DESIGN, SYNTHESIS AND EV0ALUATION OF SOME NEW SCHIFF BASE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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Abstract:

In a trial to discover potential antimicrobial agents against the increasing microbial resistance, eight new Schiff base derivatives of glycine amino acid obtained from the condensation reaction with benzaldehyde were designed and synthesized by conventional approach. The structures of all the synthesized compounds were elucidated using IR, ^{1}H NMR and ^{13}C NMR along with MS spectra data. In addition, the antimicrobial activities of the new compounds were screened with gentamycin and ketoconazole as the control against four significant representative strains including *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger*, and *Candida albicans*, using broth microdilution method. The antimicrobial activity results revealed that most of the tested compounds exhibited significant antibacterial activity. In particularly, compound **5** was found to be the most potent antibacterial agent with MIC value of 18 exhibiting better activity against *Staphylococcus aureus* than *Escherichia coli*. Additionally, compounds **4**, **6**, and **10** displayed potent antibacterial activity with MIC value of 15, 16, and 16 respectively. However, compounds **10** and **11** showed good activity against both bacterial strains along with *Aspergillus niger*, indicating their broad spectrum of activity. The structure-activity relationship analysis suggested that the electronic and lipophilic factors of aromatic substituents on the amide nitrogen significantly contributed to antibacterial activity. Moreover, the presence of aromatic heterocyclic or heterobicyclic containing more nitrogen atoms considerably influenced the antifungal activity.

Keywords:

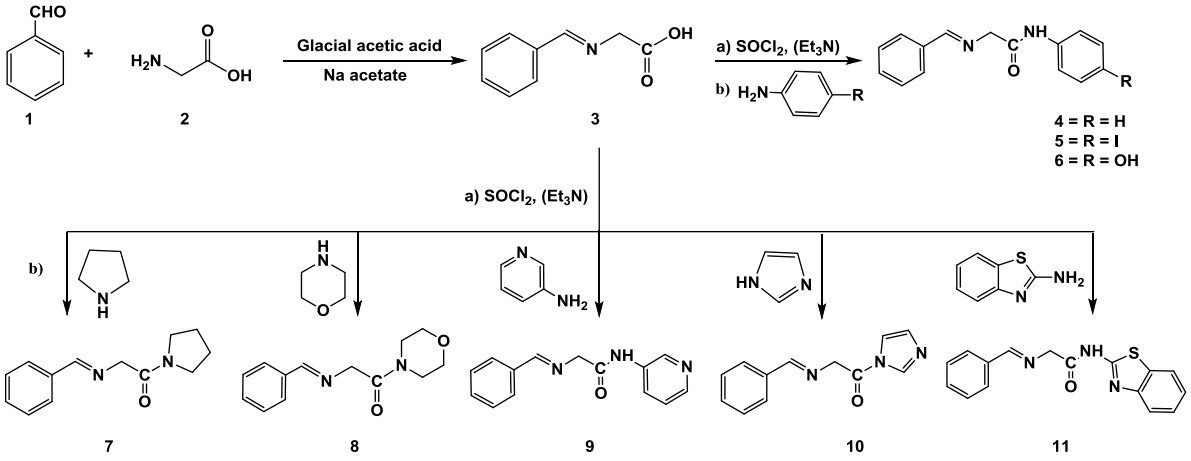
Benzaldehyde Schiff base; Amino acid Schiff base; Antimicrobial agents.

Introduction:

The complexes of amino acid Schiff bases are considered to constitute new kinds of potential antimicrobial and anticancer agents due to the existence of azomethine or imine functional group, which have been shown to be pivotal to their biological activities [Sztanke *et al*, 2013, Tabassum *et al*, 2013]. Schiff bases displayed a wide range of biological activities including antimicrobial [Wang *et al*, 2016], anti-inflammatory and analgesic [Alafeefy *et al*, 2015], anti-tubercular [Sinha *et al*, 2005], antioxidant [Valentina *et al*, 2009], antiviral, antifungal [Raman *et al*, 2011, Salama *et al*, 2015] and anticancer activities [Wang *et al*, 2009, Elshaarawy *et al*, 2016]. The antimicrobial activities of Schiff bases derived from amino acids have indicated better activities against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus polymyza* compared to *Candida albicans* [Sakiyan *et al*, 2004]. Nowadays, Schiff bases derived

from amino acids have acquired a great importance because of enhancing the lipophilicity, alleviating toxicity, and increasing bioavailability when these amino acids are introduced to the original structure [Sinha *et al*, 2008]

The yearly increase in microorganism infections lead to massive economic loss and threats to human health [Alboofetileh *et al*, 2014]. Despite of the abundance of antimicrobial drugs and other modern antibacterial agents, bacterial infections remain a major issue [Medina *et al*, 2018]. Thus, the aim of the present research is to study the effect of Schiff base derived from *L*-glycine on the activity of microorganisms with the hope that these new compounds might lead to a potential safe, effective, and potent antimicrobial agent.



Scheme 1. Synthetic routes to the benzaldehyde Schiff base of *L*-glycine amino acid and compounds **4-11**.

Materials and Methods:

1) Chemistry

All the chemicals which employed in this study were commercially available with analytical grade and used without any further purification. Glycine α-amino acid was of the *L*-series. Solvents were purified and freshly distilled before using according to the standard procedures. The progress of the reaction mixtures was monitored by thin layer chromatography (TLC). The spots on the TLC plates were visualized with a UV lamp (254 nm) and spraying with 0.2% ninhydrin in ethanol and charring after elution. Melting points were measured using Thermo Fisher Scientific. IR spectra were recorded Bruker tensor 27, FT-IR Spectrophotometer. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 and 100 MHz Spectrophotometer. Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Ultraviolet–visible (UV–vis) absorption spectra were recorded on Perkin–Elmer spectrophotometer at the wavelength of maximum absorption (kmax) in a range of DMSO at same concentrations (1×10^{-6} M). The mass spectra were run on a Shimadzu Qp 5050 Ex Spectrometer. The microanalyses for C, H and N were performed on Perkin–Elmer elemental analyzer.

General procedure for the synthesis of glycine Schiff base 3

Benzaldehyde **1** (1 mmol) was dissolved in glacial acetic acid (30 mL) then fused sodium acetate (2 mmol) and *L*-amino acid glycine **2** (1 mmol) were added. The reaction mixture was heated under reflux in a water-bath overnight and the reaction was monitored by TLC (eluent: DCM/methanol, 5:1). After completion, the reaction mixture was cooled, poured on ice then extracted with dichloromethane (DCM). The organic layer was separated using separating funnel and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to produce the compound **3**.

General procedure for the synthesis of compounds 4-11

The preparation of compounds **4-11** by a one-pot reaction was according to a reported method [Leggio *et al*, 2016]. To a solution of compound **3** (1 mmol), an appropriate primary or secondary amine (1 mmol) and triethylamine (3 mmol) in DCM, $SOCl_2$ (1 mmol) was added dropwise with stirring and cooling. The mixture was stirred for 30-45 minutes at room temperature, then the solvent was distilled off under reduced pressure. The resulted residue was taken up in DCM and washed first with aqueous HCl (5%) and then with aqueous NaOH (5%). The organic layer was separated using separating funnel, dried over anhydrous (Na_2SO_4), filtered and evaporated under reduced pressure to give to the final compounds **4-11**, which were further crystallized from ethanol.

Experimental:

2-(Benzylideneamino)acetic acid (3):

Solid, yield 66%, mp 194-196 ºC; IR (KBr, cm^{-1}): 1496 (C-N), 1617 (HC=N), 1734 (C=O), 3347-3566 (OH); ^{1}H-NMR (400 MHz, DMSO-*d6*, δ ppm): δ 12.7 (s, 1H, OH, D_2O exchangeable), 8.0 (s, 1H, CH=N), 7.0-7.6 (m, 5H, Ar-H), 4.0 (s, 2H, CH_2); ^{13}C-NMR (100 MHz, DMSO, δ ppm) δ 171.2, 160.1, 136.6, 131.4, 129.0, 128.2, 61.0; MS: (m/z) 163.35; Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58; O, 19.61; Found: C, 66.05; H, 5.96; N, 8.48; O, 19.51.

2-(Benzylideneamino)-*N*-phenylacetamide (4):

Solid, yield 62%, mp 148-150 ºC; IR (KBr, cm^{-1}): 1117 (C-N), 1618 (HC=N), 1701 (C=O), 3066 (Ar-H), 3438 (NH); ^{1}H-NMR (400 MHz, DMSO-*d6*, δ ppm): δ 10.2 (s, 1H, NH, D_2O exchangeable), 8.0 (s, 1H, CH=N), 7.0-7.6 (m, 10H, Ar-H), 4.0 (s, 2H, CH_2); ^{13}C-NMR (100 MHz, DMSO, δ ppm) δ 168.6, 160.1, 138.5, 136.2, 131.0, 129.2, 128.6, 128.5, 128.0, 121.1, 57.0; MS: (m/z) 238.35; Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76; O, 6.71; Found: C, 75.11; H, 5.62; N, 11.80; O, 6.46.

-2-(Benzylideneamino)-*N*-(4-iodophenyl)acetamide (5):

Solid, yield 69%, mp 119-121 ºC; IR (KBr, cm^{-1}): 1178 (C-N), 1587 (HC=N), 1685 (C=O), 3058 (Ar-H), 3371 (NH); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 10.1 (s, 1H, NH, D_2O exchangeable), 8.0 (s, 1H, CH=N), 7.7 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.6 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.0-7.5 (m, 5H, Ar-H), 4.0 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 168.1, 160.4, 137.5, 137.6, 136.2, 131.2, 129.6, 128.3, 121.0, 86.2, 57.0; MS: (m/z) 364.35; Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.47; H, 3.60; I, 34.85; N, 7.69; O, 4.39; Found: C, 49.12; H, 3.30; I, 34.45; N, 7.59; O, 4.79.

2-(Benzylideneamino)-*N*-(4-hydroxyphenyl)acetamide (6):

Solid, yield 71%, mp 130-132 ºC; IR (KBr, cm^{-1}): 1155 (C-N), 1592 (HC=N), 1685 (C=O), 3063 (Ar-H), 3451 (NH), 3321-3566 (OH); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 10.6 (s, 1H, NH D_2O exchangeable), 8.0 (s, 1H, CH=N), 7.9 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.6 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.0-7.5 (m, 5H, Ar-H), 5.7 (s, 1H, Ar-OH, D_2O exchangeable), 4.2 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 167.2, 160.4, 154.8, 136.7, 131.2, 131.7, 129.6, 128.3, 123.9, 116.2, 57.1; MS: (m/z) 254.11; Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02; O, 12.58; Found: C, 70.65; H, 5.53; N, 11.32; O, 12.08.

2-(Benzylideneamino)-1-(pyrrolidin-1-yl)ethan-1-one (7):

Solid, yield 67%, mp 93-95 ºC; IR (KBr, cm^{-1}): 1023 (C-N), 1617 (HC=N), 1696 (C=O), 2925 (C-H, aliphatic); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 8.0 (s, 1H, CH=N), 7.1-7.9 (m, 5H, Ar-H), 4.4 (s, 2H, CH_2), 3.1-3.2 (m, 4H), 1.6-1.7 (m, 4H); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 172.5, 160.4, 136.3, 131.1, 129.2, 128.7, 55.6, 48.3, 25.2; MS: (m/z) 216.24; Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95; O, 7.40; Found: C, 72.01; H, 7.36; N, 12.75; O, 7.20.

2-(Benzylideneamino)-1-morpholinoethan-1-one (8):

Solid, yield 73%, mp 99-101 ºC; IR (KBr, cm^{-1}): 1156 (C-N), 1207 (C-O), 1600 (HC=N), 1685 (C=O), 2925 (C-H, aliphatic); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 7.7 (s, 1H, CH=N), 7.1-7.6 (m, 5H, Ar-H), 4.2 (s, 2H, CH_2), 3.3-3.4 (m, 4H), 2.9-3.0 (m, 4H); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 169.5, 160.4, 136.3, 131.5, 129.5, 128.6, 66.6, 55.3, 47.6; MS: (m/z) 232.83; Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78; Found: C, 67.72; H, 6.64; N, 12.26; O, 13.58.

2-(Benzylideneamino)-*N*-(pyridin-3-yl)acetamide (9):

Solid, yield 64%, mp 90-92 ºC; IR (KBr, cm^{-1}): 1156 (C-N), 1617 (HC=N), 1685 (C=O), 3066 (Ar-H), 3438 (NH); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 10.5 (s, 1H, NH, D_2O exchangeable), 8.7 (s, 1H, CH=N, Ar-H), 8.2 (s, 1H, CH=N, aliphatic), 7.0-7.9 (m, 8H, Ar-H), 4.0 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 160.9, 160.3, 146.3, 143.3, 140.5, 136.6, 131.6, 129.3, 128.4, 126.7, 117.2, 57.2; MS: (m/z) 239.34; Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56; O, 6.69; Found: C, 70.78; H, 5.46; N, 17.26; O, 6.61.

2-(Benzylideneamino)-1-(1H-imidazol-1-yl)ethan-1-one (10):

Solid, yield 69%, mp 120-122 ºC; IR (KBr, cm^{-1}): 1156 (C-N), 1617 (HC=N), 1680 (C=O), 3066 (Ar-H); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 8.1 (s, 1H, CH=N), 7.5-8.0 (m, 8H, Ar-H), 4.5 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 168.2, 160.7, 136.3, 136.5, 131.5, 130.6, 129.4, 128.3, 117.4, 55.1; MS: (m/z) 213.88; Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71; O, 7.50; Found: C, 67.39; H, 5.23; N, 19.51; O, 7.55.

N-(Benzo[d]thiazol-2-yl)-2-(benzylideneamino)acetamide (11):

Solid, yield 74%, mp 154-156 ºC; IR (KBr, cm^{-1}): 1029 (C-N), 1617 (HC=N), 1685 (C=O), 3066 (Ar-H), 3423 (NH); ^{1}H NMR (400 MHz, DMSO-*d6*, δ ppm): δ 10.5 (s, 1H, NH, D_2O exchangeable), 8.6 (s, 1H, CH=N), 7.0-8.2 (m, 9H, Ar-H), 4.0 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO, δ ppm) δ 174.2, 168.0, 160.3, 153.5, 136.3, 131.6,

130.2, 129.3, 128.4, 125.1, 124.6, 121.1, 118.4, 57.0; MS: (m/z) 295.88; Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23; O, 5.42; S, 10.85; Found: C, 65.22; H, 4.34; N, 14.53; O, 5.42; S, 10.65.

2) Antimicrobial evaluation

All synthesized new compounds **4-11** were screened for their *in vitro* antimicrobial activity adopting standard broth microdilution method recommended by NCCLS [Jorgensen *et al*, 1993] using gentamycin and ketoconazole as control drugs. The tested strains include four strains of *Staphylococcus aureus* as a gram-positive bacteria, *Escherichia coli* ATCC 25955 as a gram-negative bacteria, and *Aspergillus niger*, and *Candida albicans* ATCC 10231 as fungal strains. Screening tests regarding the inhibition zone were carried out by the well diffusion method [Magaldi *et al*, 2004, Klancnik *et al*, 2010]. The inoculum suspension was prepared from colonies grown overnight on an agar plate and inoculated into Mueller-Hinton broth (fungi using malt broth). A sterile swab was immersed in the bacterial suspension and used to inoculate Mueller-Hinton agar plates. The compounds were dissolved in dimethylsulfoxide (DMSO) with different concentrations (10, 5, 2.5 mg/ml). The inhibition zone was measured around each well after 24 h at 37 ^{o}C. Controls using DMSO were adequately done.

Result and Discussion:

1) Chemistry

The Schiff base derivatives deduced from amino acid are stable compounds, they were prepared by stirring Schiff bases with an appropriate primary or secondary amines to study the effect of imine and amide moieties on the antimicrobial activity. As shown in (**Scheme 1**), the reaction of Schiff base **3** with the corresponding primary or secondary amino compounds in the presence of $SOCl_2$ and Et_3N gave compounds **4-11** according to previously reported procedure [Leggio *et al*, 2016]. All these compounds were obtained in good yields (62-74). The structures of the synthesized compounds were established with IR, ^{1}H NMR, ^{13}C NMR, along with MS spectra and microanalytical data.

The IR spectra of all synthesized compounds **4-11** showed absence of broad band of acidic OH proton at 3347-3566 cm^{-1}. Instead, IR showed the appearance of amidic C=O functional group at 1685-1701 cm^{-1}. Moreover, the characteristic band at 3371-3438 cm^{-1} indicating for the NH group of secondary amine products and disappearing for tertiary amine products. In the ^{1}H NMR spectral data, all the protons were found to be in their expected region. The ^{1}H NMR spectra of Schiff base derivatives showed the characteristic singlet signal at δ 10.2 corresponding to secondary amine proton (NH) and display the absence of the proton signals assigned to the amino moiety, indicating that the formation of tertiary amine derivatives (compounds, **7**, **8**, **10**).

2) Antimicrobial evaluation

The minimal inhibitory concentration (MIC) values of compounds **4-11** were presented in (**Table 1**). All the synthesized compounds showed a higher antibacterial activity against gram-positive bacterial strains in comparison to gram-negative bacterial strains. Among the tested compounds, compound **5** showed the highest antibacterial activity against *Staphylococcus aureus* with the MIC value of 18. On the other hand, all

the synthesized compounds showed no antifungal activity against the tested microorganisms, except compounds **10** and **11** which displayed strong antifungal activity with the MIC values of 15 and 13 respectively. Compounds **10**, and **11** contain heterocyclic nucleus with more than one heteroatoms that have -I effect and this may be the reason behind the improved antifungal activity especially against *Aspergillus niger* compared with other compounds [Kumar *et al,* 2017].

From analysis of the microbiological studies, the amide nitrogen of Schiff base derivatives and imine moiety play a critical role in their antimicrobial activities. It was important to observe that the aromatic substituents on the amide nitrogen allow overall strong antibacterial activity as compared to the aliphatic substituents. In addition, the presence of heterocyclic or heterobicyclic aromatic substituents on the amide nitrogen (compounds **10**, **11**) demonstrated strong antifungal activity as compared to other synthesized compounds [Kumar *et al,* 2017].

Furthermore, it was also important to notice that compound **5**, bearing *p*-iodophenyl substituent displayed a significant increase in the antibacterial activity as compared to the phenyl substituent (compound **4**) and *p*-hydroxyphenyl substituent (compound **6**), indicating that the presence of electron-deficient aromatic rings might be potential pharmacophores for the antibacterial activity [Naik *et al,* 2013]. Finally, the most important point was that all the potent active compounds showed good selectivity in their action against bacterial strains compared to fungal strains and the selectivity appears to be related to the presence of specific chemical features such as imine moiety, amide nitrogen moiety and electron-deficient aromatic rings.

Table 1: The MIC values of the tested compounds against the four strains (*in vitro*)

Microorganism / Compound	Escherichia Coli	Staphylococcus aureus	Aspergillus niger	Candida albicans
4	11	15	*	*
5	14	18	*	*
6	15	16	*	*
7	10	11	*	*
8	12	14	*	*
9	12	13	*	*
10	15	16	15	*
11	13	12	13	*
Gentamycin	30	24		
Ketoconazole			15	20

Positive control for fungi Ketoconazole 100 µg/ml. Positive control for bacteria Gentamycin 4 µg/ml. * (No antifungal activity was observed). The sample was tested at 10 mg/ml concentration. Mean zone of inhibition in mm beyond well diameter (6 mm) produced on a range of pathogenic microorganisms.

Conclusion

In this study, Schiff base derivatives derived from glycine amino acid were synthesized and structurally characterized using spectroscopic techniques. The investigation of antimicrobial potentials of the synthesized compounds demonstrated a moderate antibacterial activity against gram-negative and moderate to strong against gram-positive bacteria. Compounds **4**, **5**, **6**, and **10** showed strong antibacterial activity against *Staphylococcus aureus* with the MIC value ranging from 15 to 18. Furthermore, compounds **10** and **11** showed a good activity against all bacterial strains and *Aspergillus niger*. The analysis of the microbiological studies revealed that all the potent active compounds showed good selectivity in their action against bacterial strains compared to fungal strains and the selectivity appears to be related to the presence of specific chemical features. These findings indicated that imine moiety, amide nitrogen moiety and electron-deficient aromatic rings afford strong antibacterial activity and bacterial selectivity and therefore, encourage the synthesis of new amide of Schiff base derivatives.

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تصميم وتخليق وتقييم بعض مشتقات قاعدة شيف الجديدة كعوامل محتملة مضادة للميكروبات

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مـــــــن

قسم الكيمياء العضوية كلية الصيدلة جامعة الأزهر

فى محاولة لاكتشاف مضادات الجراثيم ضد المقاومة الميكروبية المتزايدة. تم تصميم ثمانية مركبات من مشتقات قاعدة شيف الجديدة المحتواة على الحمض الامينى الجلايسين المستمدة من تفاعل التكثيف للبنزالدهيد وتخليقها بواسطة الطرق التقليدية . وهذة المشتقات الجديدة تم تميزيها هيكليا من قبل مختلف التقنيات الحديثة باستخدام التحليلات الطيفية الدقيقة. بالاضافة إلى ذلك تم فحص الأنشطة المضادة للميكروبات للمركبات الجديدة باستخدام الجنتاميسين والكيتوكونازول كعنصر تحكم ضد أربعة سلالات كبيرة اثنان من البكتيريا واثنان من الفطريات. كشفت نتائج النشاط المضاد للمبكروبات أن معظم المركبات التى تم تخليقها أظهرت نشاطا مضادا للبكتيريا . وعلى وجه الخصوص وجد أن مركب ٥ هو العامل المضاد للبكتيريا الأكثر فعالية مع قيمة ١٨ مما يدل على نشاط أفضل ضد البكتيريا الموجبة والسالبة. بالإضافة الى ذلك أظهرت المركبات ٤و ٦و ١٠ عامل مضاد للجراثيم بقيمة ١٥و ١٦و ١٦ على التوالى. ومع ذلك أظهرت المركبات ١٠و ١١ نشاط جيد ضد كل السلالات البكتيرية وبعض السلالات الفطرية مما يشيرعلى واسعية المجال لهذة المركبات. كما أقترحت دراسة النشاط التركيبى لهذة المركبات أن العوامل الاكترونية والمحبة للدهون للمركبات الاروماتية المستبدلة فى رابطة الاميد تساهم بشكل كبير وفعال فى النشاط المضاد للبكتيريا . علاوة على ذلك فإن وجود مركبات حلقية أروماتية غيرمتجانسة أحادية الحلقات أو ثنائية الحلقات التى تحتوى على مزيد من ذرات النيتروجين قد أثر يشكل كبير على النشاط المضاد للفطريات.