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Synthesis, anti-inflammatory and antimicrobial activities of new 1,2,4-oxadiazoles peptidomimetics

Ana Cristina L. Leite [a,*], Renata F. Vieira [a], Antonio R. de Faria [a], Almir G. Wanderley [b], Parviz Afiatpour [b], Eulália Camelo P.A. Ximenes [c], Rajendra M. Srivastava [d], Claudia F. de Oliveira [e], M.V. Medeiros [e], Edson Antunes [e], Dalci J. Brondani [a]

[a] *Laboratório de Planejamento, Avaliação e Síntese de Fármacos, LABSINFA, Departamento de Ciências Farmacêuticas, Rua Prof. Artur Sá s/n, Cidade Universitária, Universidade Federal de Pernambuco, Recife-PE, Brazil, CEP: 50740-520*

[b] *Departamento de Fisiologia e Farmacologia, Rua Prof. Artur Sá s/n, Cidade Universitária, Universidade Federal de Pernambuco, Recife-PE, Brazil, CEP: 50740-520*

[c] *Departamento de Antibióticos, Rua Prof. Artur Sá s/n, Cidade Universitária, Universidade Federal de Pernambuco, Recife-PE, Brazil, CEP: 50740-520*

[d] *Departamento de Química Fundamental, Rua Prof. Artur Sá s/n, Cidade Universitária, Universidade Federal de Pernambuco, Recife-PE, Brazil, CEP: 50740-520*

[e] *Departamento de Farmacologia, Universidade Estadual de Campinas, Cidade Universitária, Zeferino Vaz s/n, Barão Geraldo, Campinas, São Paulo, Brazil, CEP: 13.081-970 Caixa postal 6111*

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Abstract

A new series of 1,2,4-oxadizoles **6a**–**g** have been synthesised in good yields using the peptide synthesis strategy. The prepared compounds were tested for anti-inflammatory and antimicrobial activities. The anti-inflammatory activities were determined in the rat paw oedema induced by carrageenin. Compounds **6a**, **c**, **f** and **g** (i.v.) significantly inhibited the rat paw oedema induced by carrageenin depending upon the dose employed. The compounds were also evaluated for their in vitro antimicrobial activity. Some compounds were found to have significant activity against Gram positive and Gram negative microorganisms. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Anti-inflammatory activity; Potential antimicrobial agents; 1,2,4-Oxadiazoles; Peptidomimetics; Peptide synthesis

1. Introduction

1,2,4-Oxadiazoles in general have attracted widespread attention due to their important biological activities such as antiviral [1], fungicide [2], herbicide [3], analgesic and anti-inflammatory [4]. Some of these exhibited pronounced β-adrenoreceptor blocking activity and moderate α-adrenoreceptor blocking properties [5]. Oxadiazoles are often considered as ester and amide bioisosteres in drug research, and they have also been used as dipeptidomimetics [6,7]. The optimum conditions for the synthesis of 1,2,4-oxadiazole have already been reported [8,9]. It has been shown that therapeutically active agents with small peptides or amino acid residues, exhibit reduced toxicity and enhance their therapeutic effect [10–12]. It is supposed that an amino acid transport system in the cell can be exploited to deliver the oxadiazole nucleus to target cells for the drug activity.

Considering the potential of these 1,2,4-oxadiazoles, we undertook the synthesis of 1,2,4-oxadiazoles **6a**–**g** employing the classical strategy of peptide synthesis [13]. This paper reports the synthesis of little compounds for the first time and the verification of their structures by spectroscopic means and elemental analysis. The anti-inflammatory study was carried out according to Winter et al. [14]. The antibacterial properties of these compounds were tested as well.

* Corresponding author.
E-mail address: aclb@npd.ufpe.br (A.C.L. Leite).

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2. Chemistry

1,2,4-Oxadiazoles [15–17] are most commonly synthesised from amidoximes and acetylating agents such as carboxylic acid chlorides or anhydrides [18]. In this study, the benzamidoxime was obtained as previously reported, by reaction with hydroxylamine and benzonitrile [19]. A suitable treatment of **1** with succinic anhydride gave **3** [8].

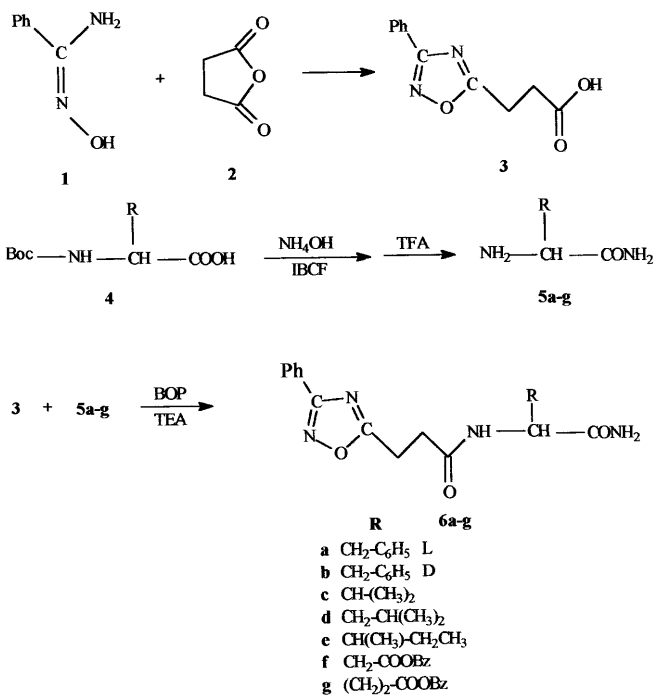
The pseudopeptide heterocyclic derivatives were synthesised from Boc-protected amino acids. The synthetic routes to afford the pseudopeptide derivatives were applied on appropriately protected lipophilic (phenylalanine D and L, valine, leucine and isoleucine) and acidic (aspartic and glutamic) amino acids. The carboxylic acid function of **4** was treated with isobutyl chloroformate in the presence of triethylamine and ammonium hydroxide to obtain the desired amide in good yield. In our strategy, we have chosen using the aspartic and glutamic amino acids whose side chain's carboxylic acid function is protected by a benzyl ester.

The expected pseudopeptides derivatives **6a–g** have been synthesised by condensation of 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid **3** with **5a–g** using benzotriazolyloxy-*tris*-(dimethylamino) phosphonium hexafluorophosphate (BOP) to activate the carboxylic acid function by generation of a highly reactive 1-hydroxybenzotriazole ester of the carboxyl component [20,21]. The 1,2,4-oxadiazol derivatives were obtained in a 40–90% yield (Scheme 1).

3. Results

3.1. Chemistry

All compounds present characteristic ^{1}H NMR signals for NH_2 and NH moiety and the proton linked to the chiral carbon. Two singlets for NH_2 group show non-equivalence of these protons. For the NH function a characteristic doublet due to coupling with proton of chiral carbon ($J = 8.0$ Hz) appeared at $\delta = 4$ ppm. Different chemical shifts for the groups next to chiral center are observed. This phenomenon is more pronounced with bulky substituents. The IR spectra showed characteristic group absorptions for νNH (3300 cm^{-1}), for νC=O, amide I band (1670 cm^{-1}), and C=N ring stretching (1573 cm^{-1}). The analytical data and proton chemical shifts of the compounds are shown in Tables 1–3.



Scheme 1.

Table 1
Analytical data of 1,2,4-oxadiazoles derivatives

Comp.	M.p. (°C) [a]	Yield (%)	$(\alpha)_D^{20}$ [b]	*Rf* [c]	Molecular formula	Calc. (%)			Found (%)		
						C	H	N	C	H	N
6a	226–8	55	+21.3	0.69	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.37	65.87	5.50	15.4
6b	235–7	86	−25.2	0.52	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.37	65.90	5.52	15.38
6c	237–9	99	+30.1	0.34	$C_{16}H_{20}N_4O_3$	60.74	6.37	17.70	60.81	6.39	17.72
6d	181–2	72	−39.0	0.40	$C_{17}H_{22}N_4O_3$	61.80	6.71	16.96	61.81	6.70	17.01
6e	230–2	90	+20.5	0.45	$C_{17}H_{22}N_4O_3$	61.80	6.71	17.70	61.72	6.7	17.01
6f	101–3	56	−62.9	0.56	$C_{22}H_{22}N_4O_5$	62.55	5.24	13.26	62.63	5.24	13.3
6g	134–6	66	+30.1	0.69	$C_{23}H_{24}N_4O_5$	63.29	5.54	12.83	63.50	5.51	12.75

[a] Crystallized from ethyl acetate/ether/hexane.
[b] Solvent: dimethylsulfoxyde; [ ] = 4 mg/ml.
[c] Solvent system: Ethyl acetate.

Table 2
IR spectral data of compounds

Comp.	IR cm^{-1} (KBr)							
	Assym. (N–H)(NH_2)	Sym. (N–H)(NH_2)	ν(N–H)(NH_2)	(C=$O_{amide\,1a}$)	(C=$O_{amide\,2a}$)	(C=C)	(C=N)	(C–N)
6a	3363.7	3286.2	3199.9	1674.5	1642	1594.6	1573.2	1346.5
6b	3363.6	3286.7	3199.7	1674.7	1642.4	1573.3	1545.4	1346.5
6c	3357.8	3283	3200.5	1674.3	1641.5	1595.2	1573.1	1345.0
6d	3371.1	3281.1	3203.6	1673.4	1641.7	1547.2	1574	1346.8
6e	3358	3287	3199.5	1673.8	1638	1424.4	1545.8	1374.3
6f	3414.1	3302.9	3211.8	1667.7	1667.7	1570.1	1550.6	1366.9
6g	3374.7	3284.5	3206.4	1672.3	1643.7	1573.4	1539.7	1346.8

Table 3
NMR spectral data of compounds

Comp	^{1}H NMR δ ppm (DMSO-d_6)
6a	2.68(t, $J = 7.29$, 2H); 2.71(dd, $J = 13.35$, 4.95, 1H, CH_2); 2.99(dd, $J = 13.35$, 4.49, 1H, CH_2); 3.06(t, $J = 7.19$, 2H); 4.30–4.45 (m, 1H); 7.06(s (NH_2), 1H); 7.10–7.30(m, 5H); 7.45(s (NH_2), 1H); 7.50–7.62(m, 3H); 7.88–8.02(m, 2H); 8.23(d (NH), $J = 8.09$ Hz, 1H)
6b	2.70(t, $J = 7.29$, 2H); 2.77(dd, $J = 13.94$, 4.49, 1H, CH_2); 3.0(dd, $J = 13.94$, 4.79, 1H, CH_2); 3.08(t, $J = 7.29$, 2H); 4.36–4.48 (m, 1H); 7.07(s (NH_2), 1H); 7.2–7.28(m, 5H); 7.44(s (NH_2), 1H); 7.53–7.62(m, 3H); 7.95–8.02(m, 2H); 8.25(d (NH), $J = 8.09$ Hz, 1H)
6c	1.23(d, $J = 5.99$, 6H), 2.3–2.45(m, 1H), 3.20(t, $J = 6.89$, 2H), 3.6(t, $J = 6.90$, 2H); 4.52(dd, $J = 8.39$, 7.49, 1H), 7.44(s (NH_2), 1H), 7.82(s (NH_2), 1H); 7.9–8.1(m, 3H); 8.3–8.5(m, 2H); 8.41(d (NH), $J = 8.39$ Hz, 1H)
6d	0.74(d, $J = 6.29$, 3H); 0.82(d, $J = 6.29$, 3H); 1.41(2ddd, $J = 7.49$, 7.19, 6.89, 2H); 1.48–1.61(m, 1H); 2.74(t, $J = 6.89$, 2H), 3.18 (t, $J = 7.19$, 2H); 4.2(ddd, $J = 8.09$, 7.34, 6.59, 1H); 6.97(s (NH_2), 1H); 7.34(s (NH_2), 1H); 7.53–7.62(m, 3H); 7.96–8.02 (m, 2H); 8.13(d (NH), $J = 8.39$ Hz, 1H)
6e	0.75 (dd, $J = 7.49$, 7.19, 3H); 0.78(d, $J = 6.59$, 3H); 0.98–1.12(m (CH_2), 1H); 1.37–1.45(m (CH_2), 1H); 1.62–1.8(m, 1H); 2.79(t, $J = 7.49$, 2H); 3.18(t, $J = 7.49$, 2H); 4.10(dd, $J = 8.09$, 7.79, 1H); 7.02(s (NH_2), 1H); 7.47(s (NH_2), 1H); 7.52–7.6(m, 3H); 7.94–8.02(m, 2H); 8.16(d (NH), $J = 8.99$ Hz, 1H);
6f	2.55(2 dd, $J = 12.89$, 5.69, 2H); 2.75(t, $J = 7.19$, 2H); 3.16(t, $J = 7.19$, 2H); 4.63(ddd, $J = 13.79$, 7.19, 6.89, 1H); 5.07(s, 2H); 6.96 (s (NH_2), 1H); 7.28–7.38(m, 5H); 7.41(s (NH_2), 1H); 7.52–7.62(m, 3H); 7.96–8.02 (m, 2H); 8.49(d (NH), $J = 7.79$ Hz, 1H)
6g	1.79–1.82(m (CH_2), 1H); 1.92–2.04(m (CH_2), 1H); 2.36(dd, $J = 8.09$, 7.79, 2H); 2.76(t, $J = 6.89$, 2H); 3.17(t, $J = 6.89$, 2H); 4.21(ddd, $J = 8.99$, 8.09, 5.69, 1H); 5.04(s, 2H); 7.09(s (NH_2), 1H); 7.29–7.37(m, 5H); 7.38(s (NH_2), 1H); 7.52–7.59(m, 3H), 7.95–8.01(m, 2H); 8.19(d (NH), $J = 8.09$ Hz, 1H)

3.2. Biological activity

3.2.1. Anti-inflammatory activity

Table 4 shows that compounds **6a**, **c**, **f** and **g** significantly inhibited the rat paw oedema induced by carrageenin depending on the dose employed. At the doses of 3 and 10 mg/kg, compounds **6a** and **c** caused marked inhibition ($P < 0.05$) of the carrageenin-induced paw oedema. At 3 mg/kg, compound **6f** showed a discrete and non-significant inhibition, but with a higher dose (10 mg/kg), it significantly inhibited the carrageenin-induced oedema (Table 4). The compound **6g** markedly ($P < 0.05$) inhibited the carrageenin-induced oedema at the dose of 3 mg/kg, but failed to affect the oedematogenic response at 10 mg/kg (Table 4).

The compound **6b** potentiated the oedematogenic activity by 20–40% at 3 mg/kg whereas at 10 mg/kg it significantly inhibited ($P < 0.05$) the oedema at 1 and 2 h of observation ($n = 6$). Compound **6d** significantly potentiated the oedema at 1 h after administration (76 ± 31 and 53 ± 9.7% potentiation for 3 and 10 mg/kg, respectively) but had no significant effects thereafter. The compound **6e** did not show any noticeable inhibitory effect on the carrageenin-induced oedema at 3 mg/kg (not shown). Higher doses of **6e** were not studied since it evoked toxic effect in the animals accompanied by death in ca. 1 min after administration.

The oral administration of the compounds **6a**, **c** and **g** was totally ineffective in inhibiting the oedema induced by carrageenin during all the observed periods of time. As expected, the indomethacin produced significant inhibition (between 30 and 45%) of the oedema (not shown).

The pharmacological results presented here demonstrate that compounds **6a**, **c** and **g** when administered

Table 4
The inhibitory effects of compounds **6a**,**c**,**f**,**g** (i.v.) on the carrageenin-induced rat oedema

Inhibition (%)					
Comp.	1 h	2 h	3 h	4 h	5 h
3 mg/kg					
6a	37 ± 14.7 *	54 ± 7 *	35 ± 7.8 *	19 ± 9.5	20 ± 8
6c	33 ± 9.3 *	38 ± 9.4 *	26 ± 5.7 *	33 ± 7.3 *	22 ± 6.7 *
6f	0	25 ± 11.3	20 ± 13.0	24 ± 11.0	20 ± 14.1
6g	44 ± 5.5 *	63 ± 7.4 *	54 ± 7.7 *	30 ± 15.5 *	8 ± 6.4
10 mg/kg					
6a	57 ± 10.7 *	68 ± 4.5 *	55 ± 4.6 *	51 ± 4.6 *	48 ± 6.8 *
6c	0	25 ± 8.6	36 ± 6.4 *	32 ± 4.4 *	33 ± 5.2 *
6f	0	57 ± 6.9 *	52 ± 6.8 *	43 ± 9.4 *	35 ± 11.6 *
6g	0	17 ± 12.8	15 ± 6.9	11 ± 5.3	9.9 ± 7.1

* $P < 0.05$ compared with the controlled animals.

intravenously are anti-edematogenic. However, when administered orally, these compounds did not modify the carrageenin-induced oedema. We do not have information on the action mechanism of these compounds, but this report suggests their possible incapability of absorption or destruction by the digestive enzymes.

3.2.2. Antimicrobial activity

The antimicrobial activity of seven synthesised compounds was determined in vitro by the disc diffusion method [22] against two strains of *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella enteritidis*, *Pseudomonas aeruginosa* and two strains of *Candida albicans*. The Mueller–Hinton, Sabouraud agar and Mueller–Hinton broth have been used as a medium of reference for antimicrobial activity tests and minimal inhibitory concentration (MIC) determination, respectively [23].

Compound **6d** was found to be the most active of them all. *E. coli* was the most sensitive and its inhibition zone was 22 mm. This compound showed to be active also against *P. mirabilis*, *S. enteritidis*, and *P. aeruginosa*. The inhibition zones were 17, 12, and 11 mm, respectively. Compound **6f** was found to be active against both strains of *S. aureus* and its inhibition zones was equal to 11 mm. *K. pneumoniae* and *B. cereus* were inhibited by **6e**; inhibition zones were 13 and 10 mm, respectively. The other compounds were either devoid of activity or the inhibition zones were inferior to 10 mm for all considered strains.

The bacteriostatic activity of compound **6d** was determined in vitro against *E. coli* and *P. mirabilis*. Ethyleneglicol was used as the solvent for the compounds and a control without the test compound was included for each tested microorganisms in the 1:10 dilution. Its MIC was 64 μg/ml against *E. coli* and 128 μg/ml against *P. mirabilis*. Compound **6d** presents an interesting bacteriostatic activity, but this activity was inferior to ciprofloxacin, the reference antibiotic whose MIC was 2 and 4 μg/ml against *E. coli* and *P. mirabilis*, respectively.

Concerning the relationships between structure and activity, it can be noted that the compounds **6d**, **e** and **f** carrying a leucine, isoleucine, and aspartic acid moieties, respectively, exhibited an antimicrobial potency, generally superior to compounds **6a**, **b**, **c** and **g**. These compounds containing an amino acid residue in side chain of 1,2,4-oxadiazoles showed a novel profile of antimicrobial activity for this class of heterocyclic compounds.

4. Experimental

4.1. Chemistry

All melting points were determined with a Thomas Hoover apparatus and are uncorrected. IR spectra were obtained on FTIR spectrophotometer Brukker, model IFS66 using KBr pellets. ^{1}H NMR spectra were measured with a Varian UNITYplus 300 MHz NMR spectrophotometer using DMSO-d_6 as solvent and tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was carried out on silica gel coated plates having fluorescence indicator F_{254} (0.2 mm, E. Merck); the spots were visualised under UV light, and by spraying with a 5% acetone solution of ninhydrin or Charing reagent. Column chromatography was carried out on using Kiesegel 60 (230–400 mesh, E. Merck). Protected amino acids (Boc and Obzl), were purchased from Bachem (Switzerland) or Propeptide (France), BOP reagent was purchased from Propeptide. All reagents used in the present work were of analytical grade.

4.1.1. 3-[3-(Phenyl)-1,2,4-oxadiazol-5-yl] propionic acid (3)

This compound was prepared according to the method reported earlier [8].

4.1.2. General procedure for the protection of the C-terminus moiety of the amino acids

To a cold (− 10–0°C) solution of N-Boc-amino acid (3.5 mmol) in dimethylformamide, were successively added isobutyl chloroformate (3.5 mmol) and ammonium hydroxide (7.0 mmol) dropwise for 20 min. Afterwards, the mixture was stirred at room temperature for 2 h. Water was added and the pure product was isolated by filtration followed by drying.

4.1.3. General procedure for the synthesis of 1,2,4-oxadiazoles containing pseudopeptide moiety

To the Boc-amino acylamide (3.0 mmol), trifluoroacetic acid was added and left to stand at room temperature for 1 h. Solvent evaporation in vacuo, and trituration with diethyl ether–hexane gave a white powder. The pure product was easily isolated by filtration and dried. TFA–amino acylamide (2.6 mmol) was dissolved in DMF (10 ml) containing **3** (2.6 mmol), BOP (2.6 mmol) and TEA (0.7 ml) was added to it. The preparation was left to stand for 4 h at room temperature. Afterwards, ethyl acetate (50 ml) was added under stirring. The organic layer was washed several times with sodium bicarbonate (50 ml), water (50 ml), 1 M citric acid (50 ml), water (50 ml), dried over sodium sulfate and concentrated in vacuo. The residue was a white powder after trituration with *n*-hexane.

4.2. Anti-inflammatory activity

4.2.1. Measurement of paw oedema

Male Wistar rats (150–200 g) were used. Oedema was induced by a single sub-plantar injection of carrageenin (1 mg/paw) into the left hind paw of the rat under light ether anaesthesia. The total volume injected was always 0.1 ml. The paw volume was measured immediately before the injection and at hourly intervals thereafter using a hydroplethysmometer (model 7150, Ugo Basile, Italy). The results were expressed as the increase in paw volume (ml) calculated by subtracting the basal volume. The compounds **6a**–**g** were intravenously administered (i.v.) at doses of 3 and 10 mg/kg each ($n = 6$ each) immediately before the subplantar injection of carrageenin. Control animals ($n = 25$) received 0.5 ml of vehicle (60% DMSO). In another experimental procedure, the compounds **6a**, **c** and **g** ($n = 6$ each) were administered by oral route (gavage) 1 h before at doses of 75 and 150 mg/kg. The control animals ($n = 8$) received 1.0 ml of the vehicle (60% DMSO) and the group reference indomethacin 10 mg/kg ($n = 6$). The Student t-test [24] was used to test for statistical significance ($P < 0.05$).

4.2.2. Antimicrobial activity

The antimicrobial activity was determined in vitro by disc diffusion method [22] against two strains of *S. aureus*, *B. cereus*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *S. enteritidis*, *P. aeruginosa* and two strains of *C. albicans*. Overnight cultures were grown at 37°C in Mueller–Hinton broth and diluted to obtain an opacity equivalent to 0.5 on the McFarland scale. It was then dispensed into Petri dishes to yield an uniform depth of 4 mm. The drugs are weighed and dissolved in ethyleneglicol to give concentrations equal to 2 mg/ml. The ciprofloxacin and cycloheximide were used to antimicrobial standard. The discs with a 6 mm diameter were saturated to 20 μl drug solutions. The discs are placed in the surface of culture medium after the complete evaporation of ethyleneglicol. The plates are incubated for 18 h at 37°C. Growth inhibition zones with diameters equal to or greater than 10 mm were considered as positive results.

4.2.3. Bacteriostatic activity

The bacteriostatic activity of compound **6d** was determined in vitro against *E. coli* and *P. mirabilis*. Overnight cultures were grown at 37°C in Mueller–Hinton broth and afterwards, diluted to obtain an opacity equivalent to 0.5 on the McFarland scale. The compound is solubilized in ethyleneglicol and a serial 2-fold dilution of compound is prepared in water to give concentrations 10-fold higher than the final one desired. The concentration of 1280 μg/ml was used as the starting one, providing a final concentration equal to 128–0.5 μg/ml. The ciprofloxacin was used as reference antibiotic. It was verified that ethyleneglicol was completely inactive against the tested microorganisms in the 1:10 dilution.

A series of tubes is prepared by mixing one part of each dilution of compound with nine parts of the Mueller–Hinton broth, previously inoculated and incubated for 18 h at 37°C. The MIC is considered to be the lowest drug concentration for which there is no microbial growth [25].

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