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SYNTHESIS AND ANTIMICROBIAL ACTIVITY EVALUATION OF NOVEL 4-THIAZOLIDINONES CONTAINING A PYRONE MOIETY

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GRAPHICAL ABSTRACT



Abstract A series of thiosemicarbazones 3a–d and 4-thiazolidinones 5a–d, 7a–d, and 9a–h were synthesized and evaluated for their in vitro antimicrobial activity. Condensation of 3-acetyl-4-hydroxy-6-methyl-2H pyran-2-one1 (dehydroacetic acid) with thiosemicarbazide 2a–d in ethanol at room temperature yielded the thiosemicarbazones 3a–d. These compounds were exploited to synthesize the 4-thiazolidinones 5a–d via their reactions with ethyl 2-bromo propionate4. Derivatives 7a–d were prepared by reaction of the thiosemicarbazones 3a–d with phenyl bromoacetate 6. The 4-thiazolidinones 9a–h were obtained by treatment of compound 3a or 3c with maleimide derivatives 8a–d in refluxing ethanol, under sulfuric acid catalysis. All compounds were screened in vitro for their antibacterial and antifungal activities against five human pathogens microorganisms: Escherichia coli ATCC 25992, Pseudomonas aeruginosa ATCC 27852, Staphylococcus aureus ATCC 43300, Staphylococcus aureus ATCC 25923, and Candida albicans.

Keywords Antimicrobial activity; maleimide; 4-thiazolidinones; thiosemicarbazones

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NOVEL 4-THIAZOLIDINONES

INTRODUCTION

In recent years, 4-thiazolidinones and their derivatives have become among the most extensively investigated compounds. They constitute an important group of heterocyclic compounds, displaying a broad spectrum of biological activity.^[1–3] They have found uses, for example, as antimicrobial^[4–6] and anti-inflammatory drugs^[7–9] and anti-HIV derivatives.^[10–12]

The thiazolidinone ring system belongs to the privileged structure in modern medicinal chemistry, particularly in discovery of new antitumor and anti-angiogenic agents.

A literature survey revealed that many different protocols have been developed in a way that allows the synthesis of 4-thiazolidinone skeletons, and several reactants or heterocyclic compounds have been employed for the preparation of 4-thiazolidinone moiety.^[13,14] The main synthesis routes to 4-thiazolidinones involve three components (an aldehyde, an amine or thiosemicarbazide, and mercaptoacetic acid or halogenoester), either in one- or two-step processes.^[15–20]

We report in this article the syntheses of a new class of structurally novel 4-thiazolidinone derivatives, incorporating two known bioactive heterocyclic nuclei such as pyrone and 4-thiazolidinone, known to be active towards (G^+ and G^-) and yeast. Pyrones and their fused derivatives have attracted a great deal of interest because of their wide range of biological activities.^[21–23] The incorporation of another heterocyclic moiety in pyrone either in the form of a substituent or as a fused component often leads to incredible diverse biological activity.

In this study, new 4-thiazolidinones **5a–d**, **7a–d**, and **9a–h** were synthesized starting from commercially dehydroacetic acid, which possesses three active sites in positions 2, 3, and 4 corresponding to ester, acetyl, and hydroxyl groups respectively for nucleophilic substitution by amine. It has been reported that the carbonyl of acetyl group in position 3 in dehydroacetic acid proved to be the more reactive site toward coupling reaction with nucleophilic reagents.^[24] In this context, we prepared thiose-micarbazones **3**, via treatment of dehydroacetic acid with thiosemicarbazides **2**, to investigate its reactivity toward some electrophilic reagents. All synthesized compounds were tested for their in vitro antimicrobial properties against Gram-positive, Gram-negative, and antifungal bacteria.

RESULTS AND DISCUSSION

Chemistry

In continuation of our ongoing work aiming at the development of efficient methods for the synthesis of heterocyclic compounds,^[25] we carried out an efficient preparation of 4-thiazolidinones derivatives 5a-d and 7a-d (Scheme 1). We also report a new synthetic route to the formation of 4-thiazolidinone compounds 9a-h, from reaction of the precursors 3a or 3c and maleimide derivatives 8a-h in refluxing ethanol.

In our study, we initially isolated the thiosemicarbazones intermediates 3a-d in quantitative yields (81–91%) after stirring the thiosemicarbazides 2a-d with dehydroacetic acid 1 in ethanol at room temperature.



Scheme 1. Synthetic pathway to generate 4-thiazolidinone derivatives 5 and 7. Reagents and conditions: (i) rt, EtOH; (ii) ethyl 2-bromopropionate 4, 3 equiv CH₃COONa anhydrous, conc. H_2SO_4 or 0.12% of keggin heteropolyacid (H₃PW₁₂O₄₀, nH₂O), CH₃CN, reflux; (iii) phenyl bromoacetate 6, 3 equiv CH₃COONa anhydrous, conc. H_2SO_4 , CH₃CN, reflux.

Spectral ¹H NMR data of thiosemicarbazones 3a-d indicated that these compounds exist as a tautomeric equilibrium between the enol (I) and the ketone (II) forms in an average ratio of 1:2, represented in Scheme 2.

For example, concerning **3a**, the chemical shift of the singlet corresponding to methyl protons of the pyrone unit was observed at δ : 2.12 ppm in form (I) and at δ : 2.16 ppm in form (II). The methylene proton (CH) appeared as a singlet at δ : 5.93 ppm (I) and at δ : 6 ppm in form (II). Methyl imine protons resonated at δ : 2.4 ppm in form (I) and at δ : 2.03 ppm in form (II). The ¹³C NMR spectrum exhibited a signal at 184 ppm assigned to the C=S bond. The infrared (IR) spectra showed bands around 1150–1156 cm⁻¹ and 1575 cm⁻¹ assigned to C=S and C=N bending vibrations, from the thiosemicarbazone fragment.

Subsequently, 4-thiazolidinone compounds **5a–d** were synthesized in good yields as described in Table 1, by reaction of the intermediates **3a–d**, ethyl 2-bromo propionate **4**, and 3 equiv of sodium acetate anhydrous in the presence of two drops of concentrated sulfuric acid or 0.12 mol% of keggin heteropolyacid^[26,27] (H₃PW₁₂O₄, n H₂O) in refluxing acetonitrile (Scheme 1).

As shown in Table 1, compounds **5a–d** were formed efficiently when we used $H_3PW_{12}O_4$, n H_2O as catalyst comparatively with sulfuric acid use. The reaction times were shortened from 2 h to 30 min for derivatives **5a–b**, 1 h to 15 min for compound **5c**, and 30 to 5 min for **5d**. However, the reaction yields are slightly lower compared with sulfuric acid use.



Scheme 2. Thiosemicarbazones 3 tautomesism.

NOVEL 4-THIAZOLIDINONES

Entry	Compound	Yield (%)	Time (min)
1	$\overset{OH}{\underset{H_{5}C}{\overset{OH}}{\overset{OH}{\overset{OH}{\overset{OH}{\overset{OH}{\overset{OH}{\overset{OH}{\overset{OH}}{\overset{OH}{\overset{OH}{\overset{OH}}{\overset{OH}{\overset{OH}}{\overset{OH}{\overset{OH}}{\overset{OH}}{\overset{OH}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}{\overset{OH}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}$	$77^{a} (72)^{b}$	$120^{a} (30)^{b}$
2	$\begin{array}{c} \begin{array}{c} OH & CH_3 \\ H_3C & O \\ \end{array} \\ \begin{array}{c} OH \\ H_5C \end{array} \\ \begin{array}{c} OH \\ O \end{array} \\ \begin{array}{c} OH \\ H_5C \end{array} \\ \begin{array}{c} OH \\ OH \end{array} \\ \begin{array}{c} OH \\ OH \end{array} \\ \begin{array}{c} OH \\ OH \\ OH \\ OH \end{array} \\ \begin{array}{c} OH \\ OH \\ OH \\ OH \end{array} \\ \begin{array}{c} OH \\ OH $	$86^{a} (80)^{b}$	$120^{a} (30)^{b}$
3	$\begin{array}{c} \begin{array}{c} \begin{array}{c} OH \\ + \\ + \\ + \\ SC \end{array} \\ \end{array} \\ \begin{array}{c} O \\ - \\ Sc \end{array} \\ \begin{array}{c} O \\ + \\ + \\ + \\ + \\ C \end{array} \\ \end{array} \\ \begin{array}{c} O \\ + \\ + \\ + \\ + \\ C \end{array} \\ \begin{array}{c} O \\ - \\ + \\ + \\ + \\ C \end{array} \\ \begin{array}{c} O \\ - \\ + \\ + \\ + \\ - \\ + \\ + \\ - \\ + \\ +$	88 ^a (84) ^b	$60^a (15)^b$
4	$H_{3C} \rightarrow H_{5C} \rightarrow H$	$90^{a} (88)^{b}$	$30^{a} (5)^{b}$
5	H ₃ C 7a	88	20
6	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \begin{array}{c} \\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \begin{array}{c} \\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \begin{array}{c} \\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \end{array}\\ \begin{array}{c} \\ \end{array}\\ \end{array}$	91	20
7	H_{3C} H	80	10
8	H_{5C} H	78	20

Table 1. Yields and reaction times of compounds 3a-d, 5a-d, and 7a-d

^{*a*}Reaction using concentrated sulfuric acid.

^bReaction using heteropolyacid H₃PW₁₂O₄₀, nH₂O.

To improve our studies, we applied the same methodology to synthesize 4-thiazolidinones 7a-d from compounds 3a-d and phenyl bromoacetate 6. The products 7a-d were isolated in excellent yields as shown in Table 1.

The appearance of the double signal at 1.53 (J=7 Hz) ppm due to $-CH_3$ and the quadruplet signal at 4.43 ppm (J=7 Hz, J=14 Hz) attributed to -CH in ¹H NMR confirms the formation of 4-thiazolidinones **5a–d**. The IR spectra of 4-thiazolidinone showed absorption bands at 1711–1718 and 1313–1357 cm⁻¹ corresponding to the C=O and the N=C-S groups of thiazolidinone ring. Moreover, in the ¹³C NMR spectrum, signals at 17.4, 43, and 178 ppm were assigned to CH₃, CH, and C=O (thiazolidinone) carbons.

The signal of methylene (CH₂) which appeared at 4.5 ppm in ¹H NMR and at 34 ppm in ¹³C NMR corroborates the structures 7a-d.

The proposed mechanism of formation of 4-thiazolidinones 5 or 7 is illustrated in Scheme 3.



Scheme 3. Mechanistic pathway proposed for the synthesis of compounds 5.

The formation of **5** or **7** was assumed to proceed through a nucleophilic attack of the sulfur atom of the thiosemicarbazones **3** onto the bromoester, followed by the intramolecular cyclization with elimination of ethanol and regeneration of sulfuric acid.

We also described a simple new strategy of the preparation of thiazolidinones **9**. The reaction of 1 equiv of the key intermediates **3a** or **3c** with the appropriate maleimide **8a-h** in the presence of two drops of concentrated sulfuric acid in refluxing ethanol for 3 to 4 h afforded structures **9a-h** in moderate yield (46–52%). The solid was obtained after purification by column chromatography (eluent: ethyle acetate) or by recrystallization in acetonitrile as represented in Scheme 4.

The formation of compounds **9a–h** results from initial attack of the sulfur atom of thiosemicarbazone group on the double bond of maleimide followed an intermediate A (not isolated). The ring opening of maleimide is obtained by nucleophic attack of nitrogen azote NR on the functional carbonyl, affording thiazolidinone structures **9a–h** (Scheme 5).

For example, in IR spectra, the formation of compound **9a** was confirmed through the presence of absorption bands around 1341 and 1704 cm^{-1} attributed to N=C-S-C=N and C=O bending vibrations. Consequently, the absence of the signal at 184 ppm in ¹³C NMR spectra, attributed to C=S, was also a parameter considered for the confirmation of the cyclization reaction. The ¹H NMR spectra



Scheme 4. Synthetic pathway to generate 4-thiazolidinone structures 9a-h.



Scheme 5. Plausible mechanism for the formation of 4-thiazolidinones 9.

exhibited signals at 2.77 ppm (${}^{3}J=9$ Hz, ${}^{2}J=17$ Hz), 3.07 ppm (${}^{3}J=4$ Hz, ${}^{2}J=17$ Hz), and 4.58 ppm (${}^{3}J=4$ Hz and 9 Hz), assigned to the H_a, H_b, and Hx appearing as double doublet (ABX pattern), due to interaction with nonequivalent methylene protons H_a and H_b with Hx proton. The signals observed at 7.09–7.58 ppm assigned to the nonequivalent amine protons were also compatible with the ring opening of the maleimide unit.

Antimicrobial Evaluation

Antibacterial activity of all compounds was determined by the well diffusion method^[28] and the diameter of inhibition zone was measured as indicated by Nataraja et al.^[29] and Vinod et al.^[30] Antimicrobial activity of the synthesized products **3a-d**, 5a-d, 7a-d, and 9a-h was evaluated against five microorganisms, known to cause some infections in humans: Escherichia coli ATCC 25992, Pseudomonas aeruginosa ATCC 27852, Staphylococcus aureus ATCC 43300, Staphylococcus aureus ATCC 25923, and Candida albicans. The results obtained (Table 2) revealed that compounds 3a, 3b, 7c, and 9a-h (except 9f) showed bactericidal activity toward Gram-positive bacteria Staphylococcus aureus ATCC43300. Compounds 7a-d (except 7b) demonstrated the greatest inhibition activity against Staphylococcus aureus ATCC 25923. All the tested compounds, 3b-d, 5a-d, 7c, 7d, and 9a-e (except 9d) are distinguished by a strong inhibitory activity on the growth of the Gram-negative bacteria Pseudomonas aeruginosa ATCC 27852. Compounds **3a–d** (except **3c**) and **7d** are the most active against Candida albicans. Very low inhibitory activity on the growth of Escherichia coli ATCC 25992 is observed for compounds 3a, 5a, 7c, and 9a, c. As shown in Table 2, some compounds did not show any activity toward Gram-positive bacteria, Gram-negative bacteria, and Candida albicans.

	Gram-positive bacteria		Gram-negative bacteria		Euroi
Compound	Staphylococcus aureus (ATCC-43300)	Staphylococcus aureus (ATCC-25923)	Escherichia coli (ATCC-25992)	Pseudomonas aeruginosa (ATCC-27852)	Candida albicans (ATCC-43300)
3a	Bactericidal activity	_	12	_	20
3b	Bactericidal activity	_	_	20	18
3c	_	_	_	17	
3d	_	_	_	20	18
5a	_	_	_	_	
5b		_	_		
5c		_	_		
5d		_	_		
7a	_	20	_	_	
7b	17	_	_		14
7c	Bactericidal activity	28	13	25	
7d	26	22	_	13	22
9a	Bactericidal activity	_	14	15	
9b	Bactericidal activity	_	_	10	12
9c	Bactericidal activity	_	15	18	
9d	Bactericidal activity	_	10	_	
9e	Bactericidal activity	_	_	25	
9f	15	_	_	_	14
9g	Bactericidal activity	_	_	_	
9h	Bactericidal activity	—	10	—	

 Table 2. Antimicrobial activity of synthesized compounds (diameter zones in mm)

Many synthetic compounds feature activity against microorganisms. The inhibitory activity increases in the compounds having substitution.^[31,32] However, it is reported that these compounds show a variety of pharmacological properties such as antibacterial, antifungal, and biological activities.^[33,34] The results obtained in this study indicate that the attachment of hydrogen, methyl, or amid groups at the 5-position of 4-thiazolidinone moiety gained the different activities of all expected compounds **3**.

From the structure–activity relationship it is clear that substituted compounds **3b** ($\mathbf{R} = C\mathbf{H}_3$), **7c** ($\mathbf{R} = C_2\mathbf{H}_5$), and **9e** ($\mathbf{R} = \mathbf{H}$, $\mathbf{R}' = \mathbf{H}$) have the broad spectrum of antibacterial activity against the Gram-positive bacteria (*S. aureus*) and Gramnegative bacteria (*P. aeruginosa*). The compound **7d** ($\mathbf{R} = C_6\mathbf{H}_5$) has the very broad spectrum of antibacterial and antifungal activity. The inhibitory activity can prevent function of some important molecules such as extracellular and intracellular enzymes and microbial metabolism. Following this activity, the synthesis of peptidoglycan in the cell wall as well as the synthesis of DNA and RNA, proteins and other important molecules can be inhibited.^[35–37]

EXPERIMENTAL

1-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)ethan-1-one N-Ethyl Thiosemicarbazone (3c)

A solution of 0.01 mol (1.68 g) of dehydroacetic acid 1 and 0.01 mol of ethyl thiosemicarbazide 2c in 20 mL of EtOH was stirred for 2 h at room temperature.

The precipitate obtained was filtered and washed with ethanol. White solid, yield 90%, mp 170–171 °C. IR (KBr, $\nu/$ cm⁻¹): 3257 (O-H), 3118 (N-H), 1718 (C=O), 1575 (C=N), 1150 (C=S). ¹H NMR (200 MHz, DMSO-d₆): δ 1.08 (t, 3H, ³J_{HH}= 7Hz, CH₂CH₃ (I, II)), 2.12 (s, 3H, CH₃(I)), 2.04 (s, CH₃(II)), 2.39 (s, 3H, NCCH₃(I)), 2.18 (s, NCCH₃(II)), 2.48 (q, 2H, ³J_{HH}= s 7Hz, CH₂(I, II)), 5.92 (s, 1H, CH(I)), 6.04 (s, CH(II)), 8.28 (t, 1H, ³J_{HH}= 7Hz, NHCH₂(I, II)); 9.43 (s, 1H, NH(I)), 10.38 (s, NH(II)). ¹³C NMR (50 MHz, DMSO-d₆): δ 14 (CH₃CH₂), 16.5 (NCCH₃), 19.3 (CH₃_{pyr}), 39.4 (CH₂), 96.2 (C=COH), 104.2 (CH), 163.1 (N=CCH₃), 163.4 (C=C-O), 167 (C=O_{pyr}), 176.8 (COH), 179.9 (C=S). MS *m/z* (%) = 269 (M⁺, 41), 166 (100), 138 (15), 151 (25), 125 (22), 43(53). HRMS *m/z* calcd. for C₁₁H₁₆N₃O₃S [M +H)⁺: 270.32010. Found: 270.32012.

General Procedure for the Synthesis of 4-Thiazolidinones (5a–d)

Thiosemicarbazones **3a–d** (0.01 mol) and 0.02 mol of ethyl 2-bromopropionate **4** were refluxed in 30 mL of acetonitrile in the presence of 0.03 mol (0.246 g) of anhydrous NaOAc and two drops of concentrated sulfuric acid for 1 to 3 h. The solid formed was recuperated by filtration and recrystallized in acetonitrile (method A).

2-{[1-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)ethylidene] hydrazinylidene}-5-methyl-1,3-thiazolidin-4-one (5a)

Yellow solid, yield 77%, mp 205 °C. IR (KBr, ν/cm^{-1}): 3443 (O-H), 1612 (C=O pyr), 1711 (C=O thiaz), 1349 (NCS). ¹H NMR (200 MHz, DMSO-d₆): δ 1.53 (d, 3H, ³J_{HH} = 7 Hz, CH_{3thiaz}), 2.14 (s, 3H, CH_{3pyr}), 2.61 (s, 3H, <u>CH₃-C=N</u>), 4.43 (q, 1H, ³J_{HH} = 7 Hz, CH_{thiaz}), 5.96 (s, 1H, CH_{pyr}), 2.19 (s, 1H, NH). ¹³C NMR (50 MHz, DMSO-d₆): δ 16.5 (CH_{3thiaz}), 18.4 (<u>CH₃CN</u>), 19 (CH_{3pyr}), 44 (CH_{thiaz}), 94.8 (<u>C</u>=COH), 104 (CH_{pyr}), 158.4 (C-O_{pyr}), 162 (H₃C-<u>C</u>=N), 163.1 (N=<u>C</u>S), 168.8 (C=O_{pyr}), 175.9 (COH), 179.9 (C=O_{thia}). MS *m*/*z* (%) = 295 (M⁺, 5), 166 (30), 138 (100), 129 (24), 101 (42). HRMS *m*/*z* calcd. for C₁₂H₁₄N₃O₄S [M+H]⁺: 296.06995. Found: 296.06992.

General Procedure for Synthesis of Compounds 7a-d

Thiosemicarbazones (0.01 mol) 3a-d and 0.02 mol of phenyl bromoacetate 6 were refluxed in 30 mL of acetonitrile in the presence of 0.03 mol (0.246 g) of anhydrous NaOAc and two drops of concentrated sulfuric acid for 1 to 3 h. The solid formed was recuperated by filtration and recrystallized in acetonitrile.

2-{2-[1-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)ethylidene] hydrazinyl}-1,3-thiazolidin-4-one (7a)

White solid, yield 88%, mp 210 °C. IR (KBr, ν/cm^{-1}): 3414 (O-H), 1614 (C=O pyr), 1704 (C=O thiaz), 1258 (NCS). ¹H NMR (200 MHz, DMSO-d₆): δ 2.13 (s, 3H, CH_{3pyr}), 2.59 (s, 3H, CH₃-C=N), 4.43 (s, 2H, CH₂), 5.96 (s, 1H, CH_{pyr}), 12.2 (s, 1H, NH). ¹³C NMR (50 MHz, DMSO-d₆): δ 16.7 (<u>C</u>H₃CN), 19.3 (CH_{3pyr}), 34.5 (CH₂), 95 (<u>C</u>=COH), 104.2 (<u>C</u>H_{pyr}), 160 (C-O), 161.8 (C<u>C</u>H₃=N), 163.8 (N=<u>C</u>S), 168.5

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(C=O_{pyr}), 173.1 (C-OH), 180 (C=O_{thia}). MS m/z (%) = 281 (M^{+,}, 7), 166 (58), 138 (100), 115 (30). HRMS m/z calcd. for C₁₁H₁₂N₃O₄S [M + H]⁺: 282.28774. Found: 282.28771.

General Method for the Synthesis of Compounds 9a-h

A mixture of thiosemicarbazones 3a or 3c (0.01 mol), appropriate maleimide 8a-d (0.01 mol), and two drops of concentrated sulfuric acid (12 N) in 30 mL of acetonitrile was refluxed for 3-4 h. The reaction mixture was then cooled at room temperature and the solid precipitated was filtered, abundantly washed with acetonitrile and ethanol, and then recrystallized, or the precipitate was purified by column chromatography using ethyl acetate as eluent.

2-(3-Ethyl-2-{2-[1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl) ethylidene]hydrazinyl}-4-oxo-1,3-thiazolidin-5-yl)acetamide (9a)

White solid, yield 48%, mp 255–256 °C. IR (KBr, ν/cm^{-1}): 3397 (O-H), 3298; 3179 (NH₂), 1673 (C=O pyr), 1704 (C=O thiaz), 1583 (NC=O), 1344 (NCS). ¹H NMR (200 MHz, DMSO-d₆): δ 1.18 (t, 3H, ³J_{HH}=7 Hz, CH₃CH₂), 2.17 (s, 3H, CH_{3pyr}), 2.68 (s, 3H, N=CCH₃), 2.77 (dd, H_a, ³J_{HH}=9 Hz, ²J_{HH}= 17 Hz), 3.07 (dd, H_b, ³J_{HH}= 4 Hz, ²J_{HH}=17 Hz), 3.75 (q, 2H, ³J_{HH}=7 Hz, CH₂), 4.58 (dd, H_x, ³J_{HH}= 4 Hz and 9 Hz), 5.98 (s, 1H, CH_{pyr}), 7.09, 7.58 (s, 2H, NH₂).¹³C NMR (50 MHz, DMSO-d₆): δ 11.4 (CH₃CH₂), 17.1 (N=CCH₃), 19.5 (CH_{3pyr}), 37.2 (CH₂CH₃), 38.2 (CH₂CONH₂), 47.2 (CH_{thiaz}), 94.5 (HOC=C), 104.1 (CH_{pyr}), 159.2 (N=CCH₃), 162.2 (CCH₃), 163.4 (C=O_{pyr}), 169.2 (N=CS), 170 (COH), 173 (CONH₂), 180.1 (C=O_{thia}). MS *m*/*z* (%) = 366 (M⁺⁻, 12), 308 (36), 166 (100), 151 (50), 58 (37). HRMS *m*/*z* calcd. for C₁₅H₁₉N₄O₅S [M+H]⁺: 367.10707. Found: 367.10690.

SUPPORTING INFORMATION

Full experimental detail, ¹H and ¹³C NMR spectra, and results of antimicrobial activity for this article can be accessed on the publisher's website.

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