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Synthesis and antimicrobial activity of substituted imidazolidinediones and thioxoimidazolidinones

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Abstract

Synthesis and physico–chemical properties of new 3-benzyl-4-thioxo-5-arylideneimidazolidine-2-ones and 3-benzyl-5-arylideneimidazolidine-2,4-dione are described. These compounds were synthesized by condensation reaction from aromatic aldehydes and 3-substituted imidazolidine-2,4-diones or 4-thioxoimidazolidine-2-ones. The *N*-alkylation of 5-benzylideneimidazolidine-2,4-dione led simultaneously to mono- and dialkylated derivatives. The nucleophilic addition of 1-methyl-3-benzylimidazolidine-2,4-dione with 2-cyano-3-(3,4-dichlorophenyl) acrylate also yielded the 3-substituted 5-arylideneimidazolidine-2,4-dione derivative. Antimicrobial in vitro activity was determined on some compounds.

Keywords: Imidazolidines; Thioxoimidazolidines; Antimicrobial activity

1. Introduction

Imidazolidinedione and thiazolidinedione derivatives are widely studied because of their pharmacological properties [1–3]. Synthesis of some 5-arylideneimidazolidine-2,4-diones, substituted in the 3-position by a benzyl group, has been previously reported [4–6]. In the present paper, we describe the synthesis and the physico–chemical characteristics of the 3-(4-fluorobenzyl)-5-(4-fluorobenzylidene)imidazolidine-2,4-dione (**7**) and of some new 3-benzyl- and 3-(4-chlorobenzyl)-4-thioxo-5-arylideneimidazolidine-2-ones (**8–14**). Antimicrobial activity of some of these compounds has been investigated against cocci and bacilli.

2. Chemistry

These compounds were synthesized by a condensation reaction between 3-(4-fluorobenzyl)imidazolidine-2,4-dione (**3**), 3-benzyl- and 3-(4-chlorobenzyl)-4-thioxoimidazolidine-2-ones (**5–6**) with aromatic aldehydes (Scheme 1). When this reaction is performed with imidazolidine-2,4-dione (**1**) and 4-bromobenzaldehyde, the resulting product (**15**) submitted to alkylation with 2-chloroacetophenone yields two derivatives: a monoalkylated one, the 3-phenacyl-5-(4-bromobenzylidene)imidazolidine-2,4-dione (**16**) and a dialkylated one, the 1,3-diphenacyl-5-(4-bromobenzylidene)imidazolidine-2,4-dione (**17**) (Scheme 1). The condensation reaction between 1-methyl-3-(4-chlorobenzyl)imidazolidine-2,4-dione (**19**) and substituted aldehydes is very difficult because the 5-position of imidazolidine ring is partially hindered by methyl group. An alternative method can be employed: thus, nucleophilic addition of **19** with ethyl-2-cyano-3-(3,4-dichlorophenyl)acrylate affords 1-methyl-3-(4-chlorobenzyl)-5-(3,4-dichlorobenzylidene)imidazolidine-2,4-dione (**20**) as a mixture of *E*/*Z* isomers in 80:20 ratio due the presence of methyl group in imidazolidine cycle. This proportion was determined by mass spectrometry coupled with GC (Scheme 2).

The 5-arylideneimidazolidine-2,4-diones can present *Z*–*E* isomerism. The condensation of imidazolidine-

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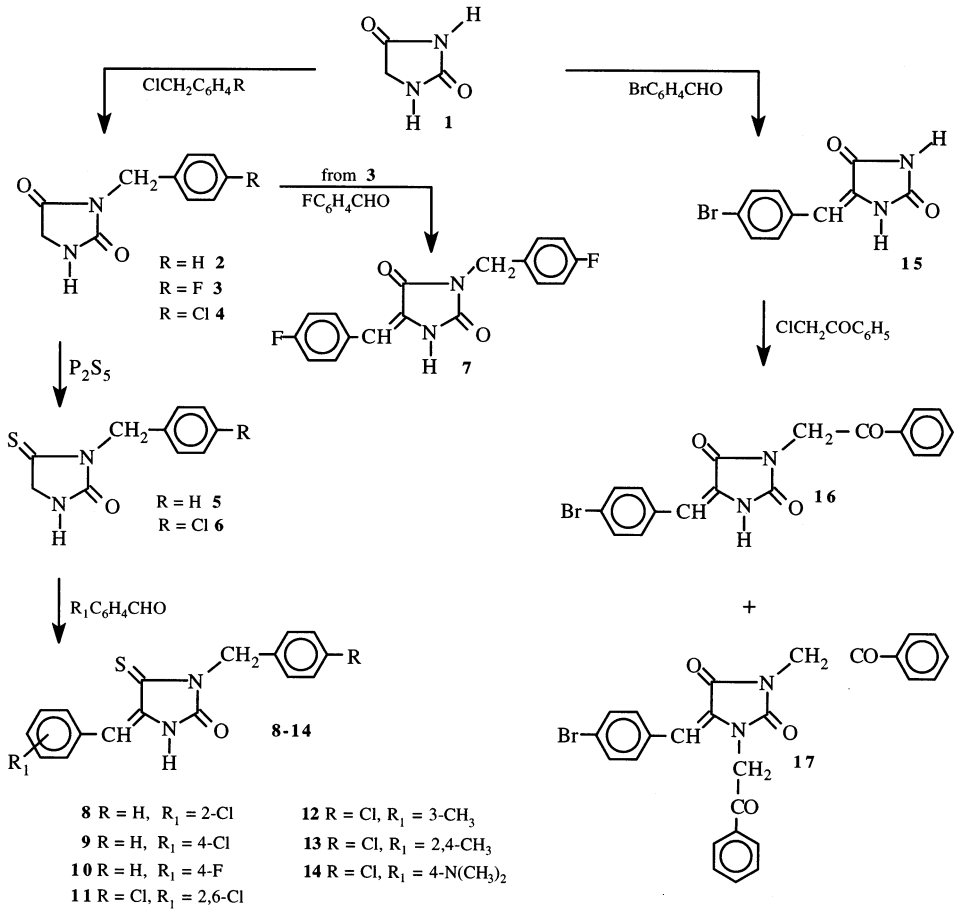
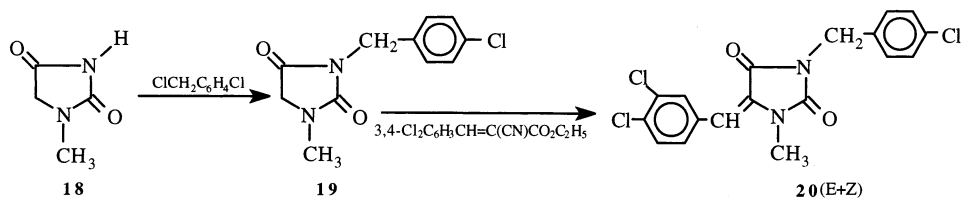


Scheme 1.



Scheme 2.

2,4-diones, unsubstituted in the 1-position, with aromatic aldehydes in acid medium, leads always to *Z* isomer [7]. The coupled ^{13}C NMR study giving the coupling constant $^{3}J_{C-H}$ (4.8–6.4 Hz) between the methylidene proton and the carbon in the 4-position shows that imidazolidine-2,4-diones present *Z* configuration [4,8]. The crystallographic study has confirmed these results [9]. The 5-arylideneimidazolidine-2,4-diones and 5-arylidene-4-thioxoimidazolidine-2-ones prepared by us show *Z* configuration, except for the above-mentioned compound **20**.

The 3-alkylation of imidazolidine takes place in two steps: firstly, the activation of the 3-position by formation of the sodium or potassium salt; then, the condensation with halides in hot ethanol [10]. By treatment of the 3-benzylimidazolidine-2,4-dione (**2**), m.p. 135°C [11], and 3-(4-chlorobenzyl)imidazolidine-2,4-dione (**4**), m.p. 164°C [12], with phosphorus pentasulfide in hot dioxane, the 3-benzyl-4-thioxoimidazolidine-2-one (**5**) and 3-(4-chlorobenzyl)-4-thioxoimidazolidine-2-one (**6**) [4] are obtained. The condensation of these thioxoimidazolidines with aromatic aldehydes is performed in acetic acid in presence of anhydrous sodium acetate. Physico–chemical and ^{1}H NMR data of the compounds **8–14** are listed in Table 1 and mass spectral data in Table 2.

3. Experimental

Melting points were determined with a capillary Büchi apparatus and are uncorrected. IR spectra were

Table 1
Physico–chemical and ^{1}H NMR data of thioxoimidazolidinones

No.	R	R_1	Reaction time (h)	M.p. (°C)	Purification method	Yield (%)	^{1}H NMR (δ ppm) (J = Hz)[b]				
							NH (s)	–CH= (s)	$-CH_2-$ (s)	$R_1-C_6H_4$	$R-C_6H_4$	CH_3 (s)
8	H	2-Cl	2	221	$CHCl_3$/MeCOMe 99/1[a]	46	8.23	7.30	5.14	7.28–7.50 (m, 9H)	7.28–7.50 (m, 9H)	
9	H	4-Cl	3	222	$CHCl_3$/MeCOMe 95/5[a]	41	9.24	7.11	5.16	7.25–7.52 (m, 9H)	7.25–7.52 (m, 9H)	
10	H	4-F	3	217	$CHCl_3$/MeCOMe 95/5[a]	40	9.16	7.14	5.17	7.12 (d, 2H), 7.31 (dd, 2H)	7.45–7.52 (m, 5H)	
11	Cl	2,6-Cl	3	183	Washed	37	11.25	6.82	5.01	7.41–7.57 (m, 3H)	7.36 (d, 2H) J = 8.2, 7.44 (d, 2H) J = 8.2	
12	Cl	3-CH_3	22	219	C_6H_6/MeCOMe 97.5/2.5[a]	69	11.37	6.98	5.05	7.19–7.55 (m, 4H)	7.34 (d, 2H) J = 8.7, 7.41 (d, 2H) J = 8.7	
13	Cl	2,4-CH_3	3	238	Washed	49	11.26	7.10	5.04	7.50 (d, 1H) J = 7.7, 7.14 (s, 1H), 7.07 (d, 1H) J = 7.7	7.35 (d, 2H) J = 8.4, 7.41 (d, 2H) J = 8.8	2.32 (3H), 2.28 (3H)
14	Cl	4-$N(CH_3)_2$	25	281	C_6H_6/MeCOMe[a]	38	11.09	7.04	5.04	7.60 (d, 2H) J = 8.9, 6.73 (d, 2H) J = 8.9	7.34 (d, 2H) J = 8.9, 7.40 (d, 2H) J = 8.7	

[a] Column chromatography with silica gel (mesh 70–230).
[b] s, singlet; d, doublet; dd, double doublet; m, multiplet. Solvent: **8**, **9**, **10** in $CDCl_3$; **11**, **12**, **13**, **14** in DMSO-d_6.

taken on a Perkin–Elmer 1310 spectrophotometer in 2% KBr pellet except for compound **20**, mixture $E+Z$, for which an IFS 66 Bruker spectrophotometer was used. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6 with a Bruker AC-200 spectrometer except for compound **20**, mixture $E+Z$, for which a Bruker AC-300P spectrometer was used. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Electronic impact mass spectra (70 eV) were measured with a R-1010C Delsi–Nermag spectrometer except for compounds **7** and **20** for which a HPG 1019A spectrometer coupled with a GC (HP 5890) was used. Thin layer chromatography was performed on silica plates pre-coated with Merck Kiesegel $60F_{254}$ and column chromatography with silica gel (mesh 70–230). No elemental analysis was performed on the new compounds, but all mass spectra agree with their proposed structure.

3.1. 3-(4-Fluorobenzyl)imidazolidine-2,4-dione (3)

A solution of hydroxide sodium (5.3 g, 0.13 mmol) in 50% ethanol (50 ml) was added dropwise to a stirred suspension of imidazolidine-2,4-dione (13.3 g, 0.13 mol) in 50% ethanol (200 ml). After 10 min, the 4-fluorobenzyl chloride (20.0 g, 0.14 mol) was added. The reaction mixture was stirred for 5 min then refluxed for 20 h. After cooling, the precipitate was filtered and recrystallized from 95% ethanol. Yield 50%. M.p. 187–188°C. TLC: ($CHCl_3$/$CH_3COOC_2H_5$ 1:1) R_f 0.50. IR (KBr): ν 3245, 1770, 1720, 1605 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.96 (s, 2H, CH_2-5); 4.50 (s, 2H, CH_2-Ph), 7.10–7.18 (m, 2H, aromatic H); 7.27–7.34 (m, 2H, aromatic H), 8.14 (s, 1H, NH).

3.2. 3-Benzyl-4-thioxoimidazolidine-2-one (5)

A mixture of 3-benzylimidazolidine-2,4-dione (**2**) (5.2 g, 27 mmol) and phosphorus pentasulfide (2.5 g, 11 mmol) in anhydrous dioxane (40 ml) is refluxed for 60 min. Then 0.1 g of zinc powder and 0.1 g of charcoal are added; the mixture is heated for another 10 min, hot filtered and concentrated to half. After addition of crushed ice, the precipitate is filtered and purified by column chromatography (C_6H_6/CH_3COCH_3 99:1). Yield 73%. M.p. 134°C. TLC: (C_6H_6/CH_3COCH_3 9:1) R_f 0.65. IR (KBr): ν 3230, 1755, 1490 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.34 (d, 2H, CH_2-5); 5.05 (s, 2H,CH_2-Ph); 6.17 (s, 1H, NH); 7.29–7.37 (m, 3H, aromatic H); 7.46–7.50 (m, 2H, aromatic H).

3.3. 3-(4-Fluorobenzyl)-5-(4-fluorobenzylidene)-imidazolidine-2,4-dione (7)

A mixture of 3-(4-fluorobenzyl)imidazolidine-2,4-dione (**3**) (3.1 g, 15 mmol), 4-fluorobenzaldehyde (2.2 g,

Table 2
Thioxoimidazolidinones: main molecular peaks and their relative intensities

No.	Formula	M^+ (%)	MS m/z (%)
8	$C_{17}H_{13}ClN_2OS$	328 (3.9)	330 (1.4), 294 (23), 293 (100), 292 (31), 91 (82)
9	$C_{17}H_{13}ClN_2OS$	328 (79.2)	329 (40.7), 330 (28.3), 293 (48), 292 (18), 91 (100), 89 (14)
10	$C_{17}H_{13}FN_2OS$	312 (100)	313 (25.5), 311 (80), 91 (77)
11	$C_{17}H_{11}Cl_3N_2OS$	397 (1.6)	398 (1.8), 361 (100), 362 (22), 363 (64), 127 (40), 125 (87), 99 (22), 90 (27), 89 (90), 86 (37)
12	$C_{18}H_{15}ClN_2OS$	342 (100)	343 (46.0), 344 (41.2), 327 (40), 125 (62), 103 (22), 90 (19), 89 (65), 86 (39)
13	$C_{19}H_{17}ClN_2OS$	356 (40.1)	358 (14.5), 343 (38), 342 (24), 341 (100), 127 (29), 125 (70), 91 (25), 90 (20), 89 (64), 86 (30)
14	$C_{19}H_{18}ClN_3OS$	371 (100)	372 (35.2), 373 (41.7), 203 (17), 160 (22), 159 (17), 125 (21), 89 (37)

18 mmol), sodium acetate (1.5 g) and glacial acetic acid (6.0 ml) is heated at 140–150°C for 3 h. After cooling, the precipitate is filtered, washed with water and recrystallized from methanol. Yield 39%. M.p. 225°C. TLC: ($CHCl_3/CH_3OH$ 9:1) R_f 0.66. IR (KBr): ν 3240, 1760, 1705, 1655 cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.64 (s, 2H, CH_2); 6.55 (s, 1H, CH=); 7.16 (t, 2H, $J = 8.7$ Hz, aromatic H); 7.23 (t, 2H, $J = 8.7$ Hz, aromatic H); 7.27–7.30 (m, 2H, aromatic H); 7.67–7.75 (m, 2H, aromatic H). MS: m/z (%) = 314 (57.2), 315 (11.0), 109 (100), 108 (9.0).

*3.4. 3-Benzyl- and 3-(4-chlorobenzyl)-4-thioxo-5-arylideneimidazolidine-2-ones (**8–14**)*

An equimolar mixture of 3-benzyl-4-thioxoimidazolidine-2-one (**5**) (0.51 g, 2.5 mmol) or 3-(4-chlorobenzyl)-4-thioxoimidazolidine-2-one (**6**) (0.24 g, 1 mmol), aldehyde, sodium acetate and glacial acetic acid is heated at 110–120°C for the time reported in Table 1. After cooling, the precipitated product is washed with water and diethyl ether. Some 3-benzyl-and 3-(4-chlorobenzyl)-4-thioxo-5-benzylideneimidazolidine-2-ones did not need another purification. Some compounds were purified by column chromatography as specified in Table 1.

*3.5. 5-(4-Bromobenzylidene)imidazolidine-2,4-dione (**15**)*

A mixture of imidazolidine-2,4-dione (**1**) (1.0 g, 10 mmol), 4-bromobenzaldehyde (2.2 g, 12 mmol), sodium acetate (3.3 g) and glacial acetic acid (14 ml) is heated at 130–140°C for 5 h. After cooling, the precipitated product is filtered, triturated with water and diethyl ether then recrystallized from acetic acid. Yield 50%. M.p. 300°C. TLC: ($CHCl_3/CH_3OH$ 96:4) R_f 0.28. IR (KBr): ν 3270, 3220, 1790, 1735, 1665 cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.36 (s, 1H, CH=C); 7.55 (s, 4H, aromatic H); 10.91 (s, 1H, NH).

*3.6. 3-Phenacyl-5-(4-bromobenzylidene)imidazolidine-2,4-dione (**16**) and 1,3-diphenacyl-5-(4-bromobenzylidene)imidazolidine-2,4-dione (**17**)*

A potassium hydroxide solution (0.3 g, 5.3 mmol) is added dropwise to a stirred suspension of 5-(4-bromobenzylidene)imidazolidine-2,4-dione (**15**) (1.3 g, 4.9 mmol) in 50 ml of absolute ethanol. The mixture is refluxed for 2 h. After cooling, the precipitated compound is filtered, washed with ethanol and dried. A mixture of potassium salt of the 5-(4-bromobenzylidene)imidazolidine-2,4-dione (1.2 g, 6.2 mmol) and of 2-chloroacetophenone (0.8 g, 5.2 mmol) in dimethylformamide (50 ml) is refluxed for 3 h. The precipitated compound is filtered, washed with minimal quantity of ethanol and purified by column chromatography with $CHCl_3/CH_3OH$ (98:2) as eluent. TLC ($CHCl_3/CH_3OH$ 98:2): two spots R_f 0.90 and 0.76.

*3.6.1. Compound **16***

Yield 25%. TLC: ($CHCl_3/CH_3OH$ 96:4) R_f 0.77. M.p. 305–306°C. IR (KBr): ν 3230, 2930, 1765, 1710, 1690, 1585 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.13 (s, 2H, CH_2); 6.58 (s, 1H, CH=); 7.62 (s, 4H, aromatic H); 7.59–7.73 (m, 3H, aromatic H); 8.07 (d, 2H, $J = 7.1$ Hz, aromatic H); 11.06 (bs, 1H, NH). MS m/z (%): 384 (10.5), 386 (8.9), 243 (60), 165 (25), 105 (100), 89 (21).

*3.6.2. Compound **17***

Yield 2%. TLC: ($CHCl_3/CH_3OH$ 98:2) R_f 0.90. M.p. 193°C. IR (KBr): ν 2930, 1775, 1725, 1695, 1600 cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.91 (s, 2H, CH_2); 5.13 (s, 2H, CH_2); 6.90 (s, 1H, CH=C); 7.02 (d, 2H, $J = 8.5$ Hz, aromatic H); 7.23 (d, 2H, $J = 8.4$ Hz, aromatic H); 7.35–7.65 (m, 8H, aromatic H); 8.02 (dd, 2H, $J = 6.6$ Hz, aromatic H). ^{13}C NMR ($CDCl_3$): δ 45.18 (CH_2), 48.33 (CH_2), 111.40 (CH), 122.53 (C), 127.48 (2 CH), 128.11 (2 CH), 128.60 (2 CH), 128.86 (2 CH), 129.54 (C), 130.54 (2 CH), 131.23 (C), 131.42 (2 CH), 133.77 (C), 133.95 (CH), 134.09 (CH), 134.17 (C), 155.35 (CO), 162.91 (CO), 190.36 (CO), 191.24 (CO). MS m/z (%): 502 (4.7), 504 (4.6), 318 (5), 208 (6), 129 (9), 105 (100), 77 (27).

*3.7. 1-Methylimidazolidine-2,4-dione (**18**)*

According to the method described by Miller and Robson [13], a mixture of *N*-methylglycine (5.4 g, 60 mmol) and potassium cyanate (4.9 g, 60 mmol) in 20 ml

of water is refluxed for 30 min. Concentrated HCl is added up to pH 3.0 and the refluxing is continued for a further 30 min. After evaporation, the residue is purified by successive crystallizations from absolute ethanol. Yield 75%.

M.p. 153–154°C (lit. [13] 155–156°C). TLC: ($CHCl_3$/CH_3OH 97:3) R_f 0.63. IR (KBr): ν 3140, 3040, 1770, 1710 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.77 (s, 3H, CH_3); 3.88 (s, 2H, CH_2); 10.68 (bs, 1H, NH).

3.8. 1-Methyl-3-(4-chlorobenzyl)imidazolidine-2,4-dione (19)

A mixture of 1-methylimidazolidine-2,4-dione (**18**) (8.8 g, 77 mmol), 4-chlorobenzyl chloride (12.4 g, 77 mmol) and sodium hydroxide (4.0 g) in ethanol at 50°C is refluxed for 20 h. After cooling, 200 g of iced water are added. The precipitated compound **19** is filtered and recrystallized from water. Yield 58%. M.p. 128–129°C. TLC ($CHCl_3$/CH_3OH 99:1) R_f 0.76. IR (KBr): ν 2920, 1775, 1700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.98 (s, 3H, CH_3); 3.85 (s, 2H, CH_2-5); 4.60 (s, 2H, CH_2-Ph); 7.27 (d, 2H, $J = 8.5$ Hz, aromatic H); 7.35 (d, 2H, $J = 8.6$ Hz, aromatic H).

3.9. 1-Methyl-3-(4-chlorobenzyl)-5-(3,4-dichlorobenzylidene)imidazolidine-2,4-dione (20, mixture E + Z)

An equimolar mixture of 1-methyl-3-(4-chlorobenzyl)imidazolidine-2,4-dione (**19**) (0.74 g, 2.7 mmol) and ethyl 2-cyano-3-(3,4-dichlorophenyl)acrylate in absolute ethanol (20 ml) is refluxed for 2 h with 0.25 ml of piperidine. After cooling, the precipitated compound is purified by column chromatography with chloroform as eluent. Yield 27%. M.p. 195–196°C. TLC ($CHCl_3$) R_f 0.60. IR (KBr, $E + Z$): ν 1762, 1710, 1631 cm^{-1}. ^1H NMR ($CDCl_3$, $E + Z$): δ 3.23 (s, 3H, CH_3); 4.73 (s, 2H, CH_2); 6.10 (s, 1H, CH=C); 7.30 (d, 1H, $J = 8.8$ Hz, aromatic H); 7.38 (d, 1H, $J = 8.4$ Hz, aromatic H); 7.44 (d, 2H, $J = 8.5$ Hz, aromatic H); 7.74 (dd, 2H, $J = 8.4$ and 2.5 Hz, aromatic H); 8.03 (d, 1H, $J = 2.2$ Hz, aromatic H). MS m/z (%): (Z 80%): 394 (43.7), 396 (43.3), 398 (15.4), 184 (12), 127 (33), 125 (100); (E 20%): 394 (36.9), 396 (36.0), 398 (12.4), 184 (12), 127 (33), 125 (100).

4. Biological activity

The antimicrobial activity of compounds **3**, **5**, **7**, **8**, **10**, and **16–20** was determined in vitro against six microorganisms (cocci, Gram-positive and Gram-negative bacilli): *Staphylococcus aureus*, *Micrococcus flavus*, *Bacillus cereus*, *Proteus vulgaris*, *Salmonella enteritidis* and *Escherichia coli*.

The Mueller–Hinton agar has been used as a medium of reference for antimicrobial activity tests [14]. Overnight cultures grown at 37°C in Mueller–Hinton broth are diluted to obtain an opacity equivalent to 0.5 on the McFarland scale. Serial 2-fold dilutions of each drug are prepared in DMSO/Tween 80/water (1:1:8) to give concentrations 10-fold higher than the final desired concentration. A concentration of 5120 or 1280 μg/ml was used as a starting concentration, providing a final concentration of 512 or 128 μg/ml in agar. A series of 8–11 dilutions (to final concentrations of 512–0.5 or 128–0.5 μg/ml) is prepared.

Plates of Petri are prepared by mixing one part of each dilution of drug with nine parts of the Mueller–Hinton agar medium. Each plate, including a drug-free control plate, is inoculated by streak using a calibrated loop (0.05 ml). The plates are examined for the presence or absence of growth after 18 h of incubation at 37°C. The minimal inhibitory concentration (MIC) is considered to be the lowest drug concentration for which there is no microbial growth [15]. It was verified that DMSO was completely inactive on the tested microorganisms at these concentrations. The ciprofloxacin was used as the reference antibiotic. Its MIC was 0.25 μg/ml against *M. flavus* and 2 μg/ml against *B. cereus*.

Compounds **18–20** presented a MIC superior to 512 μg/ml for all microorganisms tested except for compound **20** whose active concentration is 32 μg/ml against *M. flavus*. For compounds **3**, **5**, **7**, **8**, **10**, **16** and **17**, the MIC was superior to 128 μg/ml except for compound **3**, whose active concentration against *M. flavus* and *B. cereus* is inferior to 0.5 μg/ml, and for compound **7** that inhibited *B. cereus* at the concentration of 16 μg/ml.

5. Conclusion

Some new imidazolidinediones and thioxoimidazolidinones have been synthesized and characterized by their physico–chemical and spectroscopic properties. The fragments observed by electronic impact mass spectrometry are in agreement with the proposed structures.

Ten compounds were evaluated as potential antimicrobial agents against six microorganisms. They present an activity inferior to ciprofloxacin, the reference antibiotic.

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