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PECULIARITIES OF 2-AMINO-3-R-4-ARYL-4*H*-PYRANES MULTICOMPONENT SYNTHESIS DERIVED FROM 1*H*-2,1-BENZOTHIAZIN-4(3*H*)-ONE 2,2-DIOXIDE

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Abstract – The new 2-amino-3-R-4-aryl-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxides were synthesized via three-component interaction of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with arylcarbaldehydes and active methylene nitriles. Depending on the nature of an active methylene nitrile and an arylcarbaldehyde this interaction can lead either to the target 2-amino-4*H*-pyrans or to the stable triethylammonium salts of bis(1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxides) (bis-adducts). The later is a completely new product of such interaction. The structure of the bis-adduct was confirmed by the single crystal X-ray diffraction. Actually, the formation of stable triethylammonium salts (as the process competitive with the 2-amino-4*H*-pyrans formation) appeared to be reversible and their interaction with active methylene nitriles led to the formation of 2-amino-4*H*-pyrans. The extended and adjusted mechanism of three-component interaction, that includes the bis-adducts formation stage, was proposed. Taking into account the peculiarities of the mechanism of studied reaction, we were capable of controlling the reaction selectivity.

Keywords: 1*H*-2,1-benzothiazin-4(3*H*)-one, 4*H*-pyran, triethylammonium salt, benzaldehydes, active methylene nitriles, multicomponent reaction, mechanism, competing reaction, equilibrium.

1. Introduction

Multicomponent reactions (MCRs) are an extremely effective tool for the rapid generation of small-molecule libraries by creation of structural complexity in a single step from three or more reactants, providing greater efficiency and an atom economy as compared with stepwise synthesis.[1,2] Therefore, there is a continuous growth of interest in the MCRs investigations, especially for their possible application in combinatorial and medicinal science. In part, the pharmaceutical industry has fueled this resurgence because of the growing need to assemble libraries of structurally complex substances for evaluation as lead compounds for drug discovery and development.[3] However, the multicomponent processes are often associated with ambiguous reaction mechanisms and selectivity issues or unexpected outcome[4] making the design of novel MCRs as well as an extension of the scope of known MCRs to be an intriguing but challenging task.

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Electronic Supplementary Information (ESI) is available: Full spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) for compounds **5**, **7** and **8** and X-ray crystallographic data for compounds **7b** and **8b** are included in the SI file

In our previous paper [5] we described a three-component interaction of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with active methylene nitriles and isatines. This interaction led to the formation of the corresponding fused 2-amino-4*H*-pyrans spirocondensed with 2-oxindol ring. This article was the first, dedicated to the multicomponent interactions of such benzothiazinones.

1*H*-2,1-Benzothiazin-4(3*H*)-one 2,2-dioxide represents the active methylene CH-acid. Its structure is an analogue of a cyclic active methylene 1,3-dicarbonyl compounds. This makes it a very convenient and promising synthon, which opens great opportunities for building of a new heterocyclic systems based on CH_2-CO fragment in its molecule. One of the most prospective routes to achieve this goal is using of MCRs. Unlike its carbonyl analogue, 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide exists entirely in the 4-oxoform. Simultaneously, the carbonyl group of the given heterocycle is distinguished by a high propensity for enolization in the course of introducing an alkyl or an acyl groups into position 3.[6,7]

Furthermore, 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide derivatives have recently gained an additional value due to their reported biological activities such as potent antibacterial effect,[8] lipoxygenase inhibition and, so, their potential for treat heart diseases treatment.[9] Moreover, 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide core is bioisosteric to the 2,3-dihydro-4*H*-1,2-benzothiazin-4-one 1,1-dioxide (Figure 1). The last one is a core of well-known analgesic and anti-inflammatory agents (Piroxicam®, Droxicam® and Meloxicam® and its heteroanologues – Tenoxicam® and Lornoxicam®). Interestingly, isosteric benzothiazine-3-carboxamides (Figure 2(B), **d**) have been shown to posses much higher analgesic activity than Piroxicam® and Meloxicam® (Figure 2(B), **a**, **b**).[10,11,12]

Figure 1. Common scaffold of applied analgesics (left side) and 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxides possessing higher analgesic activity (right side).

Multicomponent interactions of enol-nucleophiles (1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide is one of them) with carbonyl compounds and active methylene nitriles are attracting synthetic community for a long time. The reason – is the formation of various products depending on the reaction conditions and the structure of starting compounds. In the most cases, such interaction is the direct route for the 2-amino-4*H*-pyran core construction. The main advantage of this methodology is the reduction of synthetic steps, which is of paramount importance for the preparation of intermediate unsaturated nitriles which are, in many cases,

toxic and lachrymatory.[13,14,15] To date, a lot of approaches were applied for three-component synthesis of 2-amino-4*H*-pyrans. Traditionally, the interactions of 1,3-dicarbonyl compounds with active methylene nitriles and benzaldehydes are easily carried out on heating in ethanol with basic catalysts, such as triethylamine,[16,17] piperidine,[18] morpholine,[15] which resulted into formation of 2-amino-4*H*-pyrans in good to excellent yields.

In their turn, condensed 4*H*-pyranes are ones of the most well-known natural and synthetic heterocyclic compounds. They attract considerable attention since they possess an extensive range of biological effects. Several naturally occurring pyran-annulated heterocyclic compounds display anti-inflammatory,[19] anti-HIV activity,[20] cytotoxic activity against leukemia cells,[21] antileishmania activity,[22] and slight activity against hepatitis B virus.[23]

Synthetically available 4*H*-pyranes are also used as pigments [24] and photoactive materials.[25] Furthermore, some derivatives of 4*H*-pyranes (for example cromakalim) can serve as a typical ATP-sensitive potassium channel openers or possess potent relaxant activity on blood vessels, cardiac muscle, and other smooth muscles. Thus, they may find an application in the treatment of variety of diseases such as hypertension, asthma, ischemia, and urinary incontinence.[26,27] Moreover, several representatives of this class of compounds are known to be cognitive enhancers used to treat neurodegenerative disorders, including Alzheimer's, Huntington's, and Parkinson's diseases and schizophrenia.[28,29] In previous studies, 2-amino-3-cyano-4*H*-pyran derivatives, which are closely related to the title compounds, were found to possess anticancer,[30] antibacterial,[31,32] and anti-rheumatic[33] effects; selected representatives of them are given in Figure 2(A).

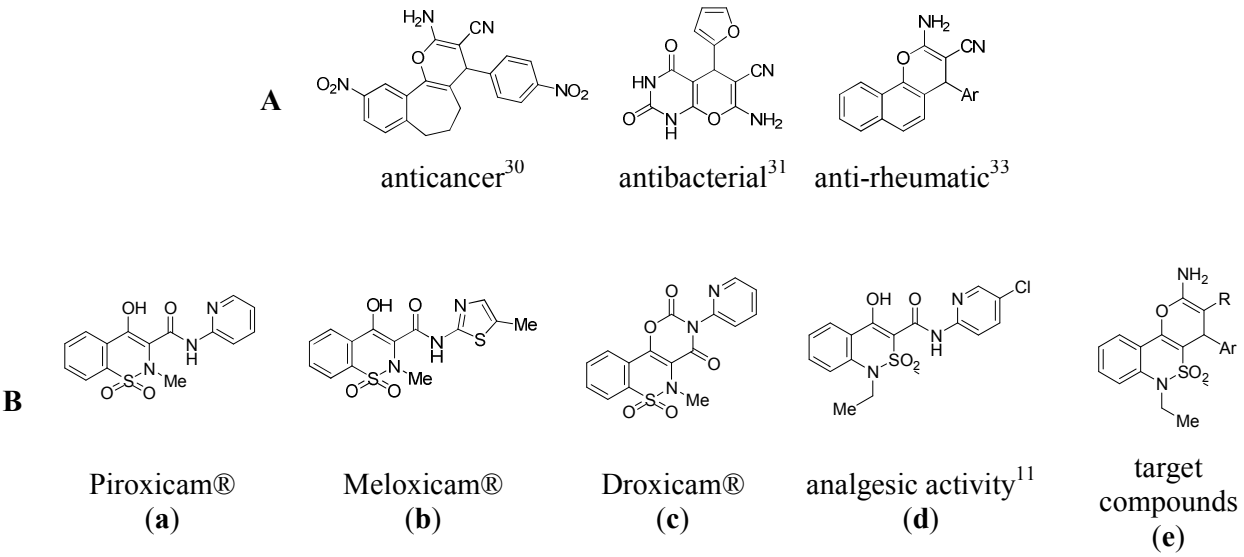


Figure 2. Examples of synthetically available bioactive 2-amino-3-cyano-4*H*-pyranes (**A**), benzothiazine (**B**) and the target compounds (**e**).

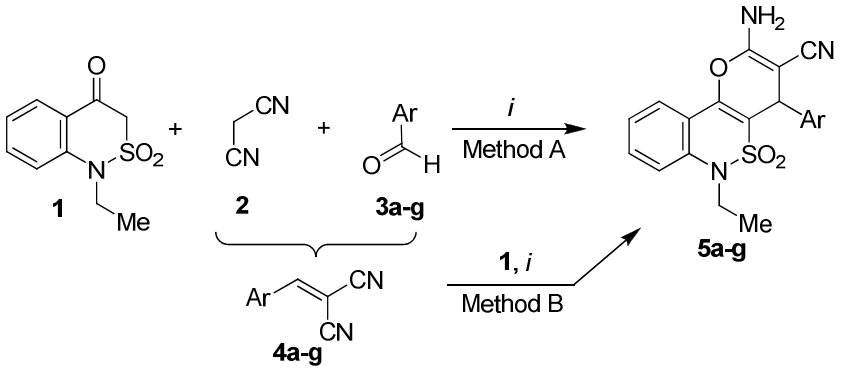
In continuation of our previous researches, the reaction of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with an active methylene nitriles and arylcarbaldehydes to synthesize corresponding 4-aryl-4*H*-pyran derivatives fused with 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (Figure 2(B), **e**) was investigated. It acquires additional value, because of, currently, 2,3-dihydro-4*H*-thiochromen-4-one is an example of six-membered sulfur containing heterocycles, based on which, 2-amino-4*H*-pyranes were obtained.[15,34]

2. Results and discussion

The first step of our researches was to find out the most suitable catalyst for three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with malononitrile and benzaldehyde. As representatives, we applied thriethanolamine (used in our previous work[5]), triethylamine (as an inexpensive and widely used organic base) and urea (as an environmentally benign organo-catalyst and since it allows to apply relatively mild reaction conditions[13]) as catalysts and ethanol or aqueous ethanol as solvents. However, the use of urea as a catalyst showed the low efficiency. The reactions with malononitrile resulted into the corresponding 2-amino-3-cyano-4-phenyl-4*H*-pyran in 30-45% yields appeared to be unsatisfactory. In this regard, thriethanolamine and triethylamine demonstrated much higher efficiency, since their applying in MCR allowed us to obtain condensed 2-amino-4-phenyl-4*H*-pyran in high yields. Triethylamine was used as more convenient in use catalyst in our further experiments.

In general, the MCR between 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1**, malononitrile (**2**) and benzaldehydes **3a-g** was carried out in refluxing ethanol during 1 hour in the presence of equimolar quantities of triethylamine and it resulted in the formation of the expected 2-amino-4*H*-pyran derivatives **5a-g** isolated in high yields (Table 1, Method A). The products precipitated from the reaction mixture were recrystallized from ethanol. For 4-nitrobenzaldehyde (**3b**), the reaction temperature and time were decreased up to 50 °C for 40 min to avoid formation of undesirable side products. Though one could expect the reactivity decreases for 4-dimethylaminobenzaldehyde (**3f**) due to its strong electron donating substituent effect[35], or for bulky 9-antraldehyde (**3g**), the high yields were also obtained in these cases. The application of the stepwise approach towards 2-amino-4*H*-pyranes **5a-g** (Table 1, Method B) resulted in the lower yields compared to those, obtained by the MCRs. The gathered results confirm the preferred applicability of the multicomponent format for synthesis of **5a-g** and serve as evidence that the formation of 2-amino-4*H*-pyran heterocycle in the course of MCR most likely proceeds via intermediate arylidenes **4**.

Table 1. Yields for the compounds **5a-g** synthesized by two methods[a]



Compound	Ar	Yields, %[b]	
		Method A	Method B
5a	C_6H_5	82	55
5b	4-NO_2-C_6H_4	95	71
5c	2-MeO-C_6H_4	85	66
5d	4-MeO-C_6H_4	84	58
5e	4-Cl-C_6H_4	89	81
5f	4-Me_2N-C_6H_4	81	63
5g	9-Anthracenyl	93	91

[a] Reagents and conditions: (*i*) EtOH, Et_3N (1.0 equiv), reflux for 1 h (for **5b** heating at 50 °C for 40 min in both methods).

[b] Isolated yield.

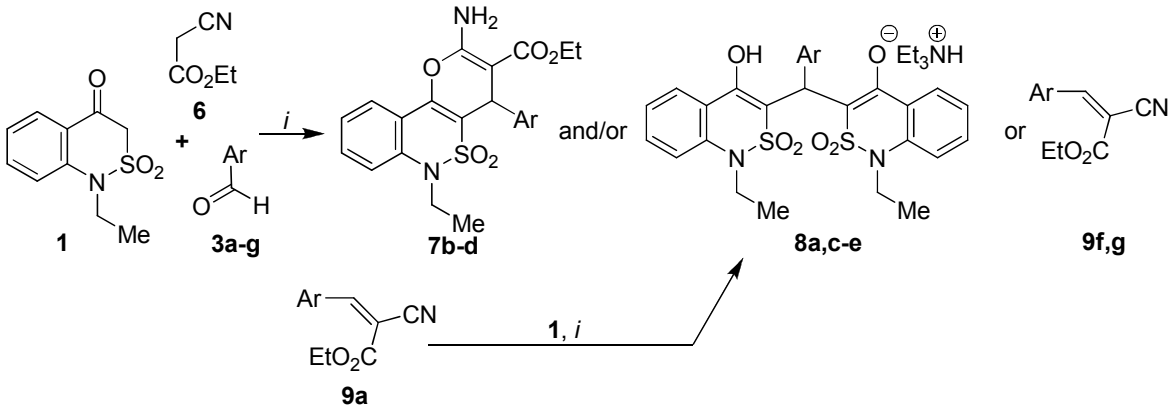
The simple performance of the reaction given above, encouraged us to introduce other active methylene nitriles into this MCR. Ethyl cyanoacetate (**6**), benzylcyanide (**12**) and N-(*p*-tolyl)cyanoacetamide (**13**) were chosen as representative building blocks to investigate the scope and limitations of this MCR.

However, for ethyl cyanoacetate (**6**) reacted under similar conditions during 4 hours, a significant decrease in the process efficiency and selectivity (Scheme 1) was observed. The only exception was the starting 4-nitrobenzaldehyde (**3b**) for which a pure target 2-amino-4*H*-pyran **7b** was isolated in 51% yield. For aldehydes **3f,g** the reaction stopped on the formation of arylidenes **9f,g**. In spite of our attempts to prolong the reaction time or to use a higher boiling point solvent (DMF), we failed to obtain the expected products **7f,g**.

When unsubstituted benzaldehyde (**3a**) and 4-chlorobenzaldehyde (**3e**) were used, it allowed us to obtain a new result of such three-component interactions, namely to get the stable triethylammonium salts **8a** and **8e** in yields 35% and 17% respectively. These salts are uncolored crystalline compounds which can be recrystallized unchanged from ethanol. The possibility of the formation of such salts is caused by the raised CH-acidic properties of methyne group (as the result of electron withdrawing influence of SO_2-group) which leads to ease of enolization.

Moreover, the intramolecular hydrogen bond formation increases the stability of triethylammonium enolates (details of the salt structures are given in X-ray diffraction experimental part). We found only one example of such three-component reaction wherein similar (but non-symmetrical) salts were formed. These salts contained 4-hydroxycoumarin core in which an increase of acidic properties is also observed as the result of 2-carbonyl group influence.[36]

In the case of benzaldehydes **3c,d**, bis-adducts **8c,d** were also formed as admixture (12-15% according to ^{1}H NMR) to the target 4*H*-pyrans **7c,d**. Pure products **7c,d** were obtained by recrystallization of crude products from ethanol with yields 50 and 39%, correspondingly.



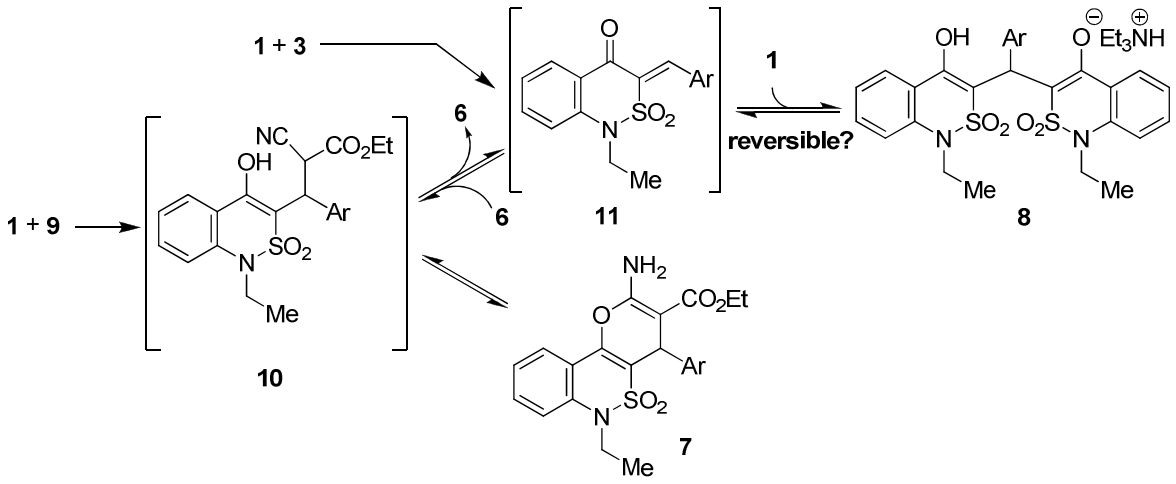
Scheme 1. Reagents and conditions: (*i*) EtOH (*i*-PrOH), Et_3N (1.0 equiv), reflux for 4 h (for **3b** – 50 °C for 2 h)

Taking into account the received information, we set the problem – to work out an efficient method for the synthesis of 3-ethoxycarbonyl-4*H*-pyrans **7**, which could avoid the formation of undesired bis-adducts **8**. However, since the bis-adducts **8** have been obtained for the first time in such three-component interactions, we also encouraged to study some aspects of their reactivity, and the role of the bis-adducts **8** in the reaction.

Based on the structure of bis-adducts **8**, it can be assumed that ethyl cyanoacetate (**6**) is not involved in three-component interaction and, consequently, in the formation of bis-adducts **8**. Therefore, initially we synthesized arylidene **9** which is an intermediate in the synthesis of 2-amino-4*H*-pyrans.[37,38] This arylidene was reacted with 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** then. We supposed, that applying such conditions, we will be able to avoid the formation of bis-adduct **8**.

To our surprise, even this stepwise format resulted in the formation of unwanted bis-adduct **8** (usage of arylidene **9a** led to **8a** with yield of 43%).

To rationalize this result one has to assume that initially formed Michael adduct **10** can be further transformed by two ways (Scheme 2). The first way – is the desired heterocyclization, that represents a cascade of proton-transfer processes: enolization of the keto group followed by chain-to-ring tautomeric transformation (*hetero*-Thorpe-Ziegler reaction, namely intramolecular nucleophilic addition of OH to CN group) and finally enamine-imine tautomerism to form product **7**.[15] The second one – is a retro-Michael reaction with elimination of ethyl cyanoacetate (**6**) and formation of enone **11**, which reacts with the second molecule of benzothiazinone **1** forming bis-adduct **8**.



Scheme 2. Presumable mechanism for the formation of compounds **7** and **8**

Enones **11** and arylidenes, similar to them, are the precursors for the synthesis of 2-amino-4*H*-pyrans while reacting with active methylene nitriles.[39,40] Arylidenes **11** formed from initial benzothiazinone **1** were described in only one publication[41] and obtained under acidic catalysis. Our attempt to obtain arylidenes **11** by interaction of benzothiazinone **1** with benzaldehydes **3a,c** (molar ratio 1:1) under basic conditions (EtOH, 1.0 of equiv Et_3N, rt) led to isolation of bis-adducts **8a,c** in low yields and of poor purity. At the same time, when this reaction was carried out under similar conditions in molar ratio 2:1 for compounds **1** and **3a,c** we isolated pure compounds **8a,c** in yields 93% and 87% correspondingly. This approach can be proposed as preparative for synthesis of salts **8**. The fact, that interaction **1** with **3** leads to the formation of bis-adducts **8** serves as evidence that the second way of three-component interaction is also possible. It involves a primary formation of enones **11** (by interaction of **1**+**3** avoiding the formation of adduct **10**). Apparently, the part of reagents reacts by this way.

Thereby, we can conclude that the arylidenes **11** are highly reactive intermediates and behave as Michael acceptors in the reaction media. Depending on the nature of the substituent in the benzaldehyde residue, these arylidenes can interact either with benzothiazinone **1** (to form

the symmetrical bis-adduct isolated as triethylammonium salt **8**) or with ethyl cyanoacetate (**6**) (to form desired 4*H*-pyrans **7**).

Since, most probably, all the stages in the mechanism (Scheme 2) are reversible[15,42] (except **11** → **8**, that required additional investigations) we attempted to take control over the selectivity of this three-component reaction (Scheme 1) by using the excess of ethyl cyanoacetate (**6**) in our further experiments to shift the reaction equilibrium towards the formation of 4*H*-pyran derivatives **7**.

As noted previously, bis-adduct **8a** was the single isolated product when benzaldehyde **3a** was used in three-component interaction (Scheme 1). Using 3.0 equiv of **6** in the reaction with **1** and **3a** in ethanol in the presence of triethylamine in one-pot under reflux during 4 h led to isolation of the desired 4*H*-pyran derivative **7a.** Though the final product was not contaminated with bis-derivative **8a** the yields appeared to be moderate (Table 2). Higher amounts of **6** did not affect the yield significantly. These unsatisfactory results compelled us to search for better reaction conditions; we tried to carry out this reaction by varying of the bases applied. In the presence of 1.0 equiv of 4-dimethylaminopyridine (DMAP) the yield of **7a** was increased up to 70%. If lower amounts of DMAP (or Et_3N) were used under abovementioned conditions, the reaction was not complete (not shown in the Table 2). The use of DMAP in the case of 4-nitrobenzaldehyde (**3b**) led to the increase of the yield of **7b** up to 68%. For the aldehyde **3c**, the pure product **7c** was formed in high yield using 2.0 equiv of **6** (Table 2). The satisfactory yield of **7d** was obtained using *i*-PrOH instead of EtOH. However, for aldehydes **3c,d** the use of 1.0 equiv of DMAP instead of Et_3N decreased the reaction efficiency. To avoid the formation of side product **8e** and to obtain pure derivative **7e** it was necessary to use 7.0 equiv of **6**. In this case, the use of DMAP significantly increased the yield of **7e** in comparison with Et_3N.

Thus, the reaction outcome is strongly dependent on the nature of the substituent in the starting benzaldehyde and the conditions applied. In the case of ethyl cyanoacetate (**6**) it was necessary to vary the reaction conditions to reach acceptable yield levels.

Table 2. Optimization steps in three-component reactions with ethyl cyanoacetate[a] (Scheme 1)

Aldehyde	Conditions of three-component reaction	Equivalents of 6	Molar ratio of products 7 and 8[b]	Yields, %[c]	
				7	8[d]
3a	EtOH, Et_3N, reflux for 4 h	1.0	0:1	–	35
		3.0	1:0	24	–
		5.0	1:0	25	–
	i-PrOH, Et_3N, boiling for 4 h	1.0	1:0.58	14	16
		3.0	1:0	24	–
	EtOH, morpholine, reflux for 4 h	1.0	1:0.67	25	34
		3.0	1:0	22	–
	EtOH, DMAP, reflux for 4 h	3.0	1:0	70	–
3b	EtOH, Et_3N, 50 °C, 2 h	1.0	1:0	51	–

	EtOH, DMAP, 50 °C, 2 h	1.0	1:0	68	–
3c	EtOH, Et_3N, reflux for 4 h	1.0	1:0.16	50	16
		2.0	1:0	84	–
		3.0	1:0	78	–
	EtOH, DMAP, reflux for 4 h	2.0	1:0[e]	62	–
3d	EtOH, Et_3N, reflux for 4 h	3.0	1:0	20	–
	i-PrOH, Et_3N, reflux for 4 h	1.0	1:0.13	39	10
		3.0	1:0	55	–
	EtOH, DMAP, reflux for 4 h	3.0	1:0[e]	62	–
3e	EtOH, Et_3N, reflux for 4 h	1.0	0:1	–	17
		3.0	1:0.36	19	14
		5.0	1:0.07	29	4
		7.0	1:0	33	–
	EtOH, DMAP, reflux for 4 h	7.0	1:0	63	–

[a] The reaction was carried out using 1 mmol of **1** and **3** in 5 mL of solvent (EtOH or *i*-PrOH).
[b] Confirmed by ^{1}H NMR spectra of isolated precipitate without purification as intensity ratio of proton in 4th position of 4*H*-pyran ring and methyne moiety proton of bis-derivative.
[c] The yields of each component **7** and **8** in the isolated product.
[d] Yields of compound **8** were calculated based on 2.0 eq. of compound **1**.
[e] The admixture of appropriate arylidenes was observed in an amount of 15-17 mol% as was confirmed by ^{1}H NMR spectra of isolated precipitates without purification as intensity ratio of proton in 4th position of 4*H*-pyran ring and CH moiety proton of arylidenes

As it was mentioned above, the mechanism of this reaction (Scheme 2) suggests the formation of the key intermediate **11** that can be transformed into both 4*H*-pyran derivatives **7** and bis-adducts **8**. Though this intermediate was neither isolated, nor identified in the reaction mixtures, its formation was additionally confirmed by studying of mutual transformations of products **5**, **7** and **8**. Among all the stages of the mechanism, the possibility of reverse transformation of **8** → **11** was unknown. To determine the possibility of the retro-reactions **8** → **7** and **8** → **5**, the interactions of bis-adducts **8** with ethyl cyanoacetate (**6**) and malononitrile (**2**) were studied. Since the products **8** were isolated for the first time, these experiments allowed us to demonstrate some aspects of their reactivity.

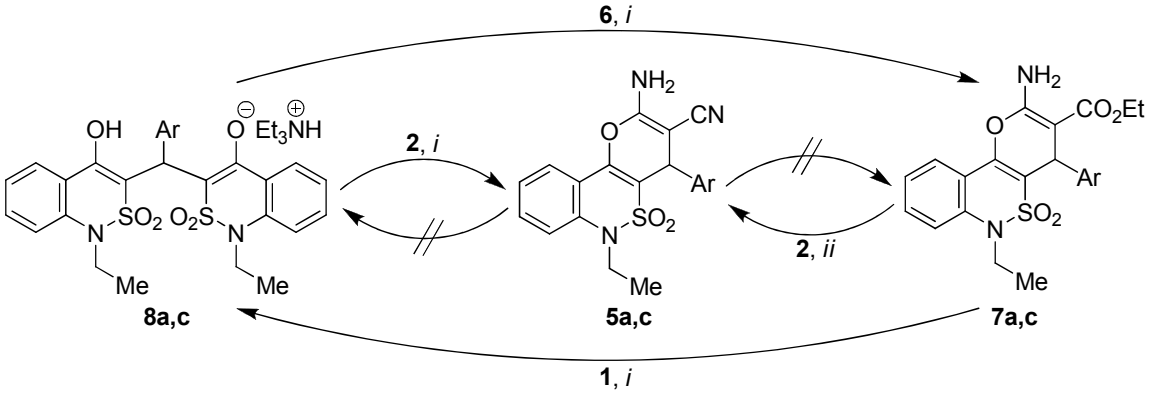
Bis-adducts **8a,c** were used to study the transformation of **8** → **7**. The reactions were carried out by the treatment of **8** with 1.0 equiv of both ethyl cyanoacetate (**6**) and triethylamine in refluxing ethanol for 6h. In the case of **8a** (Ar = C_6H_5) only the starting material was recovered after the heating, whereas when compound **8c** (Ar = 2-MeO-C_6H_4) was used, the final mixture contained the initial bis-adduct **8c**, 3-ethoxycarbonyl-4*H*-pyran **7c** and benzothiazinone **1** in molar ratio 1:2:2 (in accordance with ^{1}H NMR spectrum).

To study the transformation of **8** → **5**, the bis-adducts **8a,c** were used. The reactions of **8a,c** with 1.0 equiv of **2** under the standard reaction conditions resulted in the formation of pure compounds **5a,c** isolated in yields 53% and 61% respectively.

Thus, it was experimentally confirmed that the bis-adducts **8** can be transformed into 4*H*-pyrans **5** and **7** under reaction conditions. This fact clearly indicates the reversibility of the stage **11** ⇄ **8** and consequently all the stages of proposed mechanism (Scheme 2) are reversible.

We have also studied the possibility of reverse transformations of **7** → **8** and **5** → **8**. While there is no data about the transformation of such adducts, similar to compounds **8**, into 2-amino-4*H*-pyranes, we found only two suitable references about reverse transformations (similar to **5** or **7** into **8**)[43,44] which were carried out in AcOH/$AcONH_4$ or under heating in DMF. Transformation of **7** → **8** was achieved in the case of **7a**. It performed by treatment of **7a** with 1.0 equiv of both benzothiazinone **1** and triethylamine in refluxing ethanol for 6h. As a result, pure bis-adduct **8a** was isolated in yield 47%. However, such transformation did not proceed in the case of pyran **7c**. The reverse transformation of **5a,c** into bis-adducts **8a,c** was not achieved under similar conditions (Scheme 3).

Given the fact that 3-ethoxycarbonyl-4*H*-pyran **7a** transformed into bis-adduct **8a** and 3-cyano-4*H*-pyran **5a** did not undergo this transformation we suggested that malononitrile derived products, 3-cyano-4*H*-pyrans **5**, are more stable compared with products, derived from ethyl cyanoacetate, 3-ethoxycarbonyl-4*H*-pyrans **7**. To confirm this assumption a model reactions **7** → **5** were finally carried out using **7a,c** (Scheme 3). Thus, heating of **7a,c** at 60 °C for 1 h with 1.0 equiv of malononitrile (**2**) in ethanol in the presence of equimolar quantity of triethylamine allowed formation of **5a,c** isolated in yield 58% and 67% correspondingly. An example of this type of transformation was previously reported.[45] In opposite, the reverse interactions of **5a,c** with ethyl cyanoacetate (**6**) under the same conditions resulted in the recovery of the starting products **5a,c**.

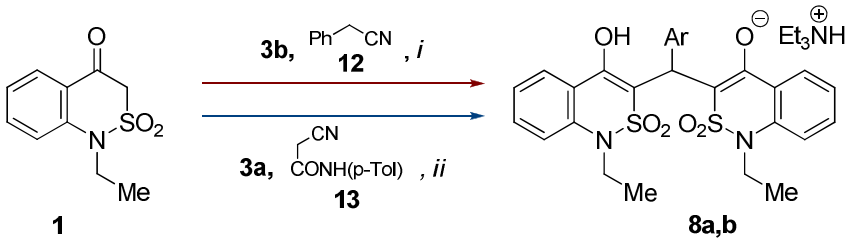


Scheme 3. Reagents and conditions: (*i*) EtOH, Et_3N, reflux, 4-6h; (*ii*) EtOH, Et_3N, 50-60°C, 1h

Therefore, when ethyl cyanoacetate (**6**) is used in three-component interaction (Scheme 1) we can conclude that in addition to the reaction conditions, the outcome of the studied MCR is controlled by the relative stability of the products **7** and **8** that is, in its turn, dictated by the substituent nature in the benzaldehyde fragment.

According to our research plan, we also used other active methylene nitriles, such as benzyl cyanide (**12**) and N-(*p*-tolyl)cyanoacetamide (**13**), in this three-component interaction

(Scheme 4). But contrary to our expectations, only bis-adducts **8a,b** in both cases were isolated in 53% and 44% yields correspondingly. In accordance with the previously established regularities, we used fivefold excess of benzyl cyanide (**12**) to obtain the target 4*H*-pyran derivative, but the bis-adduct **8b** was again the sole product of this transformation.



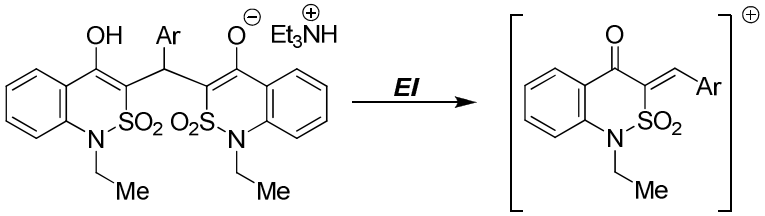
Scheme 4. Reagents and conditions: (*i*) EtOH, Et_3N, r.t., 4 h; (*ii*) EtOH, Et_3N, reflux for 4 h

The IR spectra of all the obtained compounds **5**, **7**, **8** contain two absorption bands of sulfonyl group at 1329-1296 and 1174-1102 cm^{-1} regions. The valence oscillations of amino group in compounds **5** and **7** can be observed as two bands at 3456-3285 cm^{-1}. The IR spectra of **5a-g** are characterized by the highly intense narrow band of the cyano group which can be found at 2202-2187 cm^{-1}. The frequency of the highly intense band of ester carbonyl function in position 3 of pyran ring is considerably lowered and this band appears in IR spectra of compounds **7** at 1690-1687 cm^{-1}. This is due to the conjugation with a C=C bond of the pyran ring, additionally to the formation of an intramolecular hydrogen bond with the NH_2 group.[15] The IR spectra of compounds **8** have a series of characteristic absorption bands of the OH-group (broadened band at 3456-3396 cm^{-1}), N^+–H-group of triethylammonium cation (2499-2470 cm^{-1}) and bridging CH-group (high intensity band at 3108-2973 cm^{-1}).

The narrow high-intensity singlet of the 4th position of 4*H*-pyran ring can be observed at 4.48-4.95 ppm in ^{1}H NMR spectra of compounds **5a-f** dissolved in DMSO-d_6. The same proton in compound **5g** is at 6.54 ppm, which can be explained by unshielding effect of the bulky aromatic anthracene core. The singlet of the 4th position of 4*H*-pyran ring for **7a-e** can be found in the same region, as for compounds **5**, 4.78-4.99 ppm. The signal of protons of 2-amino group for pyrans **5a-g** is situated in the range of 7.21-7.50 ppm as well as for **7a-e** the singlet of the 2-amino group is observed at 7.72-7.94 ppm. The ^{1}H NMR spectra of adducts **8a,b,e** are characterized by the presence of singlet of benzothiazine OH-group at 17.10-17.25 ppm and bridging CH-group at 5.69-5.78 ppm. The signals of triethylammonium NH-group are not found in the spectra probably due to the fast deuteroexchange. The ^{13}C NMR spectra of the synthesized compounds reveal the following general features.[15] The signal of the C-2 carbon atom of the pyran ring for compounds **5**, **7** is found at 158-159 ppm. The peak of the C-3 carbon atom of the

pyran ring for compounds **5** is observed at 55-58 ppm as well as for compounds **7** at 58-59 ppm. The C-4 carbon of compounds **5a-g** and **7a-e** gives signal at 31-37 ppm. The signal at 118-119 ppm was assigned to the nitrile carbon in the pyran ring for compounds **5** and the signal at 166-167 ppm was assigned to the carbonyl carbon of the ester group for compounds **7**. The ^{13}C NMR spectra of compounds **8** are characterized by the presence of bridged carbon peak at 35-36 ppm.

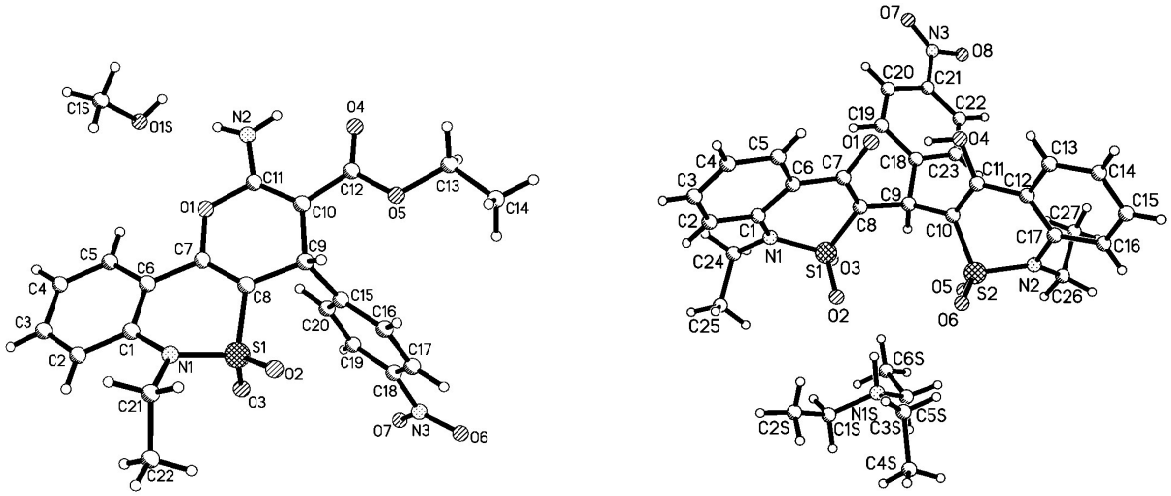
Molecular ion peaks are observed in mass spectra of 2-amino-4*H*-pyranes **5** and **7**. The mass spectra of bis-adducts **8** are characterized by the presence of the heaviest fragment of ion peak ([M-326]$^+$) corresponding to enones **11** (Scheme 5**)**.



8 **11**

Scheme 5. Characteristic mass fragmentation of compounds **8**

The structures of compounds **7b** and **8b** have been additionally confirmed by single crystal X-ray diffraction study (Fig. 3). The compound **7b** exists as methanol monosolvate in the crystal phase (more detailed information about molecular and crystal structure see in Supplementary Information). The **8b** compound corresponds to the triethylammonium salt with organic anion. The hydrogen atom at the N1s is located from the electron density difference maps. Only one peak corresponding to the hydrogen atom is observed between O1 and O4 atoms from the experimental data and it is located nearer to the O4 atom. The O1-C7 and O4-C11 bond lengths are comparable (1.309(4) Å and 1.314(4) Å, respectively) and slightly shorter than the mean value[46] for the Csp^2-OH bond (1.333 Å). The O4-H…O1 strong charge-assisted hydrogen bond (H…O 1.54 Å, O-H…O 177°) is formed. Summary, only one tautomer of organic anion with negative charge at the O1 atom may exist in the crystal phase.

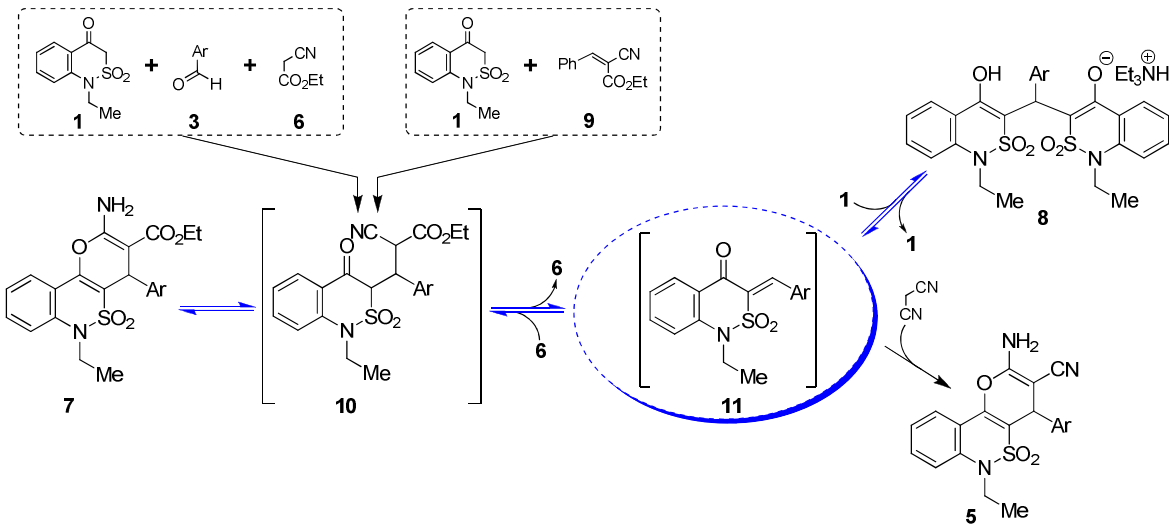


7b **8b**

Figure 3. Molecular structure of the compounds **7b** and **8b** according to the X-ray diffraction study.

3. Conclusion

In this paper the three-component interaction of 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with benzaldehydes and active methylene nitriles which led to condensed 2-amino-4-aryl-4*H*-pyrans was studied. The direction of the three-component reaction is controlled by the nature of active methylene nitrile and the nature of the substituent in the arylcarbaldehyde: the formation of either 2-amino-4*H*-pyrans or bis-adducts (or their mixture) was observed. New products of such interactions – triethylammonium salts of bis(1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide) – were obtained for the first time. The structure of these salts was proved by the single crystal X-ray diffraction study as well as their purity by the other instrumental methods. The ability of the bis-adducts to be transformed into 2-amino-4*H*-pyrans was experimentally confirmed. Based on the known mechanism of the 2-amino-4*H*-pyrans formation and on the accomplished conversions **7** → **8** and **8** → **7** we proposed the mechanism of the studied MCR which includes the bis-adduct formation stage (Scheme 6). According to the proposed mechanism, arylidenes **11** are formed in three-component reaction as highly reactive intermediates. These intermediates are the key products for the formation of bis-adducts **8** (Scheme 6). The reversibility of all stages of the mechanism allowed us to synthesize purposefully the target 2-amino-4*H*-pyrans.



Scheme 6. The general scheme of mutual transformations of compounds **7** and **8**

The one-way conversions of **7**,**8** → **5** (Scheme 3) demonstrated the highest stability of 2-amino-3-cyano-4*H*-pyrans **5** caused, probably, by the effective push-pull interaction between the strong electron donating 2-amino group and the strong electron withdrawing 3-cyano group in the product **5**.

The found regularities of three-component interaction can be more general. Currently, there is no information regarding obtaining of such bis-adducts in similar three-component condensations. Although compounds such as triethylammonium salts of bis(1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide) have not been previously reported in the literature as the possible products of synthesis of 2-amino-4*H*-pyrans, the potential of their formation should be considered in similar interactions as impurities or as main products.

4. Experimental section

4.1. General

Starting aldehydes and active methylene nitriles were obtained from commercial sources and used without further purification. Starting 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide was obtained according to the previously described procedure.[5] Arylidenes **4a-g** and **9a** were prepared via Knoevenagel condensation of the corresponding benzaldehydes **3a-g** and active methylene nitriles **2** or **6** in the presence of a base as was reported.[47] Dry DMF was prepared in accordance with standard method. Melting points were determined on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ^{1}H NMR spectra were recorded on Varian Mercury VX 200 instrument or Bruker AMX 500 spectrometer (for **8c**) using DMSO-d_6 as solvent and TMS as an internal standard. ^{13}C NMR experiments were performed using Bruker AMX 500 spectrometer or Varian Mercury MR-400 (for **7e** and **8a**). IR spectra were taken on a Perkin–Elmer 298 spectrophotometer in KBr pellets. Elemental analyses were carried out using Carlo Erba CHNS-O EA 1108 analyzer. Mass spectra were taken on a Varian 1200L DIP (EI, 70 eV).

4.2. X-ray diffraction experimental part.

The crystals of **7b** ($C_{22}H_{21}N_3O_7S \cdot CH_3OH$) are monoclinic. At 100 K a = 21.5619(7), b = 11.3694(4), c = 18.9777(7) Å, β = 93.367(3)°, V = 4642.4(3) Å^3, Mr = 500.77, Z = 1, space group C2/c, d_{calc}= 1.433 g/cm^3, μ(MoKα) = 0.194 mm^{-1}, F(000) = 2096. Intensities of 24414 reflections (6761 independent, R_{int} = 0.029) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°).

The crystals of **8b** ($C_6H_{15}NH^+ \cdot C_{27}H_{24}N_3O_8S_2^-$) are orthorhombic. At 293 K a = 13.1522(7), b = 23.496(2), c = 11.0242(5) Å, V = 3406.8(3) Å^3, Mr = 684.81, Z = 4, space group $Pna2_1$, d_{calc}= 1.335 g/cm^3, μ(MoKα) = 0.212 mm^{-1}, F(000) = 1448. Intensities of 33893 reflections

(9887 independent, R_{int} = 0.053) were measured on the«Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°).

The structures were solved by direct method using SHELXTL package[48]. Position of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl and hydroxyl groups and for water molecule and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms using 6714 (**7b**), 9840 (**8b**) reflections was converged to: wR_2 = 0.131 (R_1 = 0.048 for 5324 reflections with F>4σ(F), S = 1.046) for structure **7b** and wR_2 = 0.189 (R_1 = 0.067 for 4692 reflections with F>4σ(F), S = 0.918) for structure **8b**. The final atomic coordinates, and crystallographic data for molecules **7b** and **8b** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 1405511 for **7b** and CCDC 1405512 for **8b**).

4.3. General procedure for the synthesis of 2-amino-4-aryl-3-cyano-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxides (5a-g)

Method A. Three-component one-pot procedure. To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 mol), malononitrile **2** (0.066g, 0.001 mol) and appropriate benzaldehyde **3a-g** (0.001 mol) in ethanol (5-10 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 1 h (in case of **3b** the mixture was heated at 50 °C for 40 min). A precipitate usually formed in a few minutes after the beginning of heating. The mixture was cooled to the room temperature; the resulting precipitates of **5a-g** were filtered off, washed with ethanol then dried on air and recrystallized from ethanol.

*Method B. Synthesis using arylidenes **4a-g**.* To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 mol) and arylidenes **4a–g** (0.001 mol) in ethanol (5-10 mL), triethylamine (0.14 mL, 0.001 mol) was added. The resulted mixture was refluxed for 1 h (in case of **4b** mixture was heated at 50 °C for 40 min). During boiling precipitates of **5a-e** was gradually formed. The resulting reaction mixtures were treated as mentioned in *method A*.

The yields for the synthesized compounds **5a–g** are presented in Table 1.

*Method C (for **5a,c**). Synthesis using 2-amino-3-ethoxycarbonyl-4-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine 5,5-dioxides **7a,c**.* To a solution of 2-amino-3-ethoxycarbonyl-4-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine 5,5-dioxides **7a,c** (0.001 mol) and malononitrile **2** (0.066g, 0.001 mol) in ethanol (10 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was heated at 60 °C for 1 h and the resulting solution was cooled to the room temperature. After precipitate of **5a,c** was formed it was filtered off, washed

with ethanol, dried on air and recrystallized from ethanol. Yields of **5a,c** were 58% and 67% correspondingly.

*Method D (for **5a,c**). Synthesis using 3-[(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)(aryl)methyl]-1-ethyl-1H-2,1-benzothiazin-5-olat 2,2-dioxides **8a,c**.* To a solution of 3-[(4-hydroxy-1-ethyl-2,2-dioxido-1H-2,1-benzothiazin-3-yl)(aryl)methyl]-1-ethyl-1H-2,1-benzothiazin-5-olat 2,2-dioxides **8a,c** and malononitrile **2** (0.066g, 0.001 mol) in ethanol (10 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to 0 °C and kept at this temperature overnight. The resulting precipitate of **5a,c** was filtered off, washed with cold ethanol, dried on air and recrystallized from ethanol. Yields of **5a,c** were 53% and 61% respectively.

4.3.1. 2-Amino-3-cyano-4-phenyl-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (5a)

White needles; mp > 250 °C (from EtOH); Anal. Calcd for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07; S, 8.45. Found: C, 63.30; H, 4.39; N, 10.82; S, 8.23; IR (KBr): ν_{max}/cm^{-1} 3456, 3364, 3187, 3062, 2984, 2943, 2187, 1678, 1636, 1596, 1453, 1407, 1344, 1300, 1267, 1172, 702 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.95 (d, *J* = 7.94 Hz, 1H), 7.72 – 7.50 (m, 2H), 7.48 - 7.13 (m, 8H), 4.65 (s, 1H), 3.89 (q, *J* = 6.61 Hz, 2H), 1.02 (t, *J* = 6.87 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 158.9, 146.3, 142.6, 137.8, 132.4, 128.6, 127.8, 127.6, 124.6, 123.8, 119.3, 119.0, 117.3, 114.4, 58.2, 42.5, 37.5, 13.8; MS (EI) m/z: 379 $[M]^+$.

4.3.2. 2-Amino-3-cyano-4-(4-nitrophenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (5b)

Light yellow needles; mp 242-243 °C (decomp.) (from EtOH); Anal. Calcd for $C_{20}H_{16}N_4O_5S$: C, 56.60; H, 3.80; N, 13.20; S, 7.55. Found: C, 57.03; H, 3.53; N, 12.83; S, 7.43; IR (KBr): ν_{max}/cm^{-1} 3430, 3325, 3252, 3214, 3080, 2975, 2931, 2851, 2202, 1683, 1598, 1515, 1455, 1415, 1346, 1325, 1267, 1170, 1147, 1122 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.20 (d, *J* = 8.85 Hz, 2H), 7.96 (d, *J* = 7.63 Hz, 1H), 7.73 - 7.34 (m, 7H), 4.95 (s, 1H), 3.89 (q, *J* = 7.02 Hz, 2H), 1.04 (t, *J* = 6.87 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 158.9, 150.0, 147.0, 146.8, 137.8, 132.7, 129.4, 124.7, 123.9, 123.8, 119.3, 118.7, 117.0, 113.1, 57.0, 42.5, 37.0, 13.9; MS (EI) m/z: 424 $[M]^+$.

4.3.3. 2-Amino-3-cyano-4-(2-methoxyphenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (5c)

White needles; mp 193-195 °C (decomp.) (from EtOH); Anal. Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26; S, 7.83. Found: C, 62.04; H, 4.32; N, 10.06; S, 7.41; IR (KBr): ν_{max}/cm^{-1} 3381, 3316, 3212, 3064, 2981, 2939, 2842, 2195, 1671, 1599, 1454, 1352, 1324, 1251, 1168, 1145, 1118, 749 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.94 (d, *J* = 7.63 Hz, 1H), 7.70 – 7.49

(m, 2H), 7.39 (t, *J* = 7.33 Hz, 1H), 7.29 – 7.16 (m, 3H), 7.10 (d, *J* = 7.63 Hz, 1H), 6.98 (d, *J* = 8.24 Hz, 1H), 6.87 (t, *J* = 7.52 Hz, 1H), 4.89 (s, 1H), 3.88 (q, *J* = 6.92 Hz, 2H), 3.70 (s, 3H), 1.01 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 159.5, 157.1, 146.7, 137.7, 132.2, 130.0, 129.2, 129.0, 124.3, 123.7, 120.6, 119.4, 119.2, 117.4, 113.6, 111.9, 57.0, 55.9, 42.4, 32.4, 13.7; MS (EI) m/z: 409 $[M]^+$.

4.3.4. 2-Amino-3-cyano-4-(4-methoxyphenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (5d)

White needles; mp 236-238 °C (decomp.) (from EtOH); Anal. Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26; S, 7.83. Found: C, 61.91; H, 4.35; N, 9.83; S, 7.67; IR (KBr): ν_{max}/cm^{-1} 3412, 3322, 3252, 3213, 3070, 2957, 2930, 2836, 2202, 1678, 1598, 1512, 1407, 1329, 1246, 1164, 1146, 1117, 1027, 835 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.93 (d, *J* = 7.94 Hz, 1H), 7.72 – 7.49 (m, 2H), 7.39 (t, *J* = 7.48 Hz, 1H), 7.29 (s, 2H), 7.17 (d, *J* = 8.55 Hz, 2H), 6.87 (d, *J* = 8.55 Hz, 2H), 4.60 (s, 1H), 3.89 (q, *J* = 6.82 Hz, 2H), 3.71 (s, 3H), 1.04 (t, *J* = 6.87 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 158.7, 158.7, 145.9, 137.7, 134.6, 132.3, 129.0, 124.5, 123.7, 119.3, 119.1, 117.3, 114.7, 114.0, 58.4, 55.1, 42.4, 36.8, 13.8; MS (EI) m/z: 409 $[M]^+$.

4.3.5. 2-Amino-3-cyano-4-(4-chlorophenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (5e)

White plates; mp 234-236 °C (decomp.) (from EtOH); Anal. Calcd for $C_{20}H_{16}ClN_3O_3S$: C, 58.04; H, 3.90; N, 10.15; S, 7.75. Found: C, 58.21; H, 3.57; N, 10.08; S, 7.59; IR (KBr): ν_{max}/cm^{-1} 3381, 3316, 3254, 3189, 2969, 2935, 2191, 1671, 1643, 1596, 1489, 1416, 1354, 1315, 1253, 1167, 1143, 1119, 1075, 753 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.94 (d, *J* = 7.94 Hz, 1H), 7.73 – 7.50 (m, 2H), 7.48 – 7.23 (m, 7H), 4.72 (s, 1H), 3.89 (q, *J* = 6.71 Hz, 2H), 1.04 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 158.8, 146.3, 141.7, 137.7, 132.5, 132.2, 129.8, 128.6, 124.6, 123.8, 119.3, 118.9, 117.2, 113.9, 57.7, 42.5, 36.8, 13.9; MS (EI) m/z: 413 $[M]^+$.

4.3.6. 2-Amino-3-cyano-4-(4-(N,N-dimethylamino)phenyl))-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (5f)

Brown plates; mp 147-150 °C (decomp.) (from EtOH); Anal. Calcd for $C_{22}H_{22}N_4O_3S$: C, 62.54; H, 5.25; N, 13.26; S, 7.59. Found: C, 62.38; H, 5.02; N, 13.15; S, 7.34; IR (KBr): ν_{max}/cm^{-1} 3325, 3255, 3212, 2922, 2197, 1682, 1598, 1522, 1486, 1452, 1399, 1344, 1325, 1260, 1174, 1147, 1116, 759 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.92 (d, *J* = 6.71 Hz, 1H), 7.71 – 7.48 (m, 2H), 7.38 (t, *J* = 7.54 Hz, 1H), 7.21 (s, 2H), 7.03 (d, *J* = 8.55 Hz, 2H), 6.64 (d, *J* = 8.55 Hz, 2H), 4.48 (s, 1H), 3.89 (q, *J* = 6.82 Hz, 2H), 2.85 (s, 6H), 1.04 (t, *J* = 6.94 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 158.6, 149.8, 145.6, 137.7, 132.2, 130.0, 128.4, 124.5, 123.7, 119.3, 117.4, 115.1, 112.3, 58.8, 42.4, 40.1, 36.8, 13.9; MS (EI) m/z: 422 $[M]^+$.

4.3.7. 2-Amino-3-cyano-4-(9-anthracenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (5g)

Brown prisms; mp > 250 °C (from EtOH); Anal. Calcd for $C_{28}H_{21}N_3O_3S$: C, 70.13; H, 4.41; N, 8.76; S, 6.69. Found: C, 70.12; H, 4.24; N, 8.33; S, 6.37; IR (KBr): ν_{max}/cm^{-1} 3455, 3346, 2921, 2190, 1662, 1626, 1590, 1400, 1324, 1253, 1171, 1149, 1118, 1089, 727 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.74 – 8.57 (m, 2H), 8.25 – 7.99 (m, 4H), 7.72 – 7.28 (m, 9H), 6.54 (s, 1H), 3.76 (q, *J* = 6.41 Hz, 2H), 0.92 (t, *J* = 6.71 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 158.2, 145.5, 137.7, 132.4, 131.6, 131.1, 131.0, 131.0, 129.94, 129.86, 129.2, 129.0, 126.7, 125.7, 125.1, 124.7, 124.4, 124.2, 123.9, 123.2, 119.4, 118.7, 117.3, 115.2, 58.0, 42.4, 31.0, 13.7; MS (EI) m/z: 479 $[M]^+$.

4.4. Procedures for the synthesis of 2-amino-4-aryl-3-ethoxycarbonyl-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxides (7a-e)

Compounds **7a-e** were obtained by interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1**, ethyl cyanoacetate **6** and benzaldehydes **3a-e** in conditions submitted below. The yields for the synthesized compounds **7a–e** are presented in Table 2.

4.4.1. 2-Amino-3-ethoxycarbonyl-4-phenyl-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (7a)

To a 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 **6** (0.33 mL, 0.003 mol) and benzaldehyde **3a** (0.1 mL, 0.001 mol) in ethanol (5 mL), DMAP (0.122 g, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to 0 °C. After precipitate of **7a** was formed it was filtered off, washed with cold ethanol, dried on air and recrystallized from ethanol.

White prisms; mp 168-171 °C (from EtOH); Anal. Calcd for $C_{22}H_{22}N_2O_5S$: C, 61.96; H, 5.20; N, 6.57; S, 7.52. Found: C, 62.14; H, 5.08; N, 6.49; S, 7.19; IR (KBr): ν_{max}/cm^{-1} 3419, 3293, 3058, 2982, 2938, 2904, 1951, 1930, 1881, 1812, 1688, 1657, 1617, 1603, 1571, 1520, 1489, 1452, 1320, 1254, 1166, 1147, 1096, 1069, 757 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.04 (d, *J* = 7.63, 1H), 7.80 (s, 2H), 7.71 – 7.49 (m, 2H), 7.39 (t, *J* = 7.54, 1H), 7.32 – 7.07 (m, 5H), 4.83 (s, 1H), 4.09 - 3.79 (m, 4H), 1.11 (t, *J* = 7.17 Hz, 3H), 0.97 (t, *J* = 7.23 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 167.2, 159.5, 146.1, 144.4, 137.6, 132.1, 128.2, 127.8, 126.8, 124.5, 123.6, 119.2, 117.2, 116.9, 77.8, 59.2, 42.2, 35.8, 14.3, 13.7; MS (EI) m/z: 426 $[M]^+$.

4.4.2. 2-Amino-3-ethoxycarbonyl-4-(4-nitrophenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1] benzothiazine 5,5-dioxide (7b)

To a 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 **6** (0.11 mL, 0.001 mol) and 4-nitrobenzaldehyde **3b** (0.151 g, 0.001 mol) in ethanol (5 mL), DMAP (0.122 g, 0.001 mol) was added. The reaction mixture was heated at

50 °C for 2 h, cooled to the room temperature and allowed to stand overnight. The formed crystalline precipitate of **7b** was filtered off, washed with ethanol, dried on air and recrystallized from ethanol.

Yellow prisms; mp 170-172 °C (from EtOH); Anal. Calcd for $C_{22}H_{21}N_3O_7S$: C, 56.04; H, 4.49; N, 8.91; S, 6.80. Found: C, 56.23; H, 4.21; N, 8.60; S, 6.41; IR (KBr): ν_{max}/cm^{-1} 3430, 3396, 3304, 3076, 2976, 2933, 2449, 1949, 1812, 1689, 1657, 1515, 1347, 1316, 1255, 1166, 1146, 1100, 758 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.18 - 8.02 (m, 3H), 7.94 (s, 2H), 7.72 – 7.34 (m, 5H), 4.97 (s, 1H), 4.06 - 3.79 (m, 4H), 1.10 (t, *J* = 7.02 Hz, 3H), 0.99 (t, *J* = 6.87 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 166.9, 159.4, 152.0, 146.5, 146.4, 137.7, 132.5, 129.4, 124.7, 123.7, 123.5, 119.2, 117.0, 115.4, 76.3, 59.4, 42.3, 35.9, 14.2, 13.8; MS (EI) m/z: 471 $[M]^+$.

4.4.3. 2-Amino-3-ethoxycarbonyl-4-(2-methoxyphenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (7c)

To a 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 **6** (0.22 mL, 0.002 mol) and 2-methoxybenzaldehyde **3c** (0.136 g, 0.001 mol) in ethanol (5 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to the room temperature and allowed to stand overnight. The formed crystalline precipitate of **7c** was filtered off, washed with ethanol, dried on air and recrystallized from ethanol.

Colorless prisms; mp 175-177 °C (from EtOH); Anal. Calcd for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.30; N, 6.14; S, 7.02. Found: C, 60.88; H, 5.18; N, 6.35; S, 6.81; IR (KBr): ν_{max}/cm^{-1} 3395, 3287, 3085, 3062, 2983, 2936, 2835, 1959, 1930, 1901, 1805, 1689, 1652, 1615, 1531, 1486, 1463, 1305, 1254, 1163, 1102, 1030, 753 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.01 (d, *J* = 6.71 Hz, 1H), 7.72 (s, 2H), 7.67 – 7.32 (m, 3H), 7.12 (d, *J* = 7.32 Hz, 2H), 6.94 – 6.72 (m, 2H), 4.99 (s, 1H), 4.04 - 3.77 (m, 4H), 3.62 (s, 3H), 1.08 (t, *J* = 7.17 Hz, 3H), 0.93 (t, *J* = 6.97 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 167.7, 160.0, 157.6, 146.0, 137.6, 131.8, 131.2, 130.7, 128.3, 124.2, 123.6, 119.9, 119.3, 117.7, 115.6, 111.6, 75.8, 58.9, 55.6, 42.3, 32.4, 14.2, 13.4; MS (EI) m/z: 456 $[M]^+$.

4.4.4. 2-Amino-3-ethoxycarbonyl-4-(4-methoxyphenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (7d)

To a 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 **6** (0.33 mL, 0.003 mol) and 4-methoxybenzaldehyde **3d** (0.12 mL, 0.001 mol) in 2-propanol (5 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to 0 °C and kept at this temperature overnight. The resulting precipitate of **7d** was filtered off, washed with cold ethanol, dried on air and recrystallized from ethanol.

Colorless prisms; mp 175-177 °C (from EtOH); Anal. Calcd for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.30; N, 6.14; S, 7.02. Found: C, 60.85; H, 5.20; N, 6.09; S, 6.77; IR (KBr): ν_{max}/cm^{-1} 3399, 3285, 3072, 2981, 2935, 2901, 2848, 1927, 1844, 1812, 1690, 1656, 1608, 1509, 1450, 1321, 1300, 1255, 1168, 1102, 1032, 756 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.03 (d, *J* = 7.94 Hz, 1H), 7.75 (s, 2H), 7.69 – 7.47 (m, 2H), 7.38 (t, *J* = 7.53 Hz, 1H), 7.10 (d, *J* = 8.55 Hz, 2H), 6.80 (d, *J* = 8.55 Hz, 2H), 4.78 (s, 1H), 4.08 - 3.81 (m, 4H), 3.67 (s, 3H), 1.13 (t, *J* = 7.02 Hz, 3H), 1.00 (t, *J* = 7.17 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 167.3, 159.4, 158.1, 145.8, 137.6, 136.5, 132.1, 128.8, 124.5, 123.6, 119.1, 117.2, 117.1, 113.5, 77.9, 59.2, 55.0, 42.2, 35.0, 14.3, 13.8; MS (EI) m/z: 456 $[M]^+$.

4.4.5. 2-Amino-3-ethoxycarbonyl-4-(4-chlorophenyl)-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (7e)

To a 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 **6** (0.77 mL, 0.007 mol) and 4-chlorobenzaldehyde **3e** (0.14 g, 0.001 mol) in ethanol (5 mL), DMAP (0.122 g, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to the room temperature and allowed to stand overnight. The formed precipitate of **7e** was filtered off, washed with cold ethanol, dried on air and recrystallized from ethanol.

White fine-crystalline powder; mp 198-200 °C (from EtOH); Anal. Calcd for $C_{22}H_{21}ClN_2O_5S$: C, 57.33; H, 4.59; N, 6.08; S, 6.96. Found: C, 57.47; H, 4.33; N, 6.21; S, 6.55; IR (KBr): ν_{max}/cm^{-1} 3432, 3328, 3112, 3047, 2982, 2924, 1687, 1601, 1485, 1458, 1332, 1319, 1253, 1167, 1146, 1118, 780 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.04 (d, *J* = 7.93 Hz, 1H), 7.85 (s, 2H), 7.71 – 7.50 (m, 2H), 7.46 – 7.16 (m, 5H), 4.83 (s, 1H), 4.07 - 3.80 (m, 4H), 1.11 (t, *J* = 7.17 Hz, 3H), 0.99 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 167.5, 159.7, 146.5, 143.8, 138.0, 132.6, 131.7, 130.1, 128.5, 125.0, 124.0, 119.5, 117.5, 116.7, 77.5, 59.6, 42.6, 35.8, 14.6, 14.1; MS (EI) m/z: 460 $[M]^+$.

4.5. Isolation of 3-[(4-hydroxy-1-ethyl-2,2-dioxido-1*H*-2,1-benzothiazin-3-yl)(aryl)methyl]-1-ethyl-1*H*-2,1-benzothiazin-5-olat 2,2-dioxides (8a-c,e). These products were obtained during our attempts to synthesize the products of three-component interactions using the procedures described below.

4.5.1. 3-[(4-Hydroxy-1-ethyl-2,2-dioxido-1*H*-2,1-benzothiazin-3-yl)(phenyl)methyl]-1-ethyl-1*H*-2,1-benzothiazin-5-olat 2,2-dioxide (8a)

Procedure A. To a 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 **6** (0.11 mL, 0.001 mol) and benzaldehyde **3a** (0.1 mL, 0.001 mol) in ethanol (5 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to the room temperature and solvent was evaporated in vacuum. The oily residue was mixed with 1 mL of *i*-PrOH. Under intensive mixing the precipitate of **8a** was

formed, which was filtered off, washed with cold ethanol, dried on air and recrystallized from ethanol. Yield of **8a** was 35%.

Procedure B. To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 mol) and ethyl 2-cyano-3-phenylacrylate **9a** (0.201 g, 0.001 mol) in ethanol (5 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 4 h, cooled to 0 °C and kept at this temperature. The precipitate of **8a** was formed, washed with cold ethanol, dried on air and recrystallized from ethanol. Yield of **8a** was 43%.

Procedure C. Compound **8a** was obtained using N-(*p*-tolyl)cyanoacetamide **13** instead ethyl cyanoacetate **6** under conditions represented in *Procedure A*. Yield of **8a** was 53%.

Procedure D. To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 mol) and **7a** (0.426 g, 0.001 mol) in ethanol (5 mL), triethylamine (0.14 mL, 0.001 mol) was added. The mixture was refluxed during 6 h. Next it was treated as described in *Procedure B*. Yield of **8a** was 47%.

Preparative procedure. To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.450 g, 0.002 mol), benzaldehyde **3a** (0.1 mL, 0.001 mol) in ethanol (10 mL), triethylamine (0.14 mL, 0.001 mol) was added. The solution was stirred at the room temperature. After about 1 h a white precipitate of **8a** was formed, this was filtered off, washed with ethanol, dried on air and recrystallized from ethanol. Yield of **8a** was 93%.

White needles; mp 153-155 °C (from EtOH); Anal. Calcd for $C_{33}H_{41}N_3O_6S_2$: C, 61.95; H, 6.46; N, 6.57; S, 10.02. Found: C, 62.42; H, 6.12; N, 6.76; S, 9.63; IR (KBr): ν_{max}/cm^{-1} 3431, 3087, 2987, 2934, 2882, 2814, 2498, 1613, 1542, 1479, 1310, 1263, 1170, 1141, 1045, 758, 575 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 17.25 (s, 1H), 7.86 (d, *J* = 7.63, 2H), 7.52 – 7.35 (m, 2H), 7.34 – 6.97 (m, 9H), 5.71 (s, 1H), 3.95 (q, *J* = 7.02 Hz, 4H), 3.04 (q, *J* = 7.32 Hz, 6H), 1.33 – 1.05 (m, 15H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 160.4, 141.8, 138.7, 130.5, 128.0, 127.7, 126.8, 125.7, 124.8, 122.1, 117.5, 110.6, 46.2, 41.3, 36.2, 14.5, 9.0; MS (EI) m/z: 313 $[M-326]^+$.

4.5.2. 3-[(4-Hydroxy-1-ethyl-2,2-dioxido-1*H*-2,1-benzothiazin-3-yl) (4-nitrophenyl)methyl]-1-ethyl-1*H*-2,1-benzothiazin-5-olat 2,2-dioxide (8b)

To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.225 g, 0.001 mol), benzyl cyanide **12** (0.115 mL, 0.001 mol) and 4-nitrobenzaldehyde **3b** (0.151 g, 0.001 mol) in ethanol (5 mL), triethylamine (0.14 mL, 0.001 mol) was added. The solution was mixed at room temperature for 4 h and allowed to stand overnight. The formed yellow crystalline precipitate of **8b** was filtered off, washed with ethanol, dried on air and recrystallized from ethanol. Yield of **8b** was 44%.

Yellow prisms; mp 168-170 °C (from EtOH); Anal. Calcd for $C_{33}H_{40}N_4O_8S_2$: C, 57.88; H, 5.89; N, 8.18; S, 9.36. Found: C, 58.12; H, 5.94; N, 8.40; S, 9.14; IR (KBr): ν_{max}/cm^{-1} 3396, 3108, 2985, 2935, 2496, 1606, 1514, 1480, 1347, 1308, 1254, 1163, 1143, 1109, 1047, 751, 567 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 17.10 (s, 1H), 8.09 (d, *J* = 8.85, 2H), 7.86 (d, *J* = 6.41 Hz, 2H), 7.54 – 7.39 (m, 4H), 7.36 – 7.27 (m, 2H), 7.20 – 7.07 (m, 2H), 5.78 (s, 1H), 3.96 (q, *J* = 6.71 Hz, 4H), 3.05 (q, *J* = 7.32 Hz, 6H), 1.29 – 1.05 (m, 15H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 160.4, 150.3, 145.7, 138.4, 130.5, 128.5, 126.5, 124.2, 123.1, 121.9, 117.4, 109.5, 45.9, 41.1, 36.3, 14.1, 8.7; MS (EI) m/z: 358 $[M-326]^+$.

4.5.3. 3-[(4-Hydroxy-1-ethyl-2,2-dioxido-1*H*-2,1-benzothiazin-3-yl) (2-methoxyphenyl)methyl]-1-ethyl-1*H*-2,1-benzothiazin-5-olat 2,2-dioxide (8c).

Preparative procedure. To a solution of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **1** (0.450 g, 0.002 mol), 2-methoxybenzaldehyde **3c** (0.136 g, 0.001 mol) in ethanol (10 mL), triethylamine (0.14 mL, 0.001 mol) was added. The solution was stirred at the room temperature. After about 1 h a white precipitate of **8c** was formed, this was filtered off, washed with ethanol, dried on air and recrystallized from ethanol. Yield of **8c** was 87%.

Colorless prisms; mp 145-147 °C (from EtOH); Anal. Calcd for $C_{34}H_{43}N_3O_7S_2$: C, 60.96; H, 6.47; N, 6.27; S, 9.57. Found: C, 61.31; H, 6.46; N, 6.24; S, 9.22; IR (KBr): ν_{max}/cm^{-1} 3429, 2973, 2917, 2850, 2470, 1606, 1587, 1474, 1335, 1296, 1247, 1164, 1143, 1108, 1046, 744, 567 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 16.84 (s, 1H), 7.99 – 7.84 (m, 2H), 7.52 – 7.35 (m, 3H), 7.33 – 7.00 (m, 5H), 6.84 – 6.70 (m, 2H), 5.89 (s, 1H), 4.06 – 3.81 (m, 4H), 3.62 (s, 3H), 3.11 – 2.90 (m, 6H), 1.39 – 0.96 (m, 15H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 160.0, 156.6, 138.9, 130.4, 129.9, 129.8, 126.8, 126.4, 124.9, 121.6, 119.0, 117.5, 110.6, 110.4, 55.2, 45.9, 41.8, 31.9, 14.3, 8.7.

4.5.4. 3-[(4-Hydroxy-1-ethyl-2,2-dioxido-1*H*-2,1-benzothiazin-3-yl) (4-chlorophenyl)methyl]-1-ethyl-1*H*-2,1-benzothiazin-5-olat 2,2-dioxide (8e)

Compound **8e** was obtained using 4-chlorobenzaldehyde **3e,** instead **3a**, according to the procedure described in section 4.5.1 (*Route A*). Yield of **8e** was 17%.

Colorless prisms; mp 163-165 °C (from EtOH); Anal. Calcd for $C_{33}H_{40}ClN_3O_6S_2$: C, 58.78; H, 5.98; N, 6.23; S, 9.51. Found: C, 58.91; H, 5.87; N, 6.41; S, 9.34; IR (KBr): ν_{max}/cm^{-1} 3456, 3079, 2988, 2937, 2904, 2878, 2835, 2499, 1610, 1542, 1486, 1311, 1263, 1170, 1139, 1113, 1047, 757, 571 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ (ppm) 17.19 (s, 1H), 7.86 (d, *J* = 7.94, 2H), 7.51 – 7.36 (m, 2H), 7.34 – 7.19 (m, 6H), 7.18 – 7.06 (m, 2H), 5.69 (s, 1H), 3.95 (q, *J* = 7.22 Hz, 4H), 3.03 (q, *J* = 7.32 Hz, 6H), 1.28 – 1.05 (m, 15H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 160.1, 140.6, 138.4, 130.3, 130.0, 129.2, 127.6, 126.5, 124.3, 121.8, 117.2, 110.0, 45.9, 40.9, 35.5, 14.1, 8.7; MS (EI) m/z: 347 $[M-326]^+$.

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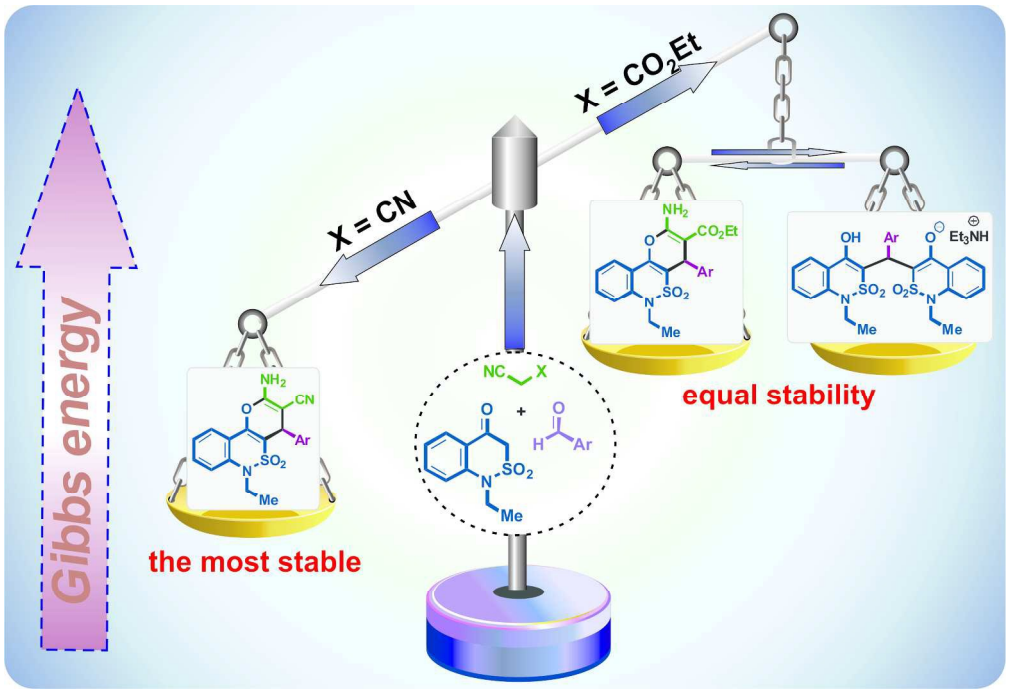

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