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An Ecofriendly and Efficient Approach through Sodium Oxalate Catalyst for the Synthesis of Azomethines and α-Aminonitriles Ligands Employing Aqueous Medium

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An ecofriendly, efficient, inorganic salt catalyzed facile method has been developed for the synthesis of potential ligands azomethines and α-aminonitriles employing aqueous medium. This procedure involves the use of $Zn(CN)_2$ an inexpensive, less toxic as compared to KCN, ecofriendly and readily available effective cyanide source. Cyanated products specially have been isolated in high yield on usual work-up procedure. In methanol and DMF solvents, all of the produced compounds were evaluated for *in vitro* antibacterial activity against certain bacterial and fungal strains. Among the compounds tested, **b** and **g** had the most promising antibacterial action against *Bacillus subtilis*. Furthermore, compounds **a** and **c** were discovered to be the most effective antifungal agents against *Candida albicans*.

Keywords: Hydrocyanation, Azomethines, Eco-friendly, Schiff base.

INTRODUCTION

The chemistry of Schiff bases and their analogues α-aminonitriles have been utilized in organic syntheses and as well as in syntheses of inorganic metal complexes [1]. These are broadly used in pharmaceutical industries to develop drugs as these exhibit a broad range of biological activities. Their synthesis involves two steps addition-elimination mechanism and these azomethines are subsequently hydrocyanated [1]. These azomethines give α-aminonitriles on their subsequent hydrocyanation reaction with ecofriendly least toxic zinc cyanide under catalyzed conditions employing sodium oxalate. The side product formed zinc salts are least toxic as compared to other reagent like KCN and other ionic cyanides, which can cause heavy damage to soil and water for the growth of fauna and flora [2]. Moreover, Schiff bases and α-aminonitriles have been synthesized involving aqueous medium by employing sodium oxalate salt for increasing polarity of water to solubilize the polar components both aldehydes and amines [3]. Thus, avoiding more toxic, costlier and carcinogenic solvents.

The synthesis of α-aminonitriles from the hydrocynation of azomethines have been carried out by employing various cyanating agents [4-12] along with a variety of catalysts in non-aqueous toxic organic solvents. The facile hydrocynation reaction is carried out by employing trimethylsilyl cyanide which is expensive moisture sensitive and can thus easily decomposes to give hydrocyanic acid gas which is toxic to its fullest extent [13]. An eco-friendly hydrocyanation of azomethines, synthetic methods of azomethines reported by various researchers [14-16] have drawbacks such as low yields, complex reactions, long reaction time and involving costly toxic organic solvents. Method reported in the present protocol involves the use of inexpensive, environmental benign solvent (*i.e.* water) and employing inorganic biodegrad-able sodium oxolate salt as catalyst. Azomethines obtained were in high yield with maximum purity.

To overcome, this difficulty some alternative arrangement of cyanating reagent was required which should be non-toxic and eco-friendly and not affected by moisture easily, besides its high efficiency in the organic synthesis. Survey of literature reveals that though many cyanating agents has been employed for hydrocyanation reactions, but $Zn(CN)_2$ which is least toxic and eco-friendly in nature has been used in organic synthesis in substitution reactions [17-22]. Cyanation of aryl halides using palladium catalyzed has been achieved [23] more conveniently than by other means like Rosenmund-von Brown reaction

[24]. Cyanation of heteroaryl chlorides using less toxic zinc cyanide as cyanting agent has been achieved more conveniently employing inexpensive $NiCl_2 \cdot 6H_2O$ as catalyst [25]. The versatility of $Zn(CN)_2$ lies in the fact that it is neither acidic, nor basic and being covalent and amphoteric in nature, the cyanide function is not hydrolyzed. The $Zn(CN)_2$ in presence of inorganic salt sodium oxalate easily gives HCN and water soluble zinc oxalate as side product which is entirely non-toxic and can be removed as compared to the usage of toxic KCN, which is difficult to remove by water as it causes a high grade of toxicity to water.

In present study, an ecofriendly hydrocyanation of azomethines have been carried out by employing $Zn(CN)_2$ in presence sodium oxalate in aqueous medium. The most interesting feature of employing $Zn(CN)_2$ is that both cyanide ions can be transferred to the substrate azomethine to provide α-aminonitrile in sufficient good yield that too in aqueous medium. Very few hydrocyanation reactions in organic solvents of azomethines have been reported [26] but the hydrocyanation reaction of substituted C-styrylcinnamalanilines does not appear in the literature employing pure aqueous medium. To explore the synthetic utility of these α-aminonitriles as ligand, present study has been taken up in this direction to employ the use of universal solvent water using sodium oxalate catalyst. In order to explore the importance of zinc cyanide as an environment friendly employing pure aqueous medium under inorganic salt catalyzed condition, the reaction of various substituted cinnamalanilines with $Zn(CN)_2$ was carried out which afforded α-aminonitriles with high yield, with constant stirring the reaction mixture about 10 to 15 min at ambient temperature. Furthermore, all compounds were evaluated for their antibacterial activities toward multi-drug resistant bacteria (MDRB) and antifungal activities.

EXPERIMENTAL

All the melting points were reported using sulphuric acid bath at normal pressure. The IR spectra were reported on Perkin Elmer RXIFT infrared spectrophotometer using KBr pallets. ^{1}H NMR spectra were recorded on 400-MHz Bruker Avance spectrometer using TMS as internal standard of these samples. Their ^{13}C NMR Spectra were recorded on 100 MHz Bruker Avance spectrometer using TMS as internal standard. Elemental analysis was carried out using Elementar Vario-Micro Cube CHN analyzer.

Synthesis of α-aminonitriles (hydrocyanation): A mixture of N-4-methoxycinnamalaniline (0.01 mol, 2.370 g) and zinc cyanide (0.01 mol, 1.170 g) was dissolved in distilled water (25 mL) in a 100 mL conical flask. A catalytic amount of sodium oxalate was added to the mixture to increase the polarity of solvent and the contents were stirred for 15 min. It resulted in a curdy mass of α-aminonitrile (**Scheme-I**). The completion of reaction was monitored by TLC. The crude product was purified by crystallization from hot aqueous solution. Similar procedure was adopted for other compounds and their appropriate quantities are mentioned. Zinc cyanide was taken (1.17 g).

Antibacterial activity: Using a paper disc plate technique, all synthesized compounds were tested *in vitro* for antibacterial activity against two Gram-positive (*Staphylococcus epidermis* and *Bacillus subtilis*) and two Gram-negative (*Acinetobacter baumannii* and *Escherichia coli*) bacterial strains. The nutritional agar medium (peptone, beef extract, NaCl and agar-agar) and Whatman filter paper discs with a diameter of 5 mm were utilized. To get the requisite concentrations, the substances under evaluation were dissolved in methanol. The filter paper discs were soaked in these solutions, dried and then placed in petri dishes that had already been seeded with the test organisms. The plates were incubated for 24 h at 28 ± 2 ºC and the inhibition zone around each disc was measured.

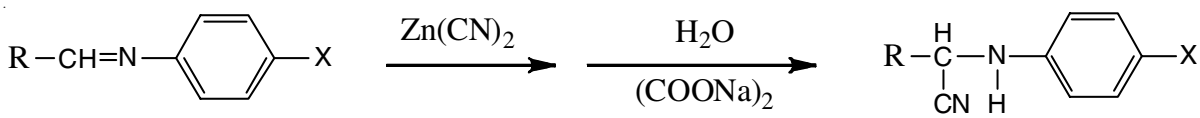
Antifungal activity: The agar plate method was used to assess antifungal activity against *Candida albicans* and *Candida glabrata*. The medium was then mixed with solutions of the compounds in various concentrations in DMF. After 96 h, the diameter of the colony was measured to determine the fungus's linear growth.

RESULTS AND DISCUSSION

In present work, various azomethines have been synthesized by condensing the substituted aromatic aldehydes with different substituted aromatic amines having both electron withdrawing and electron donating groups on both *C*-styryl and *N*-phenyl rings taking their equimolar quantities in distilled water employing sodium oxalate as inorganic salt catalyst. The main purpose of the catalyst is to provide the necessary polarity to the aqueous medium, which increases the solubility of the reactants. Moreover, after the completion of reaction the soluble sodium oxalate is easily washed away with distilled water to give maximum pure azomethines in good yield, which can be used for further reactions without any extra purification.

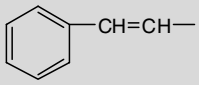
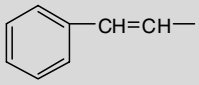
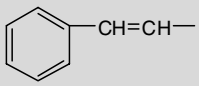
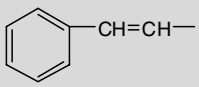
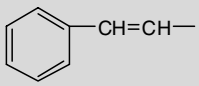
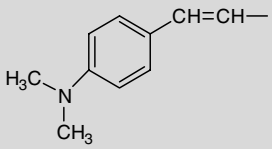
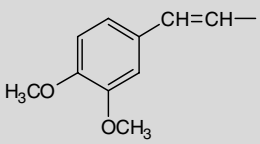
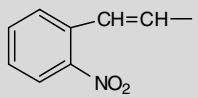
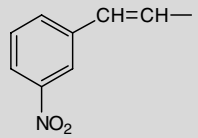
All the synthesized products were characterized through their elemental analysis using microanalysis Perkin-Elmer series II; 2400 analyzer. Results for their elemental analysis are quite satisfactory and are closed to the calculated values, indicating that these compounds have the assigned formula of α-aminonitriles. Data of their elemental analysis is recorded in Table-1. Besides this their infrared spectra, proton resonance spectra and ^{13}C NMR spectra also depict the assigned structure to be correct.

FTIR studies: In their infrared absorption spectra, these α-aminonitriles show absorption bands in same region with minor variation in their absorption bands. A strong band appearing in the range 2255-2220 cm^{-1} has been assigned to the



Scheme-I

TABLE-1
PHYSICAL CHARACTERISTICS DATA OF THE SYNTHESIZED SUBSTITUTED CINNAMALANILINES

Compd.	R	X	m.p. (°C)	Yield (%)	m.f.	m.w.	Elemental analysis (%): Calcd. (found)			
							C	H	N	X = F/Cl
a		4-H	108-109	94	$C_{16}H_{14}N_2$	234	82.05 (81.98)	5.98 (5.87)	11.96 (11.84)	–
b		4-F	114-15	89	$C_{16}H_{13}N_2F$	252	76.19 (76.11)	5.158 (5.149)	11.11 (11.02)	7.5 (7.3)
c		4-OCH_3	130-32	88	$C_{17}H_{16}N_2O$	264	77.27 (77.21)	6.06 (6.01)	10.60 (10.48)	–
d		4-Cl	126-27	79	$C_{16}H_{13}N_2Cl$	268.5	71.58 (71.49)	4.84 (4.79)	10.428 (10.413)	13.22 (13.19)
e		3-NO_2	103-104	80	$C_{16}H_{13}N_3O_2$	279	68.817 (68.817)	4.659 (4.647)	15.053 (15.020)	–
f		H	140-41	91	$C_{18}H_{19}N_3$	277	77.978 (77.892)	6.859 (6.836)	9.523 (15.114)	–
g		H	135-36	90	$C_{18}H_{18}N_2O_2$	294	73.469 (73.457)	6.122 (6.104)	15.053 (15.039)	–
h		H	129-30	87	$C_{16}H_{13}N_3O_2$	279	68.817 (68.798)	4.659 (4.634)	15.053 (15.039)	–
i		H	114-15	78	$C_{16}H_{13}N_3O_2$	279	68.817 (68.801)	4.659 (4.637)	15.053 (15.041)	–

All the melting points were taken in an open bath sulphuric acid.

nitrile function.The absorption band in the region 3460-3320 cm^{-1} has been assigned to stretching vibrations of secondary amine –N-H function. While the absorption bands in 1620-1590 cm^{-1} region has been assigned to aromatic stretching vibrations. In all their IR spectra, the characteristic absorption bands in the region 1640-1635 cm^{-1} due to azomethinic >C=N– double bond was missing indicating that hydrocyanation of these azomethines has occurred. A weak intensity absorption band in the region 1275-1245 cm^{-1} has been assigned to C–N single bond in the finger print region.

NMR studies: In ^{1}H NMR spectrum, cinnamal-4-fluroaniline displays a doublet at δ 7.92 ppm, $J \approx 16$ Hz on coupling with proton (b)-has been assigned to proton H_c. Proton H_b displays a doublet at δ 5.99 ppm, $J \approx 11$ Hz on coupling with proton H_a. While proton H_c itself appears as partially resolved doublet at δ 7.0 ppm. The coupling constants values show that proton H_a, H_b, H_c all are trans to each other. A broad signal in the range δ 7.5-7.1 ppm has been assigned to aromatic protons (9H).

In ^{13}C NMR spectrum, cinnamal-4-fluroaniline display apeak at δ 158 ppm, which has been assigned to carbon bearing fluorine, while a doublet at δ 153 ppm for two carbon atoms *ortho* to fluorine substituent. A signal at δ 141 ppm has been assigned to carbon bearing nitrogen atom, while a doublet at δ 139 ppm has been assigned to *ortho* carbon to *Ipso*-carbon bearing nitrogen. *Ipso* carbon of C-styryl moiety appears at δ 136 ppm while other carbon atom of C-styryl ring appears at δ 128 ppm.The three unsaturated sp^2-carbon appear in the range δ 116-114 ppm.

In ^{1}H NMR spectrum, α-styryl-α-(4-fluoro)anilinoacetonitrile displays signal for H_c proton as doublet at δ 8.2 ppm and for H_a a doublet at δ 6.6 ppm, while H_b appears as partially resolved quartet at δ 6.2 ppm. A broad multiplet in the range of δ 7.2-6.92 ppm has been assigned to aromatic (9H) protons. A broad signal at δ 4.08 ppm has been assigned to secondary amine proton. It is noteworthy to see that proton H_c in α-styryl-α-(4-fluoro)anilinoacetonitrile appears at higher δ value than the corresponding H_c proton of cinnamal-4-aniline by a difference δ 0.36 ppm. This is attributed to the fact that this proton is deshielded by electron withdrawing nitrile group attached to carbon bearing H_c.

Moreover, the ^{13}C NMR spectrum α-styryl-(4-fluoro)-anilinoacetonitrile displays signal at δ 157 ppm, which has been assigned to carbon bearing fluorine while poorly resolved doublet at δ 155 ppm has been assigned to *ortho* carbon atoms to the carbon bearing fluorine atom. A signal at δ 139 ppm has been assigned to carbon bearing nitrogen atom, while a doublet at δ 138 ppm has been assigned to *ortho* carbon to the nitrogen bearing carbon atom. A signal at δ 128 ppm has been assigned for rest of carbon atoms of C-styryl moiety. The sp^2-carbon atoms appear in the range δ 117-115 ppm, while, α-carbon bearing cyano group appears at δ 39 ppm. The signal for cyano carbon appears at δ 114 ppm.

Similarly in ^1H NMR spectrum, α-styryl-α-anilinoaceto-nitrile displays signal for $H_c$proton as doublet at δ 7.04 ppm and for H_a doublet at δ 6.9 ppm, while H_b appears as partially resolved quartet at δ 6.26 ppm. A broad multiplet in the range of δ 7.4-7.1 ppm has been assigned to aromatic (10 H) protons. A broad signal at δ 3.85 ppm has been assigned to secondary amine proton.

Hydrocyanation reaction seems to proceed through the formation of organozinc complex with azomethines where N-atom first coordinates with zinc cyanide with simultaneous coordination of oxalate ion to provide a possible tetrahedral geometry to the cyanating agent as zinc salts are known to form tetrahedral complexes. In the process, cyanide ion gets displaced and attacks the azomethinic carbon followed by the nucleophilic attack of water on zinc cation to displace the cyanated product leaving monocyanatedhemioxolated zinc salt. Similarly, the second mole of azomethine forms the organo zinc complex and all steps are repeated to give second molecule of hydrocyanated product. The possible path followed by reaction is shown in **Scheme-II**.

The probable route with the second azomethine molecule is shown in **Scheme-III**.

Biological activity

Antimicrobial results: All compounds examined showed varying but strong antibacterial activity against Gram-positive strains (*Bacillus subtilis* and *Staphylococcus epidermis*) and Gram-negative strains (*Acinetobacter baumannii* and *Escherichia coli*). However, none of the compounds tested demonstrated a significant antibacterial effect on another Gram-negative bacterial strain (Table-2). This is due to the intrinsic resistance of the Gram-negative bacterial membrane, which acts as a barrier and prevents the derivative molecules from penetrating.

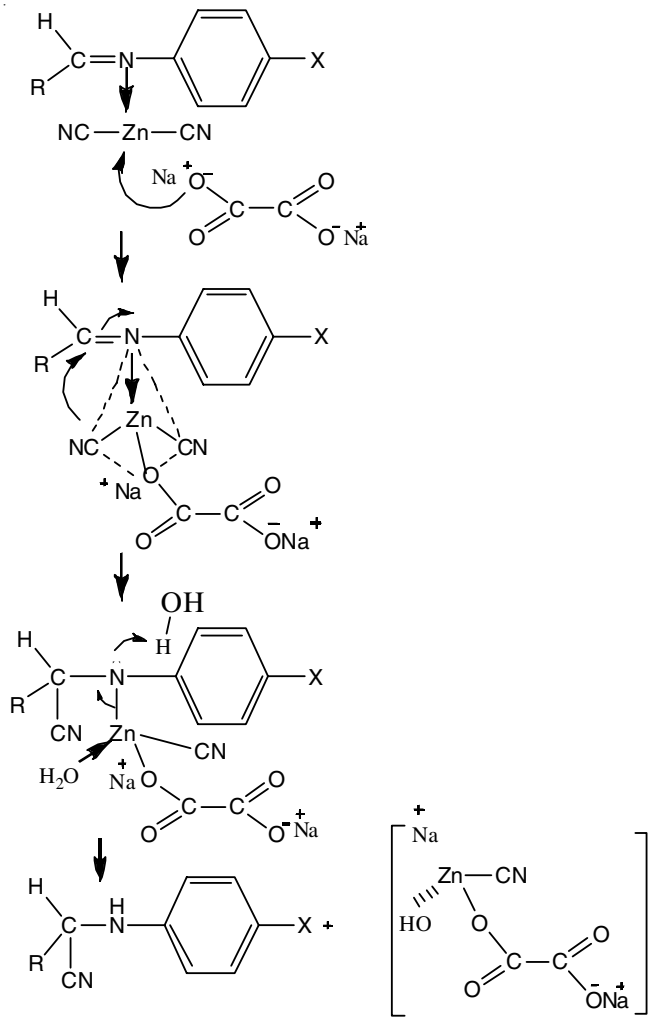
Based on the maximal inhibitory activity provided in Table-3, all compounds had good action against *B. subtilis*, with effective zones of inhibition ranging from 20 to 28 mm. Compounds **a**, **d**, **e**, **h** and **i** inhibited *S. epidermis* with a nearly excellent zone of inhibition ranging from 20.0 to 25.0 mm. Except for compound **f**, all compounds demonstrated a good zone of inhibition extending from 18-22 mm against *A. baumannii*.

Compounds **a**, **b**, **e**, **g** and **h** were shown to be extremely active against all the assessing bacterial strains except *E. coli*, while compounds **b** and **g** were found to be more effective against *B. subtilis*. The remaining compounds were likewise

TABLE-2
In vitro ANTIBACTERIAL ACTIVITIES OF COMPOUNDS **a-i**

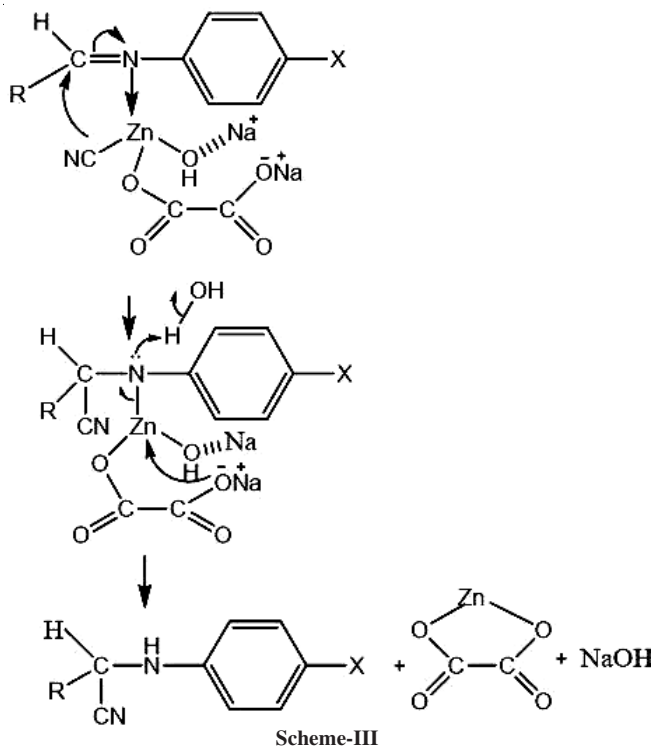
Compound[a]	Diameter of growth of inhibition zone (mm)[b]			
	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis	*S. epidermis*	*A. baumannii*	*E. coli*
a	23	23	18	14
b	25	18	24	–
c	21	–	20	–
d	20	22	21	11
e	22	25	23	21
f	24	15	17	18
g	28	13	19	–
h	22	22	23	19
i	19	21	22	23

–No activity; [a]Concentration 4.0 mg/mL; [b]Values including diameter of the well (8 mm) are means of three replicates.



Scheme-II

active against all bacterial strains except *E. coli*. Minimum inhibitory concentration (MIC) investigations were conducted on compounds that shown promising antibacterial activity (Table-4). Except for *E. coli*, all compounds had rather excellent activity, with MIC values ranging from 12.5-50.0 μg/mL against all of the examined bacterium strains. Among the compounds **a-i** tested, compounds **b**, **c** and **h** had the lowest MIC values of 12.5 μg/mL against *B. subtilis*. Compounds **a**



Scheme-III

TABLE-3
MINIMUM INHIBITORY CONCENTRATION
(μg/mL) OF COMPOUNDS **a-i**

Compound	Gram-positive bacteria		Gram-negative bacteria	
	B. subtilis	*S. epidermis*	*A. baumannii*	*E. coli*
a	25	12.5	50	6.25
b	12.5	nt	12.5	nt
c	12.5	nt	25	nt
d	50	12.5	50	nt
e	25	25	25	12.5
f	25	nt	25	nt
g	25	nt	25	nt
h	12.5	nt	25	nt
i	25	25	25	Nt

nt - Not tested

TABLE-4
In vitro ANTIFUNGAL ACTIVITIES OF COMPOUNDS **a-I**

Compound[a]	Diameter of growth of inhibition zone (mm)[b]	
	Candida albicans	*Candida glabrata*
a	30	17
b	21	16
c	28	–
d	22	19
e	23	17
f	21	15
g	20	–
h	24	22
i	20	14

– No activity; [a]Concentration 4.0 mg/mL; [b]Values including diameter of the well (8 mm) are means of three replicates.

and **d** had the lowest MIC value against *S. epidermis*, 12.5 μg/mL. Compounds **a** and **b** discovered to be the most effective against all bacterium strains.

Antifungal activity: All the synthesized compounds were tested *in vitro* for antifungal activity towards two yeast species, *C. albicans* and *C. glabrata*. Except for compounds **c** and **g**, all the examined compounds showed significant expansion of the inhibition zone against *C. albicans*, while the other compounds showed moderate growth of the inhibition zone against *C. glabrata* (Table-4). It was discovered that compounds **a** and **c** demonstrated the outstanding activity against *Candida albicans*, with zones of inhibition of 30 and 28 mm, respectively and MIC values of 6.25 and 12.5 μg/mL. Other examined compounds had good action against *C. albicans* with MIC values of 6.25-25 μg/mL and fair activity against *C. glabrata* (Table-5).

TABLE-5
MINIMUM INHIBITORY CONCENTRATION
(μg/mL) OF COMPOUNDS **a-I**

Compound	*Candida albicans*	*Candida glabrata*
a	6.25	nt
b	25	12.5
c	12.5	50
d	25	6.25
e	25	nt
f	25	50
g	25	12.5
h	25	50
i	25	12.5

nt - Not tested

Conclusion

The hydrocyanation method is equally effective with azomethines having electron withdrawing or electron donating groups on C-phenyl and N-phenyl rings. No other side product or ring substitution has been observed. The present method involves mild reaction conditions, simplicity of experimental procedure, avoidance of toxic reagent, costlier toxic organic solvents, moisture sensitive catalyst. Taking account into the biological data into account, it is possible to conclude that all of the examined compounds shown good antibacterial activity against the bacterial strains *Bacillus subtilis*, *Staphylococcus epidermis* and *Acinetobacter baumannii*. All of the compounds examined, however, were shown to be practically ineffective against *Escherichia coli*. Compounds **b** and **g** were found to be more effective inhibitors of *Bacillus subtilis* growth. All the synthesized compounds were proven to be effective at inhibiting *Candida albicans* growth. Compounds **a** and **c** were found to be more effective against fungal strain *Candida albicans*. Except for compounds **c** and **g**, all investigated compounds were effective against *Candida glabrata*. It is believed that these investigations will have a positive impact in the medical fields, spurring additional research towards the creation of innovative and effective antibacterial medicines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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