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2,1-BENZOTHIAZINE 2,2-DIOXIDES. 1. SYNTHESIS, STRUCTURE, AND ANALGESIC ACTIVITY OF 1-R-4-HYDROXY-2,2-DIOXO-1*H*-2λ^6,1-BENZOTHIAZINE-3-CARBOXYLIC ACID ESTERS

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A preparative method for the synthesis of a series of 1-R-4-hydroxy-2,2-dioxo-1H-2λ^6,1-benzothiazine-3-carboxylates has been developed. The special features of the steric structure for compounds of this class have been studied on the example of the 1-N-methyl derivative. Results of studying the analgesic properties of the substances obtained are given.

Keywords: 2,1-benzothiazines, esters, acylation, analgesic activity, heterocyclization.

Chemical modification is the simplest and the most widely applied means of improving the pharmacological and pharmaceutical properties of biologically active substances [1, 2]. This is generally accepted and became quite common for the medicinal chemistry methodology used by us fairly successfully for the optimization of several lead structures discovered among numerous derivatives of 4-hydroxyquinolin-2-ones [3-7].

An interesting extension of the studies in this direction is the replacement of carbonyl in position 2 by a sulfonyl group, i.e., the transition from 4-hydroxyquinolin-2-ones to 4-hydroxy-2,1-benzothiazine 2,2-dioxides. There are numerous examples of similar modifications reported in the literature [8, 9], including that with excellent biological results [10, 11]. The variously substituted 2,2-dioxo-2,1-benzothiazines (sulfostyrils) act as test objects in this study. Up until now, only their 4-hydroxy derivatives remain outside the field of vision for investigators. We have attempted to fill the gap by planning to carry out a set of synthetic and biological work according to designated themes. The results of the first of them, 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 [12], with only difference that upon acylation of methyl anthranilates **2** we used alkyl chlorosulfonylacetates instead of alkyl malonyl chlorides [13]. This initial step was a common synthetic procedure and was not distinguished by any special features. The sulfanilides **3** obtained were subjected directly to heterocyclization step, although if necessary it is possible to isolate them in a pure state and characterize (see Experimental for details).

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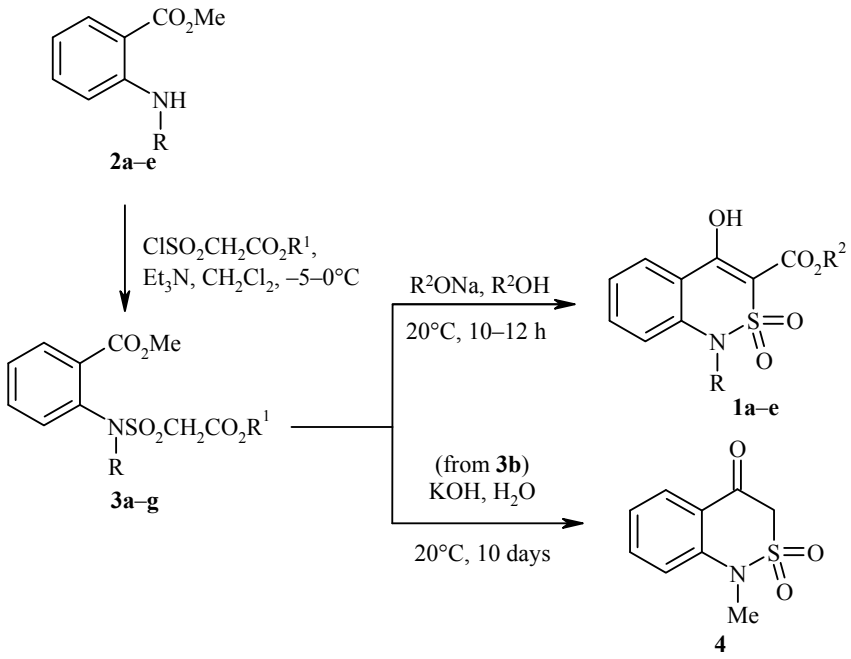
It is considered that the sulfonyl group increases the acidity of the neighboring hydrogen atoms approximately two times more than carbonyl [14]. Therefore, it was completely logical to expect that, due to the increased CH acidity of the methylene unit, cyclization of the alkyl 2-[2-(alkoxycarbonyl)phenylsulfamoyl]-acetates **3** would proceed quite readily. However, experiments showed that in reality somewhat greater energy was required for this than in the case of the seemingly less reactive alkyl 2-[2-(alkoxycarbonyl)phenyl-carbamoyl]acetates. The carbonyl analogs of sulfanilides **3**, as reported [15, 16], can be converted readily into alkyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates even at room temperature in the presence of relatively weak bases (lithium carbonate or alkylamines). However, closing the 2,1-benzothiazine ring with these catalysts was unsuccessful even on extended heating. Stronger bases, such as sodium alcoholates, were required. Under these conditions, diesters **3** displayed an enhanced inclination toward transesterification.



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

Another interesting difference in chemical properties of the acyclic alkyl 2-[2-(alkoxycarbonyl)-phenylcarbamoyl]acetates and sulfanilides **3** was discovered upon treatment with the aqueous KOH solution. Acetates, as was established previously [12], readily formed a 3-alkoxycarbonyl-substituted quinolone ring where the ester fragment was not affected. In order to eliminate ester a prolonged reflux of the reaction mixture was required. It was shown on the example of *N*-methyl derivative **3b** that sulfanilides **3** under such conditions were also capable of undergoing heterocyclization, but it proceeded far slower and was also accompanied by loss of the alkoxycarbonyl group even at room temperature, leading to the formation of 1-methyl-4-oxo-3,4-dihydro-1*H*-2λ^6,1-benzothiazine-2,2-dione (**4**).

The structures of the compounds synthesized were confirmed by ^{1}H and ^{13}C NMR spectroscopy. More interesting information was obtained with the aid of X-ray structural analysis carried out on *N*-methyl-substituted ester **1b**. As a characteristic special feature of the spatial structure of compounds of this type it should first of all be mentioned that the heterocycle on which they are based, unlike the quinolone analogs, is not planar. For example, the partially saturated thiazine ring of ester **1b** is in a "half-chair" conformation (parameters of folding [17]: S 0.52, Θ 48.0°, Ψ 27.4°). The deviations of atoms N(1) and S(1) from the mean-

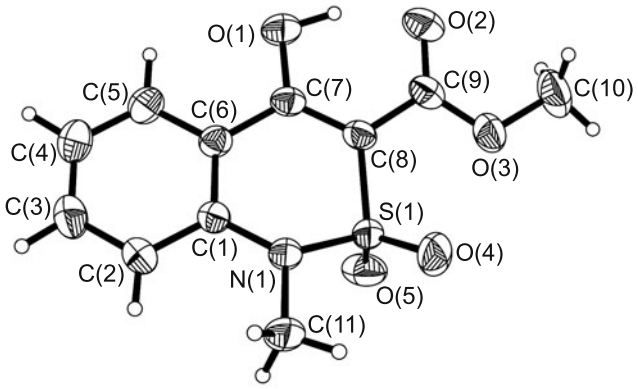


Fig. 1. The structure of the molecule of *N*-methyl-substituted ester **1b** with representation of atoms as thermal vibration ellipsoids of 50% probability.

square planarity of the remaining atoms of the ring were -0.23 and 0.35 Å, respectively (Fig. 1). It is not excluded that just this structural difference of 4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazines from the completely planar 4-hydroxy-2-oxo-1,2-dihydroquinolines [18-20] is the factor which in some degree explains the need for some larger consumption of energy in their formation.

The nitrogen atom has a pyramidal configuration, the total of the valence angles centered on it amounts to 356°. The S(1)–O(5) bond occupies an axial position, but the S(1)–O(4) bond occupies an equatorial position (torsion angles O(5)–S(1)–N(1)–C(1) -74.3(1)°, O(4)–S(1)–N(1)–C(1) 157.8(1)°). The ester substituent is practically coplanar with the endocyclic double bond (the torsion angle C(7)–C(8)–C(9)–O(2) 8.4(1)°), which enables the formation of a strong intramolecular hydrogen bond O(1)–H···O(2): H···O 1.59 Å, O–H···O 155°. The formation of a hydrogen bond also causes shortening of the O(1)–C(7) bond to 1.327(1) Å in comparison with the mean value of 1.362 Å [21] and a lengthening of the O(2)–C(9) bond to 1.230(1) Å (the mean value 1.210 Å) and C(7)–C(8) 1.374(1) Å (1.326 Å). The methyl group of the ester substituent is in the *ap* conformation relative to the C(8)–C(9) bond (the torsion angle C(10)–O(3)–C(9)–C(8) 179.2(1)°. The significant repulsion between the methyl substituent at the nitrogen atom and the atoms of the bicyclic fragment indicated by the shortened intramolecular contacts H(2)···C(11) 2.55 Å against the sum of the van der Waals radii [22] 2.87 Å, H(11b)···C(2) 2.85 Å (2.87 Å), H(11c)···C(2) 2.86 Å (2.87 Å), and the attracting interaction H(11a)···O(4) 2.38 Å (2.46 Å) assists lengthening of the N(1)–C(1) bond to 1.402(1) Å in comparison with the mean value of 1.371 Å. An attracting interaction at H(5)···O(1) 2.36 Å (2.46 Å) was also found in the molecule.

Screening investigations of the analgesic properties of esters **1a-e** were carried out on the standard model of heat-induced pain (tail-flick test) [23] enabling judgment of the central effect on the nociceptive system (see Experimental).

Analysis of the experimental data obtained showed that *N*-methyl- and *N*-phenyl-substituted esters **1b** and **1e** possessed no analgesic activity. However, the *N*-ethyl derivative **1c** displayed the activity of 23.6%, almost the level of piroxicam (+24.9%). For ester **1a**, unsubstituted at position 1, the anesthetizing properties grew to 64.0%. It was capable of suppressing the pain reaction stronger than piroxicam and diclofenac (+38.9%), reaching the level of one of the most powerful non-narcotic analgetics ketorolac (+65.4%). 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.

As a result of the investigation, we discovered a new and simple approach for the synthesis of alkyl 1-R-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylates, which might be of interest as a basis for creating new highly effective analgetics.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 solution, internal standard was TMS. Elemental analysis was carried out on a EuroVector EA-3000 microanalyzer. Melting points were determined in capillaries on a SMP10 Stuart digital melting point analyzer.

4-Hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic Acid Ethyl Ester (1a). Ethyl chlorosulfonylacetate (2.05 g, 0.010 mol) was added dropwise with stirring and cooling (-5 to 0°C) to a solution of methyl anthranilate (**2a**) (1.51 g, 0.010 mol) and triethylamine (1.54 ml, 0.011 mol) in CH_2Cl_2 (20 ml). After 5 h, water (50 ml) was added to the reaction mixture, which was then acidified to pH 4 with 1 N HCl and thoroughly mixed. The organic layer was separated, dried over anhydrous $CaCl_2$, and the solvent distilled off (at reduced pressure at the end). A solution of sodium ethylate in anhydrous ethyl alcohol (from metallic sodium (0.69 g 0.030 mol) and absolute ethanol (15 ml)) was added, the mixture was brought to boiling and stored for 10-12 h at room temperature. The reaction mixture was diluted with cold water and acidified with 1 N HCl to pH 3. The solid ester **1a** separated was filtered off, washed with water, and dried. Yield 2.53 g (94%). Colorless crystals. Mp 165-167°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.51 (2H, br. s, OH, NH); 7.92 (1H, d, *J* = 8.0, H-5); 7.63 (1H, t, *J* = 7.4, H-6); 7.23 (1H, t, *J* = 7.4, H-7); 7.15 (1H, d, *J* = 8.0, H-8); 4.40 (2H, q, *J* = 6.9, OCH_2); 1.31 (3H, t, *J* = 6.9, CH_3). ^{13}C NMR spectrum, δ, ppm: 168.2 (C-4); 167.4 (C=O); 139.4 (C-8a); 135.6 (C-7); 126.8 (C-5); 123.5 (C-6); 119.7 (C-4a); 118.4 (C-8); 105.7 (C-3); 62.2 (OCH_2); 14.6 (CH_3). Found, %: C 49.15; H 4.18; N 5.14. $C_{11}H_{11}NO_5S$. Calculated, %: C 49.07; H 4.12; N 5.20.

4-Hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid methyl ester (1b) was obtained similarly from methyl *N*-methylanthranilate (**2b**) and methyl chlorosulfonylacetate, with sodium methylate in methanol as a basic catalyst. Yield 84%. Colorless crystals. Mp 133-135°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.14 (1H, s, 4-OH); 8.03 (1H, d, *J* = 8.1, H-5); 7.73 (1H, t, *J* = 7.8, H-7); 7.39 (1H, d, *J* = 8.4, H-8); 7.32 (1H, t, *J* = 7.6, H-6); 4.00 (3H, s, OCH_3); 3.43 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 167.4 (C-4); 166.5 (C=O); 141.4 (C-8a); 135.7 (C-7); 127.2 (C-5); 123.9 (C-6); 118.3 (C-4a); 117.8 (C-8); 105.7 (C-3); 53.9 (OCH_3); 31.5 (NCH_3). Found, %: C 49.17; H 4.21; N 5.13. $C_{11}H_{11}NO_5S$. Calculated, %: C 49.07; H 4.12; N 5.20.

1-Ethyl-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid methyl ester (1c) was obtained similarly from methyl *N*-ethylanthranilate (**2c**) and isopropyl chlorosulfonylacetate. Sodium methylate in methanol was the basic catalyst. Yield 80%. Colorless crystals. Mp 111-113°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.07 (1H, s, 4-OH); 8.03 (1H, d, *J* = 8.3, H-5); 7.71 (1H, t, *J* = 7.6, H-7); 7.46 (1H, d, *J* = 8.3, H-8); 7.32 (1H, t, *J* = 7.6, H-6); 4.04 (2H, q, *J* = 7.1, NCH_2); 3.98 (3H, s, OCH_3); 1.28 (3H, t, *J* = 7.1, $NCH_2C\underline{H}_3$). Found, %: C 50.75; H 4.54; N 5.02. $C_{12}H_{13}NO_5S$. Calculated, %: C 50.88; H 4.63; N 4.94.

1-Allyl-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid methyl ester (1d) was obtained similarly from methyl *N*-allylanthranilate (**2d**) and methyl chlorosulfonylacetate, sodium methylate in methanol was the basic catalyst. Yield 82%. Colorless crystals. Mp 116-118°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.15 (1H, s, 4-OH); 8.00 (1H, d, *J* = 8.1, H-5); 7.72 (1H, t, *J* = 7.7, H-7); 7.44 (1H, d, *J* = 8.3, H-8); 7.34 (1H, t, *J* = 7.7, H-6); 6.00-5.77 (1H, m, CH); 5.26 (1H, d, *J* = 15.3) and 5.18 (1H, d, *J* = 9.3, CH=C$\underline{H}_2$); 4.58 (2H, d, *J* = 4.8, NCH_2); 3.89 (3H, s, OCH_3). Found, %: C 52.76; H 4.32; N 4.69. $C_{13}H_{13}NO_5S$. Calculated, %: C 52.87; H 4.44; N 4.74.

4-Hydroxy-1-phenyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid methyl ester (1e) was obtained similarly from methyl *N*-phenylanthranilate (**2e**) and methyl chlorosulfonylacetate, sodium methylate in methanol was the basic catalyst. Yield 77%. Colorless crystals. Mp 171-173°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.30 (1H, s, 4-OH); 8.09 (1H, d, *J* = 7.7, H-5); 7.58-7.49 (4H, m, H-7,2',4',6'); 7.36-7.29 (3H, m, H-6,3',5'); 6.73 (1H, d, *J* = 8.0, H-8); 3.96 (3H, s, OCH_3). Found, %: C 58.10; H 4.03; N 4.16. $C_{16}H_{13}NO_5S$. Calculated, %: C 58.00; H 3.95; N 4.23.

2-{[(2-Methoxy-2-oxoethyl)sulfonyl](methyl)amino}benzoic acid methyl ester (3b) was obtained similarly to sulfanilide **3a** (see synthesis of benzothiazine **1a**) from methyl *N*-methylanthranilate (**2b**) and methyl chlorosulfonylacetate. Yield 89%. Colorless crystals. Mp 60-62°C (MeOH–H_2O, 3:1). ^{1}H NMR spectrum, δ, ppm

(*J*, Hz): 7.82 (1H, d, *J* = 7.6, H-3); 7.70 (1H, t, *J* = 7.6, H-5); 7.62 (1H, d, *J* = 7.9, H-6); 7.53 (1H, t, *J* = 7.4, H-4); 4.37 (2H, s, SCH_2); 3.83 (3H, s, $CH_2COOC\underline{H}_3$); 3.72 (3H, s, $ArCOOCH_3$); 3.28 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 166.8 ($Ar\underline{C}$=O); 164.4 (CH_2–$\underline{C}$=O); 139.9 (C-1); 133.7 (C-5); 132.2 (C-3); 131.2 (C-6); 130.3 (C-4); 129.2 (C-2); 55.7 (SCH_2); 53.3 (OCH_3); 52.9 (OCH_3); 29.9 (NCH_3). Found, %: C 47.72; H 4.94; N 4.73. $C_{12}H_{15}NO_6S$. Calculated, %: C 47.83; H 5.02; N 4.65.

2-{[(2-Methoxy-2-oxoethyl)sulfonyl]amino}benzoic acid methyl ester (3f) was obtained similarly to sulfanilide **3a** (see synthesis of benzothiazine **1a**) from methyl anthranilate (**2a**) and methyl chlorosulfonylacetate. Yield 96%. Colorless crystals. Mp 95-97°C (MeOH–H_2O, 3:1). ^1H NMR spectrum, δ, ppm (*J*, Hz): 10.49 (1H, s, NH); 7.98 (1H, d, *J* = 7.7, H-3); 7.71-7.60 (2H, m, H-5,6); 7.26 (1H, t, *J* = 7.0, H-4); 4.53 (2H, s, SCH_2); 3.90 (3H, s, $CH_2COOC\underline{H}_3$); 3.61 (3H, s, $ArCOOCH_3$). ^{13}C NMR spectrum, δ, ppm: 168.3 ($Ar\underline{C}$=O); 164.0 (CH_2–$\underline{C}$=O); 139.6 (C-1); 135.4 (C-5); 131.8 (C-3); 124.5 (C-6); 119.8 (C-4); 118.0 (C-2); 56.1 (SCH_2); 53.4 (OCH_3); 53.3 (OCH_3). Found, %: C 46.08; H 4.64; N 4.95. $C_{11}H_{13}NO_6S$. Calculated, %: C 45.99; H 4.56; N 4.88.

2-{[(Isopropoxy-2-oxoethyl)sulfonyl]amino}benzoic acid methyl ester (3g) was obtained similarly to sulfanilide **3a** (see synthesis of benzothiazine **1a**) from methyl anthranilate (**2a**) and isopropyl chlorosulfonylacetate. Yield 94%. Colorless crystals. Mp 72-74°C (Me_2CO–H_2O, 3:2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 11.37 (1H, s, NH); 8.08 (1H, d, *J* = 7.8, H-3); 7.70-7.58 (2H, m, H-5,6); 7.24 (1H, t, *J* = 7.2, H-4); 4.89 (1H, m, CH); 4.46 (2H, s, SCH_2); 2.64 (3H, s, $OC\underline{H}_3$); 1.10 (6H, d, *J* = 6.4, $CH(C\underline{H}_3)_2$). Found, %: C 49.41; H 5.50; N 4.36. $C_{13}H_{17}NO_6S$. Calculated, %: C 49.52; H 5.43; N 4.44.

1-Methyl-4-oxo-3,4-dihydro-1*H*-2λ^6,1-benzothiazine-2,2-dione (4). Sulfanilide **3b** (3.01 g, 0.01 mol) was dissolved in 15% aqueous KOH solution (15 ml) and left at room temperature for 10 days. The mixture was acidified with HCl to pH 3. Solid benzothiazine **4** separated was filtered off, washed with water, and dried. Yield 1.71 g (81%). Colorless crystals. Mp 120-122°C (Et_2O) (mp 122-123°C (Et_2O) [24], mp 118-119°C [25]). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.03 (1H, d, *J* = 7.8, H-5); 7.81 (1H, t, *J* = 7.6, H-7); 7.45 (1H, d, *J* = 8.1, H-8); 7.33 (1H, t, *J* = 7.7, H-6); 5.00 (2H, s, 3-CH_2); 3.41 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 185.9 (C=O); 137.3 (C-7); 129.1 (C-8a); 128.8 (C-5); 127.9 (C-6); 124.2 (C-8); 119.4 (C-4a); 61.5 (3-CH_2); 32.4 (NCH_3).

X-Ray Structural Investigation of Compound 1b. Crystals of compound **1b** ($C_{11}H_{11}NO_5S$, *M* 269.28) were monoclinic (acetone), at 20°C: *a* 7.4863(3), *b* 18.8961(5), *c* 8.8496(3) Å; β 111.569(4)°, *V* 1164.22(7) Å^3, *Z* 4, space group $P2_1/n$, d_{calc} 1.536 g/cm^3, μ(MoKα) 0.291 mm^{-1}, *F*(000) 560. The parameters of the unit cell and the intensities of 13394 reflections (3396 independent, R_{int} 0.014) were measured on a Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ 60°). The structure was solved by the direct method with the SHELXTL set of programs [26]. The positions of the hydrogen atoms were made apparent from an electron density difference synthesis and were refined in an isotropic approximation. The structure was refined on F^2 with a full-matrix least-squares method in an anisotropic approximation for the non-hydrogen atoms to wR_2 0.092 for 3318 reflections (R_1 0.030 for 2878 reflections with $F > 4\sigma$ (*F*), *S* 1.051). The complete crystallographic information was deposited in the Cambridge Crystallographic Data Center (deposit CCDC 945496).

The analgesic activity of the compounds synthesized was studied using the tail-flick test in rats [23]. Experiments were carried out in full accord with the European Convention on protection of vertebrates used for experimental and other scientific purposes and the Ukrainian Law No. 3447-IV "On protection of animals from severe treatment" (2006). The tail tip of the experimental animal was immersed in a water bath heated to 54°. The initial duration of the latent period of immersion (jerking back) of the tail expressed in seconds was determined. The antinociceptive effect (in %) was assessed as the change in the length of the latent period of 1 h after administering the substance investigated.

All the substances under research and reference drugs (piroxicam, diclofenac, and ketorolac) were administered orally in the form of a fine aqueous suspension stabilized with Tween-80 or in solution in the dose of 20 mg/kg. The animals of the control group received the equivalent amount of the solvent.

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