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1,2-Benzoxathiin-4(3*H*)-one 2,2-dioxide – an underinvestigated building block with a high synthetic and pharmacological potential: synthesis, chemical properties, biological activity

Aim. To analyze the available literature data on the methods of synthesis, chemical transformations and the biological activity of derivatives containing a sultone core – 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide – and to show the possibilities of their further use in the construction of new molecular systems with attractive pharmacological properties.

Results and discussion. The most widespread method for the synthesis of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides is the cyclization of salicylic acid derivatives. The known chemical transformations of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides deal with all reaction centers of the heterocyclic fragment of the condensed system – C=O and CH_2 groups, SO_2–O bond, CH_2CO fragment as a whole. It should be noted that the oxathiine nucleus is prone to undergo recyclizations. The use of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides in multicomponent transformations still remains hardly explored. The "abnormal" course of some classical transformations involving 1,2-benzoxathiine 2,2-dioxides is also noteworthy. The study of the pharmacological properties of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide derivatives is scarce and mainly based on their structural similarity to the coumarin core, which led to the study of anticoagulant, antimicrobial and antitumor properties for the sultone derivatives.

Conclusions. The analysis has shown a limited number of studies in each aspect – approaches to the synthesis of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides, their chemical transformations and the study of their pharmacological activity. In addition to a small number of publications on this heterocyclic system, there have been almost no sultone studies in the last 20 years. Taking this into account 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide and its derivatives deserve close attention as objects of research for experimental chemistry and pharmacology.

Key words: sultone; oxathiine; heterocyclization; active methylene ketones; biological activity

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1,2-Бензоксатіїн-4(3*H*)-он 2,2-діоксид – малодосліджений білдинг-блок із високим синтетичним та фармакологічним потенціалом: синтез, хімічні властивості, біологічна активність

Мета. Проаналізувати наявні літературні дані щодо методів синтезу, хімічних перетворень та біологічної активності похідних, які містять у своєму складі ядро сультону – 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксиду та показати можливості їх подальшого використання у побудові нових молекулярних систем з привабливими фармакологічними властивостями.

Результати та їх обговорення. Найбільш популярний метод для синтезу ядра 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксидів – циклізація похідних саліцилової кислоти. Відомі хімічні перетворення 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксидів зачіпають усі реакційні центри гетероциклічного фрагмента конденсованої системи – C=O та CH_2 групи, SO_2-O зв'язок та CH_2CO фрагмент у цілому. Варто зазначити, що оксатіїнове ядро схильне до рециклізаційних перетворень. Використання 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксидів у багатокомпонентних перетвореннях досі залишається майже не дослідженим. Також звертає на себе увагу «аномальний» перебіг деяких класичних перетворень за участю 1,2-бензоксатіїн 2,2-діоксидів. Дослідження фармакологічних властивостей похідних 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксиду носить одиничний характер та базується на їх структурній схожості з ядром кумарину, що зумовило вивчення антикоагулянтних, протимікробних та протипухлинних властивостей для похідних цього сультону.

Висновки. Проведений аналіз засвідчив обмежену кількість досліджень щодо кожного аспекту – підходів до синтезу 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксидів, вивчення їх хімічних перетворень та фармакологічної активності. Окрім незначної кількості публікацій, де висвітлено особливості цієї гетероциклічної системи, останні 20 років майже немає робіт з досліджень сультону. З огляду на це, 1,2-бензоксатіїн-4(3*H*)-он 2,2-діоксид та його похідні заслуговують на пильну увагу як об'єкти дослідження для експериментальної хімії та фармакології.

Ключові слова: сультон; оксатіїн; гетероциклізація; метиленактивні кетони; біологічна активність

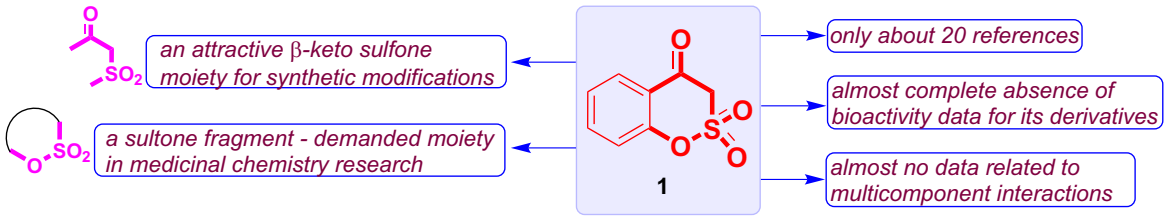


Fig. 1. The general structure and peculiarities of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**)

Nowadays, organic chemistry deals with an incredible number of molecular platforms, and it is extremely difficult to find a relatively simple organic compound, which is underinvestigated with respect to its chemical and/or biological properties. Nevertheless, 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) appeared to be one of such 'dark places' in organic chemistry (Fig. 1). To date, chemical databases provide only about 20 works concerning benzoxathiinone **1**. Moreover, issues of the biological activity and multicomponent interactions for it have been hardly studied until now. Such a state of affairs is strange as compound **1** comprises two attractive structural moieties. The first one is a β-keto sulfone fragment that allows a molecule to be a versatile synthetic intermediate used for the preparation of diverse classes of organic compounds [1]. The second one is a sultone fragment, which is responsible for many kinds of pharmacological activities mainly concerned with their toxicological, skin sensitization, antiviral, carbonic anhydrase inhibitory properties, etc. [2–4]. Furthermore, in recent decades sultones have become valuable scaffolds widely used as building blocks in the field of medicinal chemistry and were described in several reviews [5, 6].

Besides, benzoxathiinone **1** may gain the additional value due to its isosteric relationships. At the beginning of the XXth century the concept of isosterism became especially relevant in medical chemistry. It still remains a powerful tool for the purposeful search of new biologically active substances [7, 8]. The isosteric replacement changes one or more characteristics of the molecule: size, shape, hydrophobicity, solubility, pKa, reactivity. Such changes make it possible to increase the selectivity of the compound, reduce its side effects and toxicity, improve pharmacokinetic characteristics and increase the metabolic stability. From this point of view, 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) core can be considered as isostere, first of all, to such a well-known pharmacophore as 4-hydroxycoumarin **A** (Fig. 2). Among the derivatives of the latter there are anticoagulants of the indirect action, vitamin K inhibitors – warfarin, dicoumarol and others [9]. Secondly, the structural analog of this compound is 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **B**, which derivatives have shown high efficacy in the treatment of pain and inflammation, and even greater activity compared to such known NSAIDs as Piroxicam® and Meloxicam® [10, 11].

This review focuses on developments in chemistry and pharmacology of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) derivatives, including our achievements in this field. We hope the review will encourage, guide and intensify further research in the topic of sultone **1**, resulting in a breakthrough in the search for new medicines.

Results and discussion

A lot of methods have been developed for the preparation of sultones. The classical approach to their synthesis is the intramolecular cyclization of aromatic

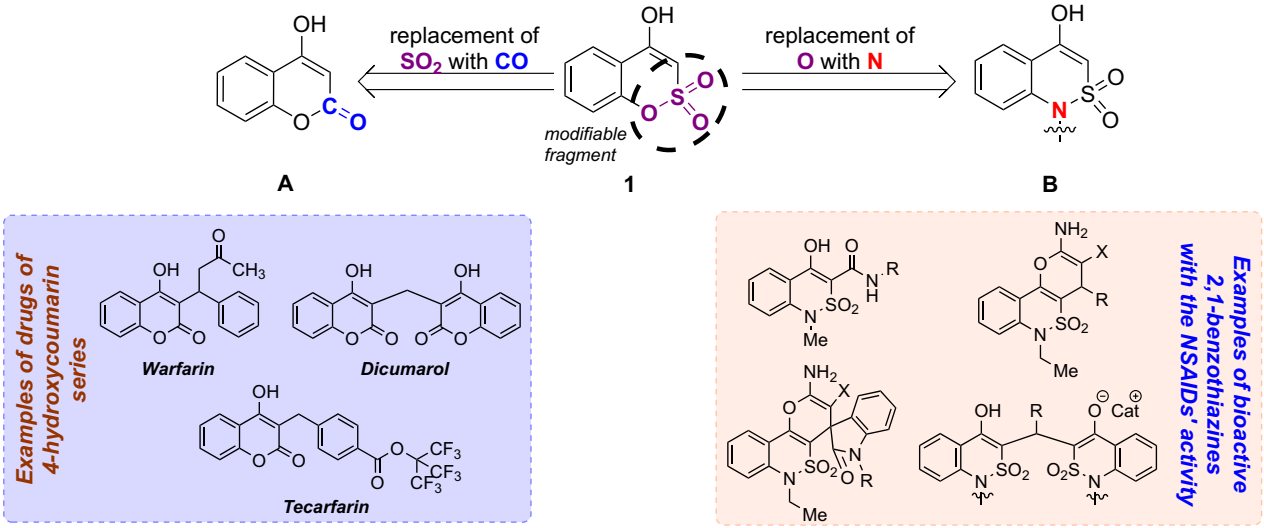
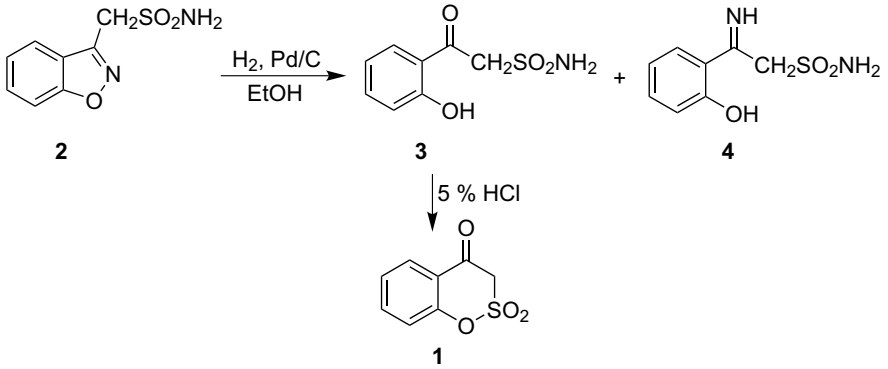


Fig. 2 Isosteric relationships of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) with 4-hydroxycoumarin **A** and 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide **B**



Scheme 1. Synthesis of sultone **1** based on 2-hydroxy-α-sulfamoylacetophenone (**3**)

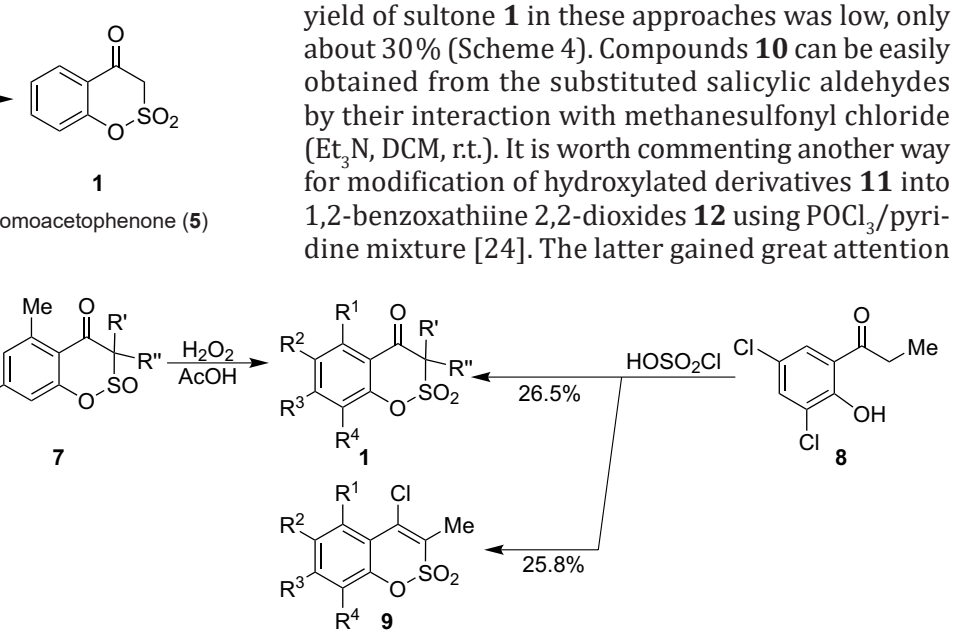
hydroxysulfonic acids under the action of the concentrated sulfuric acid, phosphorus pentachloride or phosphorus oxychloride [12]. Other methods involve the intramolecular Diels-Alder reaction of vinyl sulfonates [13], sulfonate metathesis reactions [14, 15], the cyclization reactions of sulfonates using organometallic catalysts containing copper, palladium, rhodium, ruthenium, etc. [12, 16, 17]. According to these methods sultons with different cycle sizes, mono- and polycyclic, saturated, unsaturated and condensed with aromatic systems can be synthesized.

Regarding the approaches to the synthesis of sultone **1** some works describe the methods where it was not the targeted one or turned out to be an unexpected product of another interaction studied. An example of such transformations is the acidic hydrolysis of 2-hydroxy-α-sulfamoylacetophenone (**3**) presented by the authors Uno *et al.* [18]. In the process of the catalytic hydrogenation of 3-sulfamoylmethyl-1,2-benzisoxazole (**2**) two products were obtained: 2-hydroxy-α-sulfamoylacetophenone (**3**) and its imine **4**. While studying the chemical properties of the hydrogenated products the authors tried to hydrolyze the compound **3**. In the case of using 5% solution of hydrochloric acid an unexpected cyclic product was obtained – 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) with the yield of 98% (Scheme 1).

A purposeful synthesis of this heterocyclic system was first described by King *et al.* [19] (Scheme 2). It was based on the interaction of *o*-hydroxy-α-bromoacetophenone (**5**) with hydrosulfites in the presence of phosphorus oxychloride.

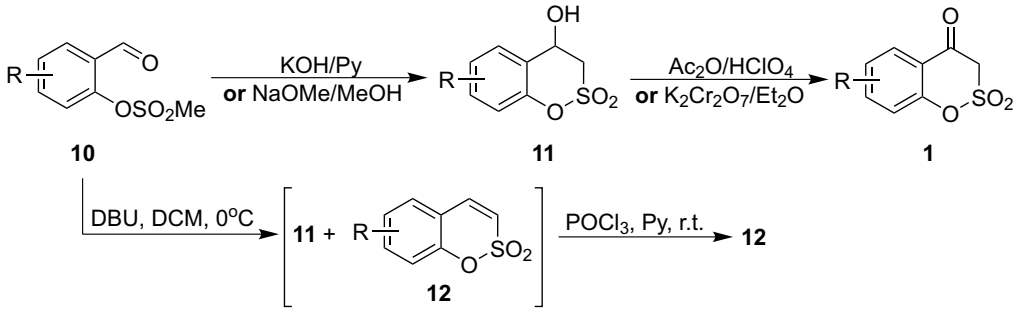
The method proposed by W. Berbiery *et al.* [20] was similar by its logic. Authors reported the synthesis of a group of stable, crystalline 1,2-benzoxathian-4-one S-oxides **7**, which could be easily obtained by refluxing the corresponding hydroxy ketones with four parts of $SOCl_2$ for 1 h. The latter were oxidized by H_2O_2 to give the target benzoxathiinones **1**. Another cyclizing agent used in the reaction with propiophenone **8** was chlorosulfonic acid [21]. A drawback of the approach is the formation of a mixture of the benzoxathiinone **1** and its 4-Cl analog **9**, which, however, can be easily separated (Scheme 3).

The papers [22, 23] presented a two-step synthesis of compound **1** by the cyclization of salicylic aldehyde methanesulfonates **10** followed by the oxidation of the product **11** formed. However, the total yield of sultone **1** in these approaches was low, only about 30% (Scheme 4). Compounds **10** can be easily obtained from the substituted salicylic aldehydes by their interaction with methanesulfonyl chloride (Et_3N, DCM, r.t.). It is worth commenting another way for modification of hydroxylated derivatives **11** into 1,2-benzoxathiine 2,2-dioxides **12** using $POCl_3$/pyridine mixture [24]. The latter gained great attention



Scheme 2. Application of *o*-hydroxy-α-bromoacetophenone (**5**) in the synthesis of sultone **1**

Scheme 3. Heterocyclizations of *o*-hydroxyphenylketones with thionyl chloride and chlorosulfonic acid in the synthesis of sultone **1**



Scheme 4. Application of salicylic aldehyde methanesulfonates **10** in the synthesis of sultone **1**

as a selective carbonic anhdydrase (CA) IX and XII inhibitors and can be successfully applied to the treatment of some cancer types [25–27].

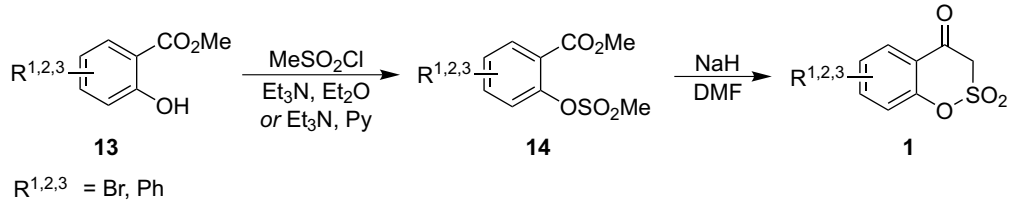
Schwender *et al.* in 1978 patented a new way to the synthesis of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide derivatives [28] (Scheme 5). According to it, methylsulfonates **14** were obtained by the interaction of the substituted methyl esters of salicylic acid **13** with methanesulfonyl chloride in the presence of a base. Further heterocyclization of the latter was carried out by its heating in DMF with sodium hydride leading to the formation of the target products **1** with a total yield of 59–76%.

This approach has gained popularity and has been applied with a variety of conditions in other synthetic investigations [29–31]. For example, authors [29] performed the heterocyclization of methanesulfonate **14** by the action of sodium hydride when cooling and modifying the conditions of the product isolation. Arava *et al.* [30] used sodium hydride in DMSO for cyclization (the yield of compounds **1** ranged from 47 to 76%). The reaction proceeded well with bromo-, chloro-, methoxy- and methyl-substituted derivatives **14**; in the presence of the NO_2-group the target derivatives **1** could not be obtained. The use of potassium *tert*-butoxide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF for the phenyl ester **16** cyclization allowed to obtain 1,2-benzoxathiin-4(3*H*)one 2,2-dioxide (**1**) with the yield of 70% [31] (Scheme 6).

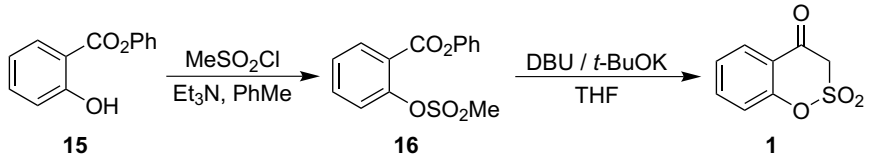
A similar approach to 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide derivatives was used in the study of Peixoto *et al.* [32]. The synthetic route to benzoxathiinone **1** is shown in Scheme 7. The authors used 2-methylresorcinol (**17**) as a starting material, which allowed obtaining **1** substituted in the benzene nucleus. After introduction of the aldehyde group into the 2-methylresorcinol molecule and its conversion into an ester, one of the hydroxyl groups was regioselectively protected with tetrahydropyran (THP). The free hydroxyl group reacted with methanesulfonyl chloride, and the resulting derivative **21** was cyclized by the action of sodium hydride in DMF. The tetrahydropyran protection was easily removed in the acidic medium to give 7-hydroxy-8-methyl-1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**).

According to the synthetic routes described above mostly 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide derivatives unsubstituted in position 3 of the sultone ring were obtained. Although the cyclization of acetophenones **6** and **8** is the way of introducing a substituent in position 3 of the oxathiine moiety, it is still unclear why various alkanesulfonyl chlorides are not used in the approach involving alkyl salicylates as starting reagents (Scheme 7).

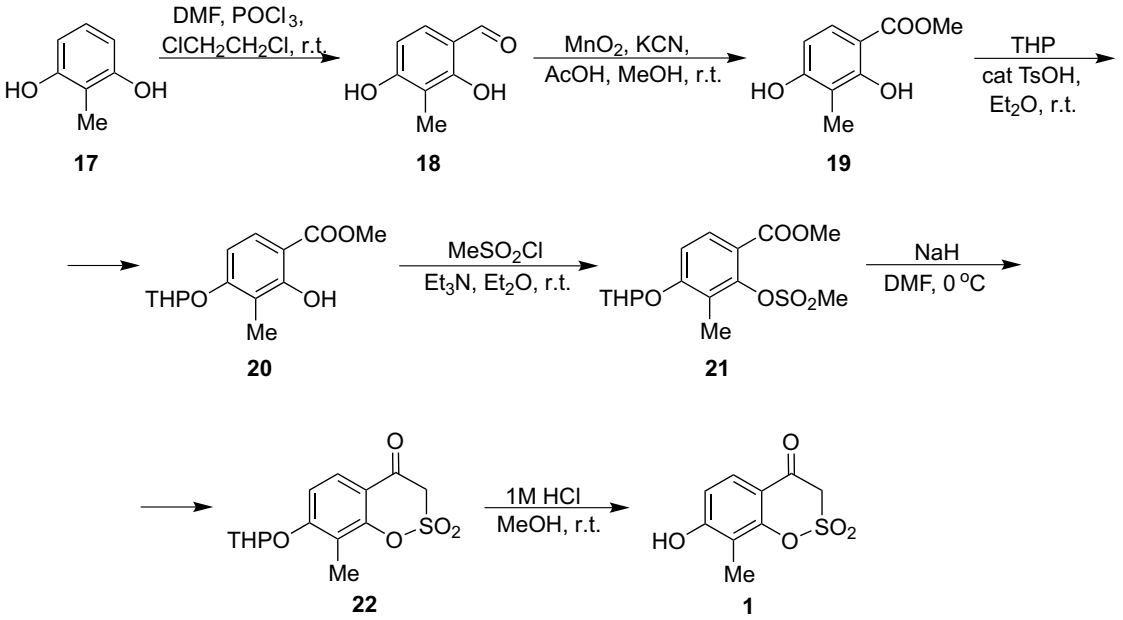
Approaches to the synthesis of the benzoxathiinone heterocyclic system functionalized in position 3 are also described in the literature. These synthetic pathways were studied in detail by Löwe *et al.* As a starting material in a number of studies 3-chromonsulfonic acid chloride (**25**), which was obtained from the corresponding acid **23**, was used [33] (Scheme 8).



Scheme 5. The two-step synthesis of sultone **1** based on methyl salicylates **13**



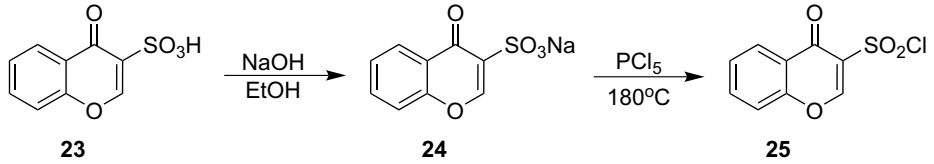
Scheme 6. The two-step synthesis of sultone **1** based on phenyl salicylate (**15**)



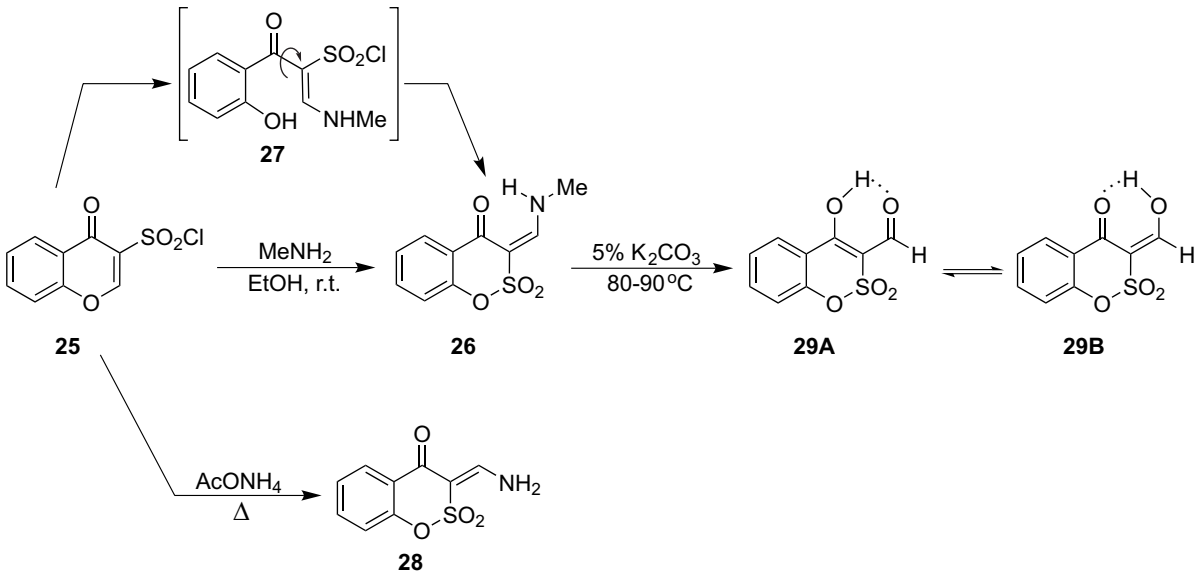
Scheme 7. 2-Methylresorcinol (**17**) in the synthesis of sultone **1**

The same authors found that the interaction of compound **25** with methylamine in ethanol at room temperature resulted in the formation of an unexpected enaminoketone – a derivative of benzoxathiinone **26** [33] (Scheme 9). The course of the transformation **25→26** was explained by the authors as an ANRORC mechanism accompanied by the opening of the pyran cycle as the result of the nucleophilic addition of methylamine (intermediate **27**) and the subsequent ring closure with the sultone nucleus formation. As it was shown in the latter study [34], the fusion of compound **25** with ammonium acetate led to the N-unsubstituted enaminone **28** apparently formed by the same ANRORC way (Scheme 9). Enaminoketone **26** exhibits properties typical for enamines and can be hydrolyzed to aldehyde **29**. The latter exists in the form of at least 2 tautomers **29A** and **29B** as it was confirmed by ^{1}H NMR spectroscopy data.

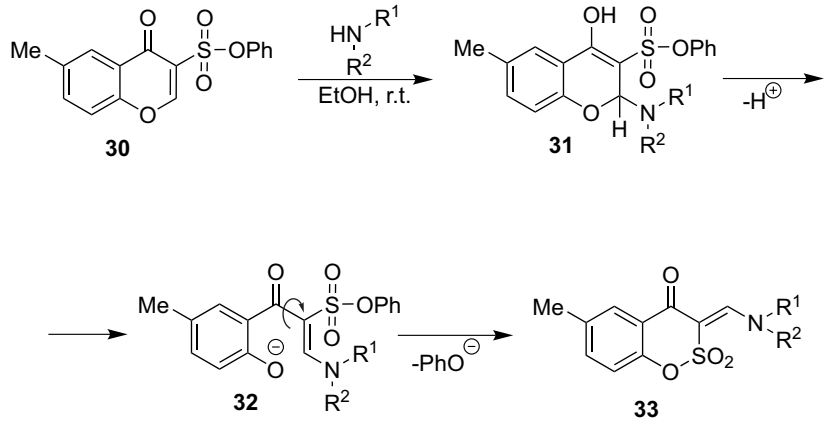
As a continuation of these studies Löwe *et al.* used the synthetic equivalent of sulfonyl chloride **25** – a phenyl



Scheme 8. The preparation of 3-chromonsulfonic acid chloride (**25**) – a starting compound in the synthesis of 3-substituted sultones **1**



Scheme 9. The recyclization of 3-chromonsulfonic acid chloride (**25**) with methylamine and ammonia



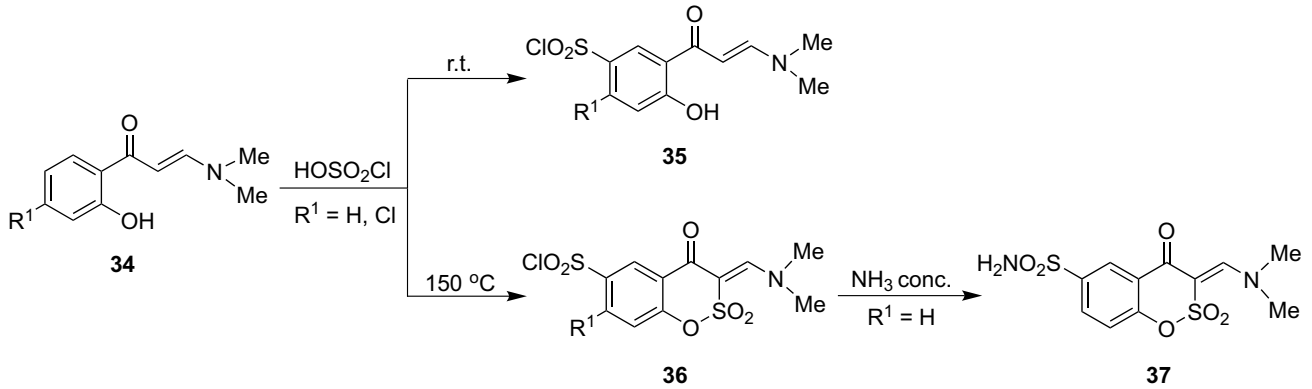
Scheme 10. The recyclization of 3-chromonsulfonic acid phenyl ester (**30**) with amines

ester **30**, and studied its interaction with a series of primary and secondary amines [35] (Scheme 10). The reaction proceeded with the formation of enaminoketones **33** by the addition-elimination mechanism similar to the case of sulfonyl chloride **25**. Also, similarly to sulfonyl chloride **25**, the fusion of phenyl ester **30** with ammonium acetate resulted in compound **28** [36].

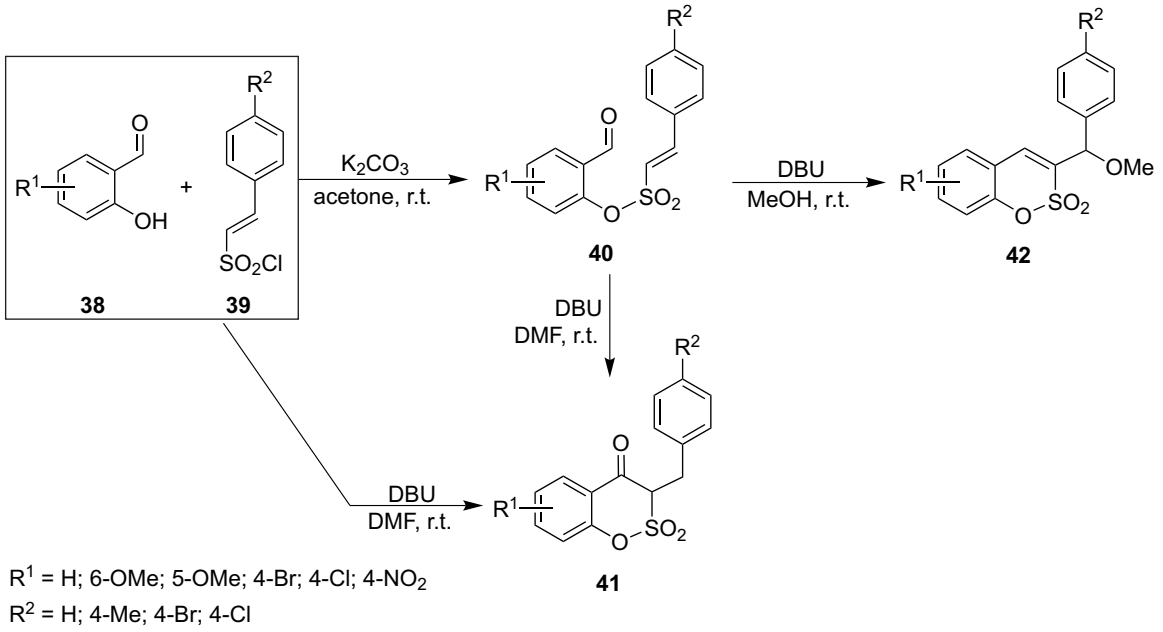
In order to obtain enaminoketones with the structure similar to **33**, another way was proposed. It consisted in the interaction of aromatic enaminones **34** with chlorosulfonic acid [37]. The result of this interaction was influenced by the temperature mode applied to it. Thus, at room temperature sulfochlorination was proceeding on the benzene ring giving derivative **35** (Scheme 11). When the mixture was heated to 150°C, two equivalents of chlorosulfonic acid were involved in the reaction so that one of them reacted with the benzene fragment, and another bridged OH and enaminone substituents of the benzene ring producing 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides **36**. The reaction of compound **36** (R^1 = H) with ammonia gave the corresponding sulfonamide **37**, while chloro-substituted derivative **36** (R^1 = Cl) was surprisingly inert in this reaction, and the formation of the sulfonamide was not observed.

Along with the results of Löwe, W. Berbiery [20] and R. Meyer [21] the synthesis of 3-substituted derivatives of 1,2-benzoxathine 2,2-dioxide is also presented in a number of studies carried out by Ghandi *et al.* Their paper [38] provide an easy-performed one-pot interaction of the substituted 2-hydroxybenzaldehydes **38** with the 4-substituted 2-phenylethenesulfonyl chlorides **39** in DMF in the presence of DBU that led to the formation of benzylbenzo[*e*][1,2]oxathiin-4(3*H*)-one 2,2-dioxides **41** (Scheme 12). Scientists also managed to isolate the intermediates – 2-formylphenyl-2-phenylethnesulfonates **40** and to investigate the effect of the solvent on the cyclization process. In the case of DBU and DMF the above-mentioned sultons were formed. The replacement of DMF with methanol gave 3-(methoxyphenylmethyl)benzo[*e*][1,2]-oxathiine 2,2-dioxides **42**. The authors suggested that the formation of **41** and **42** proceeded *via* the DBU-catalyzed *O*-sulfonylation/intramolecular Baylis–Hillman/1,3-H shift or dehydration tandem sequences, respectively.

Based on the experimental data and the results previously published the authors proposed the mechanisms for the DBU-catalyzed intramolecular Baylis-Hillman reaction described. It is illustrated in Scheme 13. For **41**, the *in situ* generated **40** undergoes the nucleophilic addition of DBU giving the zwitter-ion **A**. The subsequent nucleophilic addition of **A** to the aldehyde group affords the intermediate **B**. The generated hydroxy-derivative **C** in the next step is transformed into the final ketone **41** by the DBU-catalyzed 1,3-H shift. For **42**, the *in situ* generated methoxide



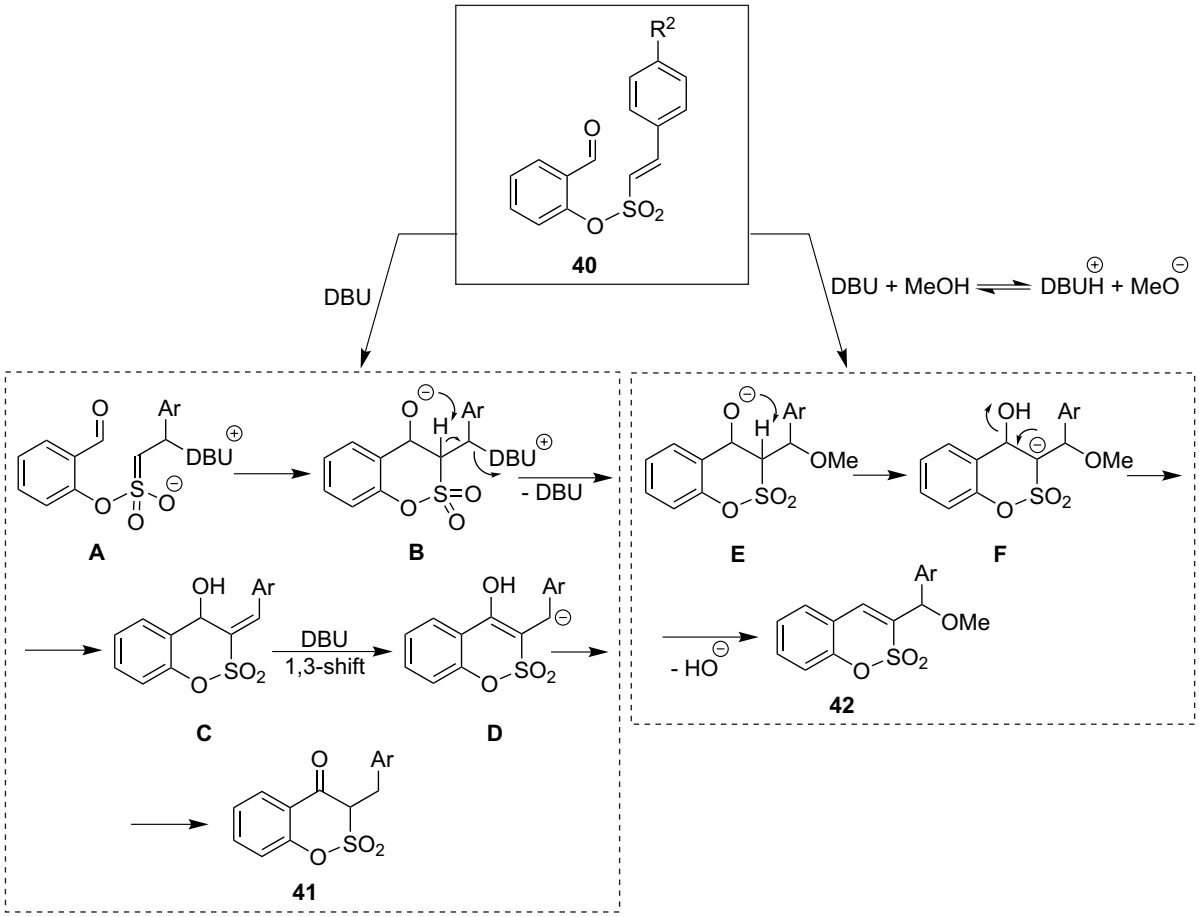
Scheme 11. The synthesis of sultone **37** involving heterocyclization of aromatic enaminones **34**



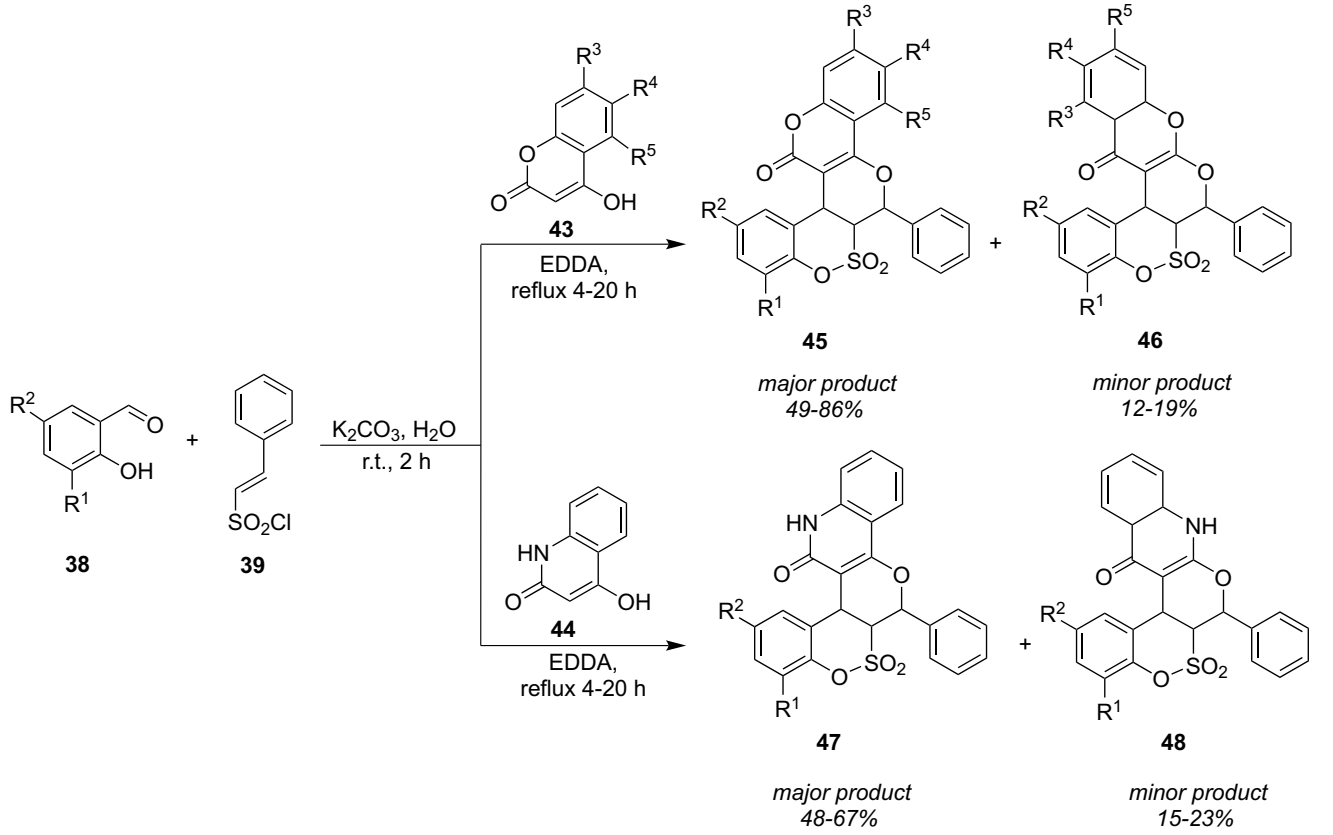
Scheme 12. The synthesis of sultone **41** based on DBU-catalyzed *O*-sulfonylation/intramolecular Baylis−Hillman/1,3-H shift tandem sequence

anion promotes the intramolecular Baylis-Hillman reaction, affording intermediates **E** and **F**. The latter is easily transformed into **42** through losing a hydroxide-anion.

Continuing the previous studies Ghandi *et al.* proposed a strategy for the one-pot synthesis of biologically interesting pentacyclic condensed 1,2-benzoxathiine 2,2-dioxide derivatives. It consisted in the interaction of the substituted 2-hydroxybenzaldehydes **38**, 2-phenylethylene sulfonyl chloride (**39**) and 4-hydroxycoumarins **43** or 4-hydroxyquinoline (**44**) in the presence of ethylenediamine-N,N'-diacetic



Scheme 13. The mechanisms of products **41** and **42** formation



Scheme 14. The one-pot synthesis of the pentacyclic condensed 1,2-benzoxathiine 2,2-dioxide derivatives **45**–**48**

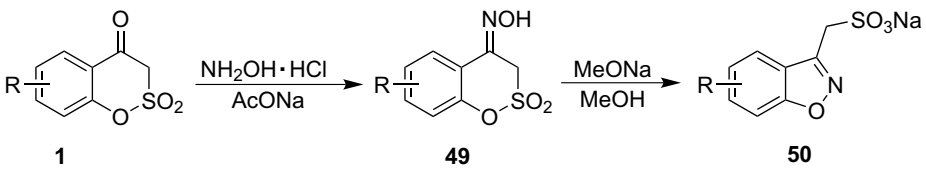
acid (EDDA) [39] (Scheme 14). The interaction presumably proceeded through the *O*-sulfonylation/Knoevenagel condensation/*hetero*-Diels-Alder reaction cascade and resulted in derivatives **45**–**48**. It should be noted that the interaction at the stage of the *hetero*-Diels-Alder reaction was non-regioselective with the participation of oxygens of the heterodiene system in the positions 2 and 4.

The reactivity of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) is connected with the presence of a carbonyl group, an activated methylene group and an endocyclic S-O bond in its structure. It is worth noting that the direct introduction of substituents in the benzene ring of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides has not been found in the literature. As it was shown above, the corresponding substituted starting compounds were used for the synthesis of the benzene-substituted derivatives.

The carbonyl group of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) exhibits the chemical properties of ketones, but currently there are only a few studies in this area. Arava *et al.* [30] showed the possibility of converting **1** to oximes **49**. The latter under the action of alkoxides undergo recyclization with the formation of 1,2-benzisoxazole-3-methanesulfonates **50**, which are important intermediates for the preparation of an anticonvulsant zonisamide (Scheme 15).

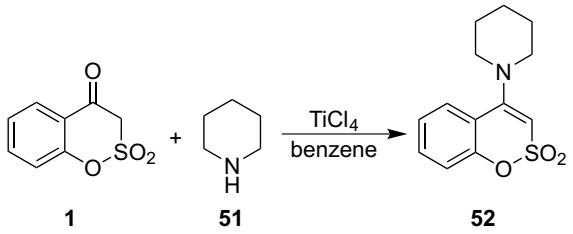
Another example of the 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide carbonyl group modification is the preparation of enamines. The authors [28] found conditions for the interaction of compound **1** with piperidine (**51**), which led to the formation of 4-(1-piperidinyl)benzoxathiine 2,2-dioxide (**52**) with the yield of 76% (Scheme 16). Considering the fact that in medicinal chemistry sultons are known because of their anti-inflammatory effects [40] the authors of the current work studied and revealed the anti-inflammatory properties of **52**, which reduced carrageenan edema when administered intraperitoneally to rats (100 mg/kg).

According to the literature data, the vast majority of chemical transformations known for 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) occurs with the participation of a methylene group, which increased



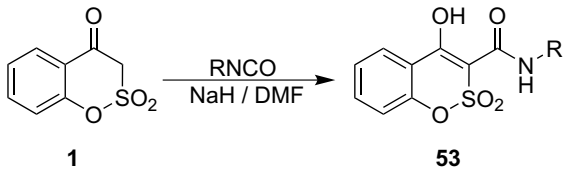
R = 5-Br, 5-Cl, 3,5-*di*Cl, 3,5-*di*Br, 3-OMe, 4-OMe, 5-OMe, 4-Me

Scheme 15. The recyclization of sultones **1** giving 1,2-benzisoxazole-3-methanesulfonates **50**



1 51 52

Scheme 16. The preparation of enamines based on sultone **1**



1 53

Scheme 17. The interaction of sultone **1** with isocyanates

reactivity is due to the presence of the neighboring C=O and SO_2-fragments. Mobility of the CH_2 moiety hydrogens results in the keto-enol tautomerism of sultone **1**, which can be easily observed in its ^{1}H NMR spectrum (Fig. 3). Therefore, 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) can be used for synthetic purposes as an enolnucleophile.

Using this property Schwender *et al.* proposed an approach to the functionalization of compound **1** in position 3, which consisted in its interaction with substituted isocyanates in DMF in the presence of sodium hydride with the formation of amides **53** (Scheme 17) [28].

In the study on the development of medicines – coumarin antibiotics, inhibitors of bacterial DNA gyrase Peixoto *et al.* [32] proposed to perform a bioisosteric substitution, namely to replace the coumarin carbonyl group with more polar SO_2, expecting that this would increase the ability of the compound to inhibit the enzyme. In addition, the high polarity of the sulfone moiety was to provide better water solubility of the compounds synthesized. For this purpose, glycosides with noviose sugar **54** and **55** (Scheme 18) were synthesized; they were further functionalized by the active methylene group of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide nucleus.

Compound **54** was obtained by the coupling of **1** with the activated noviose carbonate under BF_3–Et_2O conditions. Derivative **55** was prepared by Mitsunobu's coupling between pyrrole-containing noviose and sultone **1** (Scheme 18).

Modification of the position 3 of **54** was performed by its interaction with 3-chlorophenylisocyanate in the presence of DMAP affording the corresponding anilide **56** (Scheme 19), which was further subjected to the lithium perchlorate catalysed opening of the noviosyl carbonate portion with *O*-propargylhydroxylamine to provide a mixture of regioisomeric 3′- and 2′-N-propargyloxycarbamates **57** and **58** in the ratio 4:1, respectively. The mixture was then used in *in vitro* experiments without separation. The introduction of an acetyl group in 3-position of sultone **55** by the acetic anhydride was accompanied by the acetylation of 2′-OH of noviose. The hydrolysis of the 2′-acetate fragment with KOMe in MeOH gave 1,2-benzoxathiin 2,2-dioxide **59**.

Antibacterial properties were studied for the target derivatives **57**/**58** and **59**. According to *in vitro* studies, compound **59** had twice the ability to inhibit DNA gyrase compared to a similar compound containing the C=O group instead of the SO_2 fragment, and mixture **57**/**58** had the same *in vitro* inhibitory potency towards DNA gyrase as the aminocoumarin antibiotic novobiocin produced by the actinomycete *Streptomyces niveus*. However, the sultone derivatives were completely devoid of the antibacterial activity as their high polarity had a negative effect on the molecule ability to penetrate cell lipophilic membranes and thus on its antibacterial activity [32].

Taking into account the structural similarity of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide and 4-hydroxycoumarin cores the authors of the work [23] aimed

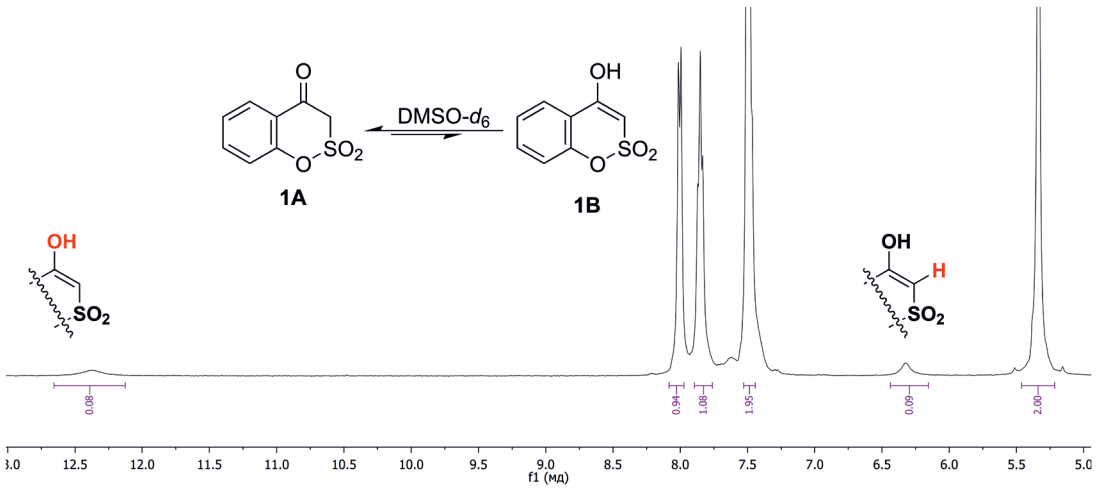
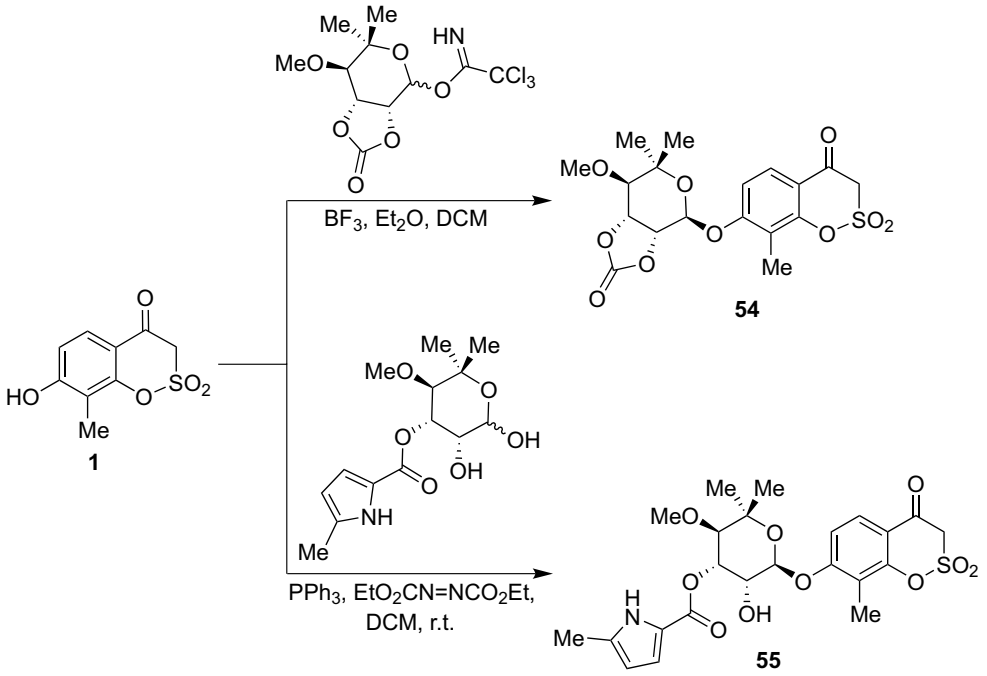
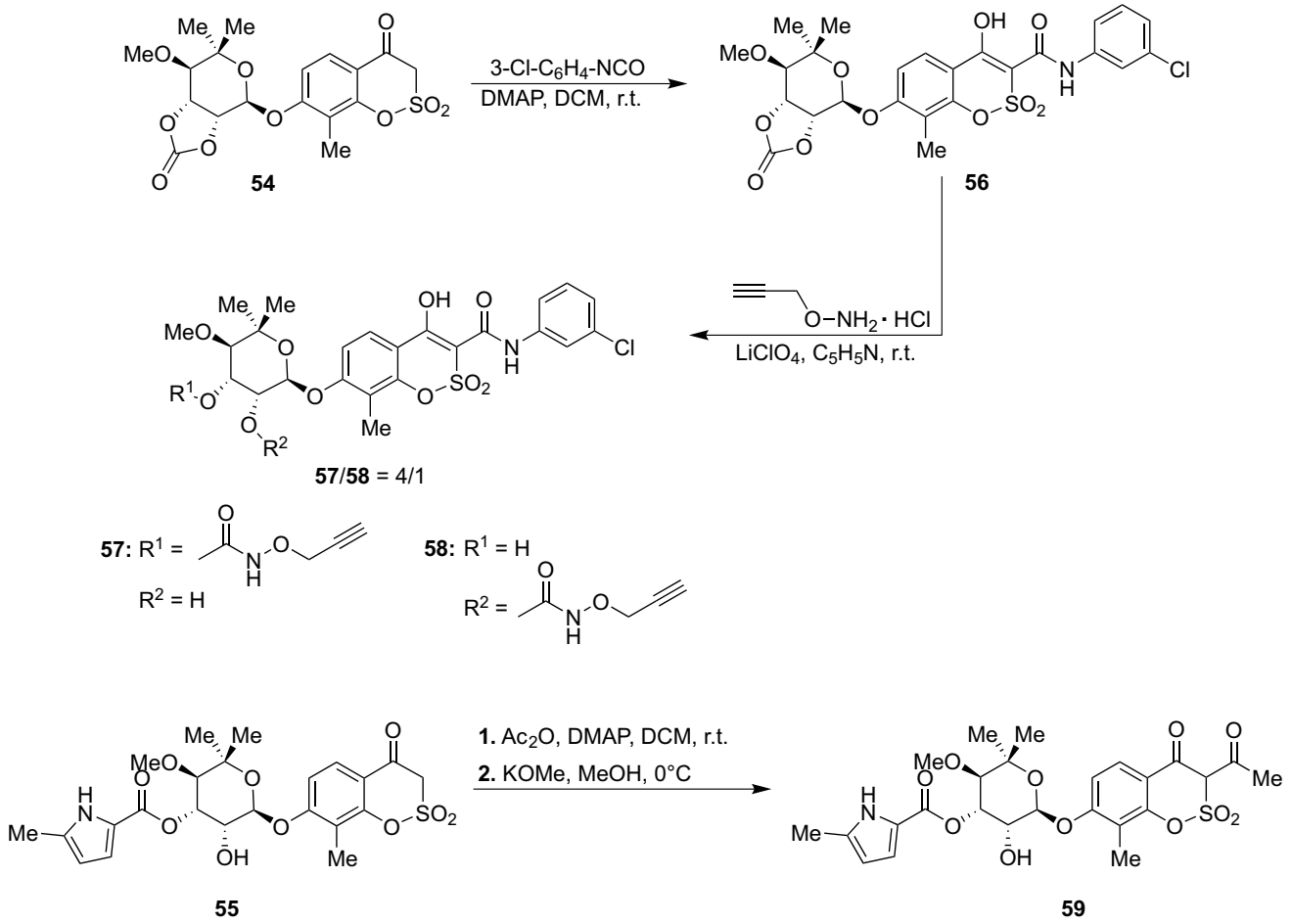


Fig. 3. The ^{1}H NMR spectrum of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) (DMSO-d_6, 400 MHz), δ, ppm

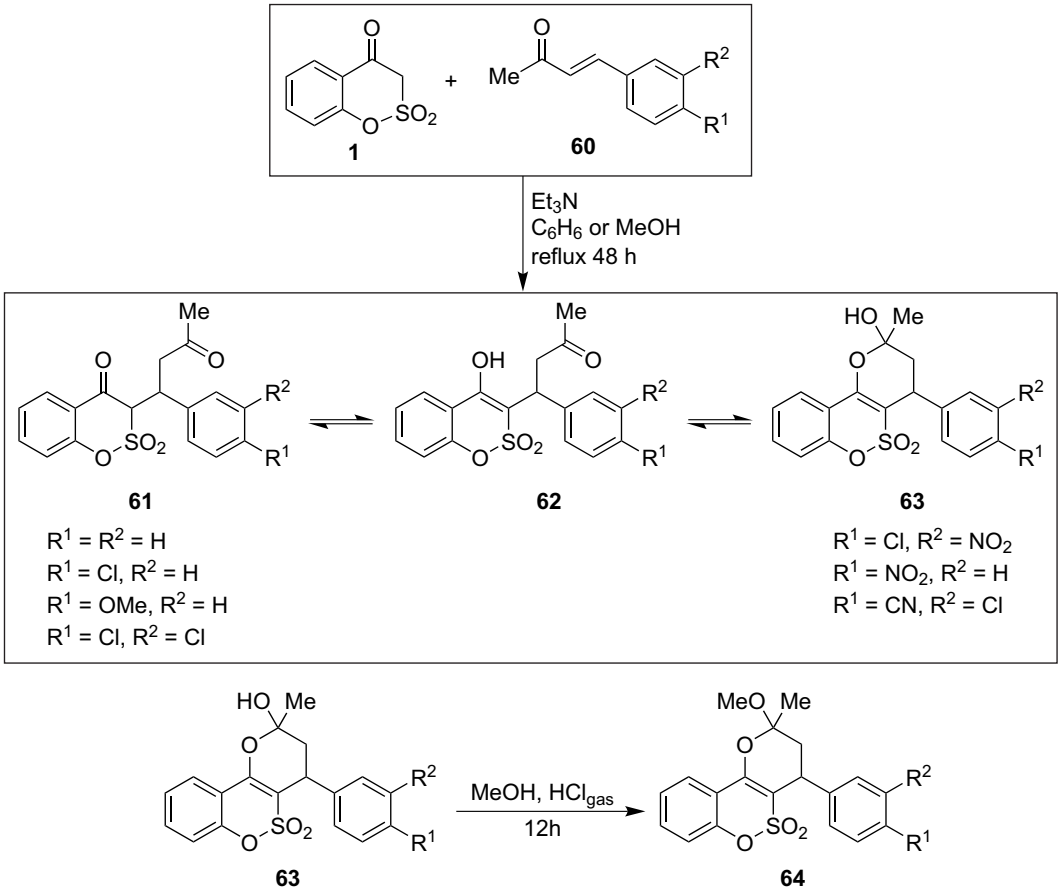


Scheme 18. The synthesis of noviose-comprising derivatives of sultone **1**

at the synthesis of coumarin anticoagulant analogs. This was achieved by the Michael addition of the substituted benzalacetones **60** to sultone **1** (Scheme 20). The structure of the products isolated strongly depended on the substituents in the benzene portion of benzalacetones. In this regard, they can exist in acyclic form **61** or hemiketal form **63**, which is apparently formed through enol form **62**. The authors discussed the stereoselectivity of the Michael addition as well. Analyzing ^{1}H NMR spectra they observed



Scheme 19. The synthesis of promising antibacterial agents comprising 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide core



Scheme 20. The synthesis of coumarin anticoagulant analogs

two sets of signals and made a conclusion about acyclic products that comprised a proton at C-3 in quasi-equatorial and quasi-axial positions. Ketals **64** can also be obtained from cyclic Michael adducts **63** by the ordinary procedure. To study anticoagulant properties, the compounds obtained were orally administered to rats (Table). As a reference drug Warfarin in the dose of 1.25 mg/kg was taken. Twelve hours after administration of a single dose (330 mg/kg) of the compounds under research the prothrombin level decreased by average 25%. The maximum level of activity was observed in 24 h. It is worth mentioning that the *dose–activity* relationship was not linear (when the dose was decreased twice, the level of activity dropped dramatically).

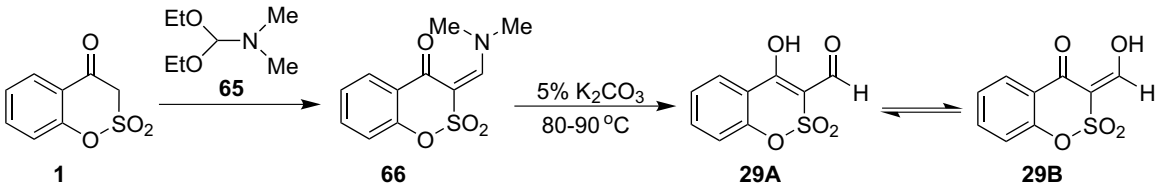
Löwe *et al.* thoroughly studied chemical properties of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides containing the 3-carbaldehyde moiety or its synthetic analogs.

Using the methylene group reactivity of the starting sultone **1** they synthesized a building block – 4-hydroxy-1,2-benzoxathiine-3-carbaldehyde 2,2-dioxide (**29**),

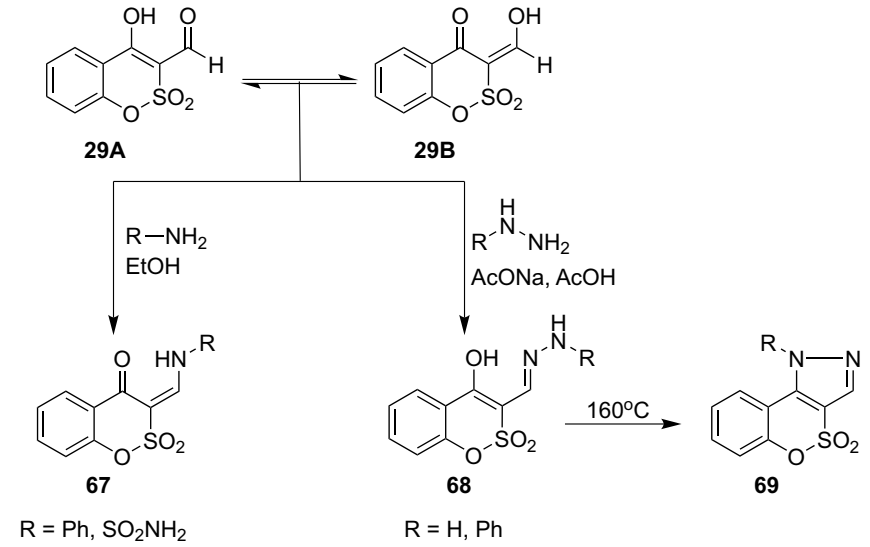
Table

The prothrombin time for warfarin and its SO_2-analogs after oral administration to rats

Cmp	R^1	R^2	Dose, mg/kg	Prothrombin time			
				12h	24h	36h	48h
61	H	H	350	25.6 ± 2.0	37.9 ± 3.5	> 50	17.3 ± 1.8
61	H	H	175	15.0 ± 1.0	14.6 ± 0.6	13.9 ± 0.5	–
61	Cl	H	330	44.4 ± 1.5	> 50	15.9 ± 0.3	–
61	OMe	H	330	24.0 ± 4.6	20.8 ± 2.3	16.6 ± 0.9	–
61	Cl	Cl	330	44.7 ± 3.9	> 50	22.7 ± 7.3	–
63	Cl	NO_2	330	18.9 ± 0.6	30.4 ± 9.1	16.4 ± 0.6	–
63	NO_2	H	330	43.8 ± 3.7	> 50	21.8 ± 10.5	–
63	CN	H	315	46.8 ± 4.2	> 50	18.6 ± 2.1	–
64	NO_2	H	330	32.4 ± 7.4	19.8 ± 3.1	18.1 ± 2.6	–
Warfarin	–	–	1.25	43.7 ± 3.4	> 50	41.8 ± 6.6	17.4 ± 0.1



Scheme 21. The synthesis of 4-hydroxy-1,2-benzoxathiine-3-carbaldehyde 2,2-dioxide (**29**)



Scheme 22. The interaction of aldehyde **29** with amines and hydrazines

crucial for their research by the interaction of **1** with N,N-dimethylformamide diethyl acetal (**65**) followed by the alkaline hydrolysis (Scheme 21) [41]. The latter, as mentioned earlier, is characterized by the existence of two tautomeric forms **29A** and **29B**.

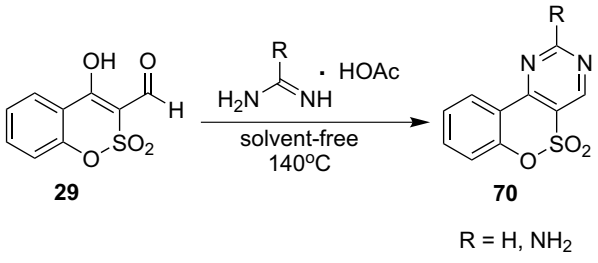
Further, the authors [41] used 4-hydroxy-1,2-benzoxathiine-3-carbaldehyde 2,2-dioxide (**29**) for the synthesis of enamines **67** by its interaction with aniline or sulfamide, as well as for the preparation of hydrazones **68** by its interaction with hydrazine and phenylhydrazine. 1,3-Dielectrophilic nature of the starting aldehyde **29** allowed hydrazones **68** to be cyclized to the condensed benzoxathiinopyrazoles **69** upon the subsequent heating (Scheme 22).

Considering the prospects of 4-hydroxy-1,2-benzoxathiine-3-carbaldehyde 2,2-dioxide (**29**) for the synthesis of condensed heterocyclic systems Löwe *et al.* used this compound in further studies to obtain 1,2-benzoxathiin[4,3-*d*]pyrimidine 5,5-dioxides **70** (Scheme 23) [42]. To form a pyrimidine ring, [3+3]-cyclocondensation was performed with amidine acetates (formamidinium acetate and guanidinium acetate) by fusing the starting compounds without the use of a solvent.

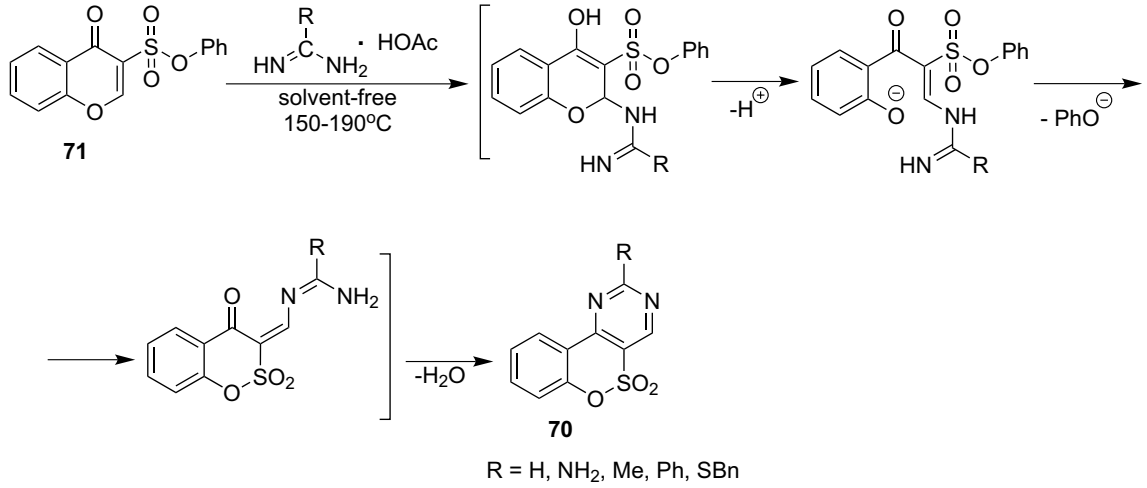
A range of 1,2-benzoxathiin[4,3-*d*]pyrimidine 5,5-dioxides **70** was then expanded by an approach involving the ability of chromone-3-sulfonic acid phenyl ester (**71**) to be recyclized by N-nucleophiles [36]. According to the mechanism proposed by the authors at the first stage there was 1,4-addition of amidine to the chromone ring with the subsequent deprotonation, recyclization and formation of a condensed system of the sultone and pyrimidine rings **70** (Scheme 24).

The ability of chromone-3-sulfonic acid phenyl ester (**71**) to recyclization transformations was also used by Löwe *et al.* to obtain a number of 1,2-benzoxathiine 2,2-dioxide derivatives condensed with the pyridine nucleus. Thus, in the work [43] the interaction of compound **71** with methyl 3-aminocrotonate (**72**) was studied. The reaction was performed by fusing the starting materials in the presence of sodium acetate. As a result, a mixture of two products was isolated, it was separated by thin layer chromatography, and the compounds were identified as methyl 2-methyl-1,2-benzoxathiin[4,3-*b*]pyridine-3-carboxylate 5,5-dioxide (**73**) and methyl 1,2-benzoxathiin[4,3-*b*]-pyridine-2-acetate 5,5-dioxide (**74**) (Scheme 25).

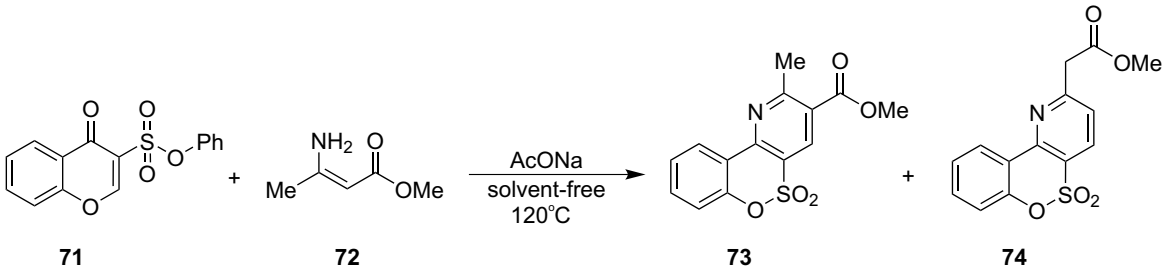
In order to explain the unusual result of forming two products in this interaction, the authors proposed several mechanisms for its course. The first path involves the Michael reaction, in which the C-2 atom of enaminoester **72** attacks the C-2 atom of chromone **71**,



Scheme 23. The synthesis of 1,2-benzoxathiin[4,3-*d*]pyrimidine 5,5-dioxides **70**



Scheme 24. The recyclization of chromone-3-sulfonic acid phenyl ester (**71**) with N-nucleophiles



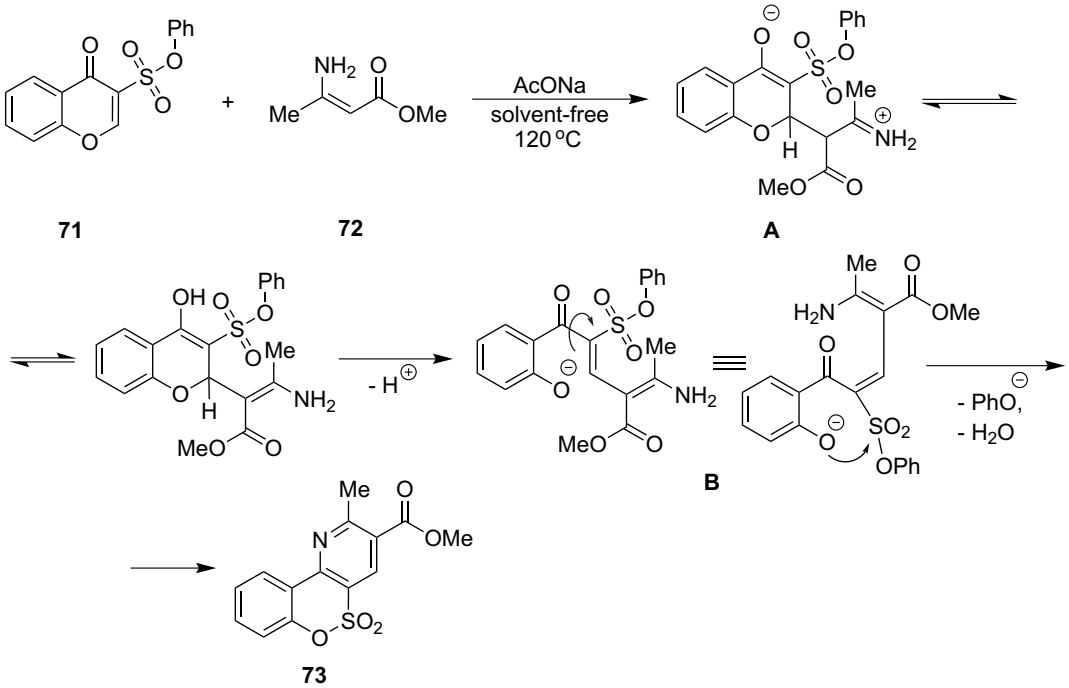
Scheme 25. The interaction of phenyl ester **71** with methyl 3-aminocrotonate (**72**)

forming the zwitter-ion **A**, which is characterized by tautomeric equilibrium (Scheme 26). It is followed by sequential deprotonation (**B**), dehydration and cleavage of the phenolate anion to form the reaction product **73**.

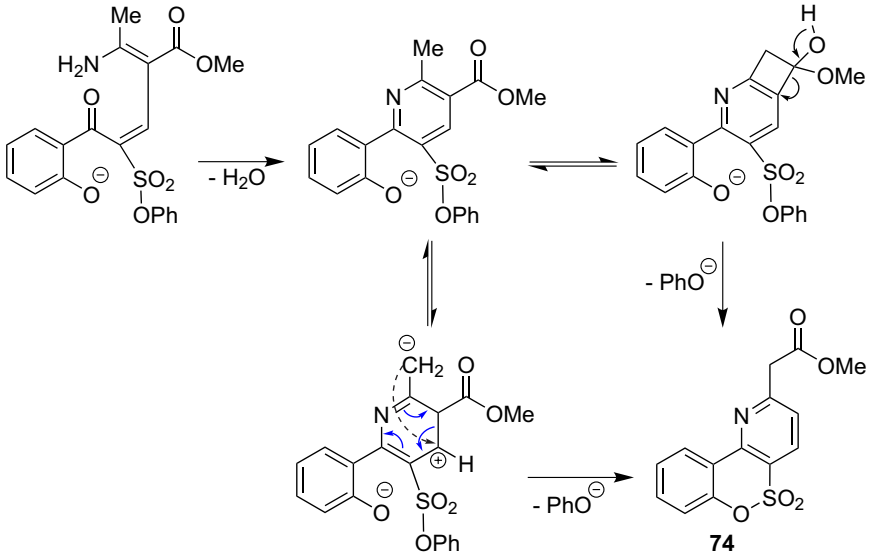
As for compound **74** isolated as a result of the interaction studied, the authors proposed two possible mechanisms of its formation. According to the first of them the rearrangement occurs in an already closed pyridine cycle (Scheme 27).

The second probable mechanism involves the nucleophilic attack of C-2 atom of chromone **71** by the C-4 atom of enaminoester **72** as a result of tautomeric transformations of the latter (Scheme 28).

As a result of the abovementioned reaction (Scheme 25), according to the authors, one could expect



Scheme 26. The mechanism of the interaction of phenyl ester **71** with methyl 3-aminocrotonate (**72**)



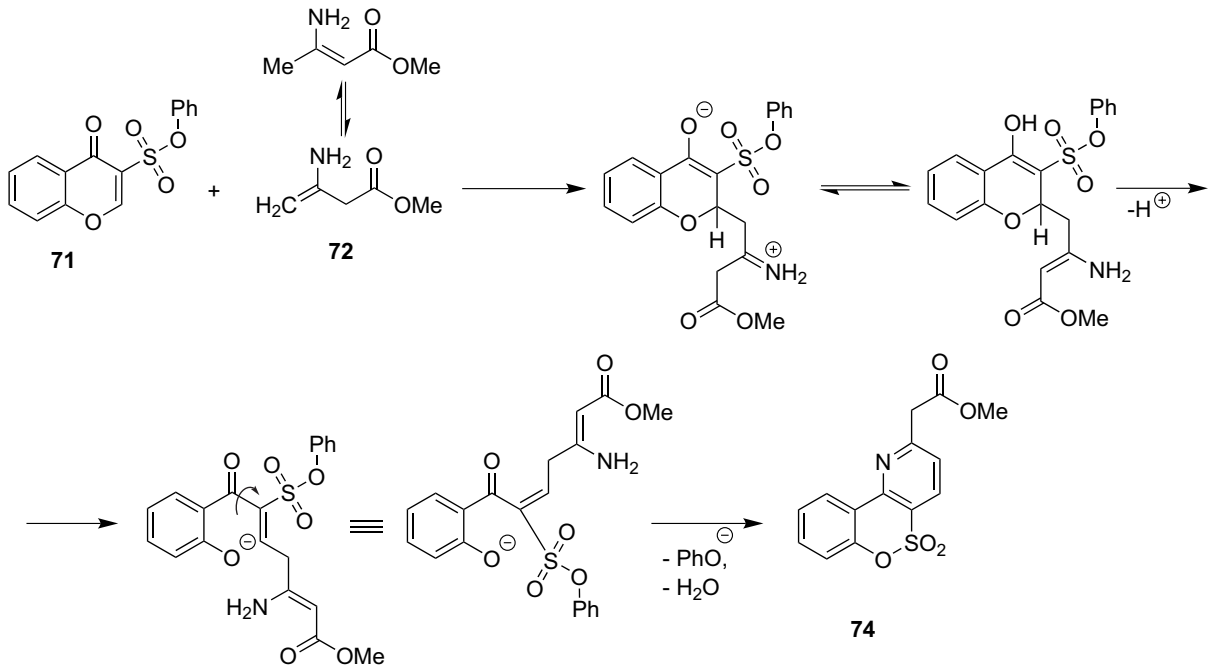
Scheme 27. The mechanism of the interaction of phenyl ester **71** with methyl 3-aminocrotonate (**72**)

the formation of another product – the structural isomer of the compounds obtained – derivative **75**. This process is possible under the condition of the nucleophilic attack of the amino group of ester **72** on the chromone ring. However, compound **75** was neither isolated nor identified (Fig. 4).

In the work [44] the authors used enaminoester **76** having one carbon atom more than aminocrotonate **72** in the reaction with chromone **71**. As the result, they isolated a mixture of three compounds containing another possible product of similar interactions – derivative **79**. The mixture was managed to be separated by chromatography on silica gel (Scheme 29).

The authors proposed the mechanism for this interaction. For compounds **77** and **78** it was consistent with the studies presented in [44] (Schemes 26–28).

The formation of compound **79**, which does not contain a nitrogen atom in the ring, is explained by the primary interaction of the amino group of enaminoester **76** with the C-2 atom of phenyl chromone-3-sulfonate (**71**) (Scheme 30). In this case, the reaction intermediate **A** is deprotonated with the opening of the cycle, the substitution of the phenolate anion and the formation of the sultone ring (**B**). Intermediate **B** undergoes the hydrolytic cleavage, and the compounds obtained then interact with each other to form an unstable intermediate **C**. The O–S bond breaking within **C** leads to disclosure of the sultone cycle and formation of zwitter-ion **D** from which a cyclic aldehyde **E** is produced by the lactone ring closure. Finally, the hydrolysis of the latter leads to the formation of the final product – 4-ethyl-5*H*-[1,2]-oxathiino[5,4-*c*]chromen-5-one 2,2-dioxide (**79**).



Scheme 28. The mechanism of the interaction of phenyl ester **71** with methyl 3-aminocrotonate (**72**)

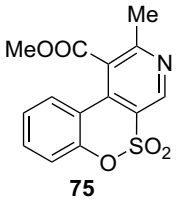


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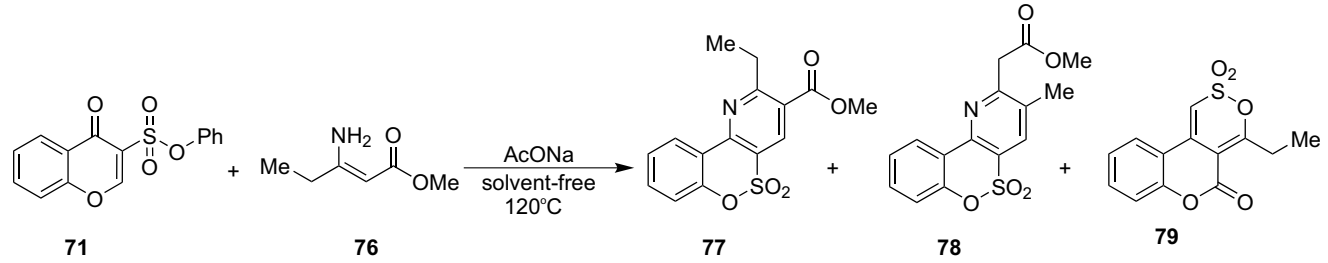
Fig. 4. Not isolated possible product of the interaction of phenyl ester **71** with methyl 3-aminocrotonate (**72**)

The mechanism proposed has been proven by the fact that enaminone **28** obtained in another way [36] when interacting with methyl 3-oxopentanoate also forms product **79**. At the same time, one cannot exclude that enaminone **28** is the product of the interaction of the starting compound **71** with ammonia formed by the *in situ* hydrolysis of methyl 3-amino-2-pentenoate (**76**).

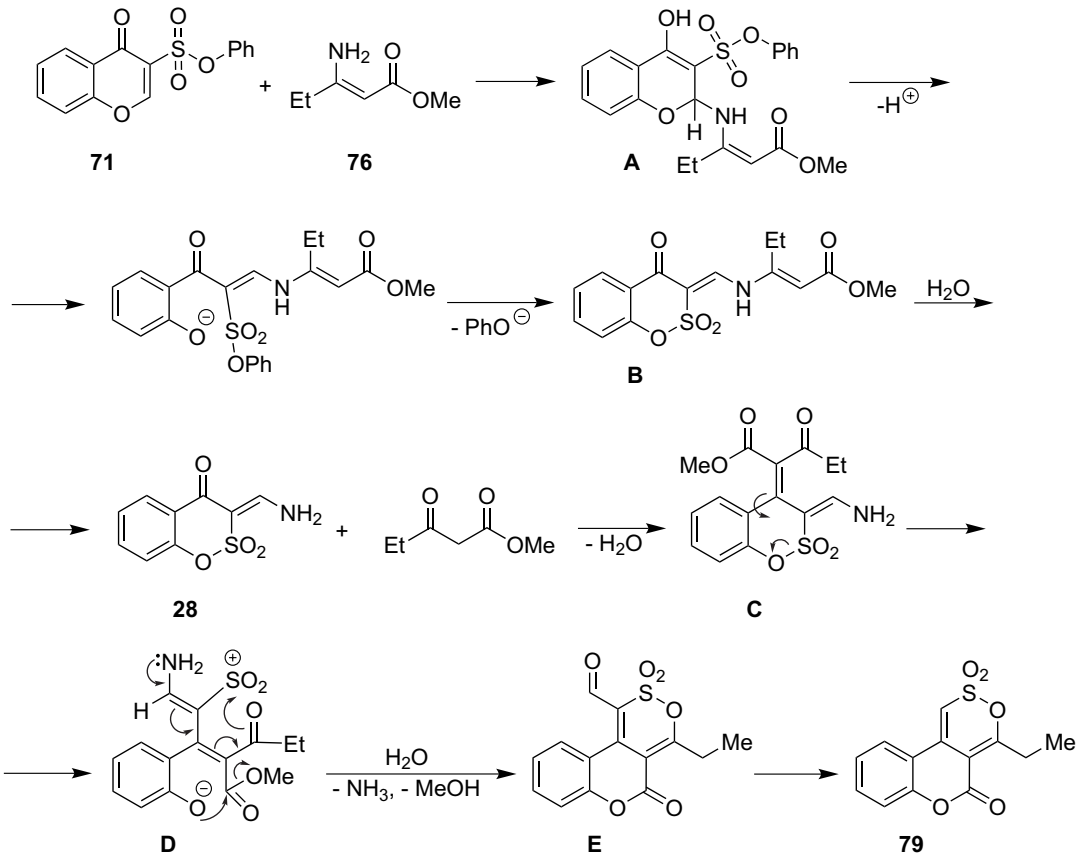
Continuing the study of enaminone **28** Löwe *et al.* studied the interaction of this compound with β-ketoesters **80**-**82** in the presence of sodium acetate under fusion [45] (Scheme 31). It was found that the outcome of such interactions strongly depended on the β-ketoester used. Thus, application of **80** led to 1,4-addition intermediate **A** which cyclized giving dibenzo annulated sultone **83**. The use of β-ketoester **81** led to the loss of selectivity. As a result of this interaction, the formation of three reaction products **84**-**86** was observed; they were separated by thin layer chromatography. For esters **82**, the reaction proceeded as 1,2-addition with the formation of condensed derivatives **87** solely. Compounds **84**, **86**, **87** were formed in accordance with mechanisms discussed before, pentasubstituted benzene **85** was the product of compound **81** self-condensation.

In many previous studies chromone and its derivatives were used to synthesize the benzoxathiine nucleus. Therefore, it should be noted that only one work describes the inverse conversion of benzoxathiine nucleus to the chromone one [46]. It was achieved by the interaction of 3-formyl-4-hydroxy-1,2-benzoxathiine



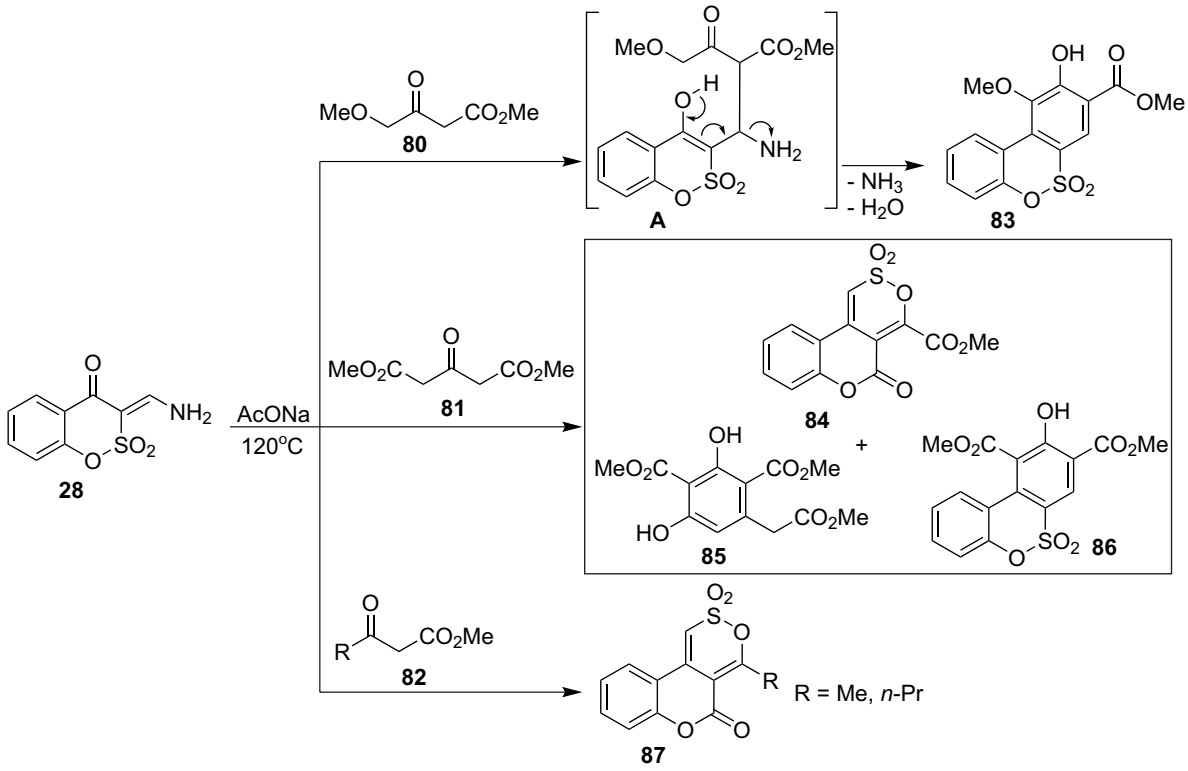
71 **76** **77** **78** **79**

Scheme 29. The interaction of phenyl ester **71** with methyl 3-aminopent-2-enoate (**76**)



71 **76** **A** **B** **28** **C** **D** **E** **79**

Scheme 30. The mechanism of compound **79** formation

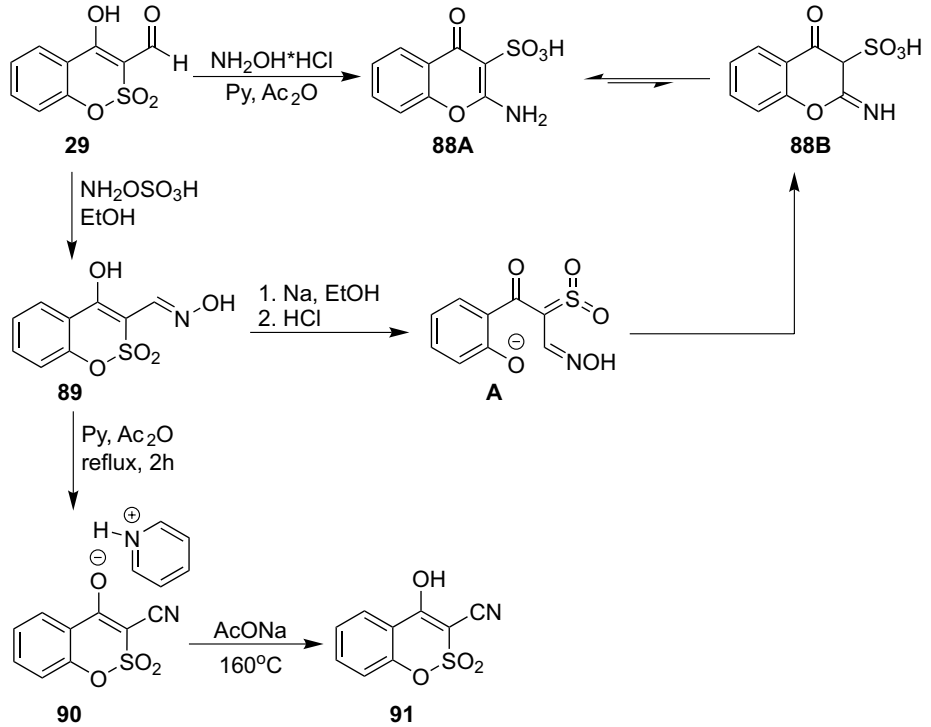


Scheme 31. The interaction of enaminone **28** with β-ketoesters

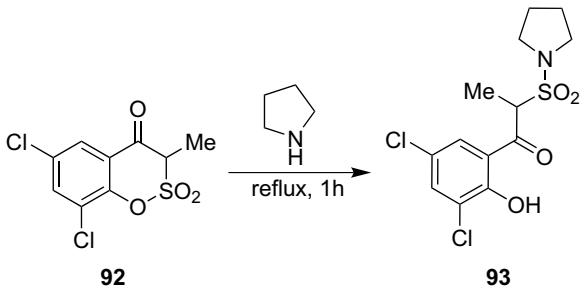
2,2-dioxide (**29**) with hydroxylamine hydrochloride in pyridine and acetic anhydride and resulted in 2-aminochromon-3-sulfonic acid (**88**) (Scheme 32). A stepwise format of the conversion with the preliminary synthesis of oxime **89** and the subsequent rearrangement under the action of sodium ethoxide is also possible. The authors believe that the conversion proceeds with the formation of acyclic intermediate **A**. Analyzing ^{1}H NMR spectra the authors make a conclusion that chromone **88** is a tautomeric compound and exists in 2 tautomeric forms – a predominating amino-form **88A** and a minor imino-form **88B.**

Another synthetic application of aldehyde **29** is the preparation of nitrile **91**. It is a two-stage process which requires isolation of the corresponding pyridinium salt **90** (Scheme 32).

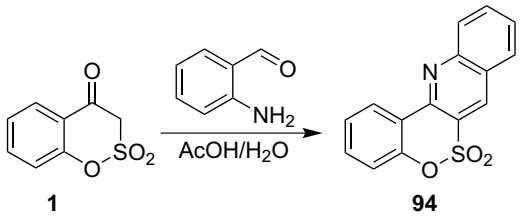
The previous transformations (Scheme 32) and some reactions mentioned before reveal a labile nature



Scheme 32. The conversion of benzoxathiine nucleus to the chromone one



Scheme 33. The ring-opening reaction of sultone **92** with pyrrolidine



Scheme 34. The interaction of sultone **1** with 2-aminobenzaldehyde

of the O–SO_2 bond, which can break under basic conditions. This property was used by R. Meyer [21] to obtain acyclic sulfonamide **93** by refluxing sultone **92** in excess of pyrrolidine (Scheme 33).

The presence of the SO_2CH_2CO fragment in the molecule of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) provides opportunities for the synthesis of the condensed heterocyclic systems based on it, but by now this synthetic direction is underinvestigated. The authors [41] used the interaction of the starting sultone **1** with 2-aminobenzaldehyde in acetic acid. As a result, a new condensed tetracyclic system – 3,4-dihydro-1,2-benzoxathiin[4,3-*b*]quinoline-6,6-dioxide (**94**) was obtained (Scheme 34).

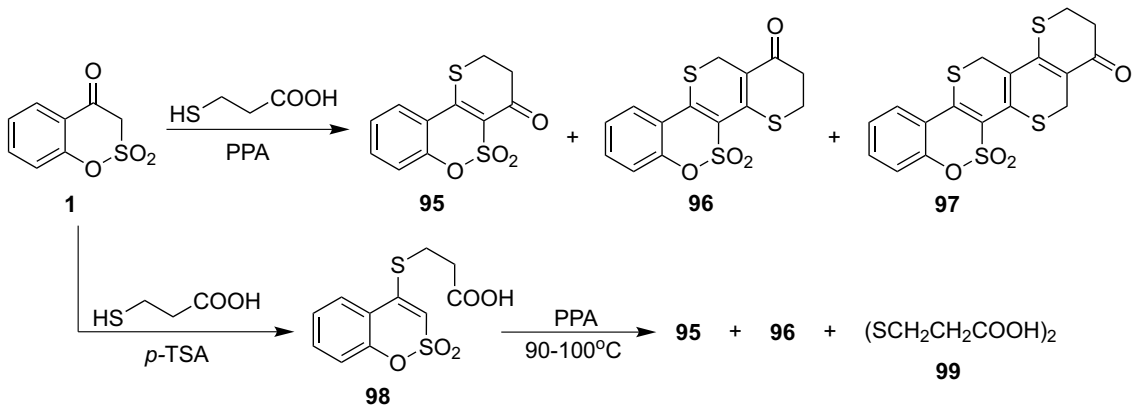
Another work [29] used the SO_2CH_2CO fragment for the synthesis of new heterosteroidic systems. A key intermediate for this purpose – 4-oxo-3,4-dihydro-2*H*-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-dioxide (**95**) was obtained by the annelation of the thiopyrane nucleus to **1** either by a direct interaction of the latter with β-mercaptopropionic acid or by the step-by-step approach with the preliminary synthesis of **98** (Scheme 35). It is worth noting that these reactions were not selective and gave rise to a mixture of products, which authors managed to separate.

The newly formed CH_2CO fragment in **95** gave great opportunities to the authors to build various heterocyclic moieties – pyrazole, isoxazole, pyrrole, thiazole (Scheme 36).

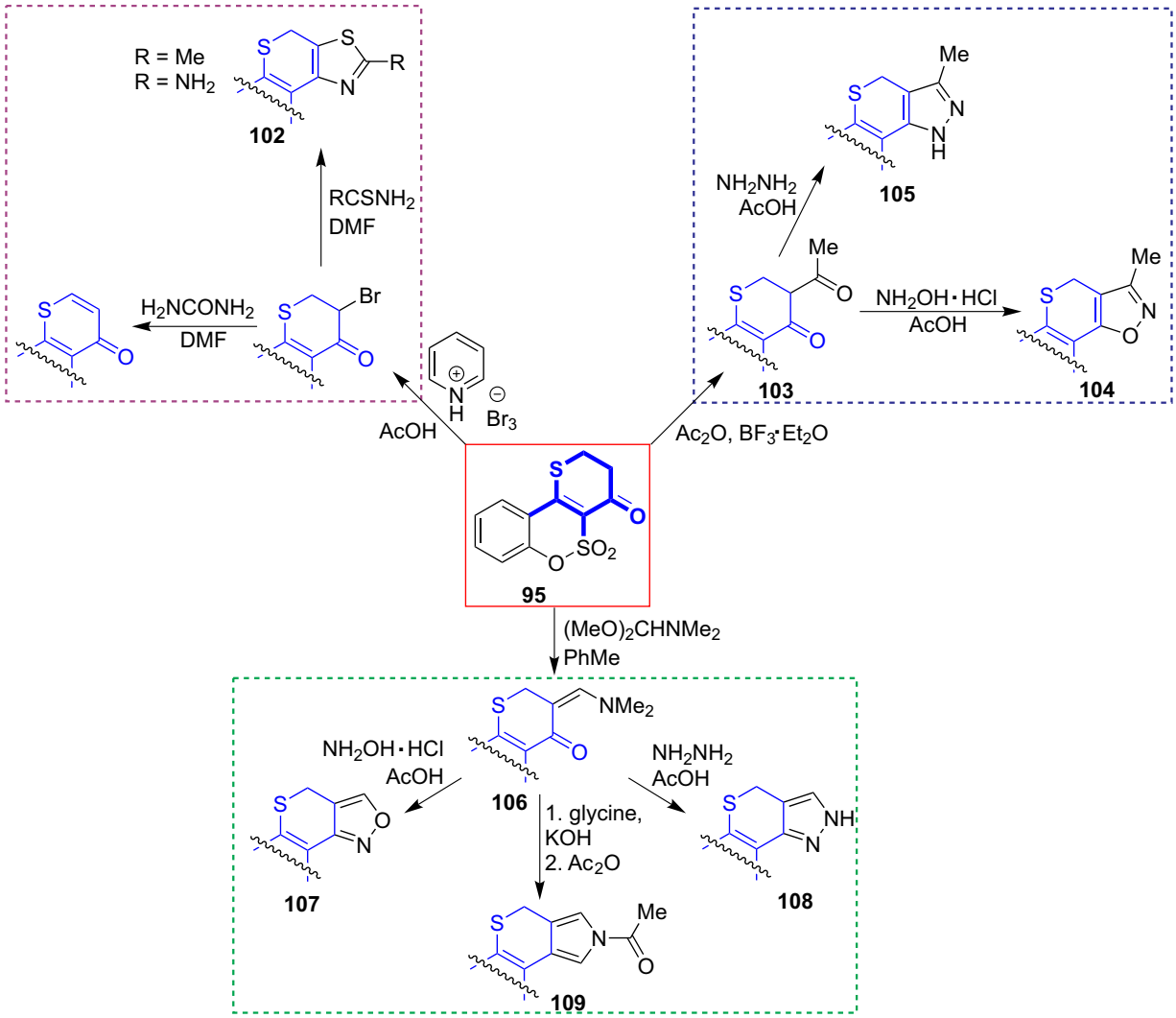
A set of works [47–53] were aimed at studying the multicomponent interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**), active methylene nitriles and carbonyl compounds in order to synthesize a new condensed heterocyclic system of 2-amino-3-R^1-4-R^2-4,6-dihydropyrano[3,2-*c*][2,1]benzoxathiine 5,5-dioxide (Fig. 5). These studies were the first and by now are the only investigations dedicated to the application of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) in multicomponent processes. Considering the target dihydropyrano[3,2-*c*][2,1]benzoxathiine 5,5-dioxides as those containing 2 promising pharmacophore units the authors also focused on determining the biological activity of the compounds synthesized.

The authors [47, 50–53] determined that the interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) with aldehydes **110** and malononitrile (**111**) gave a number of 2-amino-4-R-4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-3-carbonitrile 5,5-dioxides **112** in moderate to high yields (Scheme 37). The interaction required a base as a catalyst, which was triethylamine in most cases. It was also found that in cases of aliphatic and alicyclic aldehydes heating was redundant and might lead to fail in isolation or significant decrease in yields of the final products. The two-step approach towards the target 2-amino-4*H*-pyran-3-carbonitriles **112** with the use of α-cyanoacrylonitriles **113** is also possible as shown on examples of heteroaromatic aldehydes **99**. However, this stepwise format has no advantages comparing to the one-pot process as it leads to lower yields and requires more time to be completed.

It should be also mentioned that a successful outcome of the reaction of the synthesis of 2-amino-4*H*-pyran-3-carbonitriles **112** is limited by an aldehyde used. Thus, compounds **112** were not managed to be obtained in cases of electron-rich (hetero)aromatic



Scheme 35. The use of the SO_2CH_2CO fragment in sultone **1** for the synthesis of sulfur-containing condensed systems



Scheme 36. The modification ways of compound **95**

aldehydes (4-dimethylaminobenzaldehyde, N-methylpyrrol-2- and indol-3-carbaldehydes) or benzaldehydes with bulky substituents (9-anthracencarbaldehyde). The only products isolated were α-cyanoacrylonitriles **113**.

Taking into account the ease of forming 2-amino-4*H*-pyran-3-carbonitriles **112** in further studies the authors applied ethyl cyanoacetate (**114**) instead of malononitrile in order to expand a number of the target condensed 2-amino-4-aryl-4*H*-pyrans (Scheme 38) [47]. However, in this case the loss of the reaction selectivity was observed. The analysis of the reaction mixture by the ^{1}H NMR method evidenced the simultaneous formation of the target ethyl 2-amino-4-aryl-4*H*-pyran-3-carboxylates **115**, triethylammonium salts **116** and ethyl α-cyano-β-arylacrylates **117** (Scheme 38). These triethylammonium salts were isolated for the first time in the study on similar interactions involving N-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (nitrogen-containing analogue of compound **1**) [54, 55]. Thus, it can be assumed that this chemical behavior is a common property of cyclic SO_2-containing enolnucleophiles having a fragment of XSO_2CH_2CO.

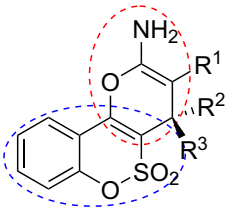
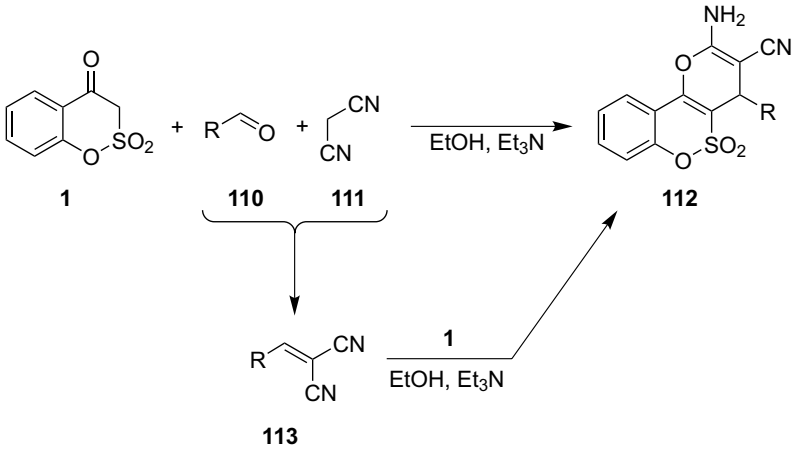


Fig. 5. 2-Amino-3-R^1-4-R^2-4,6-dihydropyrano[3,2-*c*][2,1]-benzoxathiine 5,5-dioxides – compounds containing 2 promising pharmacophore units

A number of approaches was used by the authors in order to synthesize the target compounds **115** selectively, namely the use of the ethyl cyanoacetate excess (its effectiveness was revealed earlier [55]), different heating modes, the variation of catalysts, as well as the two-component approach [47]. All of them were not successful, but the experiments carried out allowed researchers to propose a possible mechanism of the three-component interaction (Scheme 39).

According to it Michael adduct **A**, which is a recognized intermediate in these interactions, can be further transformed by two ways (Scheme 39). The first way is the desired heterocyclization (*hetero*-Thorpe–



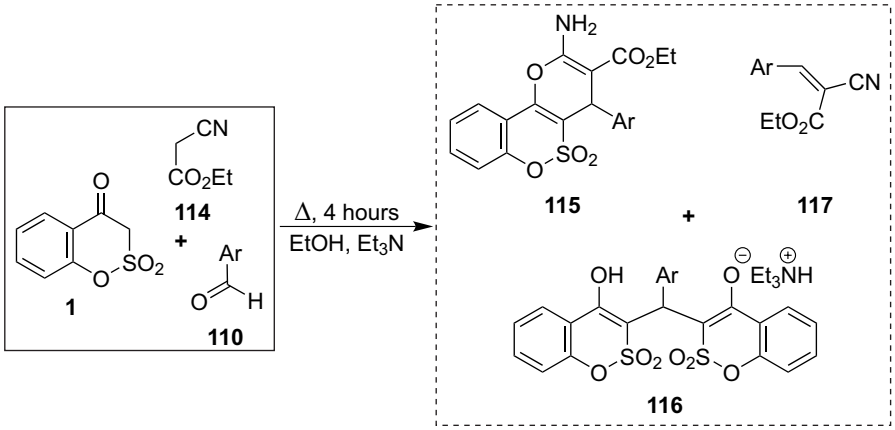
R = H, Ph, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 4-HO-3-MeO-C_6H_3, 3,4,5-*tri*MeO-C_6H_2, 2-EtO_2CCH_2O-C_6H_4, 2-$NCCH_2O$-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 3-Cl-C_6H_4, 4-F-C_6H_4, 3-F-C_6H_4, 4-HO-C_6H_4, 3-HO-C_6H_4, 4-CF_3-C_6H_4, 4-CH_3S-C_6H_4, 4-NC-C_6H_4, 4-HO_2C-C_6H_4, pyridin-3-yl, pyridin-4-yl, thienyl-2, furyl-2, 1-phenyl-3-methyl-5-chloropyrazol-4-yl, 1-phenyl-3-ethoxycarbonylpyrazol-4-yl cyclopropyl, cyclopentyl, cyclohexyl, Me, Et, *n*-Pr, *n*-Bu, *i*-Pr, *i*-Bu, 1-phenylprop-1-en-2-yl

Scheme 37. The three-component interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) with aromatic aldehydes **110** and malononitrile (**111**)

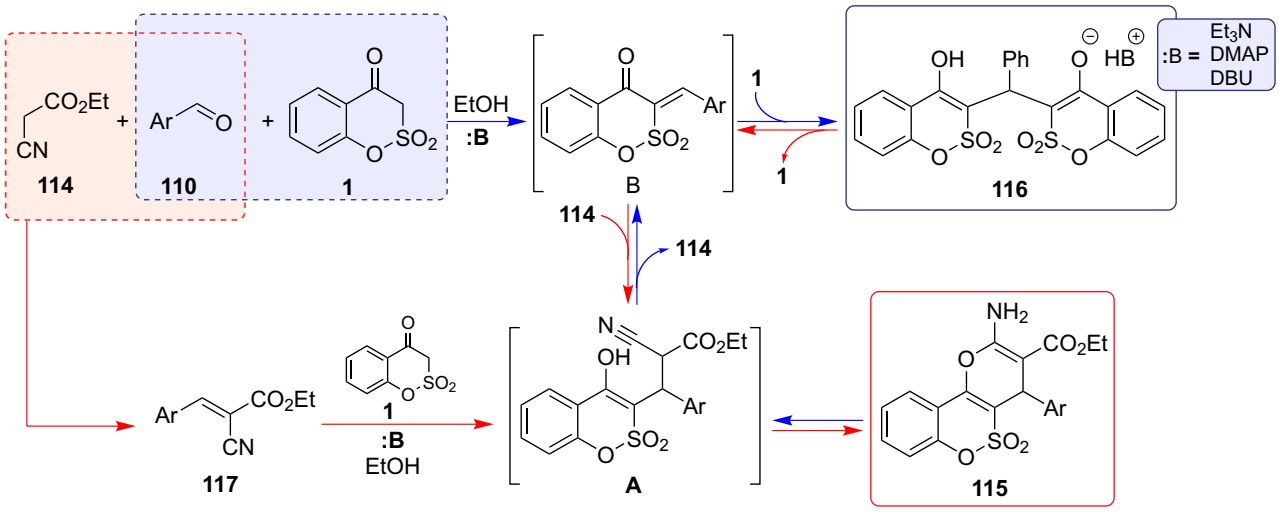
Ziegler reaction) and the enamine–imine tautomerism to form product **115**. The second one is the *retro*-Michael reaction with the elimination of ethyl cyanoacetate (**114**) and the formation of enone **B**, which reacts with the second molecule of benzothiinone **1** forming ammonium salts **116**. Apparently, the transformation of salt **116** into ethyl 2-amino-4*H*-pyran-3-carboxylates **115** is also possible by means of the reverse reactions.

The mechanism proposed is supported by a set of experiments performed in the work [47], in which the authors study the possibility of interconversions between derivatives **115**, **116** and **112** (Scheme 40). The mutual transformations of derivatives **115** and **116** prove reversibility of the key stages of the reaction mechanism (Scheme 39). Moreover, the results obtained allowed explaining the facts that the 2-amino-4*H*-pyran-3-carbonitriles **112** were formed as single products in the three-component interaction, whereas the application of ethyl cyanoacetate (**114**) resulted in the isolation of the products mixture.

Based on the data obtained it was assumed that the formation of relatively unstable salts **116** during the reaction (Scheme 39) might shift the equilibrium towards the formation of the target 2-amino-4*H*-pyrans **115**. To test this hypothesis, sodium acetate was used as a basic catalyst in the two-component interaction, assuming that the corresponding sodium salt **116** formed under the reaction conditions would be less stable as compared to the triethylammonium salts. The use of this catalyst allowed to isolate pure ethyl 2-amino-4-phenyl-4*H*-pyran-3-carboxylate **115a** (Scheme 41). A rather unexpected result was occasionally obtained during the measurement of the ^{1}H NMR spectra of **115a**. This fact refers to the stability of ethyl 2-amino-4*H*-pyran-3-carboxylate **115a** obtained. ^{1}H NMR spectra of **115a** recorded 24 h and 48 h after its dissolution in DMSO-d_6 showed the presence



Scheme 38. The three-component interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) with aromatic aldehydes **110** and ethyl cyanoacetate (**114**)



Scheme 39. The mechanism of the three-component interaction

of a high percentage of the initial benzoxathiinone **1** and ethyl α-cyano-β-phenylacrylate (**117**) increasing over time (Fig. 6). Apparently, DMSO induces the *retro*-Michael cleavage of **115a**, most probably as a result of its weak basic properties.

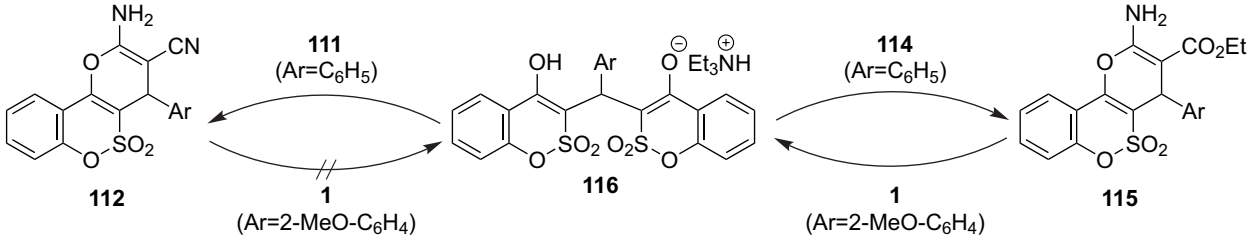
The use of hetarene-, cycloalkanecarbaldehydes and aliphatic aldehydes in the reaction with benzoxathiinone **1** and ethyl cyanoacetate (**114**) was also equivocal. In case of hetarenecarbaldehydes three different product types were isolated again depending on the aldehyde used [52]; propanal and butanal were the only aliphatic aldehydes for which ethyl 2-amino-4*H*-pyran-3-carboxylates were obtained [50]; cycloalkanecarbaldehydes gave no the target pyranes **115** [51] (Scheme 42).

Additionally, expedient two-component approaches were worked out for the synthesis of salts **116** and Hantzsch dihydropyridines **118** [47]. These routes are based on the interaction of benzoxathiinone **1** with benzaldehydes **110** in different reaction conditions (Scheme 43). It is interesting that dihydropyridine **118** (Ar = Ph) is also the product of the interaction between benzoxathiinone **1** and benzylidene **117**. Apparently, ammonium salt **116** initially formed under the reaction conditions loses 2 molecules of water and cyclizes into 1,4-dihydropyridine **118**.

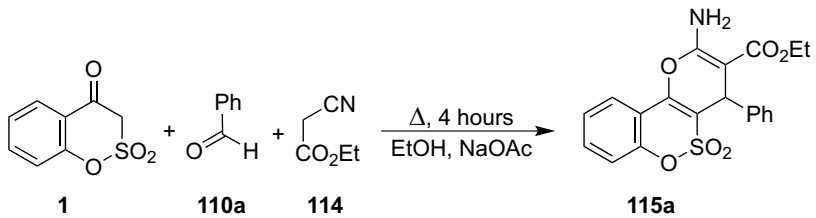
Considering isosteric relationships of the benzoxathiine **1** core with other pharmacophores (Fig. 2), 2-amino-4*H*-pyranes and ammonium salts presented in Schemes 37–43 were screened for the *in vitro* antimicrobial activity. The effect of the compounds on the blood coagulation system was also studied.

The antimicrobial activity of the compounds tested was moderate and more pronounced against gram-positive bacteria than gram-negative ones and fungi [49-52].

Studies of the effect of the compounds synthesized on the blood coagulation system were performed *in vitro* by the Burker method (Fig. 7) [53]. The results obtained turned out to be ambiguous. Thus, studies showed that compounds **112f,g** in the concentration of 1 mg/mL significantly increased the blood clotting time, indicating their anticoagulant properties. It should be mentioned that the anticoagulant effect was not dose-dependent as the same compounds in the concentration of 3 mg/mL showed a less



Scheme 40. The mutual transformations of 2-amino-4*H*-pyrans **112**, **115** and triethylammonium salts **116**



Scheme 41. The synthesis of ethyl 2-amino-4-phenyl-4*H*-pyran-3-carboxylate **115a**

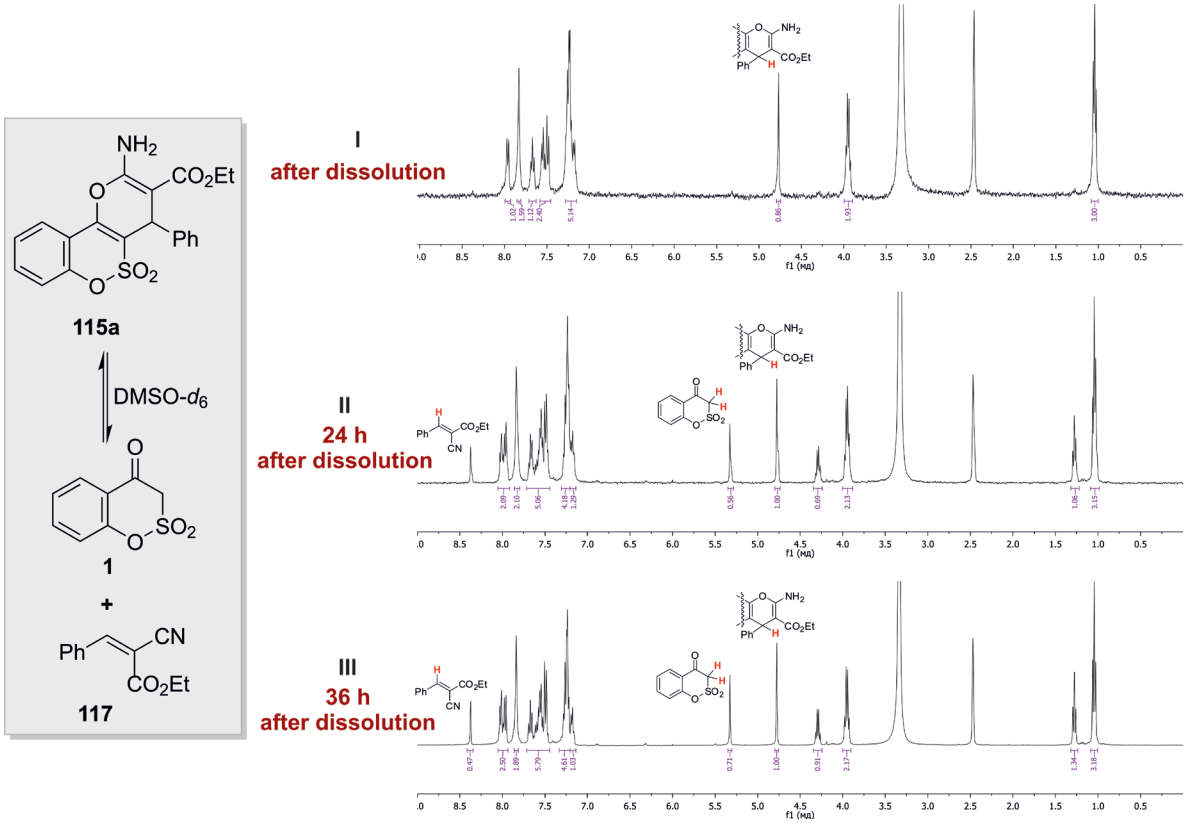
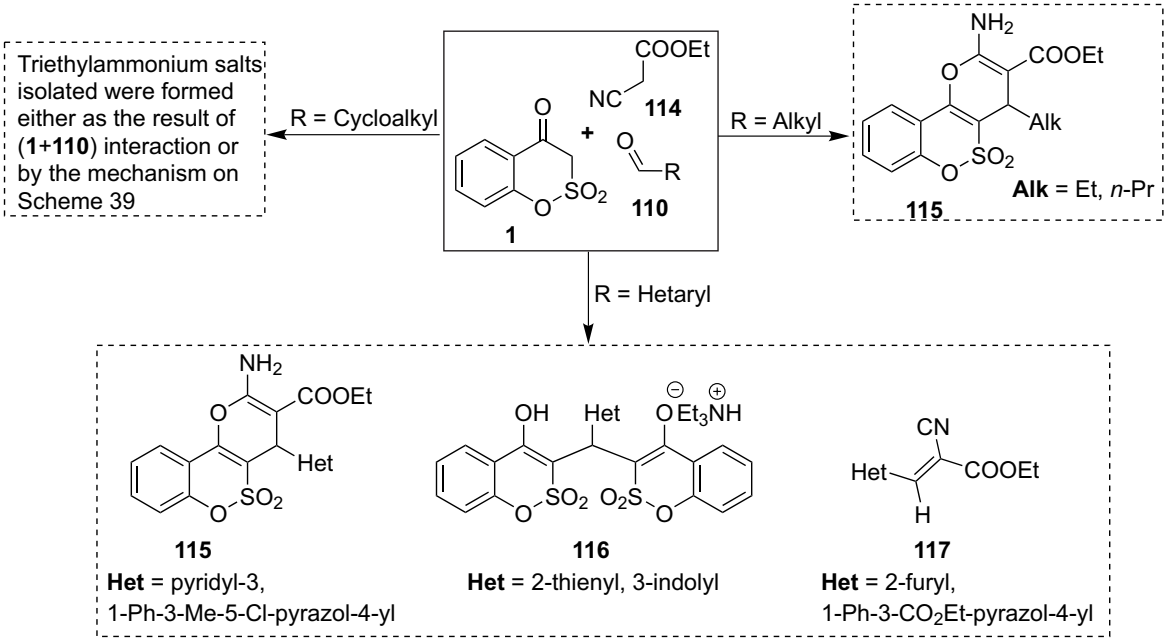


Fig. 6. The *retro*-Michael cleavage of ethyl 2-amino-4-phenyl-4*H*-pyran-3-carboxylate **115a** in DMSO-d_6 solution [47]

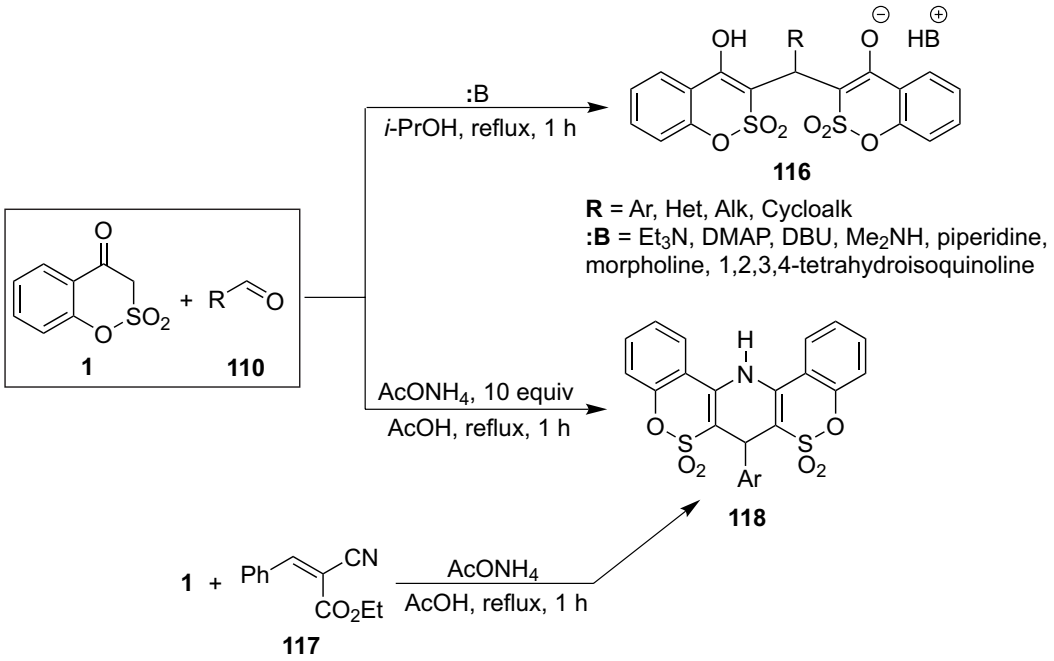
pronounced anticoagulant effect. Hemostatic substances were also found among the compounds tested; they significantly reduced the blood clotting time compared to the control.

A series of new spiro-condensed 2-amino-4*H*-pyrans were synthesized by the three-component interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**), malononitrile (**111**), and cyclic carbonyls **119**, **120** in moderate to high yields (Scheme 44) [48]. When ethyl cyanoacetate (**114**) was used, the target ethyl 2-amino-4*H*-pyran-3-carboxylate was obtained only for N-ethylisatin. Variations in catalysts, solvents and heating modes did not affect the efficiency of this interaction.

The spiro-derivatives synthesized were studied for the anti-inflammatory and analgesic activities [49]. According to the results obtained the compounds were much more promising analgesic agents than anti-inflammatory ones. The level of anti-inflammatory activity was significantly lower than for Piroxicam (Fig. 8),



Scheme 42. The use of hetarene-, cycloalkanecarbaldehydes and aliphatic aldehydes in the reaction with benzoxathiinone **1** and ethyl cyanoacetate (**114**)



Scheme 43. The synthesis of ammonium salts **116** and Hantzsch dihydropyridines **118**

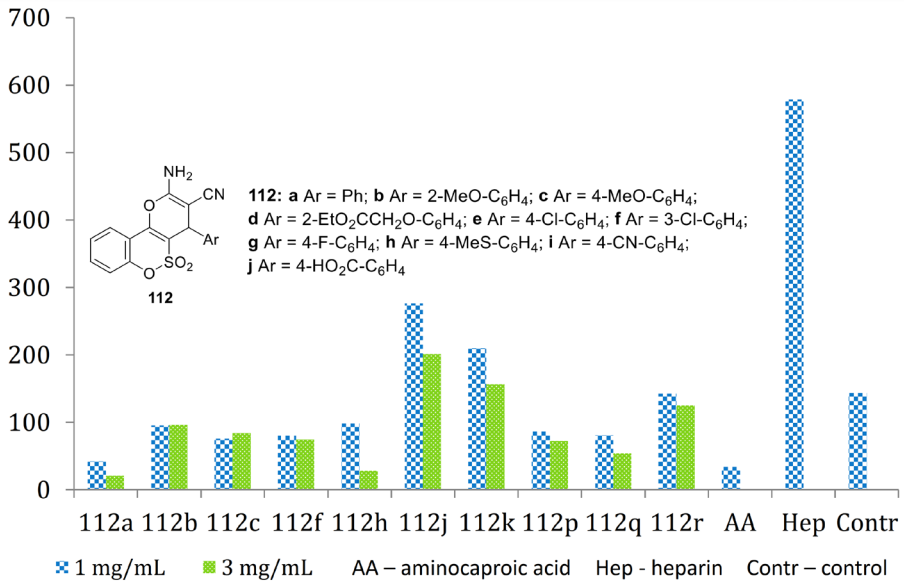
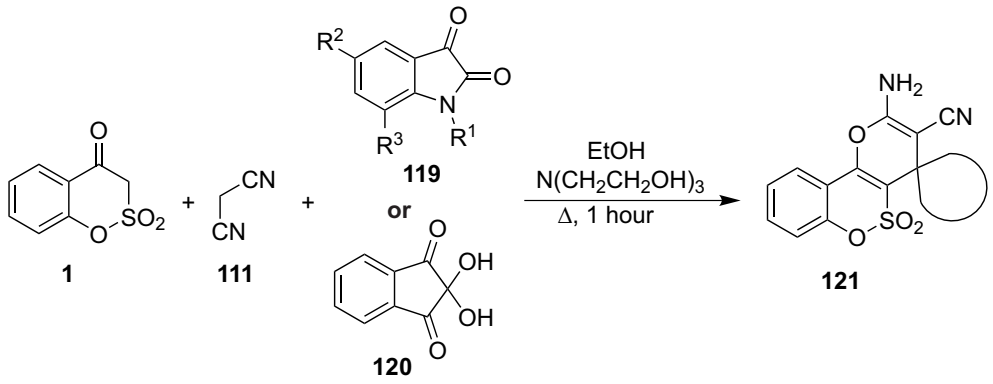


Fig. 7. The anticoagulant properties of 2-amino-4*H*-pyran-3-carbonitriles **112**



Scheme 44. The synthesis of spiro-condensed 2-amino-4*H*-pyrans

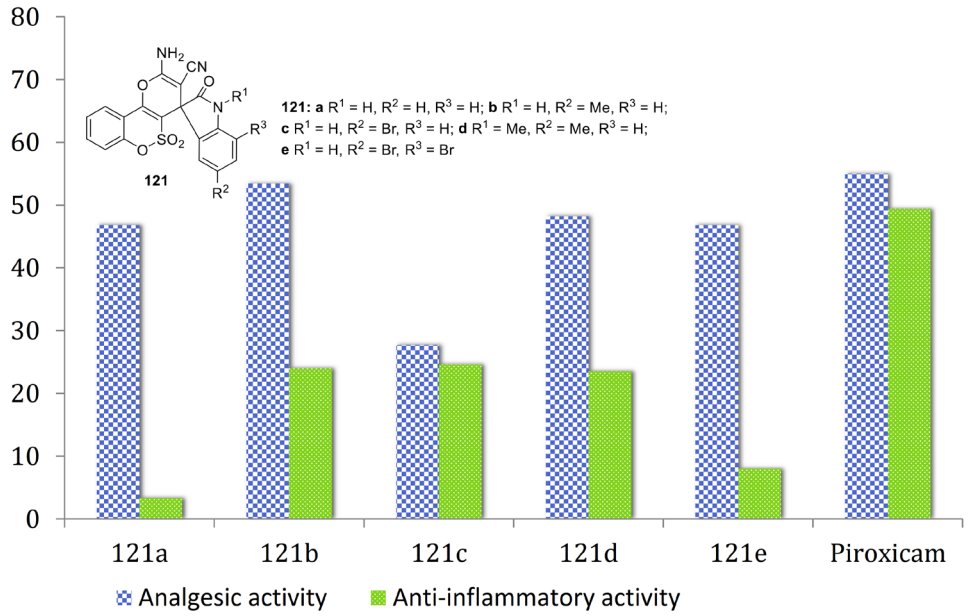


Fig. 8. The anti-inflammatory and analgesic activity of 2-amino-4*H*-pyran-3-carbonitriles **121**

whereas the analgesic activity of the test substances was about the activity of the reference drug.

Conclusions

The analysis has shown a limited number of studies in each aspect – approaches to the synthesis of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxides, their chemical transformations and the study of their pharmacological activity. In addition to a small number of publications on this heterocyclic system, there have been almost no sultone studies in the last 20 years. Taking this into account 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide and its derivatives deserve close attention as objects of research for experimental chemistry and pharmacology.

Conflict of interests: the authors have no conflict of interests to declare.

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