UDC 615.212:542.951.1:547.831.7:547.831.9

THE STUDY OF REGULARITIES OF THE STRUCTURE – ANALGESIC ACTIVITY RELATIONSHIP IN A SERIES OF 4-HYDROXY-*N*-(PYRIDIN-2-YL)-2,2-DIOXO-1*H*-2λ⁶,1-BENZOTHIAZINE-3-CARBOXAMIDES

I.V.Ukrainets, L.O.Petrushova, O.V.Gorokhova, O.O.Davydenko*

National University of Pharmacy
53, Pushkinska Str., Kharkiv, 61002, Ukraine. E-mail: uiv-2@mail.ru
* N.I.Pirogov Vinnitsa National Medical University

Key words: amidation; 2-aminopyridines; 4-hydroxy-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamides; synthesis; analgesic activity

Continuing the search for new analgesics and with the purpose of revealing the structural-biological regularities, which are important for further studies, the synthesis of a series of 4-hydroxy-N-(pyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamides unsubstituted in position 1 has been carried out. The structure of all compounds synthesized has been confirmed by elemental analysis, ¹H NMR spectra and mass spectra. Based on a detailed analysis of the mass spectra it has been concluded that 4-hydroxy-N-(pyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamides in crystals are inner salts – 3-{[(pyridinium-2-yl)amino]carbonyl}-2,2-dioxo-1H-2,1-benzothiazin-4-olates. It has been noted that spectroscopy of ¹H NMR does not allow either to confirm or disprove that in DMSO solution the substances studied exist in the form of inner salts since the signals of the active protons of OH and NH-groups that are important do not appear. According to the results of the pharmacological screening the substances – for example, 3-{[(6-methylpyridinium-2-yl)amino]carbonyl}-2,2-dioxo-1H-2,1-benzothiazin-4-olate – exceeding Piroxicam by the analgesic activity have been found. It has been unequivocally determined that removal of the 1-N-methyl group from the structure of 4-hydroxy-1-methyl-N-(pyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamides in general leads to a marked decrease in analgesic properties and may be considered inappropriate.

ВИВЧЕННЯ ЗАКОНОМІРНОСТЕЙ ЗВ'ЯЗКУ СТРУКТУРА – АНАЛГЕТИЧНА АКТИВНІСТЬ У СЕРІЇ 4-ГІДРОКСИ-N-(ПІРИДИН-2-ІЛ)-2,2-ДІОКСО-1H-2λ⁶,1-БЕНЗОТІАЗИН-3-КАРБОКСАМІДІВ
І.В.Українець, Л.О.Петрушова, О.В.Горохова, О.О.Давиденко
Ключові слова: *амідування; 2-амінопіридини; 4-гідрокси-2,2-діоксо-1H-2λ⁶,1-бензотіазин-3-карбоксаміди; синтез; аналгетична активність*
Продовжуючи пошук нових аналгетиків та з метою виявлення важливих для подальших досліджень структурно-біологічних закономірностей, ми здійснили синтез серії незаміщених у положенні 1 4-гідрокси-N-(піридин-2-іл)-2,2-діоксо-1H-2λ⁶,1-бензотіазин-3-карбоксамідів. Будову усіх синтезованих речовин підтверджено даними елементного аналізу, спектрами ¹H ЯМР та мас-спектрами. На підставі детального аналізу мас-спектрів зроблено висновок, що в кристалах 4-гідрокси-N-(піридин-2-іл)-2,2-діоксо-1H-2λ⁶,1-бензотіазин-3-карбоксаміди представляють собою внутрішні солі – 3-{[(піридиніум-2-іл)аміно]карбоніл}-2,2-діоксо-1H-2,1-бензотіазин-4-олати. Зазначено, що спектроскопія ¹H ЯМР не дозволяє ні підтвердити, ні спростувати те, що і в розчині ДМСО досліджувані речовини існують у вигляді внутрішніх солей, оскільки важливі для подібних віднесень сигнали активних протонів ОН та NH-груп у спектрах не проявляються. За результатами фармакологічного скринінгу виявлені речовини, наприклад, 3-{[(6-метилпіридиніум-2-іл)аміно]карбоніл}-2,2-діоксо-1H-2,1-бензотіазин-4-олат, які перевищують за аналгетичною активністю Піроксикам. Однозначно встановлено, що видалення 1-N-метильної групи зі структури 4-гідрокси-1-метил-N-(піридин-2-іл)-2,2-діоксо-1H-2λ⁶,1-бензотіазин-3-карбоксамідів у цілому призводить до помітного зниження аналгетичних властивостей і може бути визнане недоцільним.

ИЗУЧЕНИЕ ЗАКОНОМЕРНОСТЕЙ СВЯЗИ СТРУКТУРА – АНАЛЬГЕТИЧЕСКАЯ АКТИВНОСТЬ В СЕРИИ 4-ГИДРОКСИ-N-(ПИРИДИН-2-ИЛ)-2,2-ДИОКСО-1H-2λ⁶,1-БЕНЗОТИАЗИН-3-КАРБОКСАМИДОВ
И.В.Украинец, Л.А.Петрушова, О.В.Горохова, А.А.Давиденко
Ключевые слова: *амидирование; 2-аминопиридины; 4-гидрокси-2,2-диоксо-1H-2λ⁶,1-бензотиазин-3-карбоксамиды; синтез; анальгетическая активность*
Продолжая поиск новых анальгетиков и с целью выявления важных для последующих исследований структурно-биологических закономерностей, мы осуществили синтез серии незамещенных в положении 1. Строение всех синтезированных соединений подтверждено данными элементного анализа, спектрами ¹H ЯМР и масс-спектрами. На основании детального анализа масс-спектров сделан вывод, что в кристаллах 4-гидрокси-N-(пиридин-2-ил)-2,2-диоксо-1H-2λ⁶,1-бензотиазин-3-карбоксамиды представляют собой внутренние соли – 3-{[(пиридиниум-2-ил)амино]карбонил}-2,2-диоксо-1H-2,1-бензо-тиазин-4-олаты. Отмечено, что спектроскопия ¹H ЯМР не позволяет ни подтвердить, ни опровергнуть то, что и в растворе ДМСО исследуемые соединения существуют в виде внутренних солей, поскольку важные для подобных отнесений сигналы активных протонов ОН и NH-групп в спектрах не проявляются. По результатам фармакологического скрининга выявлены вещества, например, 3-{[(6-метилпиридиниум-2-ил)амино]-карбонил}-2,2-диоксо-1H-2,1-бензотиазин-4-олат, которые превосходят по анальгетической активности Пироксикам. Однозначно установлено, что удаление 1-N-метильной группы из структуры 4-гидрокси-1-метил-N-(пиридин-2-ил)-2,2-диоксо-1H-2λ⁶,1-бензотиазин-3-карбоксамидов в целом приводит к заметному снижению анальгетических свойств и может быть признано нецелесообразным.

By now a chemical modification (both reversible and irreversible) has become such a powerful tool for identification of promising compounds and optimization of lead compounds obtained earlier, and it is impossible to imagine practical work of medicinal chemists engaged in the search for new biologically active substances without it. Using these methodologies a variety of problems – pharmacological, pharmaceutical, technological, etc., – faced by researchers on the long and arduous road from substance to medication are being successfully solved [1-6]. Essentially, guided by these principles we have recently begun to study derivatives of 4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acids. As one of the first objects of our research N-R-amides with the general formula **I** have been chosen. Being isomers of highly effective pain killers of oxicam series **II** (e.g., Piroxicam R = pyridin-2-yl or Meloxicam R = 5-methyl-1,3-thiazol-2-yl) [7], these compounds are of interest as potential new analgesics. Their main and, at first glance, a very simple structural difference – atoms of nitrogen and sulphur in the benzothiazinone cycle changed places, thanks to it this methodology actually got the name of "flip-flop drugs" [8] – appeared to be quite difficult task for practical implementation. However, a solution was found among hetarylamides [9-10] and anilides [11-12] of 4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid **I**, highly active analgesics were really found.

The next stage of our research was an obvious, easily done removal of the N-methyl substituent from the base molecule carried out on the example of the series of 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3a-g**. The present work aims to clarify the impact of this transformation on the structure, physico-chemical and, most importantly, the biological properties of the compounds of the series studied. It is clear that obtaining the target products only looks like *N*-demethylation. In reality, from the synthetic scheme the stage of alkylation of the initial methyl anthranilate **1** is simply excluded. Based on it, ethyl 4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylate (**2**) unsubstituted in position 1 was synthesized according the method previously described [13]. The target amides **3a-g** were obtained with good yields by interaction of this ester with equimolar amounts of the corresponding 2-aminopyridines in boiling xylene.

After recrystallization from DMF amides **3a-g** synthesized are colourless or white with a yellowish tint crystalline substances with narrow intervals of melting points, when heating they are soluble in DMF and DMSO and insoluble in ethanol and water. To confirm their structure the elemental analysis, spectroscopy ^{1}H NMR, mass spectrometry were used, and in the case of 6-methylpyridine-2-ylamide **3d** the X-ray analysis was also applied. Unfortunately, the low solubility of all amides **3a-g** in DMSO-d_6 at room temperature did not allow to record ^{13}C NMR spectra.

A distinctive feature of 1-N-methylsubstituted pyridine-2-ylamides with the general formula **I** is their existence in the form of inner salts (at least in the crystal phase) [10]. However, the question whether such a structure preserves in solution is still open. One fails to solve it in the case of 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3a-g** as well. The ^{1}H NMR spectra give important and useful information about their structure. However, they do not allow either confirm or disprove that in DMSO solution the substances studied exist in the form of inner salts since the signals of the active protons OH and NH-groups that are important do not appear (obviously, due to the rapid deuterium exchange).

But in the gas phase the salt forms of amides **3a-g** are obviously preserved as evidenced by their mass spectrometric behaviour. Unlike existing conventional and therefore quite stable 4-OH forms of 4-hydroxy-1-methyl-*N*-(1,3-thiazol-2-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides [9], here by electron impact ionization the molecular ion peak was managed to be fixed in one case only and in extremely low intensity (see Scheme 2). And if the main pathway of

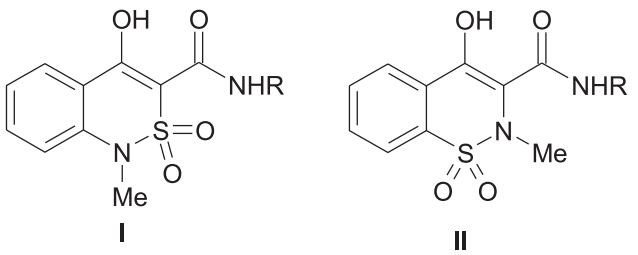
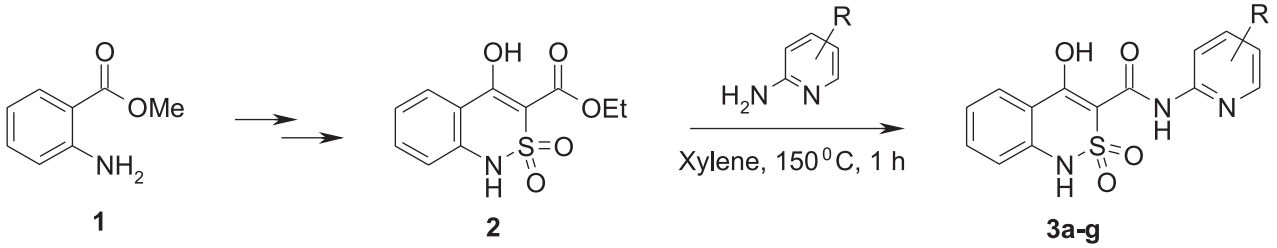
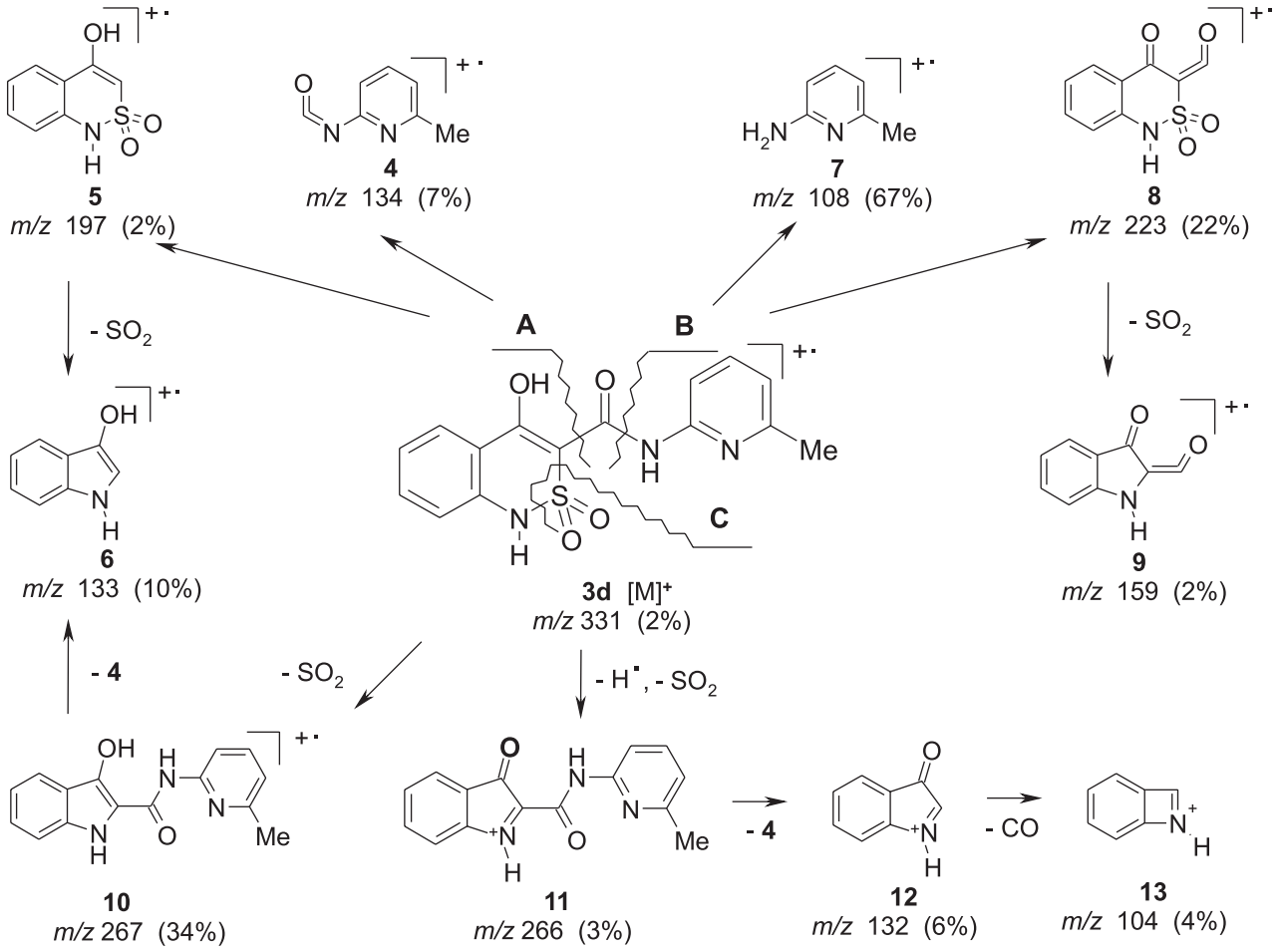


Fig. The general formula of "flip-flop" analgesics [3].



3: **a** R = H; **b** R = 4-Me; **c** R = 5-Me; **d** R = 6-Me; **e** R = 5-Cl; **f** R = 3,5-Cl_2; **g** R = 5-Br.

Scheme 1. The synthesis of 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3**.



Scheme 2. The mass spectrometric fragmentation of amide **3d** molecular ion.

the primary decomposition of molecular radical cations of thiazolyl-2-amides was breaking of the bond of the benzothiazine-carbamide fragment (pathway A), but with transition to inner salts **3a-g** the probability of such direction is considerably lost. As a result, the intensity of peaks of the corresponding fragment ions of isocyanate **4**, benzothiazine **5** and hydroxyindole **6** does not exceed 2-7%. The primary destruction of the CO-NHHet bond (pathway B) comes to the fore, as a rule, it leads to appearance of high-intensity fragment ion peaks of the corresponding 2-aminopyridines **7**, as well as ketene **8** and oxoindole **9** that are common to all samples under research. However, the main distinctive feature of the mass spectra of amides **3a-g** conditioned by their existence in the form of inner salts is an easy elimination of SO_2 from molecular ions (pathway C). It is of interest that in this case two types of products are formed: 3-hydroxyindole-2-carboxamide **10** (main) and its 3-oxo analogue **11** (minor). Apparently, their sources are different zwitterionic forms of amide **3d**.

The analgesic activity of the compounds synthesized was studied compared to Piroxicam being similar by its structure on the model of the thermal tail-flick procedure in white male rats weighing180-200 g (Tail Immersion Test) [14]. For this purpose the rat's tail tip was immersed in a water bath heated to 54ºC, and the latent period of the tail withdrawal (immersion) expressed in seconds was determined. The analgesic effect (in %) was assessed by the change of the latent period in 1 h after introduction of the test substances and the reference drug. Seven experimental animals were involved to obtain statistically reliable results (the significance level of the confidence interval accepted in this work was $p \leq 0.05$) in testing each of amides **3a-g**, the reference drug and control. All substances under research and Piroxicam were introduced orally in the form of fine aqueous suspensions stabilized with Tween-80 in a screening dose of 20 mg/kg. The animals of the control group received an equivalent amount of water with Tween-80.

All biological experiments were carried out in full accordance with the European Convention on the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and the Ukrainian Law No. 3447-IV "On protection of animals from severe treatment" (2006).

The results of our pharmacological experiments presented in Table show that removal of the 1-*N*-methyl group reflects ambiguously on the analgesic properties of 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides. In some cases –

Table

Analgesic activities of 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamides (**3a-g**) and Piroxicam

Compound	R	The latent period in 1 h after introduction of the compounds, s	Change of the latent period compared to control, %[a]
3a	H	3.52±0.11	+ 12.0 (+ 5.8)
3b	4-Me	3.46±0.10	+ 10.1 (+ 42.3)
3c	5-Me	4.08±0.12[b]	+ 29.9 (+ 3.6)
3d	6-Me	4.63±0.14[b]	+ 47.6 (+ 76.2)
3e	5-Cl	3.61±0.10	+ 15.0 (+ 96.7)
3f	3,5-Cl_2	3.92±0.11[b]	+ 24.7 (+ 25.1)
3g	5-Br	4.25±0.16[b]	+ 35.3 (+ 7.0)
Piroxicam		3.96 ± 0.15[b]	+ 26.1
Control		3.14 ± 0.14	-

[a] – The data on the analgesic activity of the corresponding 1-*N*-methyl-substituted 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxamides (**1**) are given in parentheses [10]; [b] – Significantly different from control, p≤0.05

3a,**f** amides – such chemical modification has almost no effect on the biological properties, and in other cases – **3b**,**d**,**e** amides – it causes a significant decline. At the same time there are positive examples of a substantial increase in activity – **3c**,**g** amides significantly exceed not only their 1-*N*-methyl-substituted analogues, but Piroxicam as well by the level of the analgesic effect.

Experimental Part

^{1}H NMR spectra (400 MHz) were received on a Varian Mercury-400 instrument (USA) in DMSO-d_6 solution with TMS as an internal standard. The electron impact mass spectra were recorded on a Varian 1200L mass spectrometer (USA) with complete scanning in the m/z range from 35 to 700 and direct sample inlet. The electron impact ionization was at 70 eV. Elemental analysis was performed on a Euro Vector EA-3000 microanalyzer (Great Britain). Melting points were determined in a capillary using a Stuart SMP10 digital melting point apparatus (Great Britain). The starting ethyl 4-hydroxy-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate (**2**) was prepared by our previous procedure [13]. The commercially available *o*-xylene was dried over anhydrous granular $CaCl_2$ before use and distilled.

The general procedure for the synthesis of 4-hydroxy-N-(pyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamides (3a-g). Keep the mixture of ethyl ester **2** (2.69 g, 0.01 Mol), the corresponding 2-aminopyridine (0.01 Mol), and dry *o*-xylene (5 mL) for 1 h at 150ºC on a liquid metal bath using a suitable air-cooled distilling column that allows to distill off the ethanol formed without removing the *o*-xylene solvent. Cool the reaction mixture, add EtOH (15 mL), and leave the mixture for several hours at room temperature. Filter the crystalline amide **3** precipitated, wash with cold EtOH, dry, and recrystallize from DMF. Pyridin-2-ylamides **3a**–**g** were colourless crystals or white crystals with a yellowish tint.

4-Hydroxy-N-(pyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3a). Yield – 92%. M. p. – 271-272ºC (decomp.); ^{1}H NMR, δ: 8.23 (d, J = 4.7 Hz, 1H, H-6'); 7.96-7.90 (m, 2H, H-4', 5), 7.70 (d, J = 7.2 Hz, 1H, H-3'); 7.49 (t, J = 7.7 Hz, 1H, H-7), 7.29 (t, J = 6.6 Hz, 1H, H-5'), 7.12 (t, J = 7.4 Hz, 1H, H-6), 7.06 (d, J = 8.1 Hz, H-8); MS, m/z (I_{rel}, %): 253 [M – SO_2]$^+$ (15), 252 (2), 223 (3), 197 (5), 133 (14), 132 (6), 120 (2), 106 (100), 104 (39), 77 (87); Anal. Calcd. for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: C, 53.06; H, 3.55; N, 13.17; S, 10.03.

4-Hydroxy-N-(4-methylpyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3b). Yield – 90%. M. p. – 297-299ºC (decomp.); ^{1}H NMR, δ: 8.12 (d, J = 5.7 Hz, 1H, H-6'), 7.99 (d, J = 7.8 Hz, 1H, H-5), 7.52-7.47 (m, 2H, H-7, 3'), 7.20-7.11 (m, 3H, H-6, 8, 5'), 2.35 (s, 3H, 4'-CH_3); MS, m/z (I_{rel}, %): 267 [M – SO_2]$^+$ (17), 266 (3), 223 (30), 197 (12), 159 (5), 148 (13), 134 (29), 133 (12), 132 (14), 120 (33), 119 (95), 108 (100), 104 (62), 92 (81), 81 (36), 80 (57), 77 (53); Anal. Calcd. for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68; S, 9.68. Found: C, 54.43; H, 4.02; N, 12.62; S, 9.59.

4-Hydroxy-N-(5-methylpyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3c). Yield – 91%. M. p. – 290-292ºC (decomp.); ^{1}H NMR, δ: 8.16 (s, 1H, H-6'), 7.98 (d, J = 7.6 Hz, 1H, H-5), 7.88-7.75 (m, 2H, H-4', 3'), 7.53 (t, J = 7.6 Hz, 1H, H-7), 7.21-7.08 (m, 2H, H-6, 8), 2.35 (s, 3H, 5'-CH_3); MS, m/z (I_{rel}, %): 267 [M – SO_2]$^+$ (49), 266 (7), 223 (2), 197 (3), 159 (3), 148 (17), 134 (10), 133 (16), 132 (8), 120 (32), 108 (100), 104 (18), 92 (47), 81 (25), 80 (40), 77 (22); Anal. Calcd. for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68; S, 9.68. Found: C, 54.44; H, 4.01; N, 12.60; S, 9.62.

4-Hydroxy-N-(6-methylpyridin-2-yl)-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3d). Yield – 95%. M. p. – 266-268ºC (decomp.); ^{1}H NMR, δ: 8.02-7.85 (m, 3H, H-5, 4', 3'), 7.51 (t, J = 7.4 Hz, 1H, H-7), 7.27-7.04 (m, 3H, H-6, 8, 5'), 2.50 (s, 3H, 6'-CH_3 coincides with the signals of the residual protons in DMSO-d_6); MS, m/z (I_{rel}, %): 331 [M]$^+$ (2), 267 [M – SO_2]$^+$ (34), 266 (3), 223 (22), 197 (2), 159 (2), 148 (39), 134 (7), 133 (10), 132 (6), 120 (100), 108 (67), 104 (4), 92 (84), 91 (62), 81 (88), 80 (58), 77 (17); Anal. Calcd. for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68; S, 9.68. Found: C, 54.40; H, 4.00; N, 12.59; S, 9.61.

N-(5-Chloropyridin-2-yl)-4-hydroxy-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3e). Yield – 93%. M. p. – 285-287ºC (decomp.); ^{1}H NMR, δ: 8.35

(s, 1H, H-6'), 8.17 (d, J = 8.4 Hz, 1H, H-4'), 8.00 (d, J = 7.6 Hz, 1H, H-5), 7.90 (d, J = 8.8 Hz, 1H, H-3'), 7.63 (t, J = 7.6 Hz, 1H, H-7), 7.27 (t, J = 7.2 Hz, 1H, H-6), 7.20 (d, J = 8.1 Hz, 1H, H-8); MS, m/z (I_{rel}, %): 287/289 $[M - SO_2]^+$ (34/14), 286/288 (5/7), 197 (24), 159 (6), 154/156 (48/13), 133 (22), 132 (12), 128/130 (97/43), 119 (59), 104 (70), 101 (100), 92 (58), 91 (19), 77 (79); Anal. Calcd. for $C_{14}H_{10}ClN_3O_4S$: C, 47.80; H, 2.87; N, 11.95; S, 9.12. Found: C, 47.74; H, 2.80; N, 11.88; S, 9.04.

N-(3,5-Dichloropyridin-2-yl)-4-hydroxy-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3f). Yield – 86%. M. p. – 256-258ºC (decomp.); ^{1}H NMR, δ: 8.43 (s, 1H, H-6'), 8.20 (s, 1H, H-4'), 7.98 (d, J = 7.6 Hz, 1H, H-5), 7.60 (t, J = 7.6 Hz, 1H, H-7), 7.24 (t, J = 7.2 Hz, 1H, H-6), 7.20 (d, J = 8.0 Hz, 1H, H-8); MS, m/z (I_{rel}, %): 312/323/325 $[M - SO_2]^+$ (14/10/2), 197 (18), 188/190/192 (36/24/4), 162/164/166 (98/74/14), 159 (7), 133 (15), 132 (4), 127 (60), 104 (45), 92 (61), 91 (24), 77 (38), 73 (63), 64 (100); Anal. Calcd. for $C_{14}H_9Cl_2N_3O_4S$: C, 43.54; H, 2.35; N, 10.88; S, 8.30. Found: C, 43.46; H, 2.41; N, 10.96; S, 8.23.

N-(5-Bromopyridin-2-yl)-4-hydroxy-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxamide (3g). Yield – 92%. M. p. – 291-292ºC (decomp.); ^{1}H NMR, δ: 8.41 (s, 1H, H-6'), 8.12 (d, J = 8.3 Hz, 1H, H-4'), 8.03-7.96 (m, 2H, H-5, 3'), 7.61 (t, J = 7.5 Hz, 1H, H-7), 7.25 (t, J = 7.3 Hz, 1H, H-6), 7.19 (d, J = 8.1 Hz, 1H, H-8); MS, m/z (I_{rel}, %): 331/333 $[M - SO_2]^+$ (46/45), 223 (3), 198/200 (30/27), 197 (19), 172/174 (65/61), 159 (12), 145/147 (48/44), 133 (33), 132 (18), 119 (87), 104 (76), 92 (93), 91 (31), 77 (100), 64 (44); Anal. Calcd. for $C_{14}H_{10}BrN_3O_4S$: C, 42.44; H, 2.54; N, 10.61; S, 8.09. Found: C, 42.49; H, 2.61; N, 10.68; S, 8.01.

Conclusions

1. The article presents a new series of 4-hydroxy-*N*-(pyridin-2-yl)-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxamides without substituents at the nitrogen atom of the benzothiazine cycle. The analgesic properties of all substances synthesized have been studied.

2. It has been observed that position 1 readily subjected to modification can be used for purposeful improvement of pharmaceutical or pharmacological properties of *N*-substituted 4-hydroxy-2,2-dioxo-1*H*-2λ⁶, 1-benzothiazine-3-carboxamides.

References

1. *Kubinyi H. Rossiiskii Khimicheskii Zhurnal – Russian Chemical Journal, 2006, Vol. L, No.2, pp.5-17. http://www.chem.msu.su/rus/journals/jvho/2006-2/5.pdf*
2. *Goodman A., McCall J. R., Jacocks H. M., Thompson A., Baden D., Abraham W. M., Bourdelais A. Marine drugs, 2014, Vol. 12, No.4, pp.1839-1858. DOI: 10.3390/md12041839.*
3. *Monroy C. A., Doorn J. A., Roman D. L. Chemical research in toxicology, 2013, Vol. 26, No.12, pp.1832-1839. DOI: 10.1021/tx400212q.*
4. *Banerjee S. K., Pogolotti A. Jr, Rupley J. A. The Journal of biological chemistry, 1975, Vol. 250, No.20, pp.8260-8266.*
5. *Rowland G. W., Schwartz G. G., John E. M., Ingles S. A. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research, 2012, Vol. 27, No.1, pp.187-194. DOI: 10.1002/jbmr.505.*
6. *Riverol M., Ordóñez C., Collantes M., DiCaudo C., Peñuelas I., Arbizu J., Marcilla I., Luquin M. R. Neurobiology of disease, 2014, Vol. 62, pp.250-259. DOI: 10.1016/j.nbd.2013.09.014.*
7. *Kleemann A., Engel J., Kutscher B., Reichert D. Pharmaceutical Substances: Syntheses, Patents, Applications of the most relevant APIs, 5th ed. Stuttgart, Thieme; 2008, 1800 p.*
8. *Ukrainets I. V., Gorokhova O. V., Nidal Amin Jaradat, Petrushova L. A., Mospanova E. V., Savchenkova L. V., Kuz'min V. E., Lyahovsky A. V. 4-Hydroxyquinolin-2-ones and their Close Structural Analogues as a New Source of Highly Effective Pain-killers. In book: Pain and Treatment, Racz G. B. and Noe C. E. (Ed.), Rijeka: InTech, 2014, pp.21-73. DOI: 10.5772/57402. http://www.intechopen.com/articles/show/title/4-hydroxyquinolin-2-ones-and-their-close-structural-analogues-as-a-new-source-of-highly-effective-pa*
9. *Ukrainets I. V., Petrushova L. A., Dzyubenko S. P., Sim G. Chemistry of Heterocyclic Compounds, 2014, Vol. 50, No.1, pp.103-110. doi:10.1007/s10593-014-1452-0.*
10. *Ukrainets I. V., Petrushova L. A., Dzyubenko S. P., Liu Yangyang. Chemistry of Heterocyclic Compounds, 2014, Vol. 50, No.4, pp.564-572. DOI:10.1007/s10593-014-1508-1.*
11. *Ukrainets I. V., Petrushova L. A, Dzyubenko S. P. Zhurnal Organichnoi ta Farmatsevtichnoi Khimii – Journal of Organic and Pharmaceutical Chemistry, 2014, Vol. 12, No.2(47), pp.53-58.*
12. *Petrushova L. A, Ukrainets I. V., Dzyubenko S. P., Grinevich L. A. Zhurnal Organichnoi ta Farmatsevtichnoi Khimii – Journal of Organic and Pharmaceutical Chemistry, 2015, Vol. 13, No.1(50), pp.44-48.*
13. *Ukrainets I. V., Petrushova L. A., Dzyubenko S. P. Chemistry of Heterocyclic Compounds, 2013, Vol. 49, No.9, pp.1378-1383. DOI:10.1007/s10593-013-1388-9.*
14. *Vogel H. G. Drug Discovery and Evaluation: Pharmacological Assays. – Berlin, Springer; 2008, pp.1014-1016.*

Надійшла до редакції 15.10.2015 р.