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# Zinc Tetrafluoroborate-Mediated Ring Expansion of *trans*-Aziridine-2-carboxylates to *cis*-2-Iminothiazolidines and *cis*-Thiazolidine-2-iminium Tetrafluoroborates and Evaluation of Antimicrobial Activity

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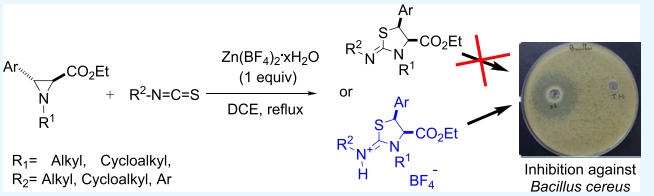
**ABSTRACT:** *Cis*-2-iminothiazolidines and *cis*-thiazolidine-2-iminium tetrafluoroborates were successfully produced from *trans*-*N*-alkyl aziridine-2-carboxylates and phenyl/alkyl isothiocyanates mediated by zinc tetrafluoroborate in refluxing DCE. Reactions were performed via a complete regio- and stereoselective process to give the title iminothiazolidines and *cis*-thiazolidine-2-iminium salts in moderate to good yields (35 to 82%) with a wide substrate scope. In addition, the antibacterial activity evaluation of these compounds, as well as the minimum inhibitory concentration (MIC) determination, revealed that only four *cis*-thiazolidine-2-iminium salts showed growth inhibition against *Bacillus cereus*.




## INTRODUCTION

Iminothiazolidines are an interesting class of molecules, which have been widely studied due to their diverse fields of application. Indeed, a large number of these five-membered heterocyclic systems play an important role in medicinal chemistry and exhibit significant physiological activities.[1] They are used as anti-inflammatory,[2] antihypertensive,[3] anti-Alzheimer,[4] and antidepressant agents.[5] They serve as progesterone receptor-binding agents[6] and act as nitric oxide synthase (NOS) inhibitors.[7] Some of them find applications as $\gamma$-radioprotective agents,[8] and others are used in agriculture as pesticides.[9] Moreover, tetramisole, a bicyclic iminothiazolidine, was found to be a competent enantioselective acylation catalyst.[10] These heterocycles are also useful intermediates in the synthesis of compounds such as iminothiazolines, possessing a wide range of biological and pharmaceutical activities.[11]

Due to the wide variety of their applications, several strategies have been developed for the synthesis of iminothiazolidines. For instance, the synthesis of these five-membered aza-heterocycles are reported from the rhodium-catalyzed reaction of thiazolidine with carbodiimides,[12] reaction integrating an iron-catalyzed nitrene transfer and domino ring-opening cyclization,[13] $BF_2OTf{\cdot}OEt_2$-catalyzed ring expansion of phenylthiranes with arylcarbodiimides,[14] a base-mediated [3 + 2] annulation involving substituted thioureas and allylic bromides,[15] and by the ring transformation of 2-(thiocyanomethyl)aziridines upon treatment with titanium(IV) chloride[11] or using a silica−water system and potassium thiocyanates.[16]

On the other hand, one of the classical methods for the synthesis of iminothiazolidines involves the reaction of aziridines and isothiocyanates. This reaction has been studied using $ZnCl_2$-, $BF_3{\cdot}OEt_2$-, $FeCl_3$-, Al(salen)Cl-, pyrrolidine-, $Bu_3P$-, and Pd(II)-based systems as catalysts or stoichiometric reagents.[17] Although a variety of strategies leading to C4 or C5 monosubstituted 2-iminothiazolidines have been developed, compounds obtained from nonactivated aziridines possessing 4,5-two vicinal stereogenic centers have rarely been reported.[18]

## RESULTS AND DISCUSSION

**Chemistry.** In a previous publication, we described the ring expansion of *trans*-aziridine-2-carboxylates into *trans*-imidazolidine-2-thiones as the major products in the absence of a catalyst, via a complete regio- and stereoselective process (Scheme 1a).[19] Herein, we show that in the presence of a Lewis acid, the behavior of aziridine-2-carboxylates and isothiocyanates is different. In fact, utilizing zinc tetrafluoroborate as a mediator in these reactions leads exclusively to *cis*-2-iminothiazolidines or *cis*-thiazolidine-2-iminium tetrafluoroborates (Scheme 1b).

In order to explore the optimum reaction conditions, we chose the reaction of phenyl isothiocyanate with *trans*-*N*-

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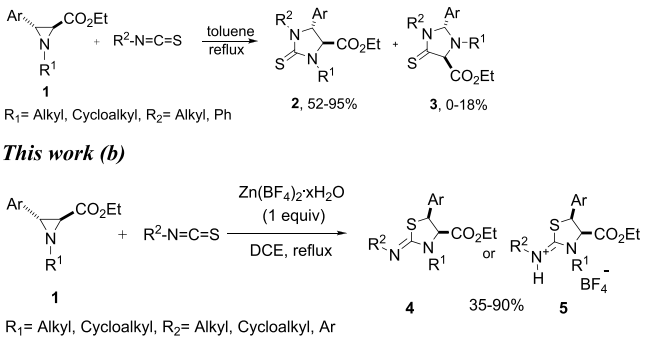
**Scheme 1. Ring Expansion of *trans*-*N*-alkyl Aziridine-2-carboxylates with Isothiocyanates in Our Previous Work (a) and This Work (b)**

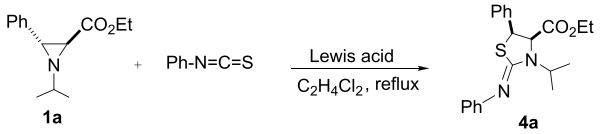



isopropylaziridine-2-carboxylate **1a** as the model substrate. Several metal halides were tested, and few of them were able to catalyze this reaction with varying degrees of success. When aziridine and isothiocyanate were mixed in the presence of a catalyst (0.1 equiv), there was no reaction at room temperature in all cases with the recovery of starting materials. Under the reflux of DCE, Lewis acids $ZnCl_2$, $BF_3{\cdot}OEt_2$, and $Cu(OTf)_2$ did not catalyze the reaction at all, with the formation of a complex mixture of unknown compounds. However, $Zn(BF_4)_2{\cdot}xH_2O$ gave 25% of 2-iminothiazolidinones **4a** under the same conditions. Catalysts $ZnBr_2$, $Cu(CF_3SO_3)_2$, and $Cu(BF_4)_2{\cdot}xH_2O$ also led to this transformation but with a lower activity. On the basis of the obtained results, $Zn(BF_4)_2{\cdot}xH_2O$ was found to be the most effective catalyst. Switching the solvent from DCE to toluene or nitromethane using this catalyst did not improve the yield of product **4a**. Increasing the amount of $Zn(BF_4)_2{\cdot}xH_2O$ from 0.1 to 0.5 equiv hardly improved the reaction yield. When larger amounts of $Cu(BF_4)_2{\cdot}xH_2O$ (1 equiv) or $Zn(BF_4)_2{\cdot}xH_2O$ (1 equiv) were used, the reaction afforded the desired *cis*-2-iminothiazolidinone **4a** in good to excellent yields, respectively. This is consistent with the results of Stoltz and co-workers who showed that a stoichiometric amount of Lewis acid is required to allow the full conversion of the starting products in cycloaddition reactions with heterocumulenes.[17a,h] It is important to note that several reactions have been described in which zinc tetrafluoroborate proved to be a suitable catalyst for various useful transformations and that a better catalytic activity of $Zn(BF_4)_2{\cdot}xH_2O$ compared to other Lewis acids was mentioned in the works of Chakraborti and co-workers[20] and Majee and co-workers.[21]

The results obtained are listed in Table 1.

As can be seen from Table 1, there is a clear superiority of $Zn(BF_4)_2{\cdot}xH_2O$ which proved to be the most effective Lewis acid used for this reaction. The cyclic structure of **4a** was established by IR and 1D NMR techniques. The presence of the C═NR group was confirmed by the appearance of a strong band at approximately 1630 $cm^{-1}$ in the IR spectrum and by a $^{13}C$ NMR resonance signal for the same group at 157.98 ppm, and no C═S signal was observed in our case. The *cis*-stereochemistry of **4a** was unambiguously confirmed from the coupling constant between the C4 and C5 protons, with $J_{cis}$ values of ∼7.9 Hz ($J_{trans}$ = 3−4 Hz), which is in agreement with those reported in the literature for *cis*-iminothiazolidine.[17b]

**Table 1. Optimization of Reaction Conditions**




| entry | Lewis acid (*x* equiv) | solvent | *t* (h) | yield (%) 2a | yield (%) 3a | yield (%) 4a |
|---|---|---|---|---|---|---|
| 1 | $ZnBr_2$ (0.1) | DCE | 2 | – | – | 13 |
| 2 | $ZnCl_2$ (0.1) | DCE | 2 | – | – | – |
| 3 | $BF_3{\cdot}OEt_2$ (0.1) | DCE | 2 | – | – | – |
| 4 | $Cu(OTf)_2$ (0.1) | DCE | 2 | – | – | – |
| 5 | $Cu(CF_3SO_3)_2$ (0.1) | DCE | 4 | – | – | 12 |
| 6 | $Zn(BF_4)_2{\cdot}xH_2O$ (0.1) | DCE | 3 | – | – | 25 |
| 7 | $Zn(BF_4)_2{\cdot}xH_2O$ (0.5) | DCE | 3 | – | – | 43 |
| 8 | $Zn(BF_4)_2{\cdot}xH_2O$ (0.1) | Toluene | 3 | 20 | 20 | trace |
| 9 | $Zn(BF_4)_2{\cdot}xH_2O$ (0.1) | $CH_3NO_2$ | 3 | – | – | trace |
| 10 | $Cu(BF_4)_2{\cdot}xH_2O$ (1) | DCE | 3 | – | – | 60 |
| 11 | $Zn(BF_4)_2{\cdot}xH_2O$ (1) | DCE | 3 | – | – | 90 |

Attempts to obtain crystals of iminothiazolidine **4a** were unsuccessful. Instead, we recovered traces of a secondary product in one of the **4a** tests, and crystals suitable for X-ray diffraction studies were obtained. However, the determination of the crystalline structure revealed that this product corresponds to a tetrafluoroborate of thiazolidine-2-iminium **4a'** with a *cis*-stereochemistry around the C═N bond (Figure 1). This very interesting result may indirectly confirm the

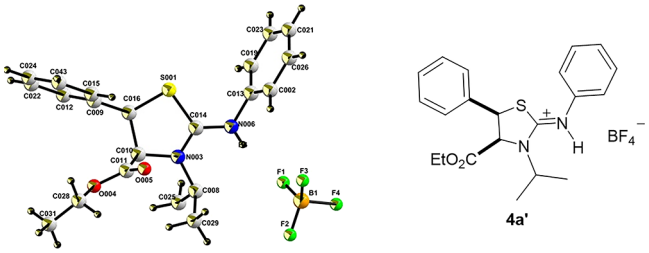



**Figure 1.** ORTEP view of compound **4a'** (**CCDC***N*° 2189951).

structure of compound **4a** and its *cis*-stereochemistry, which was further evidenced by the conversion of **4a'** to **4a** under basic conditions ($K_2CO_3$).

With the optimized reaction conditions in hand, we next evaluated the generality and scope of the methodology for the synthesis of *cis*-iminothiazolidines **4** via the cycloaddition of *N*-alkyl aziridine-2-carboxylates and *N*-aryl isocyanates mediated by zinc tetrafluoroborate (Table 2).

The results reported in Table 2 showed that good yields are always obtained (65−90%), except for **4i** (Ar = p-$MeOC_6H_4$) where the reaction proved unsuccessful, affording trace amounts of the desired product. In contrast, aziridine reactivity is not affected by the electronic influence of some aromatic substituents such as $NO_2$, $CH_3$ and Cl. In the case of **1l**, the reaction gave the expected product in a low yield (35%). This reflects the steric effect of the benzyl group in *N*-alkyl aziridine on the reaction outcome.

The successful ring-expansion reactions of *trans*-*N*-alkyl aziridine-2-carboxylates in the presence of *N*-aryl isothiocyanates inspired us to further examine the electronic effects on the reaction when the isothiocyanate aryl group was replaced with an alkyl or cycloalkyl group. Surprisingly, in contrast to


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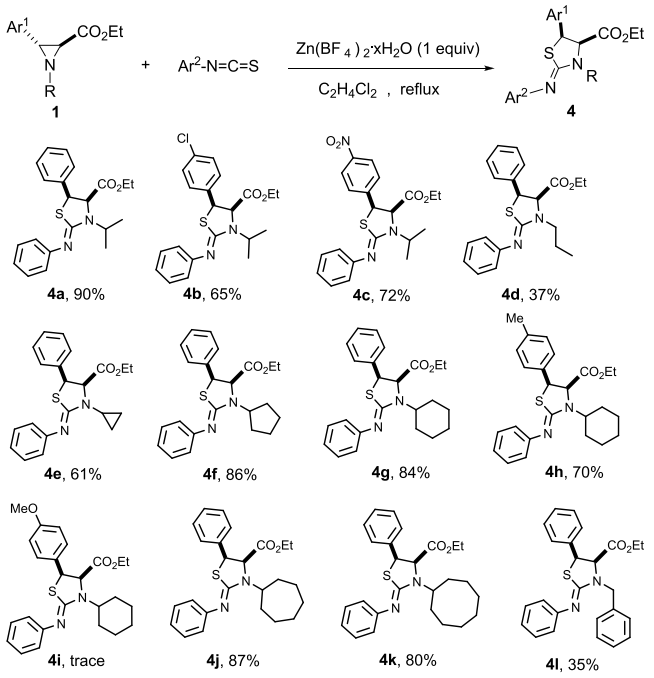
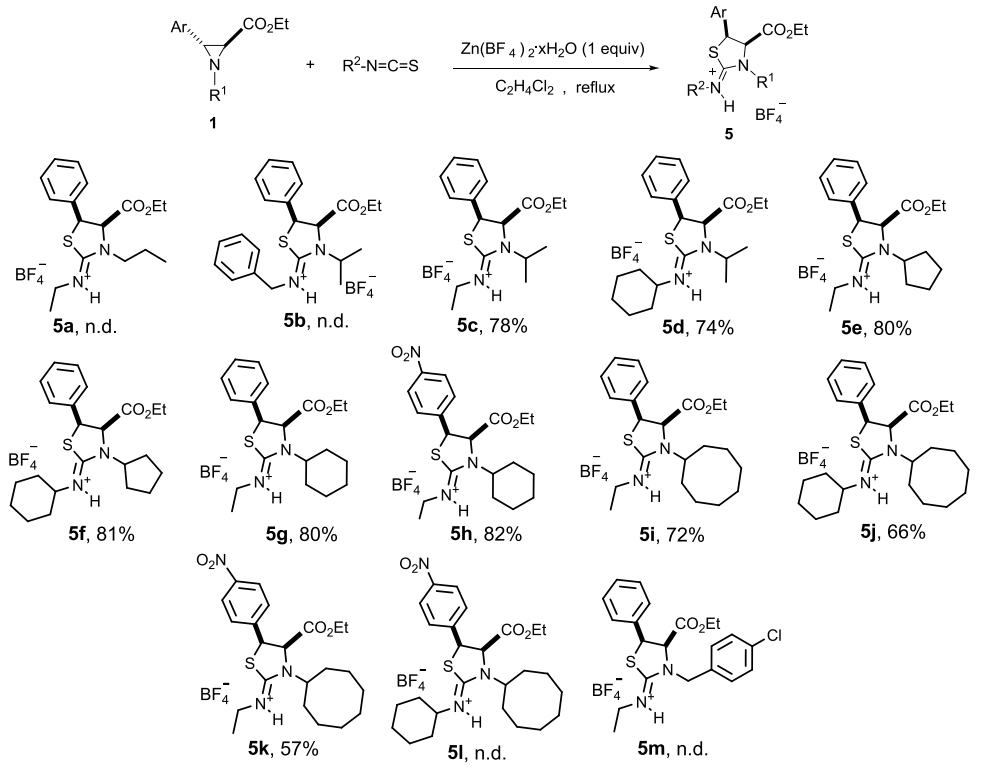
**Table 2. Scope of the Reaction of *trans*-*N*-alkyl Aziridine-2-carboxylates with *N*-aryl Isothiocyanates**




the *N*-aryl-substituted isothiocyanates, *N*-ethyl and *N*-cyclohexyl isothiocyanates reacted with *N*-alkyl aziridines **1** under the same reaction conditions to yield *cis*-thiazolidine-2-iminium tetrafluoroborates **5** as the sole products. This unexpected result was achieved in all cases (Table 3).

As shown in Table 3, when reactions were carried out in the presence of zinc tetrafluoroborate (1 equiv) and under identical conditions, they proceeded selectively to give the unexpected thiazolidine-2-iminium salts as the sole reaction products (**5c**−**5k**) in good yields (57−81%). However, when the substituent ($R^1$) on the aziridine skeleton was a primary carbon, the reaction proved unsuccessful (**5a** and **5m**). The reaction also failed for **5b** ($R^2$ = benzyl group) and **5l** ($R^1$ = *c*-$C_8H_{15}$, $R^2$ = $C_6H_{11}$, and Ar = *p*-$NO_2$−$C_6H_4$). This clearly shows the steric effect of the substituents on the reaction outcome. On the basis of our experimental results, a plausible mechanism for the formation of compounds **4** and **5** from *trans*-aziridine **1** is proposed (Scheme 2), which would involve coordination of the aziridine nitrogen with the central metal cation of the Lewis acid. This induces polarization of the aziridine C−C bond, increases the electrophilicity at these two carbons, and facilitates a regio- and stereospecific nucleophilic ring opening by the sulfur atom of the isothiocyanate at the electrophilic benzylic position, with an inversion of configuration. This attack is followed by a spontaneous intramolecular cyclization with the nitrogen atom, leading to the formation of *cis*-iminothiazolidines **4**.[14,17b,c,22] When the *N*-substituent of isothiocyanate was ethyl or cyclohexyl, thiazolidine-2-iminium tetrafluoroborate **5** is formed. Furthermore, despite the presence of two reactive sites (C═N) and (C═S) in the isothiocyanates, which in turn can be coordinated with a Lewis acid, it is obvious that the reaction occurs chemoselectively to provide compounds **4** or **5** as the sole products. The strong Lewis acid property of $Zn(BF_4)_2$·$xH_2O$, which led to the formation of a complex with the resulting iminothiazolidine, may explain the amount (1 equiv) of Lewis acid used in this reaction. Purification on a

**Table 3. Scope of the Reaction of *trans*-*N*-alkyl Aziridine-2-carboxylates with *N*-alkyl/Cycloalkyl Isothiocyanates[a,b]**




[a]Isolated yields. [b]n.d., not detected.



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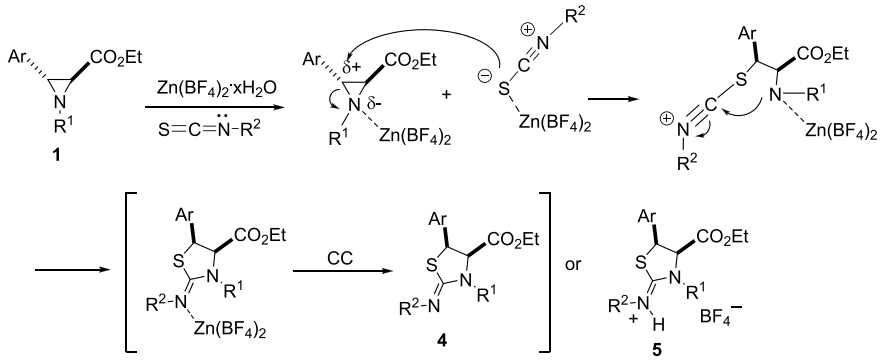
**Scheme 2. Proposed Mechanism for the Formation of *cis*-Iminothiazolidines 4 and *cis*-Thiazolidine-2-iminium Tetrafluoroborates 5**




chromatography column (CC) is needed to release iminothiazolidines **4**. Similar stereoselective Lewis acid-mediated (3 + 2) cycloaddition reactions were suggested by Stoltz[17a,23] in his works on the synthesis of *cis*-iminothiazolidines and thioimidates.

It is worth noting that we have already shown in a previous work[19] that when the reaction is conducted in the absence of a Lewis acid, the aziridine nitrogen atom, uncoordinated in this case, attacks the electrophilic carbon of the isothiocyanate to give a zwitterion as the key intermediate. This undergoes regiospecific C−N bond cleavage to give a linear zwitterionic intermediate, which cyclizes to imidazolidine-2-thione involving the attack of the highly nucleophilic nitrogen anion onto the benzylic position.

**Biological Activity.** Since the 1970s until the present, many pathogens have been reported to be resistant to a wide range of antibiotics,[24] especially because bacteria are known to persist in structured biofilms and rarely in cultures of single species.[25] In such conditions, they can intercommunicate, exchange genetic elements, and become more resistant. Consequently, in a review sponsored by the UK Department of Health and commissioned in 2014 by the UK Prime Minister, it was reported that the number of deaths attributable to global antibiotic resistance will increase from the current 700,000 annual deaths to 10 million per year until 2050.[24] Therefore, there is an urgent need to gather multiple disciplines in a one-health approach for the development of new antibiotics or new solutions that are capable of inactivating resistant microorganisms.

An ideal antibiotic is more effective if it is taken up in its target cell. However, diffusion of the antibiotic into the bacterial cytosol is limited by the membrane barriers of the bacterial cell. The negative charge of the teichoic acid residues of the cell wall of Gram-positive bacteria makes them the binding sites for positively charged molecules.[26] Unlike Gram-positive bacteria, Gram-negative bacteria, due to the membrane barrier, are less susceptible to uptake anionic and neutral molecules.[27]

Motivated by our finding of zinc tetrafluoroborate as a Lewis acid as an effective mediator for the reaction of aziridine-2-carboxylates and isothiocyanates leading exclusively to *cis*-2-iminothiazolidines or *cis*-thiazolidine-2-iminium tetrafluoroborates, these results prompted us to study the in vitro antibacterial activities of neutral iminothiazolidines **4** and positively charged thiazolidin-2-iminium tetrafluoroborates **5** against eight Gram-positive and Gram-negative bacterial strains, as detailed in the experimental section. The well diffusion test was used for the preliminary biological activity evaluation of 13 iminothiazolidines **4a**, **4f**, **4g**, and **4j** and thiazolidin-2-iminium tetrafluoroborates **5c−k**. Among these compounds, **5c** ($R^1$ = isopropyl), **5e** ($R^1$ = cyclopentyl), **5g** ($R^1$ = cyclohexyl), and **5i** ($R^1$ = cyclooctyl) showed good inhibition against *Bacillus cereus*.

Note that most molecules carrying a substituent ($R^2$ = ethyl) on the exocyclic nitrogen atom possess antibacterial activity, except for **5k** where the phenyl group at position 5 is substituted by an $NO_2$ group. Compounds **4** and **5** with a phenyl or cyclohexyl group on their endocyclic nitrogen atom are inactive and have no growth-inhibitory effects against all of the bacteria studied. On the other hand, **5c**, **5e**, **5g**, and **5i**, which have exhibited antibacterial activity, were also characterized by their minimal inhibitory concentration (MIC) values, and the results showed that these compounds inhibited *B. cereus* at MIC values ranging from 1.25 to 10 mg/mL (Figure 2). Additionally, thiazolidin-2-iminium tetrafluoroborate **5i**, substituted with a cyclooctyl group at the endocyclic *N*-position, has lower MICs than other thiazolidin-2-iminium tetrafluoroborate salts.

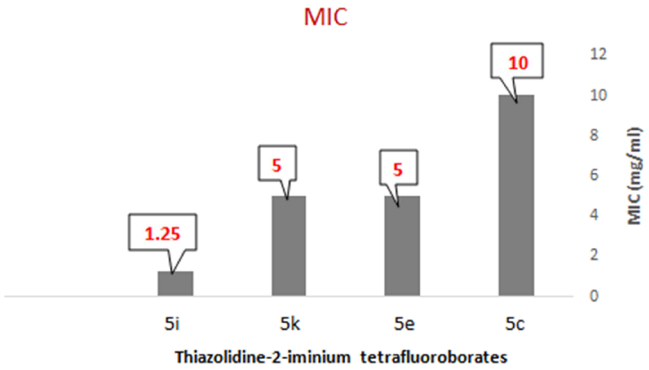



**Figure 2.** Minimum inhibitory concentration (MIC) of the active thiazolidine-2-iminium tetrafluoroborate compounds against *B. cereus*.

## CONCLUSIONS

In this study, we described the first and general method for the synthesis of new iminothiazolidines **4** and thiazolidine-2-iminium tetrafluoroborates **5** from the reaction of nonactivated aziridine-2-carboxylates with phenyl/alkyl(cycloalkyl) isothiocyanates mediated by zinc tetrafluoroborate. Our approach showed considerable efficiency compared to the previously established methods, as reactions with nonactivated trisub-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stituted aziridines gave very few examples for the desired iminothiazolidines. The assay to evaluate some of the synthesized compounds **4** and **5** with different substituents on both the endocyclic and exocyclic nitrogen atoms against eight Gram-positive and Gram-negative bacterial strains allowed us to identify four thiazolidine-2-iminium tetrafluoroborates (**5c**, **5e**, **5g**, and **5i**), which were found to be the most active derivatives against *B. cereus*. The thiazolidine-2-iminium tetrafluoroborate system also appears to be promising for other biological activities, including antiviral potential. Further research to explore Lewis acid-mediated reactions of nonactivated aziridines with other heterocumulenes will be carried out in the future.

## EXPERIMENTAL SECTION

**Chemistry.** *General Information.* All commercial products and reagents were used as purchased without further purification. Analytical thin-layer chromatography (TLC) of all reactions was performed on silica gel 60 F254 TLC plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm). Flash chromatography was carried out on silica gel 60 Å (0.063−0.2 mm). FT-IR spectra were recorded with a PerkinElmer Spectrum 1000; absorption values are given in wavenumbers ($cm^{-1}$). $^1H$ (300 MHz), $^{13}C$ (75 MHz), and NMR spectra were recorded with a Bruker AV 300 spectrometer in $CDCl_3$ as the solvent and TMS as the internal standard. $^{13}C$ chemical shifts are reported in parts per million relative to the central line of the triplet at 77.16 ppm for d-chloroform. Copies of $^1H$ and $^{13}C$ NMR spectra are provided in the Supporting Information. High-resolution mass spectra were obtained using an Autoflex III system (Bruker) with electron impact (EI) ionization methods.

*General Procedure for the Synthesis of cis-2-Iminothiazolidines **4(a−l)** and Thiazolidin-2-iminium Tetrafluoroborate **5(c−k)**.* To a mixture of *trans-N*-alkyl aziridine-2-carboxylate 1 (1.3 mmol) and isothiocyanate (1.45 mmol) in dry DCE (7 mL) was added $Zn(BF_4)_2{\cdot}xH_2O$ (1.3 mmol), and the mixture was stirred at reflux under nitrogen for 2−4 h. After the completion of the reaction (monitored by TLC), the reaction mixture was concentrated in a vacuum. The crude product was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 70/30) to give *cis*-2-iminothiazolidines **4** or thiazolidine-2-iminium tetrafluoroborates **5** as white solids.

*cis-4-Ethoxycarbonyl-3-isopropyl-N,5-diphenylthiazolidin-2-imine (**4a**).* White solid (430 mg, 90% yield); mp 106−107 °C; IR ($\nu$ $cm^{-1}$): 1719; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.84 (t, 3H, $J$ = 7.1 Hz), 1.11 (d, 3H, $J$ = 6.8 Hz), 1.25 (d, 3H, $J$ = 6.7 Hz), 3.56−3.85 (m, 2H), 4.46 (d, 1H, $J$ = 7.9 Hz), 4.67 (heptet, 1H, $J$ = 6.8 Hz), 5.05 (d, 1H, $J$ = 7.9 Hz), 6.97−7.34 (m, 10H); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 12.6, 18.7, 19.7, 46.4, 49.8, 60.1, 64.0, 121.2, 122.3, 127.5, 127.8, 132.6, 150.6, 157.0, 168.8; HRMS (ESI) $m/z$: $[M + H]^+$calcd for $C_{21}H_{25}N_2O_2S$ 369.1631; found 369.1633.

*cis-4-Ethoxycarbonyl-3-isopropyl-N-phenyl-5-parachlorophenylthiazolidin-2-imine (**4b**).* White solid (340 mg, 65% yield); mp 127−128 °C; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.97 (t, 3H, $J$ = 7.2 Hz), 1.17 (d, 3H, $J$ = 6.8 Hz), 1.31 (d, 3H, $J$ = 6.8 Hz), 3.69−3.96 (m, 2H), 4.50 (d, 1H, $J$ = 7.9 Hz), 4.62−4.75 (heptet, 1H, $J$ = 6.8 Hz), 5.07 (d, 1H, $J$ = 7.9 Hz), 7.01−7.07 (m, 3H), 7.26−7.35 (m, 7H); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 13.7, 19.6, 20.7, 47.4, 50.0, 61.2, 65.0, 122.0, 123.3, 128.7, 128.9, 129.0, 132.5, 134.7, 152.1, 157.0, 169.8; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{21}H_{24}ClN_2O_2S$ 403.1242; found 403.1246.

*cis-4-Ethoxycarbonyl-3-isopropyl-N-phenyl-5-paranitrophenylthiazolidin-2-imine (**4c**).* White solid (386 mg, 72% yield); mp 136−137 °C; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.97 (t, 3H, $J$ = 7.2 Hz), 1.19 (d, 3H, $J$ = 6.8 Hz), 1.34 (d, 3H, $J$ = 6.8 Hz), 3.67−3.97 (m, 2H), 4.59 (d, 1H, $J$ = 7.9 Hz), 4.63−4.73 (heptet, 1H, $J$ = 6.8 Hz), 5.17 (d, 1H, $J$ = 7.9 Hz), 7.01−7.09 (m, 3H), 7.28−7.33 (m, 2H), 7.60 and 8.14 (2d, 4H, $J$ = 8.7 Hz); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 13.7, 19.6, 20.7, 47.7, 49.8, 61.4, 64.7, 122.9, 123.4, 123.6, 128.9, 129.8, 141.6, 148.1, 151.9, 156.3, 169.5; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{21}H_{24}N_3O_4S$ 414.1482; found 414.1480.

*cis-4-Ethoxycarbonyl-3-n-propyl-N,5-diphenylthiazolidin-2-imine (**4d**).* White solid (177 mg, 37% yield); mp 86−87 °C; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.90 (t, 3H, $J$ = 7.2 Hz), 0.98 (t, 3H, $J$ = 7.4 Hz), 1.63−1.75 (m, 2H), 2.98−3.07 (m, 1H), 3.68−3.99 (m, 3H), 4.56 (d, 1H, $J$ = 8.1 Hz), 5.11 (d, 1H, $J$ = 8.1 Hz), 7.01−7.40 (m, 10H); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 11.5, 20.7, 29.7, 47.8, 49.5, 61.2, 68.7, 122.0, 123.2, 128.4, 128.5, 128.7, 128.9, 134.9, 152.1, 158.4, 168.5; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_2S$ 369.1631; found 369.1625.

*cis-4-Ethoxycarbonyl-3-cyclopropyl-N,5-diphenylthiazolidin-2-imine (**4e**).* White solid (290 mg, 61% yield); mp 106−107 °C; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.57−0.73 (m, 2H), 0.90 (t, 3H, $J$ = 7.2 Hz), 0.94−1.08 (m, 2H), 2.71 (quintet, 1H, $J$ = 3.8 Hz), 3.71−3.97 (m, 2H); 4.44 (d, 1H, $J$ = 7.9 Hz); 5.10 (d, 1H, $J$ = 7.9 Hz); 7.03−7.39 (m, 10H); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$):$\delta$ 5.7, 8.7, 13.7, 28.0, 49.7, 61.1, 70.2, 122.0, 123.4, 128.4, 128.5, 128.7, 128.8, 134.0, 152.2, 159.4, 168.5; HRMS (ESI) $m/z$: $[M + H]^+$calcd for $C_{21}H_{23}N_2O_2S$ 367.1475; found 367.1470.

*Cis-4-Ethoxycarbonyl-3-cyclopentyl-N,5-diphenylthiazolidin-2-imine (**4f**).* Yield (440 mg, 86% yield); white solid; mp 109−110; $^1H$ NMR (300 MHz $CDCl_3$) $\delta$ 0.82 (t, 3H, $J$ = 7.2 Hz), 1.37−2.18 (m, 2H), 3.54−3.85 (m, 2H), 4.47 (d, 1H, $J$ = 7.9 Hz), 4.56 (m, 1H), 5.09 (d, 1H, $J$ = 7.9 Hz), 6.96−7.34 (m, 10H); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$) $\delta$ 13.6, 22.8, 23.5, 29.3, 30.0, 50.6, 57.8, 61.1, 66.5, 122.2, 123.4, 128.3,128.5, 128.7, 128.8, 133.6, 151.6, 158.7,169.5; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{23}H_{27}N_2O_2S$ $(MH)^+$: 395.1788; found 395.1790.

*cis-4-Ethoxycarbonyl-3-cyclohexyl-N,5-diphenylthiazolidin-2-imine (**4g**).* White solid (445 mg, 84% yield); mp 114−115 °C; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.82 (t, 3H, $J$ = 7.2 Hz), 1.00−1.99 (m, 10H), 3.55−3.85 (m, 2H), 4.30 (m, 1H), 4.47 (d, 1H, $J$ = 7.9 Hz), 5.04 (d, 1H, $J$ = 7.9 Hz), 6.96−7.33 (m, 10H), $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 13.6, 25.6, 25.8, 30.4, 31.2, 51.0, 55.2, 61.0, 65.4, 122.3, 123.3, 128.5, 128.5, 128.7, 128.8, 133.5, 151.7, 158.1, 169.9; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{24}H_{29}N_2O_2S$ 409.1944; found 409.1942.

*cis-4-Ethoxycarbonyl-3-cyclohexyl-N-phenyl-5-paramethylphenylthiazolidin-2-imine (**4h**).* White solid (384 mg, 70% yield); mp 186−187 °C; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.97 (t, 3H, $J$ = 7.2 Hz), 1.19 (d, 3H, $J$ = 6.8 Hz), 1.34 (d, 3H, $J$ = 6.8 Hz), 3.67−3.97 (m, 2H), 4.59 (d, 1H, $J$ = 7.9 Hz), 4.63−4.73 (quintet, 1H, $J$ = 6.8 Hz), 5.17 (d, 1H, $J$ = 7.9 Hz), 7.01−7.09 (m, 3H), 7.28−7.33 (m, 2H), 7.60 and 8.14 (2d, 4H, $J$ = 8.7 Hz); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 13.76, 21.8, 25.7, 25.8, 25.9, 30.4, 31.2, 50.7, 55.0, 61.0, 65.4, 122.2, 123.0, 128.4, 128.8, 129.1, 130.5, 138.5, 152.3, 157.7, 170.1;


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HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_2S$ 423.2101; found 423.2106.

*cis-4-Ethoxycarbonyl-3-cycloheptyl-N,5-diphenylthiazolidin-2-imine (**4j**)*. White solid (477 mg, 87% yield); mp 118−119 °C; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.90 (t, 3H, $J$ = 7.2 Hz), 1.41−1.77 (m, 10H), 2.00−2.08 (m, 2H), 3.63−3.91 (m, 2H), 4.44 (m,1H), 4.54 (d, 1H, $J$ = 7.9 Hz), 5.08 (d, 1H, $J$ = 7.9 Hz), 7.01−7.39 (m, 10H); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.6, 24.8, 24.9, 27.6, 32.0, 33.7, 51.0, 57.4, 61.0, 65.7, 122.1, 123.0, 128.5, 128.5, 128.6, 128.8, 133.8, 152.3, 157.2, 169.9; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_2S$ 423.2101; found 423.2103.

*cis-4-Ethoxycarbonyl-3-cyclooctyl-N,5-diphenylthiazolidin-2-imine (**4k**)*. White solid (453 mg, 80% yield); mp 120−121 °C; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.90 (t, 3H, $J$ = 7.2 Hz), 1.39−2.01 (m, 10H), 3.63−3.91 (m, 2H), 4.42−4.51 (m,1H), 4.55 (d, 1H, $J$ = 7.9 Hz), 5.09 (d, 1H, $J$ = 7.9 Hz), 7.01−7.40 (m, 10H); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.6, 24.7, 25.1, 25.8, 26.7, 27.0, 30.5, 31.7, 51.0, 56.4, 61.0, 66.1, 122.1, 123.0, 128.5, 128.6, 128.7, 128.8, 133.9, 152.3, 157.0, 169.9; HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_2S$ 437.2257; found 437.2255.

*cis-4-Ethoxycarbonyl-3-benzyl-N,5-diphenylthiazolidin-2-imine(**4l**)*. White solid (189 mg, 35% yield); mp 75−76 °C; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.85 (t, 3H, $J$ = 7.2 Hz), 3.60−3.89 (m, 2H), 4.06 and 5.49 (AB, 2H, $J$ = 14.9 Hz), 4.33 (d, 1H, $J$ = 8.0 Hz), 5.02 (d, 1H, $J$ = 8.0 Hz), 7.04−7.37 (m, 10H), 7.35 (s, 5H); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.6, 49.3, 49.4, 61.1, 67.5, 122.0, 123.4, 127.7, 128.2, 128.4, 128.5, 128.6, 128.7, 134.8, 136.6, 151.7, 158.6, 168.1. HRMS (ESI) $m/z$: $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2S$ 417.1631; found 417.1639.

*cis-4-Ethoxycarbonyl-3-isopropyl-N-ethyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5c**)*. White solid (411 mg, 78% yield); mp 162−165 °C; IR ($\nu$ cm$^{-1}$): 3277, 2971, 1740, 1617, 1050, 988; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.83 (t, 3H, $J$ = 7.2 Hz), 1.22 (d, 3H, $J$ = 6.6 Hz), 1.43 (d, 3H, $J$ = 6.5 Hz),1.44 (t, 3H, $J$ = 7.3 Hz), 3.54−3.62 (m, 2H), 3.61−3.95 (2m, 2H), 4.37 (heptet, 1H, $J$ = 6.6 Hz), 5.03 (d, 1H, $J$ = 8.3 Hz), 5.82 (d, 1H, $J$ = 8.3 Hz), 7.38−7.51 (m, 5H), $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.4, 14.2, 19.4, 20.4, 44.9, 50.7, 52.1, 62.3, 67.7, 128.7, 129.1, 129.9, 167.1, 170.8. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{17}H_{25}N_2O_2S^+$ 321.1631; found 321.1632.

*cis-4-Ethoxycarbonyl-3-isopropyl-N-cyclohexyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5d**)*. White solid (442 mg, 74% yield); mp 215−216 °C; IR ($\nu$ cm$^{-1}$): 3275, 2922, 1742, 1607, 1063, 995; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.83 (t, 3H, $J$ = 7.2 Hz), 1.20 (d, 3H, $J$ = 6.6 Hz), 1.23−1.37 (m, 3H), 1.42 (d, 3H, $J$ = 6.5 Hz), 1.67−1.85 (m, 5H), 2.06−2.10 (m, 2H), 3.26−3.36 (m, 1H), 3.59−3.94 (2m, 2H), 4.42 (heptet, 1H, $J$ = 6.6 Hz), 5.06 (d, 1H, $J$ = 8.3 Hz), 5.84 (d, 1H, $J$ = 8.3 Hz), 7.37−7.54 (m, 5H), 8.12 (d, 1H, $J$ = 8 Hz); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.4, 19.4, 20.3, 24.5, 25.1, 31.8, 32.1, 50.5, 51.9, 61.6, 62.3, 67.5, 128.7, 129.0, 129.6, 129.8, 167.2, 169.6. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{21}H_{31}N_2O_2S^+$ 375.2100; found 462.2102.

*cis-4-Ethoxycarbonyl-3-cyclopentyl-N-ethyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5e**)*. White solid (450 mg, 80% yield); mp 142−145 °C; IR ($\nu$ cm$^{-1}$): 3275, 2959, 1740, 1617, 1049, 991; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.82 (t, 3H, $J$ = 7.2 Hz), 1.44 (t, 3H, $J$ = 7.2 Hz), 1.51−2.30 (m, 8H), 3.54−3.68 (m, 3H), 3.84−3.95 (m, 1H), 4.29 (quint, 1H, $J$ = 6.6 Hz), 5.04 (d, 1H, $J$ = 8.4 Hz), 5.82 (d, 1H, $J$ = 8.4 Hz), 7.39−7.51 (m, 5H), 8.35 (br, 1H, NH); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.4, 14.2, 22.6, 23.1, 29.3, 30.0, 44.9,51.9, 59.3, 62.4, 69.0, 128.7, 129.1, 129.7, 129.9, 167.0, 171.0. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{19}H_{27}N_2O_2S^+$ 347.1787; found 347.1788.

*cis-4-Ethoxycarbonyl-3-cyclopentyl-N-cyclohexyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5f**)*. White solid (515 mg, 81% yield); mp 192−193 °C; IR ($\nu$ cm$^{-1}$): 3258, 2939, 1743, 1611, 1064, 992; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.82 (t, 3H, $J$ = 7.2 Hz), 1.19−2.33 (m, 18H), 3.22−3.38 (m, 1H), 4.58−3.94 (2m, 2H), 4.29−4.42 (m, 1H), 5.02 (d, 1H, $J$ = 8.4 Hz), 5.80 (d, 1H, $J$ = 8.4 Hz), 7.38−7.51 (m, 5H), 8.12 (d, 1H, $J$ = 8.2 Hz); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.4, 22.5, 23.1, 24.5, 25.1, 29.2, 30.0, 31.8, 32.1, 51.8, 59.1, 61.7, 62.3, 68.8, 128.6, 129.1, 129.7, 129.9, 167.0, 170.0. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{23}H_{33}N_2O_2S^+$ 401.2257; found 401.2259.

*cis-4-Ethoxycarbonyl-3-cyclohexyl-N-ethyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5g**)*. White solid (463 mg, 80% yield); mp 171−173 °C; IR ($\nu$ cm$^{-1}$): 3274, 2928, 1741, 1617, 1055, 992; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.83 (t, 3H, $J$ = 7.2 Hz), 1.02−1.21 (m,2H), 1.44 (t, 3H, $J$ = 7.2 Hz), 1.50−1.98 (m, 8H), 3.51−3.70 (m, 3H), 3.84−4.06 (m, 2H), 5.00 (d, 1H, $J$ = 8.4 Hz), 5.76 (d, 1H, $J$ = 8.4 Hz), 7.38−7.50 (m, 5H), 8.43 (m, 1H); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.3, 14.2, 24.6, 24.8, 24.9, 30.0, 30.8, 44.8, 52.1, 58.0, 62.3, 68.0, 128.6, 129.1, 129.5, 129.9, 167.1, 171.0. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{20}H_{29}N_2O_2S^+$ 361.1944; found 361.1945.

*cis-4-Ethoxycarbonyl-3-cyclohexyl-N-ethyl-5-paranitrophenylthiazolidin-2-iminium Tetrafluoroborate (**5h**)*. White solid (526 mg, 82% yield); mp 175−176 °C; IR ($\nu$ cm$^{-1}$): 3268, 2934, 1742, 1621, 1051, 995; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.89 (t, 3H, $J$ = 7.1 Hz), 1.05−1.25 (m, 2H), 1.46 (t, 3H, $J$ = 7.3 Hz), 1.53−2.11 (m, 8H), 3.58−3.75 (m, 3H), 3.91−4.03 (m, 2H), 5.21 (d, 1H, $J$ = 8.4 Hz), 6.02 (d, 1H, $J$ = 8.4 Hz), 7.79 et 8.25 (2d, 5H, $J$ = 8.8 Hz), 8.44 (brs, 1H); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.5, 14.2, 24.7, 24.8, 29.9, 30.6, 45.0, 50.9, 58.3, 62.6, 67.8, 124.0, 130.1, 137.2, 148.6, 167.0, 170.1. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{20}H_{28}N_3O_4S^+$ 406.1795; found 406.1797

*cis-4-Ethoxycarbonyl-3-cyclooctyl-N-ethyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5i**)*. White solid (444 mg, 72% yield); mp 156−157; IR ($\nu$ cm$^{-1}$): 3268, 2927, 1744, 1617, 1053, 992; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.84 (t, 3H, $J$ = 7.1 Hz), 1.44 (t, 3H, $J$ = 7.2 Hz), 1.52−2.01 (m, 14H), 3.54−3.70 (m, 3H), 3.85−3.96 (m, 1H), 4.05−4.20 (m, 1H), 5.00 (d, 1H, $J$ = 8.2 Hz), 5.76 (d, 1H, $J$ = 8.1 Hz), 7.38−7.51 (m, 5H), 8.40 (brs, 1H); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$) $\delta$ 13.4, 14.2, 23.3, 24.3, 24.8, 26.3, 27.1, 29.7, 30.4, 44.9, 52.4, 60.3, 62.3,69.1, 128.6, 129.1, 129.5, 167.0, 170.4. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{22}H_{33}N_2O_2S^+$ 389.2257; found 389.2261.

*cis-4-Ethoxycarbonyl-3-cyclooctyl-N-cyclohexyl-5-phenylthiazolidin-2-iminium Tetrafluoroborate (**5j**)*. White solid (454 mg, 66% yield); mp 186−187 °C; IR ($\nu$ cm$^{-1}$): 3251, 2930, 1741, 1608, 1065, 976; $^1$H NMR (300 MHz $CDCl_3$): $\delta$ 0.85 (t, 3H, $J$ = 7.1 Hz), 1.26−2.08 (m, 24H), 3.22−3.40 (m, 1H), 3.61−3.97 (2m, 2H), 4.20−4.34 (m, 1H), 4.93 (d, 1H, $J$ = 8.1 Hz), 5.65 (d, 1H, $J$ = 8.1 Hz), 7.39−7.48 (m, 5H), 8.33 (d, 1H, $J$ = 8.2 Hz); $^{13}$C{$^1$H} NMR (75 MHz $CDCl_3$): $\delta$ 13.4, 23.1, 24.0, 24.4, 24.6, 25.2, 26.5, 27.5, 29.4, 30.4, 31.7, 32.0, 52.5, 59.9, 62.0,62.4, 68.8, 128.5, 129.2, 129.4, 130.0, 167.0,


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169.1. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{26}H_{39}N_2O_2S^+$ 443.2726; found 443.2732.

*cis-4-Ethoxycarbonyl-3-cyclooctyl-N-ethyl-5-paranitrophenylthiazolidin-2-iminium Tetrafluoroborate (**5k**).* White solid (377 mg, 57% yield); mp 158−160 °C; IR ($\nu$ $cm^{-1}$): 3259, 2912, 1741, 1619, 1008; $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 0.90 (t, 3H, $J$ = 7.1 Hz), 1.46 (t, 3H, $J$ = 7.2 Hz), 1.49−2.07 (m, 14H), 3.59−4.02 (2m, 4H), 4.05−4.18 (m, 1H), 5.17 (d, 1H, $J$ = 8.2 Hz), 6.00 (d, 1H, $J$ = 8.1 Hz), 7.79 et 7.24 (2d, 4H, $J$ = 8.8 Hz), 8.39 (brs, 1H); $^{13}C\{^1H\}$ NMR (75 MHz $CDCl_3$): $\delta$ 13.6, 14.3, 23.2, 24.4, 24.7, 26.3, 27.0, 29.6, 30.2, 45.1, 51.1, 60.6, 62.5, 68.8, 124.0, 130.2, 137.3, 148.6, 166.6, 169.9. HRMS (ESI) $m/z$: $[M\text{-}BF_4]^+$ calcd for $C_{22}H_{32}N_3O_2S^+$ 434.2108; found 434.2113.

*Antibacterial Activity Assay.* The *in vitro* antibacterial activities of the synthesized molecules were evaluated with respect to eight microbial strains: four Gram-positive bacteria (*Enterococcus faecalis* ATCC 29212, *Enterococcus faecium* ATCC 19436, *Staphylococcus aureus* ATCC 6538, and *Bacillus cereus* 49) and four Gram-negative bacteria (*Escherichia coli DH5α*, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa*, and *Salmonella* sp). These strains belong to the collection of the American Type Culture Collection (ATCC) and the Laboratory of Microorganisms and Active Biomolecules (LMBA-LR03ES03), University of Tunis El Manar. As a first screening, the antibacterial activities of all molecules (suspended in DMSO solution, 30%) were evaluated by the well diffusion method toward all the bacterial strains. The active molecules were evaluated by a second test for determining their minimal inhibitory concentrations (MICs). These tests were performed as described below. In all tests, the synthesized molecules were suspended in DMSO (30%), which was used as the negative control, and gentamicin was used as the reference antibacterial drug.

*Well Diffusion Method.* Suspensions (5 mL) of molten soft agar (0.75% w/v), inoculated with fresh cultures of the tested strains at a final concentration of $10^6$ CFU/mL, were poured onto the surfaces of tryptone soy agar (TSA) plates. After cooling, wells of 5 mm diameter were created, and their bases were sealed with soft agar. The wells were then filled with solutions of the synthesized molecules. After 24 h of incubation at 30 °C, samples showing growth inhibition halos around the wells were considered as active.

*Minimum Inhibitory Concentration Determination.* The MICs of the active compounds were determined using the microdilution broth method, as recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Stock solutions of the tested compounds in DMSO were serially diluted to final concentrations ranging from $10^4$ to 78.125 $\mu$g/mL in sterile 96-well microtiter plates containing Mueller−Hinton broth (MHB). Fresh culture of the bacterial strain was used at a volume of 100 $\mu$L for each well, after turbidity adjustment to 0.5 McFarland. Growth indicator (G-stain) (100 $\mu$L of 0.1%) was incorporated into each well to assess the bacterial inhibition. The wells containing inoculums alone were used as negative controls, and gentamycin was used as a positive control. All samples were tested in duplicate, and microplates were incubated at 30 °C for 24 h.

MICs were determined by at least 90% reduction in growth (IC90) compared to the control using a Biolog assay (BiologOmnilog Phenotype MicroArray) incubator, which is connected to a programmable computer allowing the tracking of the growth cycle of microorganisms, and displays the result as a growth curve.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03531.

$^1H$ NMR and $^{13}C$ NMR of compounds and X-ray crystallographic data of compound **4a'** (PDF)

Single-crystal X-ray diffraction data for **4a'** (CIF)

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### Notes

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