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THE SYNTHESIS, ANTI-INFLAMMATORY, ANALGESIC AND ANTIMICROBIAL ACTIVITIES OF ETHYL 2-AMINO-4-ALKYL-4,6-DIHYDROPYRANO[3,2-*c*][2,1]BENZOTHIAZIN-3-CARBOXYLATE 5,5-DIOXIDES AND TRIETHYLAMMONIUM 3-[(4-HYDROXY-1-ETHYL-2,2-DIOXIDO-1*H*-2,1-BENZOTHIAZIN-3-YL)ALKYL]-1-ETHYL-1*H*-2,1-BENZOTHIAZIN-5-OLAT 2,2-DIOXIDES

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Key words: 2,1-benzothiazine 2,2-dioxide; aliphatic aldehydes; ethyl cyanoacetate; 2-amino-4H-pyran; triethylammonium; enolate; antimicrobial activity; anti-inflammatory activity; analgesic activity

The search for new groups of anti-inflammatory and analgesic drugs is a topical issue of the current medicinal chemistry. It is caused by numerous diseases that are accompanied by pain and inflammation, as well as by imperfection of the existing drugs aimed to provide treatment of these pathological conditions. Derivatives of 1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide are promising chemicals to search and develop drugs with the pharmacological properties required. This heterocyclic system is structurally close to 2H-1,2-benzothiazin-4-one 1,1-dioxide, which is the core of the famous non-steroidal anti-inflammatory drugs related to the "oxicam" group. Moreover, derivatives of 1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide are also considered to be promising structures for searching effective antimicrobial substances among them. The present article is devoted to the synthesis of new derivatives of 1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide, namely ethyl 2-amino-4-alkyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxides and triethylammonium 3-[(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)alkyl]-1-ethyl-1H-2,1-benzothiazin-5-olat 2,2-dioxides. Condensed 2-amino-4-alkyl-4H-pyran-3-carboxylates were synthesized via the three-component one-pot interaction of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide with ethyl cyanoacetate and aliphatic aldehydes. The abovementioned triethylammonium salts were obtained by the two component interaction of 1-ethyl-1H-2,1-benzothiazin-4(3H)-one 2,2-dioxide with aliphatic aldehydes in the presence of the equimolar amount of triethylamine. The study of the anti-inflammatory and analgesic activity has demonstrated high prospects of new effective drugs when searching among two classes of the compounds synthesized. The screening of the antimicrobial activity has shown that the compounds synthesized are the most active against the fungal strain of C. albicans.

СИНТЕЗ, ПРОТИЗАПАЛЬНА, АНАЛГЕТИЧНА ТА АНТИМІКРОБНА АКТИВНІСТЬ ЕТИЛ 2-АМІНО-4-АЛКІЛ-4,6-ДИГІДРОПІРАНО[3,2-c][2,1]БЕНЗОТІАЗИН-3-КАРБОКСИЛАТ 5,5-ДІОКСИДІВ І ТРИЕТИЛАМОНІЙ 3-[(4-ГІДРОКСИ-1-ЕТИЛ-2,2-ДІОКСИДО-1Н-2,1-БЕНЗОТІАЗИН-3-ІЛ)АЛКІЛ]-1-ЕТИЛ-1Н-2,1-БЕНЗОТІАЗИН-5-ОЛАТ 2,2-ДІОКСИДІВ

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***Ключові слова**: 2,1-бензотіазин 2,2-діоксид; аліфатичні альдегіди; етилціаноацетат; 2-аміно-4Н-піран; триетиламоній; єнолят; антимікробна активність; протизапальна активність; аналгетична активність*

Пошук нових груп протизапальних та аналгетичних лікарських препаратів є актуальним завданням сучасної медичної хімії. Це обумовлено великою кількістю захворювань, що супроводжуються болем і запаленням, а також недосконалістю існуючих на теперішній час препаратів для боротьби з даними патологічними станами. Однією з перспективних хімічних груп для пошуку і розробки препаратів з даними фармакологічними властивостями є похідні 1Н-2,1-бензотіазин-4(3Н)-он 2,2-діоксиду. Вказана гетероциклічна система є структурно близькою до 2Н-1,2-бензотіазин-4-он 1,1-діоксиду, що лежить в основі комерційно успішних нестероїдних протизапальних засобів ряду оксикамів. Крім того, похідні 1Н-2,1- бензотіазин-4(3Н)-он 2,2-діоксиду розглядаються як перспективні сполуки для пошуку серед них ефективних антимікробних субстанцій. Запропонована стаття присвячена синтезу нових похідних 1Н-2,1-бензотіазин 2,2-діоксиду, а саме етил-2-аміно-4-алкіл-4,6-дигідропірано[3,2-с][2,1]бензотіазин-3-карбоксилат 5,5-діоксидів і триетиламоній 3-[(4-гідрокси-1-етил-2,2-діоксидо-1Н-2,1-бензотіазин-3-іл) алкіл]-1-етил-1Н-2,1-бензотіазин-5-олат 2,2-діоксидів. Синтез конденсованих етил-2-аміно-4-алкіл-4Н-піран-3-карбоксилатів був здійснений за допомогою трикомпонентної взаємодії між 1-етил-1Н-2,1-бензотіазин-4(3Н)-он 2,2-діоксидом, етилціаноацетатом та аліфатичними альдегідами. Синтез триетиламонієвих солей проведений шляхом двокомпонентної взаємодії 1-етил-1Н-2,1-бензотіазин-4(3Н)-он 2,2-діоксиду з аліфатичними альдегідами у присутності еквімолярної кількості триетиламіну. Вивчення протизапальної та аналгетичної активності показало високу перспективність пошуку серед двох класів синтезованих сполук нових ефективних лікарських субстанцій. Скринінг антимікробної активності показав, що найбільшу активність тестовані сполуки виявляють проти грибкового штаму C. albicans.

СИНТЕЗ, ПРОТИВОВОСПАЛИТЕЛЬНАЯ, АНАЛЬГЕТИЧЕСКАЯ И АНТИМИКРОБНАЯ АКТИВНОСТЬ ЭТИЛ 2-АМИНО-4-АЛКИЛ-4,6-ДИГИДРОПИРАНО[3,2-c][2,1]БЕНЗОТИАЗИН-3-КАРБОКСИЛАТ 5,5-ДИОКСИДОВ И ТРИЭТИЛАММОНИЙ 3-[(4-ГИДРОКСИ-1-ЭТИЛ-2,2-ДИОКСИДО-1Н-2,1-БЕНЗОТИАЗИН-3-ИЛ)АЛКИЛ]-1-ЭТИЛ-1Н-2,1-БЕНЗОТИАЗИН-5-ОЛАТ 2,2-ДИОКСИДОВ

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***Ключевые слова**: 2,1-бензотиазин 2,2-диоксид; алифатические альдегиды; этилцианоацетат; 2-амино-4Н-пиран; триэтиламмоний; фенолят; антимикробная активность; противовоспалительная активность; анальгетическая активность*

Поиск новых групп противовоспалительных и анальгетических лекарственных препаратов является актуальной задачей современной медицинской химии. Это обусловлено большим количеством заболеваний, которые сопровождаются болью и воспалением, а также несовершенством существующих препаратов для борьбы с данными патологическими состояниями. Одной из перспективных химических групп для поиска и разработки препаратов с такими фармакологическими свойствами являются производные 1Н-2,1-бензотиазин-4(3Н)-он 2,2-диоксида. Данная гетероциклическая система является структурно схожей с системой 2Н-1,2-бензотиазин-4-он 1,1-диоксида, которая лежит в основе коммерчески успешных нестероидных противовоспалительных препаратов ряда оксикамов. Кроме того, производные 1Н-2,1-бензотиазин-4(3Н)-он 2,2-диоксида рассматриваются как перспективные соединения для поиска среди них эффективных антимикробных субстанций. Предложенная статья посвящена синтезу новых производных 1Н-2,1-бензотиазин 2,2-диоксида, а именно этил 2-амино-4-алкил-4,6-дигидропирано[3,2-c][2,1] бензотиазин-3-карбоксилат 5,5-диоксидов и триэтиламмоний 3-[(4-гидрокси-1-этил-2,2-диоксидо-1Н-2,1-бензотиазин-3-ил)алкил]-1-этил-1Н-2,1-бензотиазин-5-олат 2,2-диоксидов. Синтез конденсированных этил 2-амино-4-алкил-4Н-пиран-3-карбоксилатов был осуществлен с помощью трехкомпонентного взаимодействия между 1-этил-1Н-2,1-бензотиазин-4(3Н)-он 2,2-диоксидом, этилцианоацетатом и алифатическими альдегидами. Синтез триэтиламмониевых солей проведен путем двухкомпонентного взаимодействия 1-этил-1Н-2,1-бензотиазин-4(3Н)-он 2,2-диоксида с алифатическими альдегидами в присутствии эквимолярного количества триэтиламина. Изучение противовоспалительной и анальгетической активности показало высокую перспективность поиска среди двух классов синтезированных соединений новых эффективных лекарственных субстанций. Скрининг противомикробной активности показал наибольшую активность тестируемых веществ против грибкового штамма C. albicans.

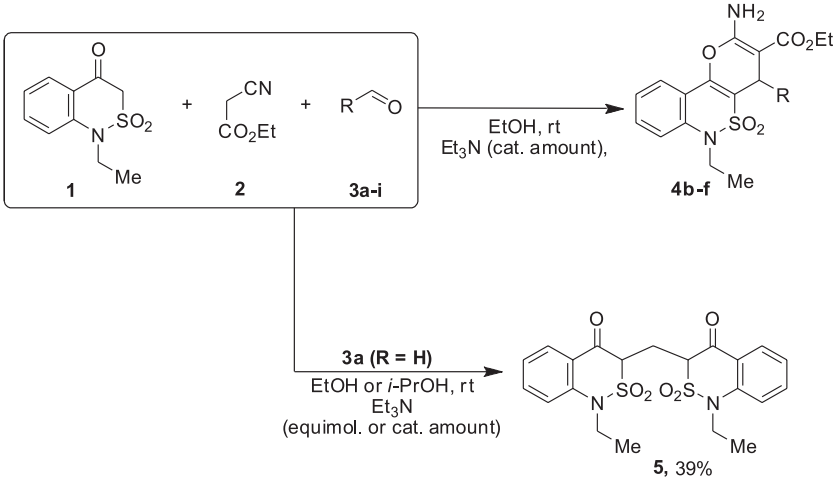
The inflammatory process is a natural host-defensive process in the innate immunity response, and it is usually associated with pain as a secondary process resulting from release of pain mediators [1]. These disease states involve a series of events that can be elicited by numerous stimuli such as infectious agents, ischemia, antigen-antibody interaction and a thermal or physical injury.

The most common drugs currently used for the treatment of pain and inflammatory conditions are non-steroidal anti-inflammatory drugs (NSAIDs). Over the past years a lot of NSAIDs have been prepared and marketed through design and development of new drug substances. These drugs play the immense role in management of various inflammatory conditions such as rheumatism, arthritis and others associated with pain. Currently, more than 30 million people worldwide take NSAIDs every day, and 40% of these patients are aged over 60 years; about 20% of inpatients receive NSAIDs [2, 3]. The high prevalence of NSAIDs is caused by the unique combination of analgesic and anti-inflammatory activities. However, these drugs are known to provoke numerous adverse effects, among them gastrointestinal irritation is the most widespread. In particular, 30-40% of patients taking NSAIDs note the presence of dyspeptic disorders, 10-20% of patients have erosions and ulcers of the stomach and duodenum, and 2-5% of them have gastrointestinal bleeding and perforation [4, 5]. In this regard, intensive studies concerning design and development of new highly efficient and safe NSAIDs continue worldwide.

Derivatives of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide are very promising for searching new substances to treat inflammatory disorders and states accompanied with pain. This heterocyclic system is structurally close to 2*H*-1,2-benzothiazin-4-one 1,1-dioxide, which is the core of famous NSAIDs related to the "oxicam" group. *N*-R-1*H*-2,1-benzothiazin-3-carboxamides have been shown to possess a high level of the analgesic activity [6]. Moreover, 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxides are a prospective core structure for creating new antimicrobial drugs as previously reported [7, 8]. Therefore, the present article is devoted to the synthesis of new derivatives of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide and evaluation of their anti-inflammatory, analgesic activities and antimicrobial properties.

The first step of our investigations was to synthesize 1*H*-2,1-benzothiazine 2,2-dioxides condensed with 4-alkyl substituted ethyl 2-amino-4*H*-pyran-3-carboxylate core via the three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**1**) with ethyl cyanoacetate (**2**) and aliphatic aldehydes **3** (Scheme 1). In our previous works [9, 10] we showed that application of malononitrile in the three-component interaction with 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide and aldehydes unambiguously led to 2-amino-3-cyano-4*H*-pyrans condensed with 1-ethyl-1*H*-2,1-benzothiazine 2,2-dioxide core, while utilization of ethyl cyanoacetate in this reaction was accompanied with side processes and lower yields of target products, namely fused ethyl 2-amino-4*H*-pyran-3-carboxylates.

The results of the three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (**1**) with ethyl cyanoacetate (**2**) and aliphatic alde-



Cmp	R	Yield, %
4b	Me	—
4c	Et	29
4d	*n*-Pr	43
4e	*n*-Bu	30
4f	*i*-Pr	48
4g	*i*-Bu	49
4i		—

Scheme 1. Aliphatic aldehydes in the three-component interaction with 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide and ethyl cyanoacetate.

hydes **3a-i** are presented in Scheme 1. As one can see, we managed to obtain the target 2-amino-4*H*-pyrans **4** only in the cases of aldehydes **3c-g**. In the cases of acetaldehyde **3b** and glutaric aldehyde **3i** we were unable to identify isolated products. The desired 2-amino-4*H*-pyranes **4c-g** were formed at the room temperature in the presence of catalytic amounts of triethylamine, but apparently in low to moderate yields. We failed in our attempts to increase the yields of the products **4** despite the application of different reaction conditions.

When formaldehyde **3a** was introduced in the three-component interaction with **1** and **2** under conditions shown in Scheme 1, the isolated product was bis(1-ethyl-1*H*-2,2-dioxido-2,1-benzothiazin-4(3*H*)-on-3-yl) methane **5**. It is interesting that product **5** was obtained as a dicarbonyl form though one could expect to isolate it as a triethylammonium salt since the equimolar amount of triethylamine was applied in the reaction, and it was in our results previously reported [10]. If the interaction of **3a** with **1** and **2** was carried out at 35-40°C, the admixture of triethylammonium salt **7a** was observed in the isolated product (not shown in Scheme 1).

The structure of bis-product **5** was proven by ^{1}H NMR and ^{13}C NMR-spectroscopic data (Fig. 1).

As one can see, protons of the CH_2 group bridging appear in the ^{1}H NMR-spectrum as a set of signals in the spectral range of 2.77-3.10 ppm (Fig. 1a), and it can be explained by the existence of compound **5** as two diastereomers (Fig. 2). This also explains the appearance of the signals in the ^{13}C NMR-spectrum (Fig. 1b) having highly similar chemical shifts, which relate to the same carbons of two diastereomeric forms.

Based on the ^{1}H NMR-spectroscopic data it has been also found that compound **5** exists exclusively in the diketoform in solutions of compounds unable to form hydrogen bonds (such as chloroform, see Fig. 1a), while such solvent as dimethylsulfoxide (DMSO) entails formation of the equilibrium between diketo-form **5** and keto-enol form **6** (Scheme 2). The molar ratio of these forms according to the ^{1}H NMR (DMSO-d_6) spectrum is about 1:0.55.

According to our research plan, we also aimed to obtain triethylammonium salts of 3-[(4-hydroxy-1-ethyl-2,2-dioxido-1*H*-2,1-benzothiazin-3-yl)alkyl]-1-ethyl-1*H*-2,1-benzothiazin-5-olat 2,2-dioxides. These salts are new derivatives of 1*H*-2,1-benzothiazine-4(3*H*)-one 2,2-dioxide and, so, they are of interest for evaluation of their biological activity in order to develop new effective anti-inflammatory, analgesic and antimicrobial substances.

In our previous works [9, 10], similar triethylammonium salts were synthesized in high yields via the interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with (het)arylcarbaldehydes (the molar ratio – 2:1) in the alcoholic solution in the presence of the equimolar amount of triethylamine. Such conditions were applied for the interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** with aliphatic aldehydes **3**. Thus, when formaldehyde **3a** was introduced into the reaction, the mixture of triethylammonium salt **7a** and bis-product **5** in the approximate molar ratio of 1:0.2 was isolated (Scheme 3). To avoid formation of undesirable products **5** the ten-fold excess of triethylamine was used; the reaction was carried out under reflux for 7 h. But the mixture of **7a** and **5** was isolated in this case too. This result serves as evidence that a formaldehyde derived product is not inclined to easy enolization and thereby to formation of enol salts.

Utilization of other aliphatic aldehydes **3b-i** allowed to obtain the desired triethylammonium salts **7b-i** in good yields. Reactions in all cases were conducted in refluxing alcohol (ethanol or 2-propanol) in the presence of the equimolar quantity of triethylamine. The yields of compounds **7b-i** synthesized are presented in Scheme 3.

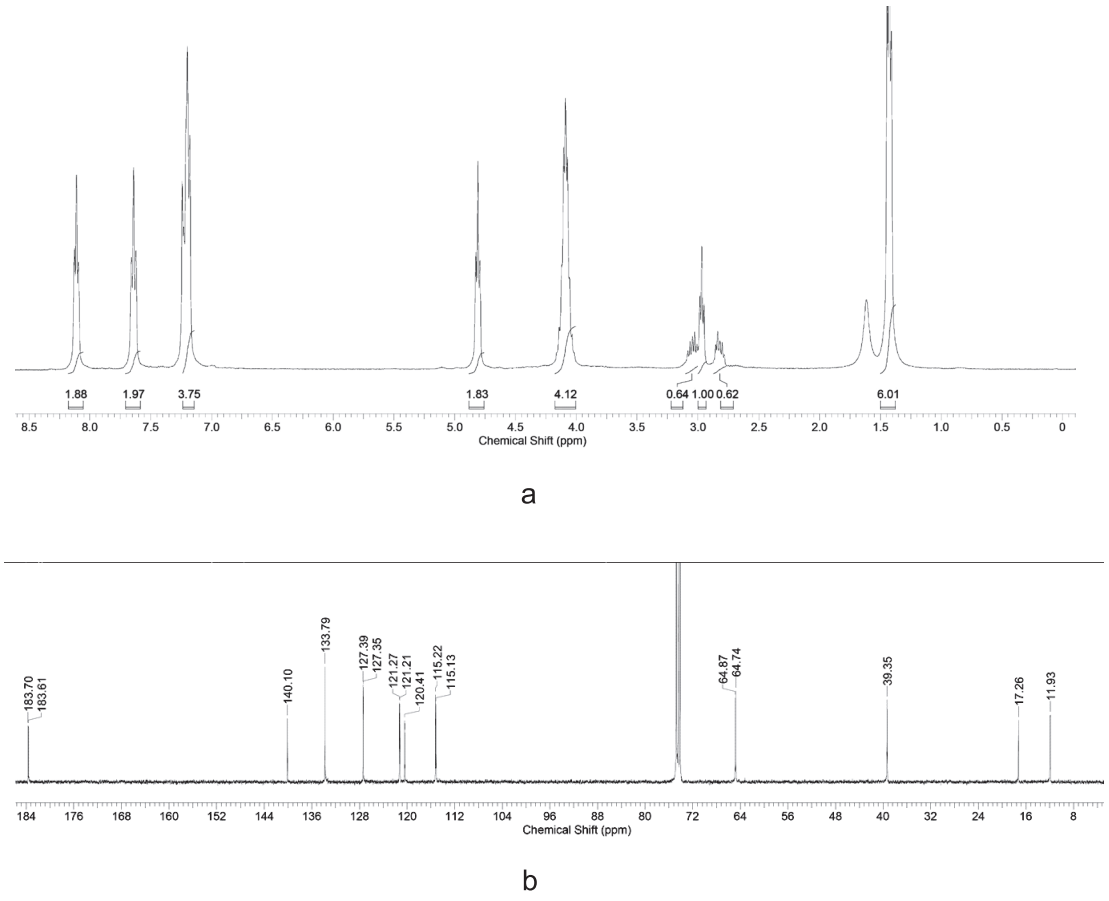


Fig. 1. ^{1}H NMR (a) and ^{13}C NMR (b) spectra of **5** (solvent – $CDCl_3$).

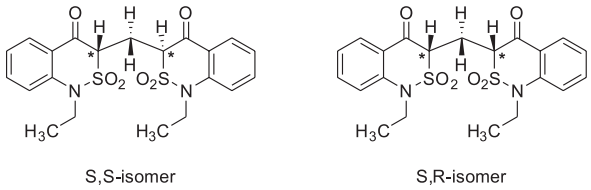
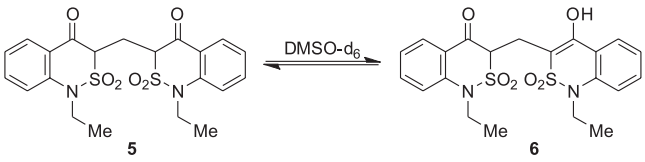


Fig. 2. Two possible diastereomers of compound **5**.

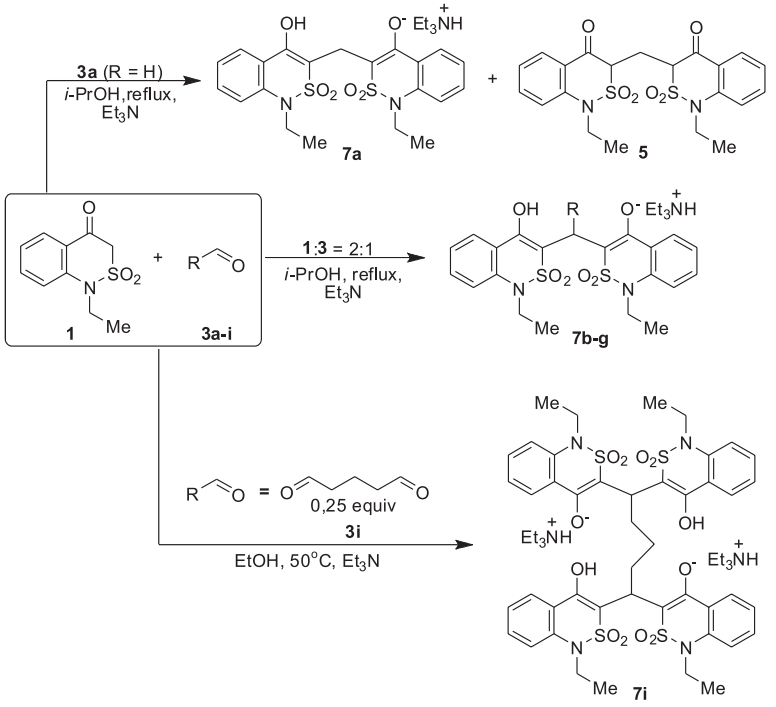


Scheme 2. The equilibrium between diketoform **5** and keto-enol form **6** in DMSO-d_6 solution.

The next stage of our investigations was evaluation of the anti-inflammatory (AIA) and analgesic (AA) activity. Compounds **4g** and **7g** as representatives of each group of the derivatives synthesized were used for this purpose. The anti-inflammatory and analgesic properties of **4g** and **7g** were studied in albino adult rats weighing 200-240 g in full compliance with the Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010 on the protection of animals used for scientific purposes [11] and with the Ukrainian Law No. 3447-IV "On protection of animals from severe treatment" [12].

AIA was studied on the model of carrageenan-induced paw edema [13, 14], and AA was determined on the model of local inflammatory hyperalgesia [14, 15]. Pathology in both cases was reproduced by the intraplantar injection of 0.1 mL of 1% solution of λ-carrageenan ("Fluka", Switzerland) into the right hind limb of the rats [14, 15]. Piroxicam (Sopharma, Bulgaria) was used as a reference drug because of its 2*H*-1,2-benzothiazin-4-one 1,1-dioxide core being structurally similar to the compounds tested. The substances under research and the reference drug were introduced orally one hour before the carrageenan injection in the form of fine aqueous suspensions stabilized with Tween-80 (0.5 mL/100 g). The screening dose of Piroxicam was 2 mg/kg, the compounds studied were introduced in doses that were equimolar to Piroxicam. The control group received the equivalent amount of Tween-80 water solution. Seven experimental animals were involved in each experimental group to obtain statistically reliable results.

The initial and final paw volumes were measured by the water displacement method using a plethysmometer, the final value of the paw volume was obtained in three hours after the phlogogen agent injection. The anti-inflammatory activity (%) was calculated as the percentage of edema inhibition in the animals treated with the substances studied and Piroxicam compared to the control rats.

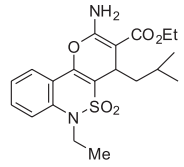
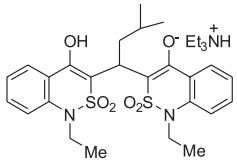


Cmp	R	Yield, %
7b	Me	73
7c	Et	57
7d	*n*-Pr	55
7e	*n*-Bu	40
7f	*i*-Pr	74
7g	*i*-Bu	78
7i		73

Scheme 3. The synthesis of triethylammonium salts.

Table 1

The data of the anti-inflammatory and analgesic activity for 4g and 7g

Compound	Dose, mg/kg	Volume of edema, %	AIA, %	Decrease of PT, %	AA, %
 **4g**	2.4	53.0±4.8*/**	29.6±6.3**	37.5±3.1*	41.4±4.8
 **7g**	3.7	48.2±3.7*	35.9±4.9	33.0±4.0*	48.5±6.2
Piroxicam	2.0	40.1±2.6*	46.7±3.5	29.4±3.4*	54.1±5.3
Control	–	75.2±7.8	–	64.1±4.0	–

Note: * – differences were significant at $p<0.05$ compared to the control group; ** – differences were significant at $p<0.05$ compared to Piroxicam.

The analgesic effect (in %) was assessed by the change of the pain threshold (PT) checked on the inflamed paw in rats receiving **4g**, **5g** and Piroxicam in three hours after administration of the test substances compared to the vehicle-treated animals.

The comparative analysis of the experimental data is given in Tab. 1. The results were calculated using standard math procedures and presented in the form of *arithmetic mean±standard error of the mean*. The results of biological tests were also processed by the method of variation statistics using Student's t-criterion.

Carrageenan-induced pathology is commonly used as an experimental model in animals for acute inflammation and indicated the anti-exudative activity of the compounds synthesized, as well as their ability to inhibit the action of pain mediators. This is connected with biphasic evolution of the disease process in this case [16, 17]. The initial phase of the carrageenan model is mainly mediated by histamine, serotonin and the increased synthesis of prostaglandins in the damaged tissue. The next phase is supported by prostaglandin release and mediated by bradykinin,

Table 2

The data of the antimicrobial activity for compounds 4 and 7

Compound	MIC (μg/mL)				
	S. aureus (ATCC 6538)	*E. coli* (ATCC 8739)	*B. subtilis* (ATCC 6633)	*P. aeruginosa* (ATCC 9027)	*C. albicans* (ATCC 10231)
4c	250	250	250	500	250
4d	500	250	125	250	250
4e	250	250	125	125	125
4f	250	500	250	62.5	62.5
4g	125	125	250	125	62.5
7b	250	250	250	125	125
7c	250	125	125	125	62.5
7d	growth	growth	growth	growth	growth
7f	250	250	125	125	62.5
7g	250	250	125	125	125
7i	250	250	250	125	125
DMSO*	275	137.5	137.5	275	550

Note: *– the concentration for DMSO was calculated based on its density value of 1.1 mg/mL.

leukotrienes, polymorphonuclear cells and prostaglandins produced by tissue macrophages. All of the mediators released are the main inflammation factors and act at their receptors to increase permeability of small blood vessels and thereby to support the progress of exudation. The chemosensitivity of nociceptors allows the released mediators to act on these neurons and causes the appearance of hyperalgesia. These features allow to determine the inhibition effect of the test compounds at the second (exudative) stage of inflammation, as well as to identify the peripheral component affecting the nociceptive system in the mechanism of the analgesic effect of the substances studied.

During pharmacological studies of anti-inflammatory and analgesic agents (especially during the screening phase), a substantial level of the pharmacological activity must be not less than 20% [7]. In this regard, the results of AIA of the compounds assessed are promising (Tab. 1). Compound **4g** administered in the dose of 2.4 mg/kg moderately decreased development of edema (29.6±6.3%) in 3 h after the phlogogen injection, whereas triethylammonium salt **7g** was slightly more active and in the equimolar dose of 3.7 mg/kg decreased development of edema at the level of 35.9±4.9%.

The similar results were obtained for the study of AA. Both of the compounds studied showed the high level of AA (Tab. 1). While 4*H*-pyran annulated derivative **4g** showed AA of 41.4±4.8%, triethylammonium salt **7g** (48.5±6.2%) was almost as good as the reference drug Piroxicam (54.2±5.3%).

The results obtained allow considering 4*H*-pyran annulated derivatives **4** and triethylammonium salts **7** as the basis for design of highly effective substances which will be useful for treatment of various diseases accompanied by inflammation and pain such as inflammatory arthropathies, injuries, etc.

The antimicrobial activity of 2-amino-4*H*-pyranes **4** and triethylammonium enolates 7 in vitro was studied according to the requirements of the State Pharmacopoeia of Ukraine (1 ed.) by the double serial dilution method in the liquid growth medium. The compounds synthesized were tested against Pharmacopoeial Gram positive (*S. aureus* – ATCC 6538, *B. subtilis* – ATCC 6633) and Gram negative (*E. coli* – ATCC 8739, *P. aeruginosa* – ATCC 9027) strains of bacteria, as well as against the fungal strain of C. albicans (ATCC 10231) [18, 19]. The solutions of the compounds studied with the concentrations of 500, 250, 125, 62.5, 31.25, 15.62 μg/mL were prepared using dimethylsulfoxide (DMSO) as a solvent and the broth as a growth medium. Since DMSO exhibits a moderate antimicrobial activity [20], it is used as a reference drug. Inocula of the bacterial and fungal cultures were prepared according to the optical turbidity standard of 0.5 ME from a daily agar culture. The microbial load was 150×10^6 microbes per mL. The test-tubes containing bacterial cultures were kept in the thermostat at 37°C for 24 h, and test-tubes containing C. albicans culture were kept in the thermostat at 25°C for 48 h and observed for the presence of turbidity. The lowest concentration when no growth of microorganisms was observed was taken as the minimum inhibitory concentration (MIC) value. The MIC values detected for the solutions studied are presented in Tab. 2.

From the activity report it can be noticed that most of the test compounds did not reveal any activity or

displayed a slight antimicrobial activity against the bacterial strains. Furthermore, it is interesting that DMSO solutions of the derivatives studied showed the higher MIC values against bacterial strains compared to the reference DMSO.

At the same time, all of the compounds studied exhibited a moderate or high antifungal activity against *C. albicans*. Among 2-amino-4*H*-pyrans **4** the most active were isobutiric and isovaleric aldehyde derived products **4f,g**; in addition, compound **4g** was also moderately active against *P. aeruginosa* strain. Isobutiric and isovaleric aldehyde derived products **7f,g** and propionaldehyde derived compound **7c** displayed the lowest values of MIC among triethylammonium salts **7**. Thus, 4*H*-pyran derivatives **4** and triethylammonium salts **7** containing the branched alkyl chain were the most active compounds studied. These results are of interest for discovering a new class of compounds to treat fungal related diseases.

Experimental Part

Chemical Part

The starting aldehydes and ethyl cyanoacetate were obtained from commercial sources and used without further purification. The starting 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide was obtained according to the procedure previously described [21]. The new compounds are characterized by the data of melting points (obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes), ^{1}H and ^{13}C NMR-spectroscopic data (recorded on a Varian WXR-400 spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard, chemical shifts in parts per million) and elemental analysis (carried out using a Carlo Erba CHNS-O EA 1108 analyzer).

The general procedure for the synthesis of ethyl 2-amino-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxides (4c-g). To the solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 Mol), ethyl cyanoacetate **2** (0.112 g, 0.001 Mol) and appropriate aldehyde **3c-g** (0.001 Mol) in ethanol (5-10 mL) add the catalytic amount of triethylamine. Allow the mixture to stand at the room temperature. Filter the resulting precipitates of **4c-g**, wash with cold ethanol and dry on the air.

Ethyl 2-amino-4,6-diethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxide (4c). Yield – 0.11 g (29%), colourless prisms. M. p. – 163-165°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.67 (t, *J* = 7.34 Hz, 3H, $CHCH_2C\underline{H}_3$), 1.12-1.24 (m, 6H, $NCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.58-1.73 (m, 2H, $CHC\underline{H}_2CH_3$), 3.90 (t, *J* = 3.67 Hz, 1H, $C\underline{H}CH_2CH_3$), 3.97-4.19 (m, 4H, $NC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$), 7.33 (t, *J* = 7.52 Hz, 1H, Ar-H), 7.51-7.56 (m, 1H, Ar-H), 7.58-7.64 (m, 1H, Ar-H), 7.71 (s, 2H, $N\underline{H}_2$), 7.92 (d, *J* = 8.07 Hz, 1H, Ar-H). Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40; S, 8.47. Found: C, 57.25; H, 5.71; N, 7.54; S, 8.23.

Ethyl 2-amino-4-propyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxide (4d). Yield – 0.17 g (43%), colourless prisms. M. p. – 180-182°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.77 (t, *J* = 7.17 Hz, 3H, $CHCH_2CH_2C\underline{H}_3$), 1.03-1.27 (m, 8H, $NCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$, $CHCH_2C\underline{H}_2CH_3$), 1.50-1.69 (m, 2H, $CHC\underline{H}_2CH_2CH_3$), 3.88 (t, *J* = 3.73 Hz, 1H, $C\underline{H}CH_2CH_2CH_3$), 3.96-4.20 (m, 4H, $NC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$), 7.32 (t, *J* = 7.48 Hz, 1H, Ar-H), 7.49-7.56 (m, 1H, Ar-H), 7.57-7.64 (m, 1H, Ar-H), 7.69 (s, 2H, $N\underline{H}_2$), 7.92 (d, *J* = 7.63 Hz, 1H, Ar-H). Anal. Calcd for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14; S, 8.17. Found: C, 58.30; H, 6.03; N, 7.08; S, 8.41.

Ethyl 2-amino-4-butyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxide (4e). Yield – 0.12 g (30%), colourless prisms. M. p. – 131-133°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.69-0.81 (m, 3H, $CHCH_2CH_2CH_2C\underline{H}_3$), 0.98-1.32 (m, 10H, $NCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$, $CHCH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.53-1.73 (m, 2H, $CHC\underline{H}_2CH_2CH_2CH_3$), 3.86-3.93 (m, 1H, $C\underline{H}CH_2CH_2CH_2CH_3$), 3.97-4.22 (m, 4H, $NC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$), 7.33 (t, *J* = 7.14 Hz, 1H, Ar-H), 7.50-7.57 (m, 1H, Ar-H), 7.58-7.65 (m, 1H, Ar-H), 7.69 (s, 2H, $N\underline{H}_2$), 7.93 (d, *J* = 7.68 Hz, 1H, Ar-H). Anal. Calcd for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89; S, 7.89. Found: C, 59.23; H, 6.70; N, 7.07; S, 7.52.

Ethyl 2-amino-4-(propan-2-yl)-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxide (4f). Yield – 0.19 g (48%), colourless prisms. M. p. – 160-162°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.70 (d, *J* = 6.60 Hz, 3H, $CHCH(C\underline{H}_3)_2$), 0.79 (d, *J* = 6.97 Hz, 3H, $CHCH(C\underline{H}_3)_2$), 1.11-1.24 (m, 6H, $NCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.88-2.02 (m, 1H, $CHC\underline{H}(CH_3)_2$), 3.84 (d, *J* = 2.93 Hz, 1H, $C\underline{H}CH(CH_3)_2$), 3.96-4.19 (m, 4H, $NC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$), 7.33 (t, *J* = 7.52 Hz, 1H, Ar-H), 7.50-7.56 (m, 1H, Ar-H), 7.57-7.64 (m, 1H, Ar-H), 7.70 (s, 2H, $N\underline{H}_2$), 7.95 (d, *J* = 7.70 Hz, 1H, Ar-H). Anal. Calcd for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14; S, 8.17. Found: C, 58.34; H, 6.21; N, 7.27; S, 8.30.

Ethyl 2-amino-4-(2-methylpropyl)-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazin-3-carboxylate 5,5-dioxide (4g). Yield – 0.20 g (49%), colourless prisms. M. p. – 155-157°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.78 (d, *J* = 6.24 Hz, 3H, $CHCH_2CH(C\underline{H}_3)_2$), 0.85 (d, *J* = 6.24 Hz, 3H, $CHCH_2CH(C\underline{H}_3)_2$), 1.13-1.24 (m, 6H, $NCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.32-1.41 (m, 1H, $CHCH_2C\underline{H}(CH_3)_2$), 1.46-1.63 (m, 2H, $CHC\underline{H}_2CH(CH_3)_2$), 3.84 (dd, *J* = 6.42, 4.22 Hz, 1H, $C\underline{H}CH_2CH(CH_3)_2$), 3.97-4.23 (m, 4H, $NC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$), 7.32 (t, *J* = 7.52 Hz, 1H, Ar-H), 7.50-7.54 (m, 1H, Ar-H), 7.57-7.63 (m, 1H, Ar-H), 7.71 (s, 2H, $N\underline{H}_2$), 7.95 (d, *J* = 7.70 Hz, 1H, Ar-H). Anal. Calcd for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89; S, 7.89. Found: C, 59.01; H, 6.32; N, 7.13; S, 7.72.

The synthesis of bis(1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-4(3H)-on-3-yl)methane (5). To the solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 Mol) in 2-propanol (10 mL)

add 40% water solution of formaldehyde **3a** (0.075 g, 0.001 Mol), ethyl cyanoacetate (0.112 g, 0.001 Mol) and triethylamine (0.101 g, 0.001 Mol). Allow the solution to stand at the room temperature for 48 h. After that evaporate the solvent in vacuum, dissolve the residue in methanol, and cool the solution to 5°C. Filter the precipitate formed, wash with cold methanol and dry on the air to obtain a pure product. Yield – 0.09 g (39%), a white powder. M. p. – 147-149°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.43 (t, *J* = 6.79 Hz, 6H, 2×$NCH_2C\underline{H}_3$), 2.77-3.10 (m, 2H, CH_2 bridged), 4.01-4.17 (m, 4H, 2×$NC\underline{H}_2CH_3$), 4.81 (t, *J* = 6.79 Hz, 2H, 2×$SO_2C\underline{H}CO$), 7.13-7.23 (m, 4H, Ar-H), 7.64 (t, *J* = 7.70 Hz, 2H, Ar-H), 8.11 (t, *J* = 6.97 Hz, 2H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 11.93 (2×$NCH_2\underline{C}H_3$), 17.26 ($\underline{C}H_2$ bridged), 39.29 ($N\underline{C}H_2CH_3$), 39.25 ($N\underline{C}H_2CH_3$), 64.74 ($SO_2\underline{C}HCO$), 64.87 ($SO_2\underline{C}HCO$), 115.13, 115.22, 120.36, 120.41, 121.21, 121.27, 127.35, 127.39, 133.79, 140.10, 140.12, 183.61 ($SO_2CH\underline{C}O$), 183.70 ($SO_2CH\underline{C}O$) Anal. Calcd for $C_{21}H_{22}N_2O_6S_2$: C, 54.53; H, 4.79; N, 6.06; S, 13.86. Found: C, 54.42; H, 4.85; N, 5.91; S, 13.58.

The general procedure for the synthesis of triethylammonium 3-[(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)alkyl]-1-ethyl-1H-2,1-benzothiazin-4-olat 2,2-dioxides (7b-g). To the solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.450 g, 0.002 Mol) and aldehyde **3b-g** (0.001 Mol) in 2-propanol (10 mL) add triethylamine (0.14 mL, 0.001 Mol). Stir the solution and reflux for 2 h, and cool the mixture to the room temperature. Filter the precipitates formed, wash with 2-propanol and dry on the air. Recrystallize the crude products from 2-propanol to obtain pure products **7b-g**.

Triethylammonium 3-[1-(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)ethyl]-1-ethyl-1H-2,1-benzothiazin-4-olate 2,2-dioxide (7b). Yield – 0.42 g (73%), a white crystalline powder. M. p. – 110-112°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.06-1.16 (m, 15H, 2×$NCH_2C\underline{H}_3$, $HN^+(CH_2C\underline{H}_3)_3$), 1.57 (d, *J* = 7.32 Hz, 3H, $C\underline{H}_3CH$), 3.00 (q, *J* = 7.32 Hz, 6H, $HN^+(C\underline{H}_2CH_3)_3$), 3.86 (q, *J* = 6.92 Hz, 4H, 2×$NC\underline{H}_2CH_3$), 7.12 (t, *J* = 7.48 Hz, 2H, Ar-H), 7.22 (d, *J* = 7.93 Hz, 2H, Ar-H), 7.35-7.41 (m, 2H, Ar), 7.92 (d, *J* = 7.63 Hz, 2H, Ar-H), 17.58 (br. s, 1H, O$\underline{H}$). Anal. Calcd for $C_{28}H_{39}N_3O_6S_2$: C, 58.21; H, 6.80; N, 7.27; S, 11.10. Found: C, 58.34; H, 6.93; N, 7.38; S, 11.32.

Triethylammonium 3-[1-(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)propyl]-1-ethyl-1H-2,1-benzothiazin-4-olate 2,2-dioxide (7c). Yield – 0.34 g (57%), a white crystalline powder. M. p. – 121-123°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.73 (t, *J* = 7.32 Hz, 3H, $C\underline{H}_3CH_2CH$), 1.05-1.15 (m, 15H, 2×$NCH_2C\underline{H}_3$, $HN^+(CH_2C\underline{H}_3)_3$), 2.09 (quin, *J* = 7.48 Hz, 2H, $CH_3C\underline{H}_2CH$), 2.98 (q, *J* = 7.12 Hz, 6H, $HN^+(C\underline{H}_2CH_3)_3$), 3.85 (q, *J* = 7.02 Hz, 4H, 2×$NC\underline{H}_2CH_3$), 4.20 (t, *J* = 8.09 Hz, 1H, $CH_3CH_2C\underline{H}$), 7.09 (t, *J* = 7.48 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.24 Hz, 2H, Ar-H), 7.33-7.39 (m, 2H, Ar), 7.89 (d, *J* = 7.93 Hz, 2H, Ar-H), 17.53 (br. s, 1H, O$\underline{H}$). Anal. Calcd for $C_{29}H_{41}N_3O_6S_2$: C, 58.86; H, 6.98; N, 7.10; S, 11.84. Found: C, 58.70; H, 7.11; N, 7.21; S, 11.93.

Triethylammonium 3-[1-(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)butyl]-1-ethyl-1H-2,1-benzothiazin-4-olate 2,2-dioxide (7d). Yield – 0.33 g (55%), a white crystalline powder. M. p. – 118-120°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.79 (t, *J* = 7.34 Hz, 3H, $C\underline{H}_3CH_2CH_2CH$), 1.06-1.18 (m, 17H, 2×$NCH_2C\underline{H}_3$, $HN^+(CH_2C\underline{H}_3)_3$, $CH_3C\underline{H}_2CH_2CH$), 2.06 (q, *J* = 7.99 Hz, 2H, $CH_3CH_2C\underline{H}_2CH$), 3.01 (q, *J* = 7.34 Hz, 6H, $HN^+(C\underline{H}_2CH_3)_3$), 3.85 (q, *J* = 6.85 Hz, 4H, 2×$NC\underline{H}_2CH_3$), 4.34 (t, *J* = 8.19 Hz, 1H, $CH_3CH_2CH_2C\underline{H}$), 7.09 (t, *J* = 7.46 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.07 Hz, 2H, Ar-H), 7.34-7.40 (m, 2H, Ar-H), 7.87-7.93 (m, 2H, Ar-H), 17.47 (br. s, 1H, O$\underline{H}$). Anal. Calcd for $C_{30}H_{43}N_3O_6S_2$: C, 59.48; H, 7.15; N, 6.94; S, 10.59. Found: C, 59.39; H, 7.27; N, 7.03; S, 10.75.

Triethylammonium 3-[1-(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)pentyl]-1-ethyl-1H-2,1-benzothiazin-4-olate 2,2-dioxide (7e). Yield – 0.25 g (40%), a white powder. M. p. – 170-172°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.75 (t, *J* = 7.15 Hz, 3H, $C\underline{H}_3CH_2CH_2CH_2CH$), 1.07-1.26 (m, 19H, 2×$NCH_2C\underline{H}_3$, $HN^+(CH_2C\underline{H}_3)_3$, $CH_3C\underline{H}_2C\underline{H}_2CH_2CH$), 2.08 (q, *J* = 7.70 Hz, 2H, $CH_3CH_2CH_2C\underline{H}_2CH$), 3.29-3.36 (m, 6H, $HN^+(C\underline{H}_2CH_3)_3$), 3.85 (q, *J* = 6.97 Hz, 4H, 2×$NC\underline{H}_2CH_3$), 4.31 (t, *J* = 8.07 Hz, 1H, $CH_3CH_2CH_2CH_2C\underline{H}$), 7.09 (t, *J*=7.34 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.07 Hz, 2H, Ar-H), 7.33-7.40 (m, 2H, Ar-H), 7.89 (d, *J* = 7.70 Hz, 2H, Ar-H), 17.54 (br. s, 1H, O$\underline{H}$). Anal. Calcd for $C_{31}H_{45}N_3O_6S_2$: C, 60.07; H, 7.32; N, 6.78; S, 10.35. Found: C, 59.93; H, 7.48; N, 6.59; S, 10.53.

Triethylammonium 3-[1-(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)-2-methylpropyl]-1-ethyl-1H-2,1-benzothiazin-4-olate 2,2-dioxide (7f). Yield – 0.45 g (74%), white prisms. M. p. – 157-159°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.81 (d, *J* = 6.50 Hz, 6H, $(C\underline{H}_3)_2CHCH$), 1.10-1.19 (m, 16H, 2×$NCH_2C\underline{H}_3$, $HN^+(CH_2C\underline{H}_3)_3$, $(CH_3)_2C\underline{H}CH$), 3.02-3.10 (m, 6H, $HN^+(C\underline{H}_2CH_3)_3$), 3.82-3.90 (m, 5H, 2×$NC\underline{H}_2CH_3$, $(CH_3)_2CHC\underline{H}$), 7.08 (t, *J* = 7.34 Hz, 2H, Ar-H), 7.19 (d, *J* = 8.07 Hz, 2H, Ar-H), 7.33-7.39 (m, 2H, Ar-H), 7.86-7.90 (m, 2H, Ar-H), 17.65 (br. s, 1H, O$\underline{H}$). Anal. Calcd for $C_{30}H_{43}N_3O_6S_2$: C, 59.48; H, 7.15; N, 6.94; S, 10.59. Found: C, 59.58; H, 7.14; N, 7.10; S, 10.41.

Triethylammonium 3-[1-(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)-3-methylbutyl]-1-ethyl-1H-2,1-benzothiazin-4-olate 2,2-dioxide (7g). Yield – 0.48 g (78%), white prisms. M. p. – 120-122°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.80 (d, *J* = 6.71 Hz, 6H, $(C\underline{H}_3)_2CHCH_2CH$), 1.07-1.16 (m, 15H, 2×$NCH_2C\underline{H}_3$, $HN^+(CH_2C\underline{H}_3)_3$), 1.28-1.39 (m, 1H, $(CH_3)_2C\underline{H}CH_2CH$), 1.97 (t, *J* = 7.32 Hz, 2H, $(CH_3)_2CHC\underline{H}_2CH$), 3.02 (q, *J* = 7.32 Hz, 6H, $HN^+(C\underline{H}_2CH_3)_3$), 3.85 (q, *J* = 6.92 Hz, 4H, 2×$NC\underline{H}_2CH_3$), 4.43 (t, *J* = 8.09 Hz, 1H,

$(CH_3)_2CHCH_2C\underline{H}$), 7.09 (t, *J* = 7.48 Hz, 2H, Ar-H), 7.20 (d, *J* = 8.24 Hz, 2H, Ar-H), 7.33-7.39 (m, 2H, Ar-H), 7.89 (d, *J* = 7.93 Hz, 2H, Ar-H), 17.49 (br. s, 1H, O$\underline{H}$). Anal. Calcd for $C_{31}H_{45}N_3O_6S_2$: C, 60.07; H, 7.32; N, 6.78; S, 10.35. Found: C, 59.91; H, 7.48; N, 6.54; S, 10.50.

The procedure for the synthesis of di(triethylammonium) 3,3′-[1,5-bis(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)pentane-1,5-diyl]bis(1-ethyl-1H-2,1-benzothiazin-4-olat 2,2-dioxide) (7i). To the solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.450 g, 0.002 Mol) and 50% water solution of glutaric aldehyde **3i** (0.105 g, 0.0005 Mol) in ethanol (10 mL) add triethylamine (0.101 g, 0.001 Mol). Stir the solution at 50°C for 30 min, cool to the room temperature and allow it to stand overnight. Treat the oily precipitate formed with water until it becomes solid. Filter it, wash with water and dry on the air to obtain a pure product **5i**. Yield – 0.42 g (73%), a pink powder. M. p. – 125-127°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.05-1.17 (m, 32H, 4×$NCH_2C\underline{H}_3$, 2×$HN^+(CH_2C\underline{H}_3)_3$, $CHCH_2C\underline{H}_2CH_2CH$), 2.02 (q, *J* = 7.32 Hz, 4H, $CHC\underline{H}_2CH_2C\underline{H}_2CH$), 3.00 (q, *J* = 7.21 Hz, 12H, 2×$HN^+(C\underline{H}_2CH_3)_3$,), 3.63-3.73 (m, 4H, 2×$NC\underline{H}_2CH_3$), 3.76-3.86 (m, 4H, 2×$NC\underline{H}_2CH_3$), 4.19 (t, *J* = 7.89 Hz, 2H, $C\underline{H}CH_2CH_2CH_2C\underline{H}$), 7.08 (t, *J* = 7.34 Hz, 4H, Ar-H), 7.16 (d, *J* = 8.07 Hz, 4H, Ar-H), 7.34 (t, *J* = 7.52 Hz, 4H, Ar-H), 7.85 (d, *J* = 7.70 Hz, 4H, Ar-H), 17.48 (br. s, 2H, O$\underline{H}$). Anal. Calcd for $C_{57}H_{78}N_6O_{12}S_4$: C, 58.64; H, 6.73; N, 7.20; S, 10.99. Found: C, 58.52; H, 6.81; N, 7.03; S, 11.12.

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