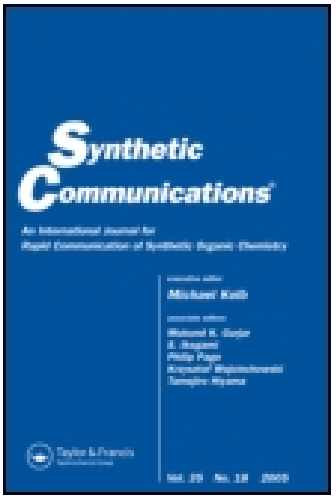

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Synthesis, Antibacterial, and Antifungal Activities of Imidazo[2,1-c][1,2,4]triazoles and 1,2,4-Triazolo[4,3-a]pyrimidinones

Monia Aouali [a], Fatma Allouche [a], Imen Zouari [b], Dhekra Mhalla [b], Mohamed Trigui [b] & Fakher Chabchoub [a]

[a] Laboratoire de Chimie Appliquée: Hétérocycles, Corps Gras et Polymères, Faculté des Sciences de Sfax, Université de Sfax, Sfax, Tunisia

[b] Biopesticides Team (LPIP), Center of Biotechnology of Sfax, University of Sfax, Sfax, Tunisia

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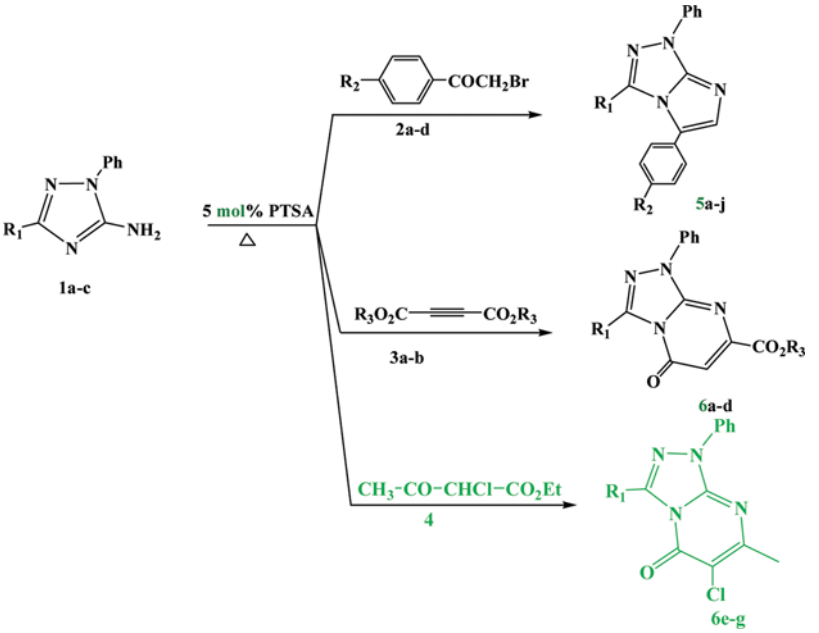
SYNTHESIS, ANTIBACTERIAL, AND ANTIFUNGAL ACTIVITIES OF IMIDAZO[2,1-c][1,2,4]TRIAZOLES AND 1,2,4-TRIAZOLO[4,3-a]PYRIMIDINONES

Monia Aouali,[1] Fatma Allouche,[1] Imen Zouari,[2] Dhekra Mhalla,[2] Mohamed Trigui,[2] and Fakher Chabchoub[1]

[1]*Laboratoire de Chimie Appliquée: Hétérocycles, Corps Gras et Polymères, Faculté des Sciences de Sfax, Université de Sfax, Sfax, Tunisia*
[2]*Biopesticides Team (LPIP), Center of Biotechnology of Sfax, University of Sfax, Sfax, Tunisia*

GRAPHICAL ABSTRACT



Abstract *A straightforward method has been developed for the synthesis of 1-phenyl-imidazo [2,1-c][1,2,4]triazole derivatives* ***5a–j*** *and 1-phenyl-[1,2,4]triazolo[4,3-a]pyrimidinones derivatives* ***6a–g*** *starting from 5-amino-1-phenyl[1,2,4]triazole and p-toluenesulfonic acid (PTSA). This methodology affords a number of 1-phenyl-imidazo [2,1-c][1,2,4]triazoles*

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Address correspondence to Fatma Allouche, Laboratoire de Chimie Appliquée: Hétérocycles, Corps Gras et Polymères, Faculté des Sciences de Sfax, Université de Sfax, 3018 Sfax, Tunisia. E-mail: fatma.mallek_allouch@yahoo.fr

5a–j and 1-phenyl-[1,2,4]triazolo[4,3-a]pyrimidinones 6a–g in reasonable yields and short reaction times. The structures of all new compounds were elucidated using infrared, ^{1}H and ^{13}C NMR, and high-resolution mass spectrometry. Some of the newly synthesized compounds were screened for their antimicrobial activity.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 5-Amino-1-phenyl[1,2,4]triazole; antimicrobial activity; imidazo[2,1-c][1,2,4]-triazole; triazolo[4,3-a] pyrimidinones

INTRODUCTION

There exist a number of [1,2,4]triazoles having a wide range of pharmacological activities, some of them are applied in medicine: alprazolam (tranquilizer), estazolam (hypnotic, sedative, tranquilizer), rilmazafon (hypnotic, anxiolytic, used in the case of neurotic insomnia), benatradin (diuretic), trapidil (hypotensive), trazodon (antidepressant, anxiolytic), etoperidone (antidepressant), nefazodone (antidepressant, 5-HT2A antagonist), anastrozole, letrozole, vorozole (antineoplastics, nonsteroidal competitive aromatase inhibitors), ribavirin (the potent antiviral N-nucleoside), fluconazole, itraconazole, and terconazole (the powerful azole antifungal agents).[1] It follows from the literature survey that, depending on the type of substituent, the derivatives of [1,2,4]triazole have a high potential for biological activity, possessing a wide range of antimicrobial[2] and antitumor[3] properties. The other ones show anti-inflammatory,[4] antihypertensive,[5] anticonvulsant and antiviral,[6] and analgesic[7] activities. Previous studies by Sztanke et al.[8] concerning bridgehead nitrogen–heterocyclic compounds obtained by fusion of the 1-hydroimidazole and [1,2,4]triazole nuclei have identified compounds containing a group at position 3 and aryl substituent at position 7 with significant antibacterial activity. This heterobicycle was strongly active against *Staphylococcus aureus* ATCC 25923, with a minimum inhibition concentration (MIC) value of 31.7 mM and showed superior antibacterial activity to ampicillin.[8a] On the other hand, some derivatives having the same heterocyclic skeleton are bioactive molecules[9] and imidazo-fused heterocycles, revealing promising anticancer activities.[10] It seemed worthwhile to synthesize some novel biheterocyclic derivatives containing the imidazotriazole and triazolopyrimidine nuclei as possible compounds of high biological potency. In a second study, bridgehead nitrogen–heterocyclic compounds obtained by fusion of the 1,5-dihydro pyrimidine and [1,2,4]triazole lead to 1,2,4-triazolo[4,3-a]pyrimidine carboxylate derivatives. The synthesis and biological activities of these compounds have been interesting topics in the fields of medicinal and agricultural chemistry for many years.[11] Some triazolopyrimidine derivatives are known as cardiovascular vasodilators,[11a] dual thrombin/factor Xa inhibitors[11b], and human adenosine A_{2a} and A_3 receptor ligands.[11c,d]

The present work describes an interesting approach to substituted imidazotriazoles and triazolopyrimidinones derivatives having antifungal and antibacterial activities. In particular, we were interested in the synthesis of *para*-toluenesulfonic acid (PTSA)–catalyzed 1-phenyl-imidazo[2,1-c][1,2,4] triazoles **5** and 1-phenyl[1,2,4] triazolo[4,3-a] pyrimidinones **6** from easily accessible 5-amino-1-phenyl[1,2,4]triazole.

Table 1. Yields of the compounds according to the catalyst

Catalyst	R_1	R_2	Yield (%)	Compound
PTSA	CH_3	H	83	5a
CH_3COOH	CH_3	H	63	5a
$Sc(OTf)_3$	CH_3	H	72	5a

RESULTS AND DISCUSSION

Chemistry

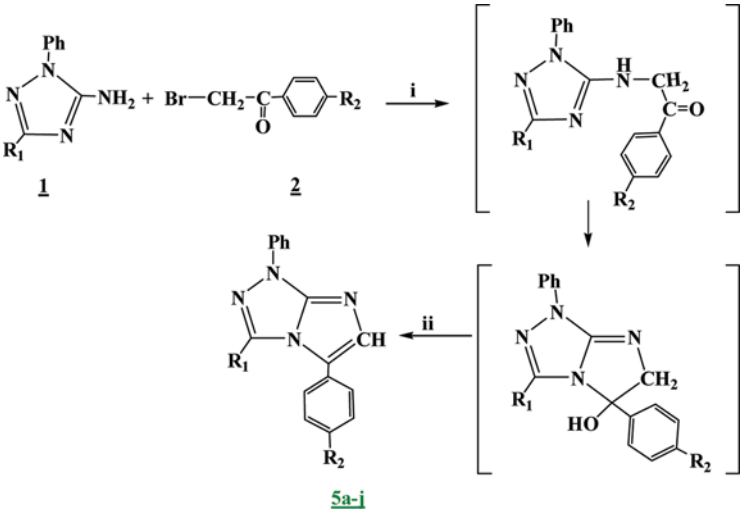
The 5-amino-1-phenyl [1,2,4] triazoles derivatives **1a–c** were synthesized according to the literature.[12]

The general synthetic procedure employed for 1-phenyl-imidazo[2,1-c][1,2,4]triazole **5** involves the reaction of appropriate 5-amino-1-phenyl[1,2,4]triazole **1** with α-bromocetophenone **2** in the presence of a catalytic amount of PTSA (5 mol%) in refluxing ethanol. 1-Phenyl imidazo[2,1-c][1,2,4]triazole derivatives **5** were isolated as stable compounds in good yields. Three amino triazoles and different *para*-substituted bromoacetophenones have been tested successfully (Table 1).

We show the different imidazo[2,1-c][1,2,4]triazole derivatives **5** obtained by the condensation. We examined this reaction with a variety of Brønsted acid (CH_3CO_2H) and Lewis acids (PTSA and $Sc(OTf)_3$). The reactions were run by mixing 5-amino-1-phenyl[1,2,4]triazole **1** and α-bromacetophenone **2** in an appropriate solvent, adding the acid catalyst, and monitoring the reaction progress by thin-layer chromatography (TLC). To our delight, in all the cases studied, the anticipated product **5a** was formed. While substantial formation of this product was achieved using a catalytic amount of acid, PTSA was found to be superior in terms of both the purity of the product mixtures and the isolated yield.

We tried to prove the mechanism of the reaction by carrying out the reaction using a Dean–Stark apparatus and we found water. This proves that the reaction occurs when a primary amino group intercepts a bromine atom, liberating HBr, followed by intracyclization and elimination of a water molecule to give 1-phenyl-imidazo[2,1-c][1,2,4]triazole **5a–j**. Bromoacetophenone proved to be more efficient, for example, in the synthesis of **5a** and **5h**, the yields were 83% and 71%, respectively, for using methyl and benzyl amino triazole, and for the other imidazotriazoles synthesized from 3-benzyl-5-amino[1,2,4] triazole the yields are lower. From these results, we conclude that the electronic nature of the substituent on the bromoacetophenone has a significant role on the reaction outcome. The correct identity of compound as imidazo[2,1-c][1,2,4]triazole was confirmed by ^1H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS).(Scheme 1, Table 2).

As starting materials we use 5-amino-1-phenyl[1,2,4]triazole derivatives **1a–c**. First, it was subjected to condensation with dimethyl or diethyl acetylene dicarboxylate **3**, in the presence of a catalytic amount of PTSA (5 mol%). The mixture was refluxed overnight in ethanol to produce 1,2,4-triazolo[4,3-a]pyrimidines carboxylates **6a–d**, obtained after chromatographic purification. The structure and yields of the products formed are independent of the nature of the substituent at aminotriazole. Triazolo[4,3-a]pyrimidines carboxylate **6a–d** were isolated in 62 to 67% yield.



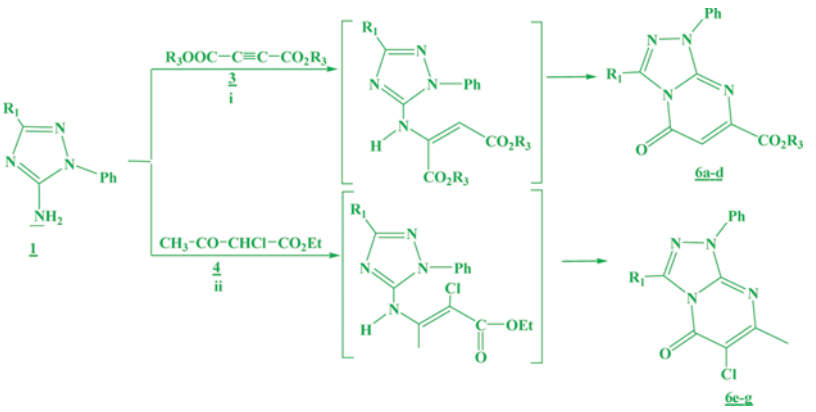
Scheme 1.

The reaction mechanism has been explicitly discussed when studying the condensation of imidazolecarboxamides and dithioesters with diethyl acetylene dicarboxylate.[13] Second, it is known that the synthesis of triazolopyrimidines is generally performed by condensation of amino triazoles with β-keto esters in glacial acetic acid under reflux.[14] Therefore, we investigated the reaction of 5-amino-1-phenyl[1,2,4]-triazole derivatives **1** with ethyl-2-chloro-3-oxobutanoate **4** in the presence of a catalytic amount of PTSA (5 mol%) to probe the possibility of synthesis of biheterocyclic compounds.

The spectroscopic analysis revealed that compounds **6e–g**, isolated from the reaction, were formed when initially heating compounds **1** and **4** to reflux in xylene. Upon further heating, the enaminoester intermediate gradually disappeared. These latter compounds are usually not isolatable because of rapid cyclization into [1,2,4]triazolo[4,3-a]pyrimidin-5-ones **6e–g**. Following isolation and recrystallization from ethanol, **6e–g** are obtained in 65% yield (Scheme 2, Table 3).

Table 2. Synthesis of 1-phenyl-imidazo[2,1-c][1,2,4]triazoles **5a–j** recrystallized from ethanol

Compounds	R_1	R_2	Yield (%)	Mp (°C)
5a	CH_3	H	83	170
5b	CH_3	4-CH_3	63	179
5c	CH_3	4-Cl	57	177
5d	CH_3	4-OCH_3	70	170
5e	C_2H_5	4-CH_3	62	206
5f	C_2H_5	4-Cl	65	210
5g	C_2H_5	4-OCH_3	60	226
5h	C_6H_5-CH_2	H	71	206
5i	C_6H_5-CH_2	4-CH_3	53	208
5j	C_6H_5-CH_2	4-OCH_3	53	205



Scheme 2.

Antimicrobial Activity

The in vitro antimicrobial activity was qualitatively assessed by the determination of the inhibition zone diameters. The antibacterial and antifungal potency of the compounds under similar conditions were compared with gentamicin and amphotericin B, which served as positive controls for bacteria and fungi, respectively. Among the tested compounds, **5d** showed a wide range of antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi (Table 4). Nine out of the 11 tested strains were inhibited by **5d**. It inhibit the growth of clinically important Gram-negative bacteria such as *E. coli* and food spoilage bacteria such as *Salmonella enterica* (food isolate) and the Gram-positive bacteria *L. monocytogenes* (food isolate) with inhibition zones of 14, 11, and 14 mm, respectively. The compound **5 h** showed a high antibacterial activity against the Gram-positive bacteria *S. aureus* with an inhibition zone of 22 mm, slightly less than the inhibition zone of gentamicin (25 mm). However, **5a, 5b, 4c**, and **5j** failed to show any antibacterial activity at the tested concentration. The Gram-positive bacteria were more susceptible to the antimicrobial properties of synthesized compounds than Gram-negative ones. These differences could be attributed in part to the great complexity of the double membrane-containing cell envelope in Gram-negative bacteria compared to the single membrane structure of positive ones.[15] The strong antibacterial activity

Table 3. Synthesis of 1-phenyl-[1,2,4] triazolo[4,3-a] pyrimidinones **6a–g**

Compounds	R_1	R_3	Yield (%)	Mp (°C)
6a	CH_3	CH_3	67	180
6b	C_2H_5	CH_3	66	139
6c	C_2H_5	C_2H_5	62	149
6d	C_6H_5-CH_2	CH_3	65	178
6e	CH_3	—	66	160
6f	C_6H_5-CH_2	—	65	159
6g	C_2H_5	—	62	164

Table 4. Antibacterial and antifungal activities of **5c, d, h** and reference drugs against fungi and food-borne and spoiling bacteria using the agar well diffusion method

Strain	Inhibition zone diameter (mm)[a]			
	5c	5d	5h	Reference compound
Bacterial strains				**Gentamicin**[b]
Gram positive				
Bacillus cereus ATCC 14579	0	11	7	20
Staphylococcus aureus ATCC 25923	0	12	22	25
Enterococcus faecalis ATCC 29212	0	11	0	12
Listeria monocytogenes (food isolate 2132)	0	14	11	15
Gram negative				
Salmonella enterica (food isolate)	0	11	0	18
Escherichia coli ATCC 25922	0	14	0	21
Fungal strains				**Amphotericin B**[c]
Aspergillus niger CTM 10099	0	0	0	15
Fusarium oxysporum CTM10402	11	11	0	14
Botrytis cinerea CTM10410	0	11	0	12.5
Pythiumsp LPAP032	0	0	0	Nt
Alternaria alternata CTM 10230	0	8	0	14

[a]Diameter of inhibition zones of synthesized compounds including diameter of well, 6 mm.
[b]The used concentation of gentamicin was 10 μg/well.
[c]The used concentation of amphotericin B was 20 μg/well.

of the synthesized compound **5d** indicated that methoxy-substituent might mediate greater potency than methyl or chloride substituents against bacteria. These results indicate that moderate lipophilicity is needed to exert antibacterial activity and to disrupt the permeability barrier of cell membrane[16].

Contamination by fungal strains such as *Fusarium oxysporum* and *Botrytis cinerea* and their respective mycotoxins is considered as a challenge for agriculture and food industries. As with the antibacterial activity, we evaluated antifungal activity by means of inhibition zone diameters compared to the positive control, amphotericin B. Among the tested synthesized compounds, **5d** exhibited antifungal activity with inhibition zone of 11 mm against *F. oxysporum* and *B. cinerea*. The compound **5c** showed activity against only *F. oxysporum*. These results suggest that, as in the case of antibacterial activity, the methoxy-substituent at the 4-position influences strongly both the antifungal spectrum and degree of activity.

CONCLUSION

In conclusion we designed a simple synthesis of substituted new 1-phenyl-imidazo[2,1-c][1,2,4]triazoles **5a–j** and 1-phenyl-[1,2,4]triazolo[4,3-a] pyrimidinones **6a–g** in good yields. The synthesized compounds were tested for their antibacterial and antifungal activities. Results showed that the compound **5d** exhibited strong antibacterial and moderate antifungal activities. Taking into account the significant antibacterial and antifungal activities of the presented compounds, the research in this field will be continued.

EXPERIMENTAL

Melting points were measured on an Electrothermal apparatus. Progress of the reactions was monitored with thin-layer chromatography (TLC) using aluminium sheets with silica gel 60 F254 from Merck. Spectra infrared (IR) were recorded on a Perkin-Elmer Paragon FT-IR spectrometer covering field 400–4000 cm^{-1}. The spectra of ^{1}H NMR and ^{13}C NMR were recorded in solution in $CDCl_3$ or in dimethylsulfoxide (DMSO-d_6) on a Bruker spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz). The chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (TMS) as internal reference. The multiplicities of the signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quadruplet; and m, multiplet, and coupling constants are expressed in hertz.

5-Amino-1-phenyl[1,2,4]triazole **1a–c** were prepared from the corresponding cyanamide and phenyle hydrazonates according to the literature[12] by gently refluxing in methanol.

α-Bromoacetophenone **2**, dimethyl acetylenedicarboxylate **3**, ethyl-2-chloro-3-oxobutanoate **4**, PTSA, Sc(OTf)3, CH_3COOH, and solvents used in this work were obtained from Aldrich and Fluka and were used without further purification.

General Procedure for the Synthesis of Substituted Imidazo [2,1-c][1,2,4]triazoles 5a–j

p-TsOH · H_2O (5 mol%) was added to a mixture of 5-amino-1-phenyl[1,2,4] triazole **1** (1 mmol)[12] and α-bromacetophenone **2** (1 mmol) in 3 mL of ethanol. It was refluxed for 12 h. After completion of the reaction, as indicated by TLC (EtOAc–hexane, 90:10), the precipitated solid was separated by filtration, washed with ethanol, and crystallized from a suitable solvent to obtain the pure product.

General Procedure for the Synthesis of Substituted [1,2,4]Triazolo [4,3-a]pyrimidine Carboxylate 6a–d

p-TsOH · H_2O (5 mol %) was added to a mixture of 5-amino[1,2,4]triazole **1** (1 mmol) and dimethyl or diethyl acethylenedicarboxylate **3** (1 mmol) in 3 mL of ethanol. It was refluxed for 12 h. After completion of the reaction, as indicated by TLC (EtOAc–hexane, 90:10), the deposited solid was filtered, washed with ether, and recrystallized from an appropriate organic solvent to give the triazolo[4,3-a]pyrimidine carboxylate derivatives.

General Procedure for the Synthesis of Substituted [1,2,4]Triazolo [4,3-a]pyrimidinones 6e–g

PTSA (5 mol %) was added to a mixture of 5-amino[1,2,4] triazole **1** (1 mmol) and ethyl-2-chloro-3-oxobutanoate **4**, (1 mmol) in 3 mL of xylene and refluxed for 12 h. After completion of the reaction, as indicated by TLC (EtOAc–hexane, 90:10), The deposited solid was filtered, washed with ether, and recrystallized from an appropriate organic solvent to give the triazolo[4,3-a]pyrimidinones derivatives **6e–g**.

Antimicrobial Test

Six bacterial and five fungal strains were used in this study. The tested pathogenic bacteria were *Bacillus cereus* ATCC 14579, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Listeria monocytogenes* (food isolate 2132), *Esherichia coli* ATCC 25922, and *Salmonella enterica* (food isolate 824). The tested fungi were *Aspergillus niger* CTM 10099, *Fusarium oxysporum* CTM10402, *Botrytis cinerea* CTM10410, *Pythium* sp. LPAP032, and *Alternaria alternata* CTM 10230. The bacterial strains were cultivated in Muller–Hinton agar (MH) (Oxoid Ltd, UK) at 37 °C except for *Bacillus* species, which were incubated at 30 °C. The fungi were cultured on potato dextrose agar medium (PDA) and incubated at 28 °C. Working cultures were prepared by inoculating a loopful of each tested bacteria in 3 ml of MH and were incubated at 37 °C for 12 h. For the test, final inoculum concentration of 10^7 CFU/ml of bacteria was used. Fungal spore suspensions were collected from the surface of such fungal colonies by gently scraping with a loop and suspended in 10 ml potato dextrose broth (PDB). Each suspension was mixed vigorously by vortexing for 15–20 min. The spore suspension stock was diluted to obtain a concentration of 10^6 spores/ml (measured by Thoma blade).

Antibacterial and antifungal tests were performed using agar well diffusion method as described by Güven et al.[17] One hundred µl of freshly prepared cell suspension adjusted to 10^7 CFU/ml for bacteria and 10^6 spores/ml for fungi were inoculated onto the surface of agar plates. Thereafter, wells with 6 mm in diameter were punched in the inoculated agar medium with sterile Pasteur pipettes and the molecules were added to each well. Negative control consisted of DMSO, which was used to dissolve the compounds. Gentamicin (10 µg/wells) was used as positive control for bacteria while amphotericin B (20 µg/well) was used as positive control for fungal strains. The plate was allowed to stand for 2 h at 4 °C to permit the diffusion of the molecule followed by incubation at 37 °C for 24 h for bacterial strains and 72 h for fungi at 28 °C. The antimicrobial activity was evaluated by measuring the inhibition zones (clear zone around the well) against the tested microorganisms. All tests were repeated three times.

SUPPLEMENTARY DATA

Supplementary data (experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR) associated with this article can be found in the online version.

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