

Article

New Water-Soluble Condensed Heterocyclic Compounds with Antimicrobial Activity Based on Annulation Reactions of 8-Quinolinesulfonyl Halides with Natural Products and Alkenes

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Abstract: The annulation reactions of 8-quinolinesulfonyl halides with natural products and alkenes affording new water-soluble [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium derivatives in high or quantitative yields are developed in this study. The reactions with styrene derivatives and terminal alkenes including allyl arenes proceed in a regioselective manner but with the opposite regiochemistry. The reactions with terminal alkenes including allyl arenes occur in an anti-Markovnikov fashion (regarding addition of the 8-quinolinesulfonyl electrophile to the double bond) to give 2-organyl-2*H*,3*H*-[1,4]thiazino[2,3,4-*ij*]quinolin-4-ium halides, while the reactions with styrene derivatives proceed in a Markovnikov fashion, leading to 3-substituted condensed heterocyclic compounds. In general, styrene derivatives demonstrate higher reactivity in the annulation reactions compared to the terminal alkenes. Antimicrobial activity of novel water-soluble compounds against *Enterococcus durans*, *Bacillus subtilis* and *Escherichia coli* are evaluated. The compounds with high antimicrobial activity are found. The annulation products of the reactions of 8-quinolinesulfonyl halides with 1*H*-indene, eugenol, methyl eugenol and 1-heptene, are superior in their activity compared to the antibiotic gentamicin.

Keywords: annulation reactions; [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium derivatives; 8-quinolinesulfonyl chloride; heterocycles; natural products; alkenes



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1. Introduction

The quinoline skeleton occurs in many natural products, including alkaloids. Some containing the quinoline ring natural products have been used as lead molecules for the development of novel biologically active compounds and drugs [1–5]. Many modern drugs have been designed based on the quinoline scaffold. The quinoline scaffold has often been used for the design and synthesis of various synthetic compounds with pharmacological properties [1–8].

The quinoline ring is a structural part of many biologically active compounds. Quinoline derivatives exhibit a variety of biological activities including antibacterial, antiviral, anticancer, antifungal, antimalarial, cardiovascular, anticonvulsant, analgesic, antimycobacterial, anti-inflammatory, antihelminthic, antiprotozoal and antioxidant properties [1–10]. Such antimalarial drugs as chloroquine, hydroxychloroquine, amodiaquine, and primaquine have been developed based on the quinoline scaffold [1–8].

Fluoroquinolone drugs are some of the most commonly used antibiotics in modern pharmacotherapy. These drugs are broad-spectrum bacteriocidals, which exhibit high activity against both Gram-negative and Gram-positive bacteria [1–7]. A number of fluoroquinolone antibiotics have a tricyclic core structure (pazufloxacin, rufloxacin, nadifloxacin),

in which the quinoline ring is condensed with six-membered cycles (2,3-dihydro-1,4-thiazine, 2,3-dihydro-1,4-oxazine, Figure 1).

A variety of biologically active compounds are based on scaffolds in the form of a combination of nitrogen and sulfur heterocycles [11–20]. Pazufloxacin, rufloxacin and nadifloxacin antibiotics have the quinoline core structure condensed with six-membered heterocycles (Figure 1) [17–19]. The well-known antibiotics penicillin and cephalosporin are examples of drugs containing fused nitrogen and sulfur heterocycles.

The [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium scaffold can be considered as being a result of annulation of the quinoline core structure with the thiazine heterocycle. The [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium derivatives exhibit a broad spectrum of biological activities [18–23], including anticancer [21], antibacterial [22] and anti-tuberculosis [23] properties. The commonly used fluoroquinolone antibiotic rufloxacin belongs structurally to this class of compounds (Figure 1).

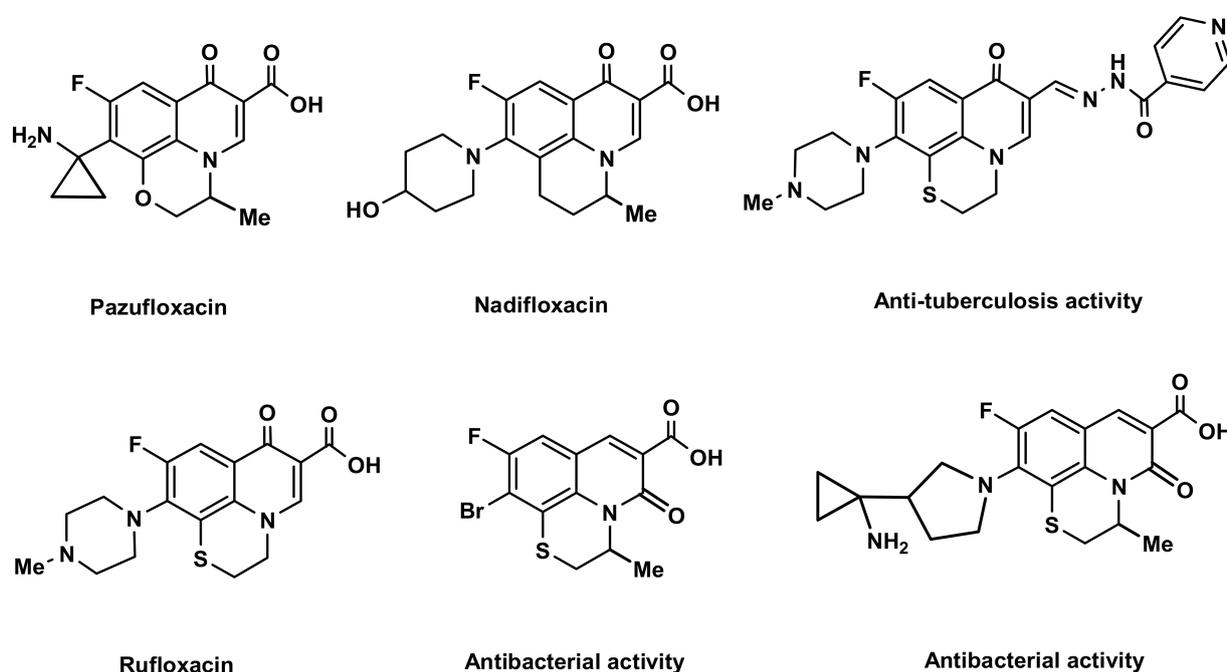
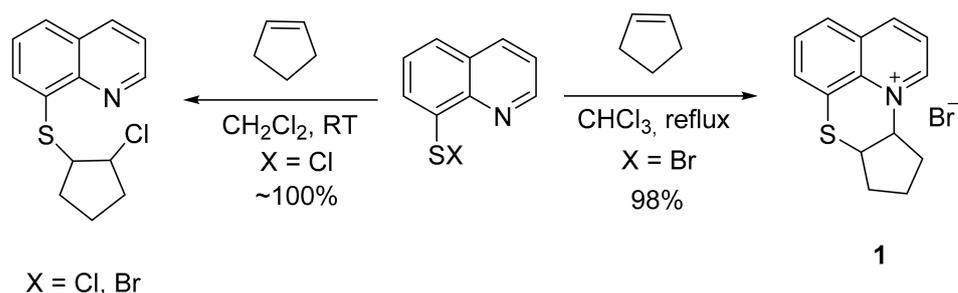


Figure 1. Known biologically active compounds structurally related to the 2*H*,3*H*-[1,4]thiazino[2,3,4-*ij*]quinolin-4-ium scaffold, which have the quinoline ring condensed with six-membered cycles (fluoroquinolone antibiotics [17–19], compounds with antibacterial [22] and anti-tuberculosis [23] activity).

In the last decade, we have developed efficient regioselective approaches to novel heterocyclic and condensed organochalcogen compounds by means of cyclization and annulation reactions based on chalcogen-containing reagents and unsaturated compounds [24–33]. Recently, we carried out the annulation reactions of 8-quinolinesulfonyl halides with vinyl heteroatom compounds and cycloalkenes to obtain novel [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium derivatives in high yields [32,33]. For example, the annulation reactions with divinyl sulfide and divinyl selenide proceeded with the addition of the sulfur atom of 8-quinolinesulfonyl electrophile at the β -position of the vinylchalcogenyl group (the Markovnikov direction), affording 3-(vinylsulfanyl)- and 3-(vinylselanyl)-2*H*,3*H*-thiazinoquinolin-4-ium chlorides in 94% and 50% yields, respectively. However, in the case of tetravinyl silane, the attachment of the sulfur atom occurred at the α -carbon atom of the vinylsilyl group (the anti-Markovnikov direction), leading to 2-(trivinylsilyl)-2*H*,3*H*-[1,4]thiazino[2,3,4-*ij*]quinolin-4-ium chloride in a 98% yield [32].

The reactions of 8-quinolinesulfonyl halides (chloride and bromide) with cycloalkenes (cyclopentene, cyclohexene, and cyclooctene), depending on the nature of the halogen and

the reaction conditions, gave products of electrophilic addition or annulation products in high yields [33]. The reactions of 8-quinolinesulfonyl chloride with cycloalkenes afforded 8-[(2-chlorocycloalkyl)sulfonyl]quinolines in quantitative yields, while condensed tetracyclic compounds were synthesized in 90–100% yields from 8-quinolinesulfonyl bromide and cycloalkenes. Thus, the reaction of 8-quinolinesulfonyl chloride with cyclopentene at room temperature in methylene chloride gave 8-[(2-chlorocyclopentyl)sulfonyl]quinoline in a quantitative yield, whereas condensed tetracyclic compound, 8,9,10,10a-tetrahydro-7a*H*-cyclopenta[5,6][1,4]thiazino[2,3,4-*ij*]quinolin-11-ium bromide (**1**), was obtained in a 98% yield by the annulation reaction of 8-quinolinesulfonyl bromide with cyclopentene in chloroform under reflux (Scheme 1) [33].



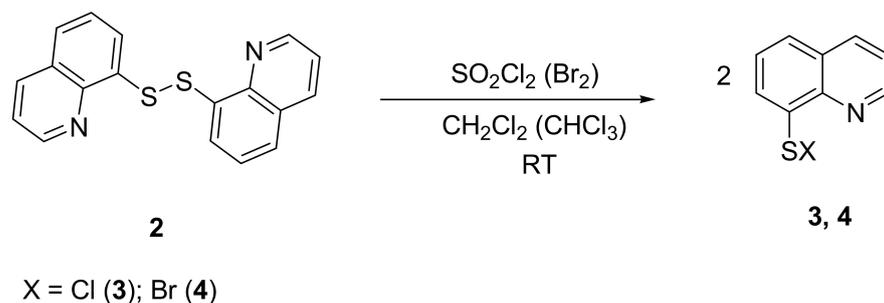
Scheme 1. The annulation reactions of 8-quinolinesulfonyl chloride and bromide with cyclopentene.

Although some synthetic methods for the preparation of [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium derivatives have been developed [32–40], the annulation reactions of 8-quinolinesulfonyl halides with natural products such as eugenol, isoeugenol, methyleugenol, anethole as well as with 1*H*-indene, styrene derivatives (4-methylstyrene and α -methylstyrene) and simple alkenes (1-hexene and 1-heptene) have not been described in the literature.

The development of efficient selective methods for the preparation of new [1,4]thiazinoquinolin-4-ium derivatives with promising biological activity is an urgent task. The aim of this research is the development of the regioselective synthesis of new derivatives of [1,4]thiazino[2,3,4-*ij*]quinolin-4-ium based on annulation reactions of 8-quinolinesulfonyl halides with natural products (eugenol, isoeugenol, methyleugenol, *trans*-anethole) as well as with 1-hexene, 1-heptene, 1*H*-indene and styrene derivatives (4-methylstyrene and α -methylstyrene) and the evaluation of their antimicrobial activity.

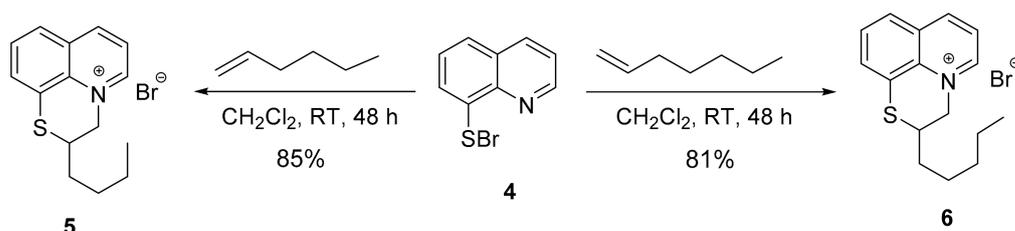
2. Results and Discussion

The starting compounds, 8-quinolinesulfonyl chloride **3** and bromide **4**, were generated in situ from di(8-quinolinyl) disulfide (**2**) in methylene chloride or chloroform and used without isolation in further reactions with alkenes and natural products (eugenol derivatives, *trans*-anethole) (Scheme 2).



Scheme 2. The generation of 8-quinolinesulfonyl chloride **3** and bromide **4** from di(8-quinolinyl) disulfide **2** by the action of sulfuryl chloride or bromine.

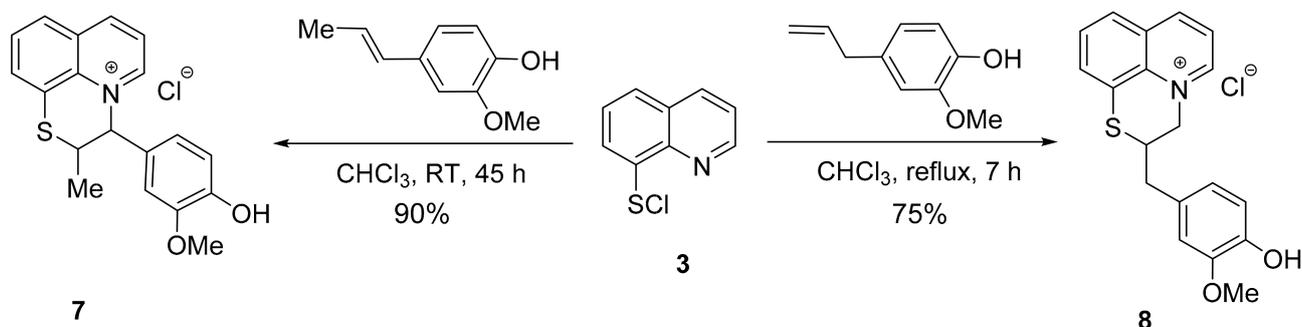
Taking into account the known data on the reactions of 8-quinolinesulfenyl halides with cycloalkenes [33], which produced electrophilic addition products of sulfenyl chloride **3** and annulation products in the case of sulfenyl bromide **4** (Scheme 1), it could be assumed that the reactions of 8-quinolinesulfenyl halides with 1-alkenes would proceed similarly. However, the reactions of sulfenyl chloride **3** with 1-alkenes gave a complex mixture of compounds including electrophilic addition products under the same conditions as indicated in Scheme 1. Nevertheless, the reactions of sulfenyl bromide **4** with 1-alkenes at room temperature in methylene chloride led to annulation products **5** and **6** in 85% and 81% yields, respectively (Scheme 3).



Scheme 3. Synthesis of 2-butyl- and 2-pentyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium bromides **5** and **6** from sulfenyl bromide **4** and 1-alkenes.

Compounds **5** and **6** are water-soluble light-yellow powders with a melting point of about 120 °C.

The naturally occurring products eugenol (4-allyl-2-methoxyphenol) and isoeugenol (2-methoxy-4-(1-propenyl)phenol) were involved in the annulation reactions with 8-quinolinesulfenyl chloride **3**. The reaction of sulfenyl chloride **3** with isoeugenol smoothly proceeded at room temperature in chloroform, giving compound **7** in a 90% yield (Scheme 4).

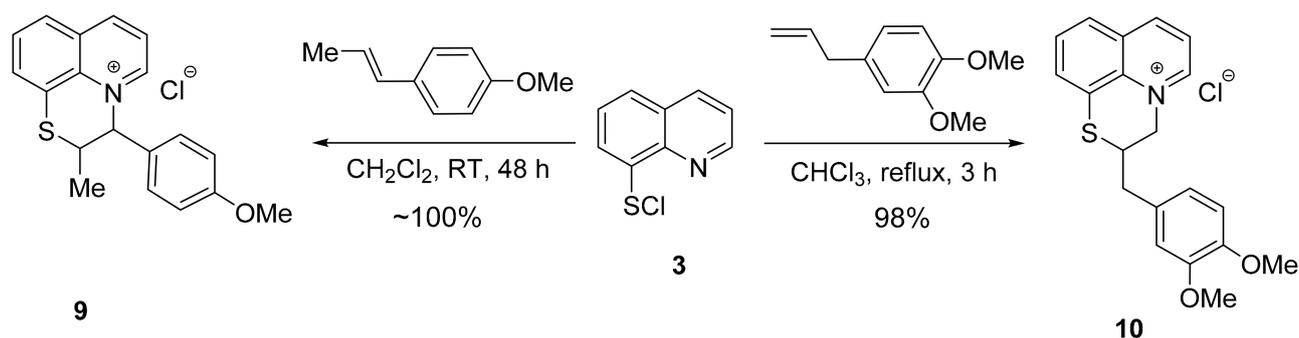


Scheme 4. Synthesis of compounds **7** and **8** by the annulation reactions of sulfenyl chloride **3** with isoeugenol and eugenol.

The reaction of sulfenyl chloride **3** with eugenol under the same conditions as the synthesis of compound **7** was very sluggish (40% yield of the annulation product). However, carrying out the reaction of sulfenyl chloride **3** with eugenol under reflux in chloroform for 7 h allowed us to obtain annulation product **8** in a 75% yield (Scheme 4).

The reaction of sulfenyl chloride **3** with eugenol includes electrophilic addition of the sulfur atom of sulfenyl electrophile to the α -carbon atom of the vinyl group (the anti-Markovnikov direction), while the opposite regiochemistry is observed in the annulation reaction of sulfenyl chloride **3** with isoeugenol.

Another naturally occurring compound, *trans*-anethole (1-methoxy-4-(*E*-1-propenyl)benzene), appears to be very reactive in annulation reactions. The reaction of sulfenyl chloride **3** with *trans*-anethole was carried out at room temperature in methylene chloride, affording quinolinium chloride **9** in a quantitative yield (Scheme 5).



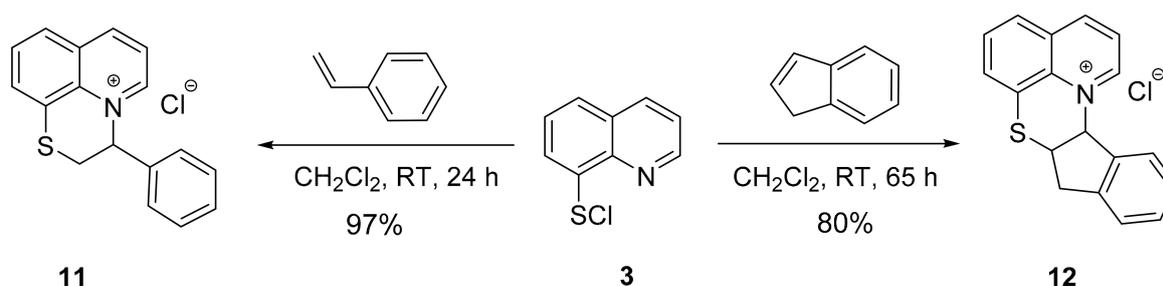
Scheme 5. Synthesis of compounds **9** and **10** by the annulation reactions of sulfenyl chloride **3** with *trans*-anethole and methyl eugenol.

The reaction of sulfenyl chloride **3** with methyl eugenol (4-allyl-1,2-dimethoxybenzene) seems to proceed more slowly than with eugenol. Under the same conditions as the synthesis of product **9**, the reaction of sulfenyl chloride **3** with methyl eugenol afforded the annulation product in a 57% yield. However, after refluxing the mixture of sulfenyl chloride **3** with methyl eugenol in chloroform for 3 h, annulation product **10** was obtained in a 98% yield (Scheme 5).

The double bond in *trans*-anethole and isoeugenol occurs in conjugation with the benzene ring, and these compounds demonstrate higher activity in the annulation reactions compared to eugenol and methyl eugenol bearing the allyl fragment without conjugation of the double bond.

Such substrates as styrene, 4-methylstyrene and α -methylstyrene and 1*H*-indene also have the double bond, which is in conjugation with the benzene ring. We assumed that these substrates may be active in the annulation and carried out the reactions of sulfenyl chloride **3** with them.

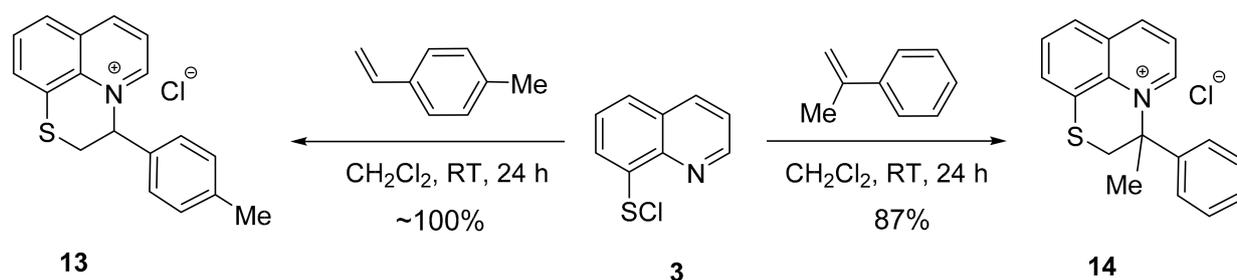
The reactions of quinoline sulfenyl chloride **3** with styrene proceeded smoothly in methylene chloride at room temperature for 24 h to give quinolinium chloride **11** in a 97% yield (Scheme 6).



Scheme 6. Synthesis of compounds **11** and **12** by the annulation reactions of sulfenyl chloride **3** with styrene and 1*H*-indene.

Under the same conditions, the reactions of sulfenyl chloride **3** with 1*H*-indene afforded the condensed five-membered product in only a 43% yield. Refluxing the reaction mixture resulted in the formation of a small amount of by-product along with the target compound. However, when the reaction time was increased to 65 h at room temperature, pure annulation product **12** was obtained in an 80% yield (Scheme 6).

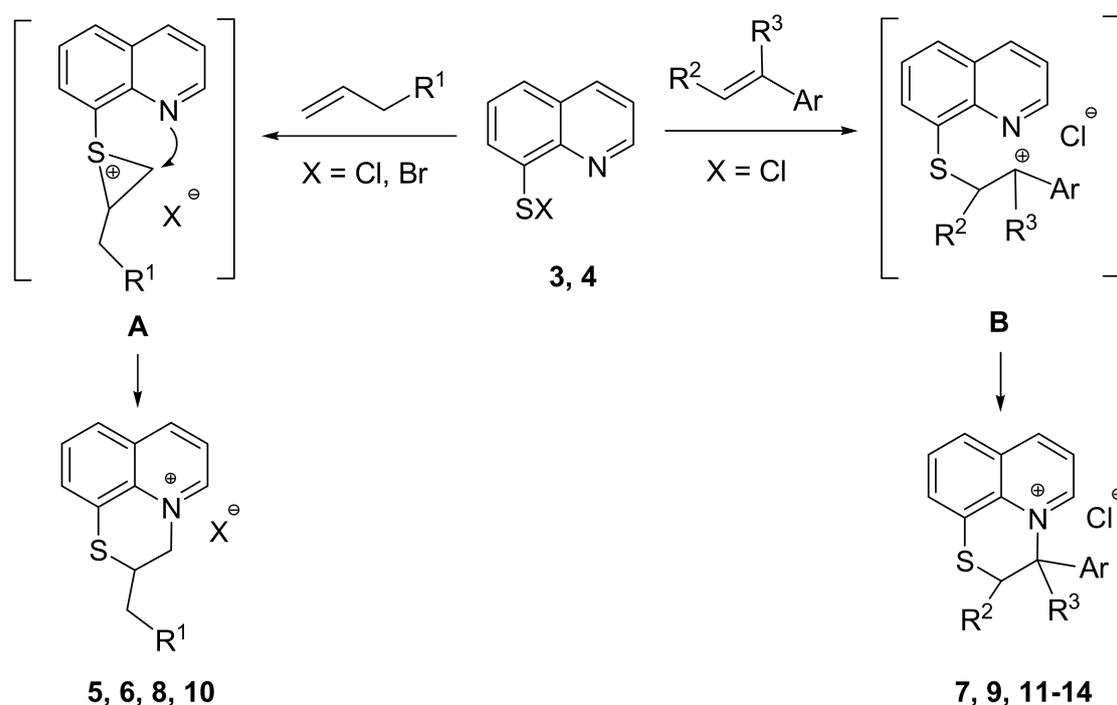
The reaction of sulfenyl chloride **3** with 4-methylstyrene was carried out at room temperature for 24 h in methylene chloride affording compound **13** in quantitative yield (Scheme 7). Under the same conditions as the synthesis of product **13**, the reaction of sulfenyl chloride **3** with α -methylstyrene gave annulation product **14** in an 87% yield (Scheme 7).



Scheme 7. Synthesis of compounds **13** and **14** by the annulation reactions of sulfenyl chloride **3** with 4-methylstyrene and α -methylstyrene.

The reaction of sulfenyl chloride **3** with α -methylstyrene seems to proceed more slowly than with 4-methylstyrene and styrene. The methyl substituent at position 4 of the benzene ring has little influence on the yield of the product, and compounds **11** and **13** (derived from both styrene and 4-methylstyrene) were obtained in 97% and quantitative yields, while the introduction of the methyl substituent to the α -position of the double bond affects on the annulation reaction and slightly decreases the the annulation product yield to 87% under the same conditions.

All the studied substrates can be schematically divided into two groups: terminal alkenes including allyl arenes and styrene derivatives, which contain the double bond in conjugation with the benzene ring. In general, the latter group of compounds demonstrates the higher activity in the annulation reactions compared to the terminal alkenes (Scheme 8).



$\text{R}^1 = \text{C}_4\text{H}_9$ (**5**), C_5H_{11} (**6**), 4-HO(3-MeO) C_6H_3 (**8**), 3,4-(MeO) $_2\text{C}_6\text{H}_3$ (**10**),
 $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, Ar = 4-HO(3-MeO) C_6H_3 (**7**); $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, Ar = 4-(MeO) C_6H_4 (**9**);
 $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, Ar = C_6H_5 (**11**); $\text{R}^2\text{CH}=\text{C}(\text{R}^3)\text{Ar} = 1H\text{-indene}$ (**12**);
 $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, Ar = 4-Me C_6H_4 (**13**), $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$, Ar = C_6H_5 (**14**)

Scheme 8. Directions of the reactions of sulfenyl chloride **3** and bromide **4** with natural products and alkenes.

The annulation reactions with the terminal alkenes, whose double bond is not in conjugation with the benzene ring, proceed with the attachment of the sulfur atom of sulfenyl halides **3**, **4** at the α -position of the double bond (the anti-Markovnikov direction). In the case of styrene derivatives, the addition of the sulfur atom occurs at the terminal carbon atom of the double bond (the Markovnikov direction). Possible intermediates **A** and **B**, which correspond to two directions of these reactions, can be considered for the explanation of these trends (Scheme 8).

We assume that the reactions with terminal alkenes proceed via three-membered thiiranium intermediates **A**. It is known that the electrophilic addition reactions of sulfenyl chlorides [41–54] with linear 1-alkene mainly give anti-Markovnikov products [41–43], and thiiranium cations are regarded as intermediates of these reactions [42–45]. Nucleophilic attack of the nitrogen atom of the quinoline ring occurs at the unsubstituted carbon atom of thiiranium intermediates **A** due to the steric factor, which determines the anti-Markovnikov direction of the reactions (Scheme 8).

It is assumed that linear carbocations **B** are involved as intermediates in the reactions with styrene derivatives. In this case, linear carbocations **B** are energetically favorable due to their stabilization by the benzene ring that provides the Markovnikov direction of the reactions (Scheme 8). It is known that electrophilic addition of sulfenyl chlorides to styrene leads to Markovnikov products [52,53].

The antibacterial activity of the synthesized compounds was evaluated. The minimal inhibitory concentration (MIC) was determined using the broth standard microdilution method [55].

The obtained results are presented in Table 1. Compounds **1**, **5–14** were tested in vitro for antimicrobial activity against strains of the Gram-positive bacteria *Bacillus subtilis* B-406 and *Enterococcus durans* B-603 (which are similar in properties and taxonomic affiliation to bacteria *Staphylococcus aureus*) and the Gram-negative bacteria *Escherichia coli* B-1238 (the bacterial strains were taken from the All-Russian Collection of Microorganisms).

Table 1. The evaluation of antibacterial activity of compounds **1**, **5–14**.

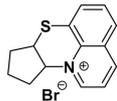
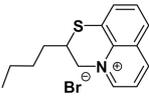
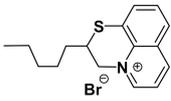
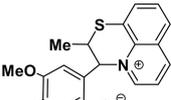
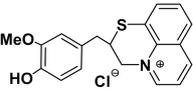
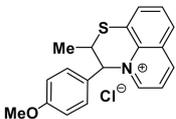
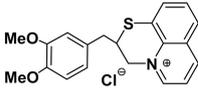
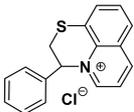
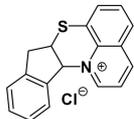
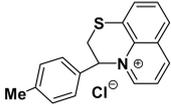
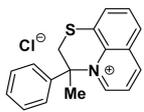
Compound	Minimum Inhibitory Concentration ($\mu\text{g/mL}$)			
	<i>Enterococcus durans</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	
1		31.2	>1000	>1000
5		250	250	250
6		3.1	62.5	12.5
7		310	310	>1000
8		3.1	3.1	62.5

Table 1. Cont.

Compound	Minimum Inhibitory Concentration ($\mu\text{g/mL}$)			
	<i>Enterococcus durans</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	
9		250	125	>1000
10		3.1	25	1000
11		6.2	250	125
12		0.6	3.1	250
13		6.2	125	250
14		62.5	250	125
Gentamicin		25	50	100

As can be seen from the presented data (Table 1), compound 1 is active against *Enterococcus durans*, but has low activity against other microorganisms. Compounds 5 and 6 differ only by one group, CH_2 , but the activity of these compounds varies considerably. Compound 5 with a shorter carbon chain shows low activity, while compound 6 is superior to antibiotic gentamicin against both the Gram-positive *Enterococcus durans* and the Gram-negative *Escherichia coli* (Table 1).

The obtained results were compared with the activity of standard aminoglycoside antibiotic gentamicin, the minimal inhibitory concentrations of which are 25, 50 and 100 $\mu\text{g/mL}$ against *Enterococcus durans*, *Bacillus subtilis* and *Escherichia coli*, respectively.

Having the same molecular formula, products 7 and 8 are isomeric compounds obtained by the reactions of sulfonyl chloride 3 with isoeugenol and eugenol, respectively. These compounds differ significantly (by about 10 times) in activity (Table 1). The eugenol-derived product 8, as well as that obtained from methyl eugenol, compound 10, are highly active against bacteria *Enterococcus durans* and *Bacillus subtilis* and are superior in their activity compared the antibiotic gentamicin against these microorganisms.

The structurally related compounds 7 and 9 (obtained from methyl isoeugenol and *trans*-anethole), which formally differ in one hydroxyl group, show activity against Gram-positive bacteria *Enterococcus durans* and *Bacillus subtilis*, but are inferior to gentamicin (Table 1).

Comparison of the structurally related compounds 11, 13 and 14 reveals the higher activity of products 11 and 13 (obtained from styrene and 4-methylstyrene), which are superior to the activity of gentamicin against bacteria *Enterococcus durans*. α -methylstyrene-derived product 14 shows lower activity (Table 1).

The highest level of activity was shown by product 12 (obtained from 1*H*-indene), which significantly exceeds the activity of gentamicin and all the obtained compounds

against the bacteria *Enterococcus durans* and is more than 15 times higher than the activity of this antibiotic against *Bacillus subtilis*.

The structural assignments of synthesized compounds were made using ^1H - and ^{13}C -NMR spectroscopy including J -modulation ^{13}C -NMR experiments and confirmed by elemental analysis (see more in Supplementary Materials).

The groups $\text{SCH-CH}_2\text{N}^+$, $\text{SCH}_2\text{-CHN}^+$ and SCH-CHN^+ provide characteristic signals in the ^1H - and ^{13}C -NMR spectra. Thus, the carbon atoms of these groups, bonded with one or two protons, reveal characteristic signals in the ^{13}C -NMR spectra. For example, the CH_2N^+ group manifests itself at ~ 62 ppm, while signals of the CHN^+ moiety are observed in the lowfield region of ~ 69 – 75 ppm in the ^{13}C -NMR spectra of the obtained compounds. The regiochemistry of the products was determined based on the ^1H - and ^{13}C -NMR spectra, taking into account the number of protons bonded with the carbon atoms of these groups.

3. Experimental Section

3.1. General Information

^1H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker DPX-400 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) in a 2–5% solution with D_2O or $\text{DMSO-}d_6$. ^1H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm), relative to tetramethylsilane (external) or to the residual solvent peaks of D_2O ($\delta = 4.79$) and $\text{DMSO-}d_6$ ($\delta = 2.50$ and 39.52 ppm for ^1H and ^{13}C NMR, respectively). Elemental analysis was performed on a Thermo Scientific FLASH 2000 Organic Elemental Analyzer (Thermo Fisher Scientific Inc., Milan, Italy). Melting points were determined on a Kofler Hot-Stage Microscope PolyTherm A apparatus (Wagner & Munz GmbH, München, Germany). Absolute solvents were used in the reactions.

3.2. Synthesis of Products 5 and 6 from 1-Alkenes

2-Butyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium bromide (5). A solution of bromine (0.072 g, 0.45 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.144 g, 0.45 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of hexene-1 (0.076 g, 0.9 mmol) in methylene chloride (10 mL) was added dropwise. The reaction mixture was stirred for 48 h at room temperature and left overnight. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was washed with cold hexane and dried in vacuum, giving the product (0.248 g, 85% yield) in the form of a yellow powder, mp 220–221 °C.

^1H -NMR (400 MHz, $\text{DMSO-}d_6$): δ 0.90 (t, $J = 7.3$ Hz, 3H, CH_3), 1.31–1.39 (m, 2H, CH_2), 1.47–1.54 (m, 2H, CH_2), 1.61–1.68 (m, 1H, CH_2), 1.80–1.89 (m, 1H, CH_2), 3.94 (m, 1H, SCH), 5.01 (dd, $J = 13.9, 8.5$ Hz, 1H, NCH_2), 5.36 (d, $J = 13.9$ Hz, 1H, NCH_2), 7.88–7.92 (m, 1H, H_{quino}), 8.12–8.14 (m, 1H, H_{quino}), 8.18–8.22 (m, 2H, H_{quino}), 9.28–9.30 (m, 1H, H_{quino}), 9.39–9.41 (m, 1H, H_{quino}).

^{13}C -NMR (101 MHz, $\text{DMSO-}d_6$): δ 13.75 (CH_3), 21.65 (CH_2), 28.03 (CH_2), 30.81 (CH_2), 36.21 (SCH), 62.05 (NCH_2), 122.25 (C_{quino}), 126.40 (C_{quino}), 126.87 (C_{quino}), 129.39 (C_{quino}), 130.59 (C_{quino}), 133.14 (C_{quino}), 133.61 (C_{quino}), 148.65 (C_{quino}), 150.23 (C_{quino}).

Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{BrNS}$: C 55.56, H 5.59, N 4.32, Br 24.64, S 9.89. Found: C 55.69, H 5.96, N 4.44, Br 24.86, S 10.10.

2-Pentyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium bromide (6). A solution of bromine (0.130 g, 0.80 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.261 g, 0.80 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of heptene-1 (0.157 g, 1.6 mmol) in methylene chloride (10 mL) was added dropwise. The reaction mixture was stirred for 48 h at room temperature and left overnight. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was washed with cold hexane and dried in vacuum, giving the product (0.438 g, 81% yield) in the form of a yellow powder, mp 219–220 °C.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 0.88 (s, 3H, CH_3), 1.30–1.32 (m, 4H, CH_2), 1.49–1.56 (m, 2H, CH_2), 1.58–1.65 (m, 1H, CH_2), 1.81–1.84 (m, 1H, CH_2), 3.94 (m, 1H, SCH), 5.01 (dd, $J = 13.7, 8.3$ Hz, 1H, NCH_2), 5.35 (d, $J = 13.7$ Hz, 1H, NCH_2), 7.88–7.92 (m, 1H, H_{quino}), 8.12–8.13 (m, 1H, H_{quino}), 8.18–8.22 (m, 2H, H_{quino}), 9.27–9.30 (m, 1H, H_{quino}), 9.39–9.41 (m, 1H, H_{quino}).

$^{13}\text{C-NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ 13.78 (CH_3), 21.82 (CH_2), 25.48 (CH_2), 30.60 (CH_2), 31.01 (CH_2), 36.18 (SCH), 61.97 (NCH_2), 122.21 (C_{quino}), 126.36 (C_{quino}), 126.81 (C_{quino}), 129.33 (C_{quino}), 130.54 (C_{quino}), 132.54 (C_{quino}), 133.10 (C_{quino}), 148.60 (C_{quino}), 150.19 (C_{quino}).

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{BrNS}$: C 56.80, H 5.96, N 4.14, Br 23.62, S 9.48. Found: C 57.02, H 6.11, N 4.24, Br 23.97, S 9.72.

3.3. Synthesis of Compounds 7–10 from Natural Products

3-(4-Hydroxy-3-methoxyphenyl)-2-methyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (7). A solution of sulfuryl chloride (0.113 g, 0.83 mmol) in chloroform (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.268 g, 0.83 mmol) in chloroform (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of isoeugenol (0.274 g, 1.6 mmol) in chloroform (10 mL) was added dropwise, and the reaction mixture was stirred for 45 h at room temperature and left overnight. The formed precipitate was filtered off, washed with hexane and dried in vacuum, giving the product (0.54 g, 90% yield) in the form of a yellow powder, mp 156–159 °C.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 1.40 (d, $J = 7.0$ Hz, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.96 (m, 1H, SCH), 5.73 (m, 1H, NCH), 6.58 (m, 1H, Ar), 6.61 (m, 1H, Ar), 6.80 (m, 1H, Ar), 7.94–7.98 (m, 1H, H_{quino}), 8.14–8.16 (m, 1H, H_{quino}), 8.24–8.27 (m, 1H, H_{quino}), 8.32–8.34 (m, 1H, H_{quino}), 9.43–9.45 (m, 1H, H_{quino}), 9.48–9.50 (m, 1H, H_{quino}).

$^{13}\text{C-NMR}$ (101 MHz, $\text{DMSO-}d_6$): δ 20.04 (CH_3), 37.46 (SCH), 55.74 (OCH_3), 73.69 (NCH), 110.39, 115.40, 117.77, 122.94, 124.85, 127.68, 129.08, 129.70, 130.87, 132.96, 133.95, 147.17, 148.03, 150.25, 151.10.

Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{NClO}_2\text{S}$: C 63.41, H 5.04, N 3.89, Cl 9.85, S 8.91. Found: C 63.69, H 5.23, N 4.07, Cl 10.09, S 9.21.

2-[(4-Hydroxy-3-methoxyphenyl)methyl]-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (8). A solution of sulfuryl chloride (0.167 g, 1.2 mmol) in chloroform (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.396 g, 1.2 mmol) in chloroform (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of eugenol (0.394 g, 2.4 mmol) in chloroform (10 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature and 7 h at reflux and left overnight. The formed precipitate was filtered off, washed with hexane and dried in vacuum, giving the product (0.648 g, 75% yield) in the form of a yellow powder, mp 195–197 °C.

$^1\text{H-NMR}$ (400 MHz, D_2O): δ 2.88–2.94 (m, 1H, CH_2), 3.02 (dd, $J = 14.2, 6.0$ Hz, 1H, CH_2), 3.68 (s, 3H, CH_3), 3.92–3.97 (m, 1H, SCH), 4.94 (dd, $J = 14.4, 6.8$ Hz, 1H, NCH_2), 5.21 (dd, $J = 14.4, 2.4$ Hz, 1H, NCH_2), 6.48–6.53 (m, 2H, Ar), 6.68 (s, 1H, Ar), 7.69–7.73 (m, 1H, H_{quino}), 7.80–7.82 (m, 1H, H_{quino}), 7.92–7.98 (m, 2H, H_{quino}), 8.96–9.00 (m, 2H, H_{quino}).

$^{13}\text{C-NMR}$ (101 MHz, D_2O): δ 36.84 (CH_2), 37.18 (SCH), 55.34 (CH_3), 61.78 (CH_2N), 112.80, 114.59, 121.35, 121.70, 125.61, 126.51, 127.91, 129.14, 130.46, 132.69, 133.07, 143.36, 146.56, 148.55, 148.68.

Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{NClO}_2\text{S}$: C 63.41, H 5.04, N 3.89, Cl 9.85, S 8.91. Found: C 63.73, H 5.21, N 4.01, Cl 10.31, S 9.29.

3-(4-Methoxyphenyl)-2-methyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (9). A solution of sulfuryl chloride (0.103 g, 0.76 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.243 g, 0.76 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of *trans*-anethole (0.226 g, 1.52 mmol) in methylene chloride (10 mL) was added dropwise, and the reaction mixture was stirred for 48 h at room temperature. The solvent was removed

by rotary evaporator. The residue was dried in vacuum, giving the product (0.523 g, quantitative yield) in the form of a yellow powder, mp 97–100 °C.

¹H-NMR (400 MHz, D₂O): δ 1.43 (d, *J* = 7.0 Hz, 3H, CH₃), 3.65 (s, 3H, OCH₃), 3.92 (dd, *J* = 7.0, 3.1 Hz, 1H, SCH), 6.39 (d, *J* = 3.1 Hz, 1H, NCH), 6.70 (d, *J* = 9.0 Hz, 2H, Ar), 6.74 (d, *J* = 9.0 Hz, 2H, Ar), 7.84–7.88 (m, 1H, H_{quino}), 7.93–7.95 (m, 1H, H_{quino}), 8.04–8.08 (m, 1H, H_{quino}), 8.18–8.20 (m, 1H, H_{quino}), 9.15–9.16 (m, 1H, H_{quino}), 9.21–9.23 (m, 1H, H_{quino}).

¹³C-NMR (101 MHz, D₂O): δ 19.25 (CH₃), 38.18 (SCH), 55.23 (OCH₃), 74.33 (NCH), 114.17, 122.18, 124.12, 126.68, 127.75, 129.65, 130.30, 131.09, 133.18, 134.52, 150.10, 150.25, 159.10.

Anal. Calcd for C₁₉H₁₈NCIOS: C 66.36, H 5.28, N 4.07, Cl 10.31, S 9.33. Found: C 66.46, H 5.34, N 4.15, Cl 10.84, S 9.91.

2-[(3,4-Dimethoxyphenyl)methyl]-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (10). A solution of sulfuryl chloride (0.067 g, 0.50 mmol) in chloroform (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.160 g, 0.50 mmol) in chloroform (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of methyl eugenol (0.178 g, 1.0 mmol) in chloroform (10 mL) was added dropwise, and the reaction mixture was stirred for 1 h at room temperature and 3 h at reflux temperature. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was washed with cold hexane and dried in vacuum, giving the product (0.366 g, 98% yield) in the form of a yellow powder, mp 179–180 °C.

¹H-NMR (400 MHz, D₂O): δ 2.76–2.82 (m, 1H, CH₂), 2.93–2.98 (m, 1H, CH₂), 3.56 (s, 3H, OCH₃), 3.57 (s, 3H, OCH₃), 3.83–3.86 (m, 1H, SCH), 4.82–4.85 (m, 1H, NCH₂), 5.12–5.16 (m, 1H, NCH₂), 6.45–6.51 (m, 2H, Ar), 6.56 (s, 1H, Ar) 7.56–7.65 (m, 2H, H_{quino}), 7.80–7.82 (m, 1H, H_{quino}), 7.90–7.92 (m, 1H, H_{quino}), 8.89–8.94 (m, 2H, H_{quino}).

¹³C-NMR (101 MHz, D₂O): δ 37.20 (CH₂), 37.56 (SCH), 55.43 (OCH₃), 55.53 (OCH₃), 62.18 (CH₂N), 111.22, 112.45, 121.79, 121.92, 125.95, 126.85, 128.63, 129.49, 130.72, 132.92, 133.20, 146.92, 147.55, 148.92, 149.03.

Anal. Calcd for C₂₀H₂₀NCIO₂S: C 64.25, H 5.39, N 3.75, Cl 9.48, S 8.58. Found: C 63.73, H 5.21, N 4.01, Cl 10.01, S 8.99.

3.4. Synthesis of Compounds 11–14 from Styrene Derivatives and 1H-Indene

3-Phenyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (11). A solution of sulfuryl chloride (0.042 g, 0.31 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.100 g, 0.31 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of styrene (0.065 g, 0.62 mmol) in methylene chloride (5 mL) was added dropwise, and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was washed with cold hexane and dried in vacuum, giving the product (0.18 g, 97% yield) in the form of a light-yellow oil.

¹H-NMR (400 MHz, D₂O): δ 3.78 (dd, *J* = 14.3, 3.5 Hz, 1H, SCH₂), 3.98 (dd, *J* = 14.3, 3.0 Hz, 1H, SCH₂), 6.79–6.83 (m, 1H, NCH), 6.89–6.96 (m, 2H, Ar), 7.36–7.44 (m, 3H, Ar), 7.91–7.95 (m, 1H, H_{quino}), 8.08–8.13 (m, 2H, H_{quino}), 8.23–8.25 (m, 1H, H_{quino}), 9.21–9.27 (m, 2H, H_{quino}).

¹³C-NMR (101 MHz, D₂O): δ 29.77 (SCH₂), 69.32 (NCH), 121.99, 125.76, 126.34, 128.05, 129.14, 129.23, 129.32, 129.45, 133.91, 134.12, 136.95, 149.62, 150.31.

Anal. Calcd for C₁₇H₁₄ClNS: C 68.10, H 4.71, Cl 11.82, N 4.67, S 10.70. Found: C 67.81, H 4.53, Cl 12.01, N 4.48, S 10.48.

7aH,8H,12bH-Indeno[1',2':5,6][1,4]thiazino[2,3,4-ij]quinolin-13-ium chloride (12). A solution of sulfuryl chloride (0.071 g, 0.53 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinolinyl) disulfide (0.169 g, 0.53 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of 1H-indene (0.140 g, 1.06 mmol) in methylene chloride (10 mL) was added dropwise, and the reaction mixture was stirred for 65 h at room temperature. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was washed with cold

hexane and dried in vacuum, giving the product (0.266 g, 80% yield) in the form of a yellow powder, mp 158–160 °C.

$^1\text{H-NMR}$ (400 MHz, D_2O): δ 3.07 (d, $J = 16.8$ Hz, 1H, CH_2), 3.61 (d, $J = 16.8$ Hz, 1H, CH_2), 4.52 (d, $J = 4.2$ Hz, 1H, SCH), 6.71 (s, 1H, NCH), 6.77–6.79 (m, 1H, Ar), 7.13–7.17 (m, 1H, Ar), 7.33–7.36 (m, 1H, Ar), 7.45–7.46 (m, 1H, Ar), 7.68–7.72 (m, 1H, H_{quino}), 7.81–7.83 (m, 1H, H_{quino}), 8.04–8.06 (m, 1H, H_{quino}), 8.19–8.22 (m, 1H, H_{quino}), 9.20–9.22 (m, 1H, H_{quino}), 9.43–9.44 (m, 1H, H_{quino}).

$^{13}\text{C-NMR}$ (101 MHz, D_2O): δ 36.27 (CH_2), 39.61 (SCH), 72.47 (NCH), 121.6, 122.27, 125.14, 126.38, 127.22, 127.33, 129.12, 129.49, 131.04, 132.50, 138.22, 138.68, 138.71, 149.35, 149.81.

Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{NClS}$: C 69.33, H 4.53, N 4.49, Cl 11.37, S 10.28. Found: C 69.46, H 4.68, N 4.63, Cl 11.81, S 10.56.

3-(4-Methylphenyl)-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (13). A solution of sulfonyl chloride (0.097 g, 0.71 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinoliny) disulfide (0.230 g, 0.71 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of 4-methylstyrene (0.168 g, 1.42 mmol) in methylene chloride (10 mL) was added dropwise, and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was dried in vacuum, giving the product (0.445 g, quantitative yield) in the form of a yellow powder, mp 73–75 °C.

$^1\text{H-NMR}$ (400 MHz, D_2O): δ 2.21 (s, 3H, CH_3), 3.67 (dd, $J = 14.2, 3.2$ Hz, 1H, SCH₂), 3.89 (dd, $J = 14.2, 2.4$ Hz, 1H, SCH₂), 6.72 (m, 3H, NCH, Ar), 7.10 (d, $J = 8.0$ Hz, 2H, Ar), 7.84–7.88 (m, 1H, H_{quino}), 7.98–8.00 (m, 1H, H_{quino}), 8.04–8.08 (m, 1H, H_{quino}), 8.19–8.21 (m, 1H, H_{quino}), 9.15–9.16 (m, 1H, H_{quino}), 9.22–9.24 (m, 1H, H_{quino}).

$^{13}\text{C-NMR}$ (101 MHz, D_2O): δ 20.11 (CH_3), 29.67 (SCH₂), 69.05 (NCH), 121.93, 125.57, 125.97, 127.93, 129.38, 129.41, 129.57, 131.37, 133.73, 133.90, 139.64, 149.48, 150.16.

Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{NClS}$: C 68.89, H 5.14, N 4.46, Cl 11.30, S 10.22. Found: C 69.00, H 5.21, N 4.54, Cl 11.56, S 10.68.

3-Methyl-3-phenyl-2H,3H-[1,4]thiazino[2,3,4-ij]quinolin-4-ium chloride (14). A solution of sulfonyl chloride (0.108 g, 0.8 mmol) in methylene chloride (10 mL) was added dropwise to a solution of di(8-quinoliny) disulfide (0.256 g, 0.8 mmol) in methylene chloride (10 mL), and the mixture was stirred for 10 min at room temperature. A solution of α -methylstyrene (0.189 g, 1.6 mmol) in methylene chloride (10 mL) was added dropwise, and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered, and the solvent was removed by rotary evaporator. The residue was washed with cold hexane and dried in vacuum, giving the product (0.436 g, 87% yield) in the form of a yellow oil.

$^1\text{H-NMR}$ (400 MHz, D_2O): δ 1.58 (s, 3H, CH_3), 3.57 (d, $J = 14.6$, 1H, SCH₂), 3.78 (d, $J = 14.6$ 1H, SCH₂), 6.58–6.64 (m, 1H, Ar), 6.66–6.72 (m, 2H, Ar), 7.00–7.05 (m, 2H, Ar), 7.77–7.62 (m, 1H, H_{quino}), 7.98–8.03 (m, 1H, H_{quino}), 8.07–8.13 (m, 1H, H_{quino}), 8.21–8.25 (m, 1H, H_{quino}), 8.90–8.94 (m, 1H, H_{quino}), 9.00–9.04 (m, 1H, H_{quino}).

$^{13}\text{C-NMR}$ (101 MHz, D_2O): δ 28.80 (CH_3), 50.91 (SCH₂), 74.85 (NCH), 122.00, 124.79, 126.84, 127.22, 127.86, 129.28, 129.41, 130.14, 136.99, 141.46, 143.67, 144.20, 148.31.

Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{NClS}$: C 68.89, H 5.14, N 4.46, Cl 11.30, S 10.22. Found: C 69.12, H 4.99, N 4.27, Cl 11.19, S 9.96.

4. Conclusions

A new family of water-soluble [1,4]thiazino[2,3,4-ij]quinolin-4-ium derivatives in 75–100% yields have been developed based on the annulation reactions of 8-quinolinesulfonyl halides with natural products (eugenol, isoeugenol, methyl eugenol, *trans*-anethole) and alkenes (1-hexene, 1-heptene, styrene, 4-methylstyrene, α -methylstyrene and 1H-indene).

The annulation reactions of 8-quinolinesulfonyl halides with styrene derivatives, which contain the double bond in conjugation with the benzene ring, and terminal alkenes including allyl arenes proceed in a regioselective fashion but with the opposite regiochemistry. The annulation reactions with styrene derivatives occur with the attachment of the sulfur atom of the 8-quinolinesulfonyl electrophile at the β -position of the vinyl

group, whereas the opposite regiochemistry is observed in the case of terminal alkenes and allyl arenes.

The formation of possible intermediates in the annulation reactions of 8-quinolinesulfonyl halides with styrene derivatives and terminal alkenes including allyl arenes has been discussed. Three-membered thiiranium cations are assumed as intermediates in the reactions of 8-quinolinesulfonyl halides with terminal alkenes and allyl arenes. Nucleophilic attack of the nitrogen atom of the quinoline ring occurs at the unsubstituted carbon atom of thiiranium intermediates due to the steric factor. Linear carbocations are regarded as intermediates in the reactions with styrene derivatives. In this case, linear carbocations are energetically favorable due to their stabilization by the benzene ring.

Based on the evaluation of antimicrobial activity of novel water-soluble compounds against bacteria *Enterococcus durans*, *Bacillus subtilis* and *Escherichia coli*, the compounds with high activity have been found. A number of the obtained compounds are superior in their activity compared to the antibiotic gentamicin.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/app11188532/s1>, examples of ¹H- and ¹³C-NMR spectra of the obtained compounds.

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