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Synthesis, characterization and biological evaluation of some new amlodipine derivatives

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Abstract

Background and objective: The Schiff base compound is formed by the condensation reaction of a primary amine with aldehydes or ketones to form the azomethine group RCH=N-R. This study aims to synthesize some new compounds as Schiff bases from amlodipine derivatives and study their biological activity.

Methods: Ether derivatives of benzaldehyde were synthesized using the Williamson ether synthetic method to react with 3-*O*-ethyl 5-*O*-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (amlodipine). Another type of Schiff bases was synthesized from some derivatives of benzaldehyde without the ether group.

Results: The series of Schiff base compounds (6a–k) were obtained from the reaction of benzaldehyde derivatives (5a–k) with amlodipine (4). IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy were used for the characterization of the synthesized compounds. The antibacterial activities of both types of Schiff base compounds against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* were compared.

Conclusion: All of the synthesized ether derivatives (6a–f) showed more antibacterial activity than the derivatives of benzaldehyde (6g–k), and all of the synthesized compounds were more active against Gram-negative bacteria (*Escherichia coli)* than Gram -positive *Staphylococcus aureus*.

Keywords: Amlodipine; Schiff bases; Williamson ether synthesis.

Introduction

Schiff bases are known by the R–N=CH–R (imine) group, where R can be an alkyl or aryl group, and have a great role in the mechanism of transformation in biological systems. Many studies have been conducted on the ability of these compounds to form complexes with various metals, and their behavior has been studied.[1]

These types of compounds are of great importance in many fields, as they are considered the bases for the preparation of a large number of heterocyclic compounds and the synthesis of new drug designs.[2] Many studies have shown that imine compounds have distinct biological activities, such as antifungal, antiviral, antioxidant,[3] antibacterial,[1,4] and anticancer properties.[1,5]

Depending on their uses, application in different fields and biological activity of Schiff bases and heterocyclic compounds and their importance in pharmaceutical and biological fields,[6] the heterocyclic amine (amlodipine) was linked with alkyloxy and aryloxy group to synthesize a new series of Schiff base (imine) compounds with enhanced biological activity.[7-9]

4-Hydroxybenzaldehyde reacted with different alkyl halides and aryl halides in the first step of this study for the synthesis of compounds (3a–f).

The second step was the synthesis of a series of new Schiff bases (6a-k)

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derived from 3-*O*-ethyl-5-*O*-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (amlodipine) (4). Then, after the antibacterial activity of the synthesized compounds was studied on pathogenic strains of Gram-positive bacteria (*S.aureus)* and Gram-negative bacteria *(E. coli)*

Methods

This experimental study was conducted at the College of Pharmacy / Hawler Medical University between 10th of October 2019 to 1st of November 2020, starting from different alkyl and benzyl halides, *p*-hydroxybenzaldehydes, and amine (amlodipine).

Electrothermal melting point apparatus from Stuart Scientific was used for the determination of melting points (Table 1). A spectroscopy-specific Jasco FT-IR 4600 Spectrometer was used to record infrared spectra at the College of Pharmacy (Hawler Medical University). ^{1}H-NMR and ^{13}C-NMR spectra were measured using a Bruker ultra shield 300 MHz with internal TMS (Central Lab., University of Jordan) and a Bruker 400 MHz with internal TMS (Day Petronic Company, Iran); Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. NMR spectra were recorded in solutions of deuterated dimethyl sulfoxide (DMSO-d6).

Synthesis of 4-alkoxy and aryloxybenzaldehydes(3 a–f)[10-12]

K_2CO_3 (0.11mol) was mixed with 4-hydroxybenzaldehyde (0.05mol) and dissolved in 10ml of absolute ethanol, stirred at room temperature for 2 hours, then (0.05 mol) of alkyl halide and substituted benzyl halide was added, and the mixture was refluxed for 7 hours. Finally, the mixture was poured into crushed ice, and the product filtered off. Dried and recrystallized from appropriate solvents. The physical properties are listed in Table 1.

A general method for the synthesis of Schiff bases(6 a–k)

Aldehyde derivative (0.0025 mol) was dissolved in 5 ml of absolute ethanol, and then amlodipine (0.0025mol) was dissolved in 5 ml of absolute ethanol and added to the first solution, which was stirred and heated under reflux for 5 hours. The product was cooled, filtered off, dried, and recrystallized from absolute ethanol. The physical properties are listed in Table 1.

Antibacterial Study

The disk diffusion method was used to study the antibacterial activity of Schiff bases (6a–k) against two types of bacteria, gram-positive *S. aureus* and gram-negative *E. coli.* For this test, Muller-Hinton agar and nutrient agar were used for the preparation of a medium for the maintenance of pure culture, then sterilized by autoclave and poured into a petri dish to a depth of 4 mm. The bacteria were spread on the culture after activation of each type of bacteria on nutrient agar in nutrient broth for 24 hours at 37°C. The agar plate was streaked. The solid powder of the synthesized compounds was mixed with KBr powder (1:3) and converted to a disc by pressing them under pressure. KBr has been used as a blank disc, and four dried discs were placed on the surface of the cultured media per petri dish. The plates were then incubated at 37°*C*for 18 to 24 hours, and the inhibition zone was measured in mm. [13]

Results

The first step of this study was the synthesis of *p*-alkyloxybenzaldehyde and *p*-aryloxybenzaldehyde (3a–f) using the Williamson ether synthesis method for substitution reactions. The ether products are characterized by their physical properties; all of the synthesized compounds were obtained as powders or crystals with a good percentage of yield and a low melting point, only *p*-butyloxybenzaldehyde was collected as a colorless liquid. The synthesized Schiff bases (6a–k) showed a higher melting

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point than the aldehyde, as shown in Table 1.

The results of the IR spectra showed the characteristic peaks of compounds (6a–k) at 1581–1645 cm^{-1} and at 1180–1234 cm^{-1} for azomethines' N=C and C-O bands for ether groups, respectively. The peaks of the carbonyl C=O group in the structure of amlodipine (4) were observed in the region between 1699 and 1670 cm^{-1}, and the N-H bond was observed at 3151 and 3394 cm^{-1}. The vibration frequency of hydrogen attached to C=N was found at (2811-2901) cm^{-1}, as shown in Table 2.

The appearance of signals related to all of the groups existing in the structure of the synthesized compounds (6a-k) in the ^{1}H-NMR and ^{13}C-NMR spectra of Schiff bases and the absence of signals related to aldehyde compounds C=O with the shifting of CH_2 protons attached to the nitrogen atom of the amino group in amlodipine base to the downfield in the ^{1}H-NMR spectra of Schiff bases demonstrated the formation of the products. All of these results indicated that the condensation reaction was carried out successfully. Table 3 contains the ^{1}H-NMR and ^{13}C-NMR spectra data.

Table 1 Some physical constants of compounds 3a-f and 6a-k

Compounds	R	Formula	M.p	Colour	%Yield
3a	$C_6H_5CH_2$-	$C_{14}H_{12}O_2$	63-65	white	90
3b	3-$NO_2C_6H_4$-CH_2-	$C_{14}H_{11}NO_4$	53-56	yellow	86
3c	3-ClC_6H_4-CH_2-	$C_{14}H_{11}ClO_2$	53-55	white	84
3d	C_4H_9-	$C_{11}H_{14}O_2$	258 **	Colorless	82
3e	C_5H_{11}-	$C_{12}H_{16}O_2$	58-60	white	85
3f	HC≡C-CH_2-	$C_{10}H_8O_2$	66-67	yellow	89
6a	C_6H_5-CH_2O-	$C_{34}H_{35}ClN_2O_6$	89-90	yellow	90
6b	3-$NO_2C_6H_4CH_2O$	$C_{34}H_{34}ClN_3O_8$	143-144	yellow	88
6c	3-$ClC_6H_4^-$-CH_2O-	$C_{34}H_{34}Cl_2N_2O_6$	182-183	yellow	86
6d	C_4H_9O-	$C_{31}H_{37}ClN_2O_6$	158-159	yellow	65
6e	$C_5H_{11}O$-	$C_{32}H_{39}ClN_2O_6$	160-165	green	85
6f	HC≡C-CH_2O-	$C_{30}H_{31}ClN_2O_6$	86-87	yellow	83
6g	4-CH_3O	$C_{28}H_{31}ClN_2O_6$	107-119	yellow	90
6h	4-Cl-	$C_{27}H_{28}ClN_2O_5$	129-130	yellow	88
6i	3- NO_2-	$C_{27}H_{28}ClN_3O_8$	155-156	yellow	87
6j	3-OH-	$C_{27}H_{29}ClN_2O_6$	121-123	yellow	90
6k	*Cinn	$C_{29}H_{31}ClN_2O_5$	127-128	yellow	85

*Cinnamaldehyde **(b.p)

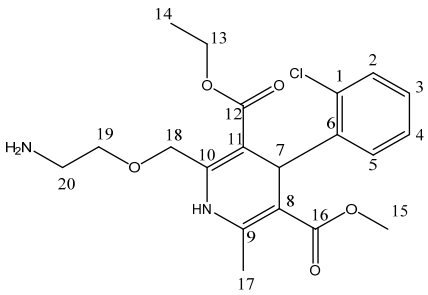
https://doi.org/10.15218/zjms.2024.048

Table 2 The IR data of investigating compounds (6a-k)

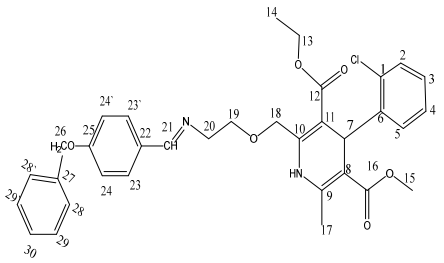
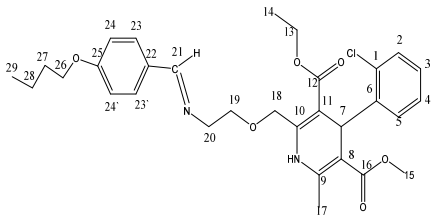
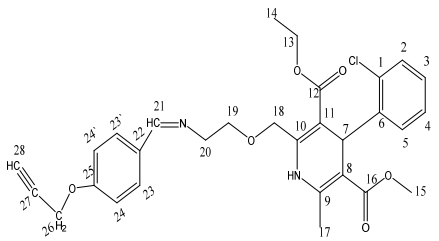
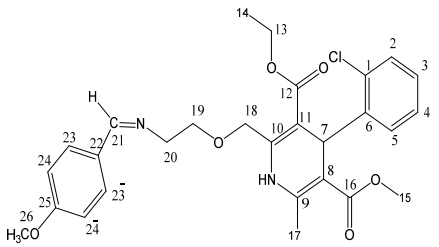
Compound No.	R	v N-H	v CH=N	v C≡C vC-H	v C=O	v C=N	v N-O asym. str.	v N-O sym. str.	v C-O ether
6a	C_6H_5-CH_2O-	3151	2830		1670	1612			1180
6b	3-$NO_2C_6H_4$-CH_2O-	3378	2815		1670	1633	1528	1388	1204
6c	3-ClC_6H_4-CH_2O-	3193	2811		1670	1604			1203
6d	C_4H_9O-	3367	2869		1679	1592			1234
6e	$C_5H_{11}O$-	3380	2849		1697	1607			1202
6f	HC≡C-CH_2O	3367	2861	2121 3324	1685	1604			1203
6g	4-CH_3O-	3358	2833		1699	1581			
6h	4-Cl	3282	2833		1690	1623			
6i	3-NO_2	3375	2901		1696	1645	1590	1393	
6j	3-OH	3358	2900		1687	1638			
6k	*Cinn	3394	2833		1685	1635			

*Cinnamaldehyde

Table 3 Diagnostic peaks in ^{1}H-NMR and ^{13}C-NMR spectra for some synthesized compounds (6a-k) solvent DMSO d^6 ,Chemical shift (ppm)

Comp.	Structure	Chemical Shift (ppm)
4		^{1}H-NMR ($CDCl_3$): 7.8 (s, 1H, N-H), 7.03-7.38 (m, 4H, Ar), 5.3 (s, 1H, CH C_7), 4.05 (q, 2H, CH_2, C_{13}), 4.72 (dd, 2H, CH_2O, C_{18}), 3.56 (s, 3H, CH_3OC=O, C_{15}), 3.5 (t, 2H, CH_2, C_{19}), 2.93 (t, 2H, CH_2, C_{20}), 2.34 (s, 3H, CH_3, C_{17}), 1.31 (2H), 1.18 (t, 3H, CH_3, C_{14} ^{13}C-NMR: 14.56 (C_{14}), 18.49 (C_{17}), 37.19 (C_7), 41.38 (C_{20}), 50.94 (C_{15}), 59.76 (C_{13}), 66.77 (C_{18}), 73.60 (C_{19}), 101.86-146.95 (10C) Ar-C, 166.83 (C_{12}), 167.68 (C_{16}).

https://doi.org/10.15218/zjms.2024.048

Comp.	Structure	Chemical Shift (ppm)
6a		^{1}H-NMR: 8.49 (s, 1H, NH), 8.3 (s, 1H, CH=N, C_{21}), 7-7.8 (m, 12H, Ar-H), 5.2 (s, 1H, CH, C_7), 4.5-4.6 (dd, 2H, CH_2O, C_{18}), 4 (q, 2H CH2, C_{13}), 3.8 (t, 2H, CH_2-N, C_{20}), 3.7 (t, 2H, CH_2-CH_2N, C_{19}), 3.5 (s, 3H, CH_3OC=O,C_{15}), 2.2 (s, 3H, CH_3, C_{17}), 1(t,3H,CH_3, C_{14}) . ^{13}C-NMR: 14.56 (C_{14}), 18.69 (C_{17}), 37.19 (C_7), 50.97 (C_{15}), 59.85 (C_{13}), 60.4 (C_{20}), 66.77 (C_{18}), 69.78 (C_{26}), 70.66 (C19), 102-146 (17C) Ar-C, 160.78 (C_{21}), 162. (C_{25}), 166 (C_{12}), 166.85 (C_{16}).
6d		^{1}H-NMR: 8.44 (s, 1H, N-H). 8.29 (s,1H,CH=N, C_{21}), 7.7.67 (m, 8H, Ar-H), 5.3 (s,1H, CH, C_7), 4.6 (dd,2H, CH_2O, C_{18}), 4 (t,2H, CH_2-N, C_{20}), 4(t, 2H, CH_2O, C_{26}), 3.7(s,3H, CH_3, C_{15}), 3.4 (q,2H,CH_2, C_{13}), 3.4 (t,2H, CH_2, C_{19}), 2.18 (s,3H, CH_3, C_{17}), 1.7 (p,2H, CH_2, C_{27}), 1.46 (h, 2H, CH_2, C_{28}), 1.1(t, 3H, CH_3,C_{14}), 0. 96 (t, 3H, CH_3, C_{29}). ^{13}C-NMR: 14.13(C_{29}), 14.51 (C_{14}), 18.69(C_{17}), 19.02 (C_{28}), 31.14 (C_{27}), 37.19 (C_7), 50.93 (C_{15}), 59.85 (C_{13}), 60.4(C_{20}), 66.79 (C_{18}), 67.75 (C_{26}), 70.7 (C_{19}), 102-146 (13C) Ar-C, 161.16(C_{21}), 162.11 (C_{25}), 166.76 (C_{12}), 166.85 (C_{16}).
6f		^{1}H-NMR: 8. 46 (s, 1H, N-H), 8.3 (s, 1H, CH=N, C_{21}), 7. -7.7 (m, 8H, Ar-H), 4.68 (s,2H, CH_2-O,C_{26}), 5.3(s,1H,C-H, C_7), 6(dd, 2H, ,CH_2O, C_{18}), 4.1 (q, 2H, CH_2,C_{13}), 4(t,2H, CH_2-N, C_{20}) 3.7 (t, 2H, CH_2CH_2N,C_{19}), 3.5 (s,3H, CH_3OC=O, C_{15}) 3.4(s,1H, C_{28}), 2.2 (s, 3H,CH_3,C_{17}), 1.1 (t,3H,CH_3 , C_{14}). ^{13}C-NMR:14.42 (C_{14}). 18.59 (C_{17}), 37.9 (C_7), 55.98 (C_{15}), 59.85 (C_{26}), 66.76 (C_{13}), 67.16 (C_{20}), 70.64 (C_{18}), 73.39 (C_{19}),78.91 (C_{28}), 79.39 (C_{27}), 101.80-146.81 (13C) Ar-C, 159.5 (C_{25}), 162.02 (C_{21}), 166.76 (C_{12}), 166.83 (C_{16})
6g		^{1}H-NMR:8.49 (s,1H,N-H), 8.29 (s,1H,CH=N, C_{21}) 7-8 (m, 8H, Ar-H), 5.3(s,1H,C-H, C_7),4.6(dd,2H, CH_2,C_{18}), 4(q,2H CH_2,C_{13}), 3.8 (t ,2H, CH_2- N, C_{20}), 3.8 (s,3H, CH_3O, C_{26}), 3.48 (t,2H, CH_2CH_2N,C_{19}), 3.4 (s,3H, CH_3OC=O, C_{15}), 2.17(s, 3H,CH_3 ,C_{17}), 1.1(t, 3H, CH_3, C_{14}). ^{13}C-NMR: 13.80 (C_{14}), 17.98 (C_{17}), 34.55 (C_7), 50 (C_{15}), 55 (C_{26}). 59.10 (C_{13}), 59.69 (C_{20}), 66.10 (C_{18}),70 (C_{19}), 113-145(13C) Ar-C, 160 (C_{21}), 161.39 (C_{25}), 166 (C_{12}), 166.85 (C_{16})

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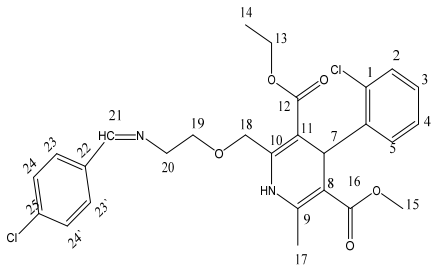
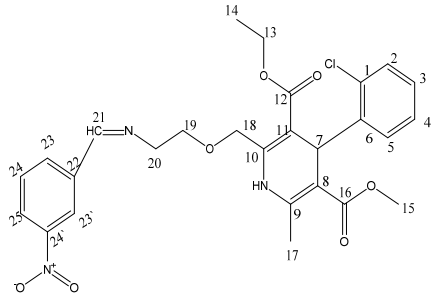
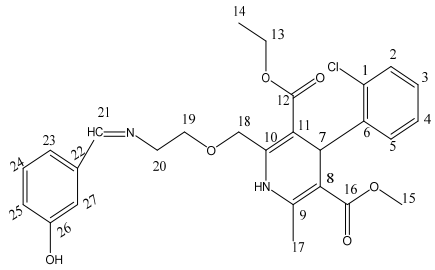
Comp.	Structure	Chemical Shift (ppm)
6h		^{1}H-NMR: 8.43 (s, 1H, N-H), 8.36 (s, 1H, CH=N, C_{21}), 7-7.72 (m, 8H, Ar-H), 5.26 (s, 1H, CH, C_7), 4.5 (dd, 2H, CH_2O (C_{18}) 3.98 (q 2H CH_2O, C_{13}), 3.75 (t,2H, CH_2-N, C_{20}), 3.75 (t,2H, CH_2CH_2-N ,C_{19}), 3.47 (s,3H, CH_3OC=O,C_{15}),2.17 (s,3H,CH_3,C_{17}),1.3 (t 3H,CH_3,C_{14}). ^{13}C-NMR: 13.76 (C_{14}), 17.88 (C_{17}), 36.49 (C_7), 50.19 (C_{15}), 59.06 (C_{13}), 59.64 (C_{20}), 66.01 (C_{18}), 69.66 (C_{19}), 113-145.47 (14C) Ar-C, 160.98 (C_{21}), 166.01 (C_{12}) 166.75 (C_{16}).
6i		^{1}H-NMR: 8.62 (s,1H,N-H), 8.5 (s,1H,CH=N), 7.18-.8.64 (m, Ar-H), 5.3(s,1H,C-H C_7),4.5-4.6 (dd,2H, -CH_2O- C_{18}), 4(q,2H,CH_2,C_{13}), 3.9 (t ,2H, CH_2-N, C_{20}), 3.8(t,2H,CH_2CH_2N, C_{19}), 3.5 (s,3H, CH_3OC=O, C_{15}), 2.2(s, 3H,CH_3, C_{17}), 1.1 (t,3H,CH_3, C_{14}). ^{13}C-NMR: 14.15 (C_{14}), 18.21 (C_{17}), 36.88 (C_7), 50.55 (C_{15}), 59.16 (C_{13}), 60.30 (C_{20}), 66.22 (C_{18}), 69.93 (C_{19}), 101-148.23 (16C) Ar-C, 160.77 (C_{21}), 166.40 (C_{12}). 167.16 (C_{16})
6j		^{1}H-NMR: 9.56(s,1H,OH),8.41s(1H, N-H), 8.28 (s, (1H,CH=N,C_{21}), 6.8-7.72(m,8H,Ar-H), 5.26 (s,1H, CH, C_7), 4.5 (dd,2H, CH_2O, C_{18}), 3.94 (q,2H, CH_2, C_{13}),3.7 (t,2H, CH_2- N, C_{20}), 3.7(t,2H,CH_2CH_2N, C_{19}), 3.5 (s, 3H, CH_3OC=O,C_{15}), 2.17 (s,3H, CH_3, C_{17}), 1(t,3H,CH_3,C_{14}). ^{13}C-NMR: 18.76 (C_{14}), 23.3 (C_{17}), 41.03 (C_7), 55.33 (C_{15}), 64.75 (C_{13}), 64.75 (C_{20}), 71.15 (C_{18}), 74.55 (C_{19}) 106.52-150.64 (15C) Ar-C, 162.43 (C_{26}), 167.37 (C_{21}), 171.16 (C_{12}), 171.95 (C_{16}).

s= singlet, d= doublet, m= multiplet, Ar= aromatic.

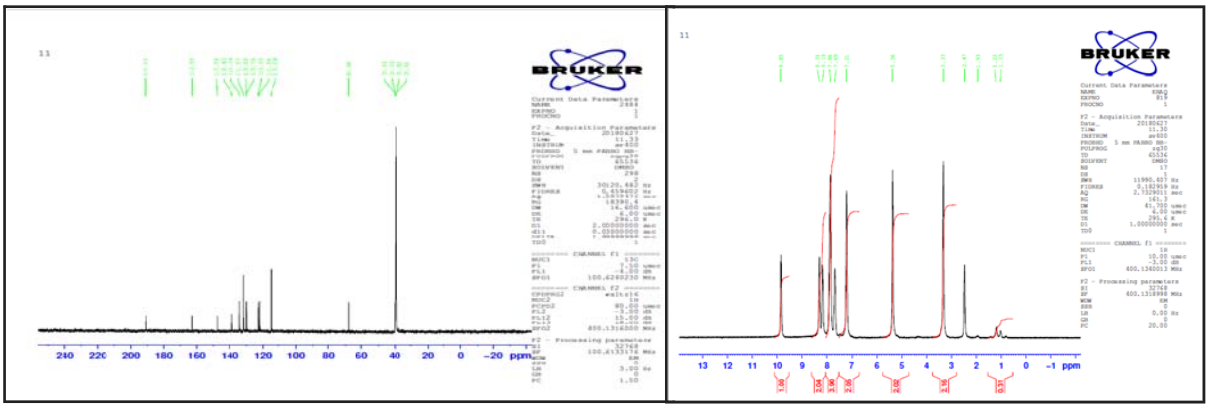


Figure 1 ^{1}H-NMR and ^{13}C-NMR spectra of compound 3b

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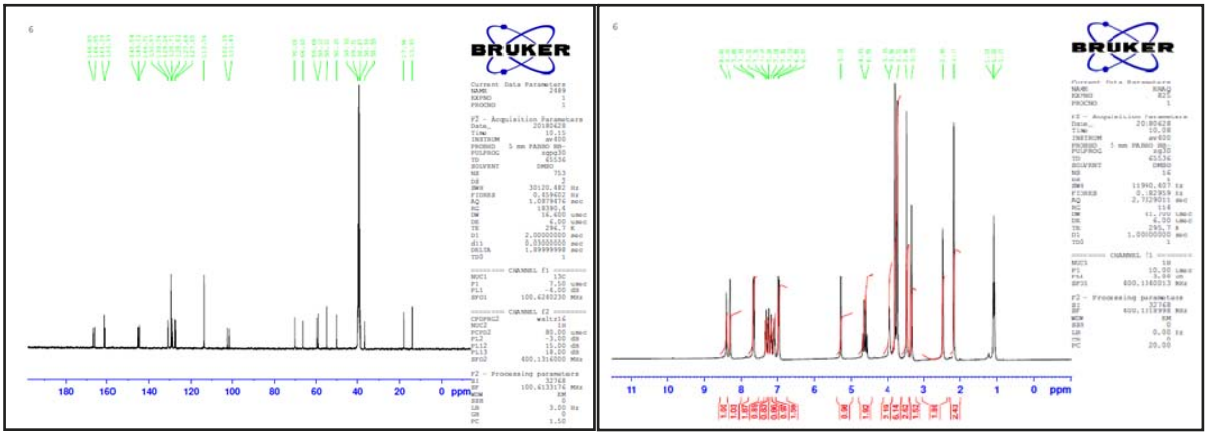

Figure 2 ^{1}H-NMR and ^{13}C-NMR spectra of compound 6g

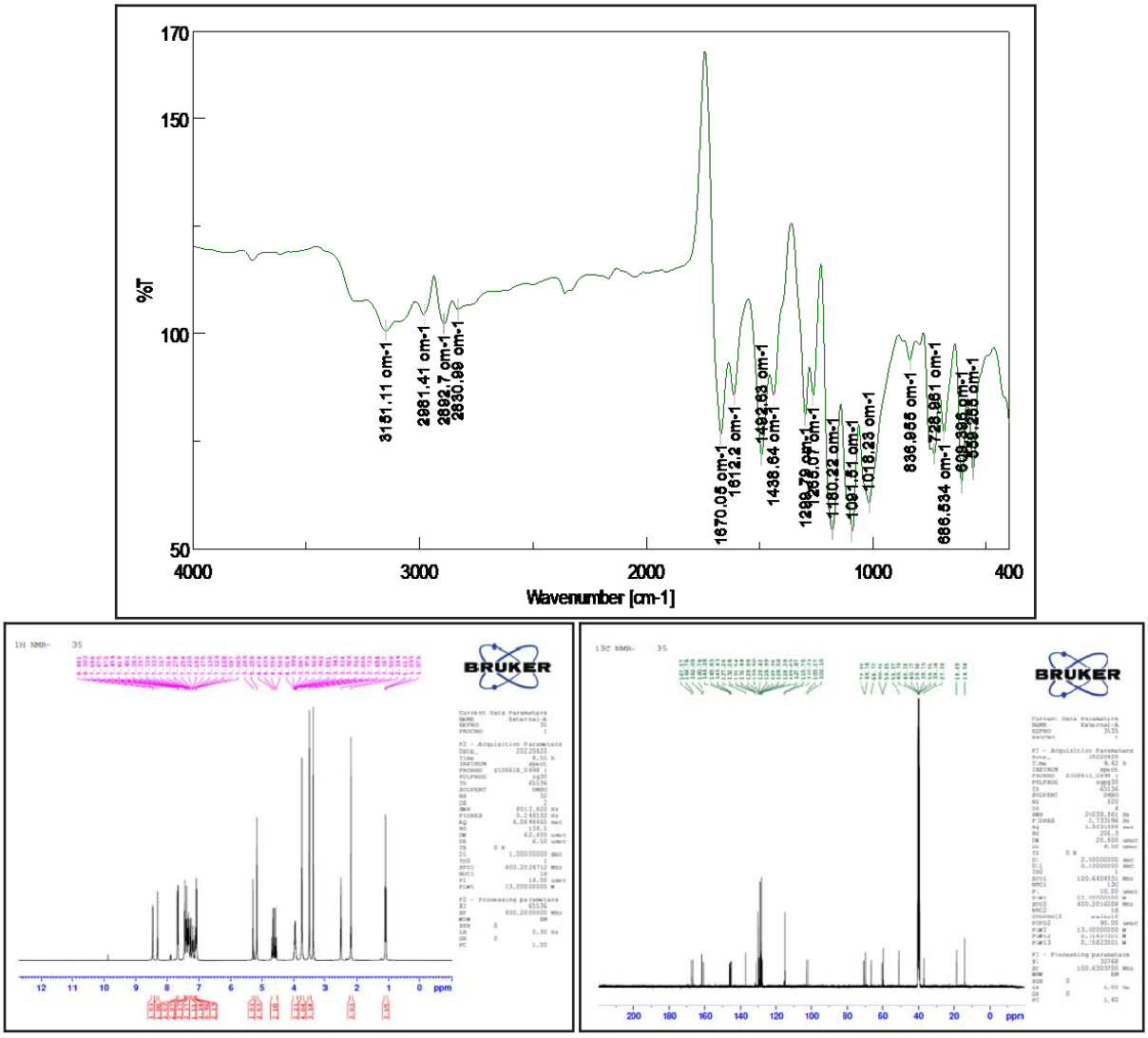

Figure 3 IR,^{1}H-NMR and ^{13}C-NMR spectra of compound 6a

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The results of antibacterial activities describe the effect of the additive functional groups in the structure of amlodipine (4) through the inhibition zones of growth of bacteria for each compound that is measured by mm unit. Compounds (6a-d) and 6g showed higher activity against *E.Coli* than *S-aureus*, while the compounds (6h-k) were less reactive against both kinds of Microorganism, The KBr disk was used as a negative control, and two medications were chosen as a positive control for this test ciprofloxacin and amoxicillin. The synthesized compounds (6a-c) and 6j showed similar activity to amoxicillin against both types of bacteria while being less reactive than ciprofloxacin.

Table4 Antibacterial activity of the amlodipine derivatives against *Staphylococcus aureus* and *Escherichia coli*

Compound	***E. coli***	***S.aureus***
6a	+++	++
6b	+++	++
6c	+++	++
6d	+++	-
6g	+++	-
6h	-	+
6i	++	-
6j	-	++
6k	-	-
Ciprofloxacin	27 mm	23 mm
Amoxicillin	18 mm	12 mm

Inhibition zone (mm), highly reactive +++ (20 to 24 mm), active ++ < 20mm, less reactive (10-0.5), – no inhibition zone

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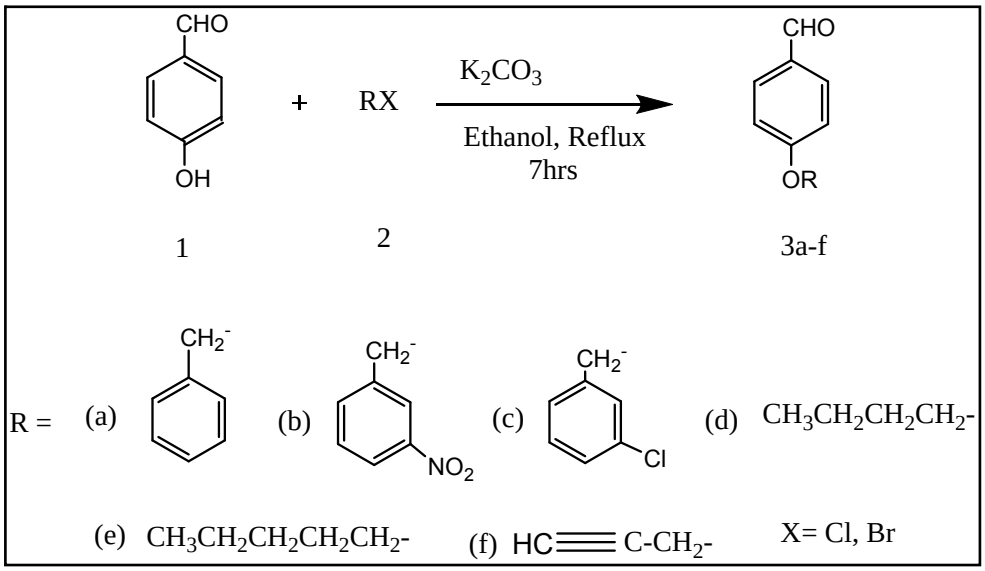
Discussion

p- Hydroxybenzaldehyde was treated with various alkyl and aryl halides in absolute ethanol in the presence of K_2CO_3. The mixture was heated under reflux for 7 hours to afford products 3a–f, which are represented in Scheme 1. The synthesized compounds were characterized by IR spectroscopy, and from their physical properties, the absence of the vibration frequency of the OH group at 3400 cm^{-1} in the IR spectra of compounds 3a–f was a piece of great evidence for a successful substitution reaction. Another indication of the formation of these compounds was obtained from the observation of a new absorption band at 1180–1234 cm^{-1} related to C–O bond vibration. [10,6]

The structure of compound (3b) in Figure 4 was characterized by the ^{1}H-NMR spectra, which revealed a singlet signal related to methylene (CH_2) protons at δ 5.3 ppm with multiple signals at δ 7-8 ppm, which indicated the presence of phenyl rings.
The ^{13}C-NMR spectrum in DMSOd^6 confirmed the structure of this compound through the appearance of a characteristic signal at 68 ppm for the CH_2 carbon atom, 10 signals for 10 carbon atoms in the aromatic region, and a signal related to the CH=O carbon atom at 191 ppm (Figure 1). In this spectroscopic technique, DMSOd^6 was used as a solvent to measure ^{1}H and ^{13}C-NMR spectral data; its ^{1}H-NMR spectrum revealed three signals at chemical shifts 2, 2.5, and 3.3 ppm for water molecules found with the solvent.



Scheme 1 Synthetic pathway of *p*-aryloxybenzaldehyde and *p*-alkyloxybenzaldehyde

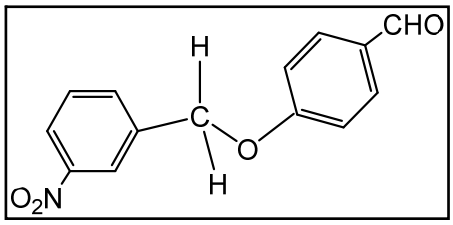


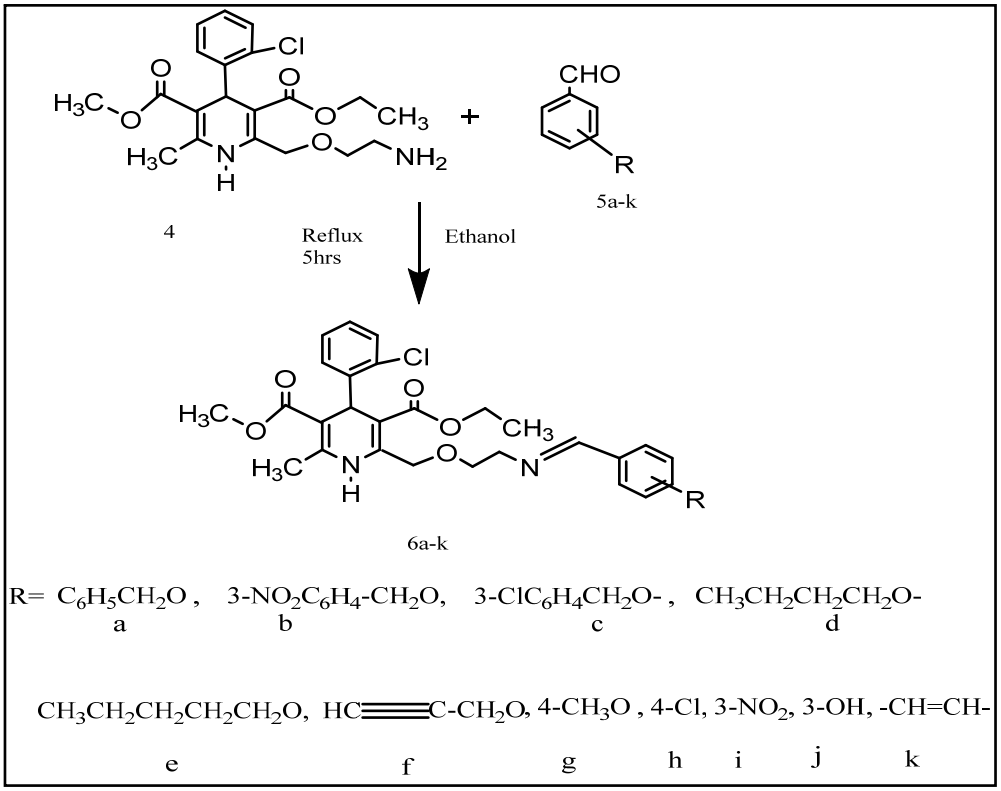
Figure 4 Compound 3b

https://doi.org/10.15218/zjms.2024.048

As shown in Scheme 2, the compounds (6a-k) were synthesized by reacting amlodipine base (4) with substituted benzaldehyde (5a-k) at reflux temperature without the use of a catalyst. and their structure has been confirmed by physical and chemical properties, including IR, ^{1}H-NMR, and ^{13}C-NMR spectra.

The IR spectra of compounds (6a–k) showed the absence of the vibration frequency of (-NH_2, C=O) groups in the region at 3235–3282 $cm^{-1}$and at 1710 cm^{-1}, respectively, due to the primary amino group for amlodipine (4) and substituted benzaldehyde. In addition, the appearance of a new peak between 1592–1645 cm^{-1} characterized the azomethines bond (-N=C), Figure 3. As shown in Table 2, the absorption band of C-H stretching vibrations for the benzene ring and the N-H of the heterocyclic ring was observed between 3000 and 3100 cm^{-1} and 3151 and 3394 cm^{-1}, respectively.

^{1}H-NMR and ^{13}C-NMR spectral data were compared with that recorded in the literature and were in agreement with the formation of the expected compound. The^{1}H-NMR spectra data (Figures 2 and 3) supported the infrared through the appearance of two characteristic signals at a chemical shift between 8.2 and 8.4 ppm as a singlet signal related to the imine proton (CH=N) [14,15], and N-H proton of the 1-hydropyridine ring, the presence of an aromatic ring characterized by signals at 6.8–8.64 ppm.



Scheme 2 Synthetic pathway of Schiff bases compounds

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The signals due to methyl groups and methylene were observed at different chemical shifts depending on their positions, for example in compound (6 g) Figure 5 showed four singlet signals at chemical shifts 2.17 (2-CH_3 pyridine ring), 2.5 ppm for DMSOd[6] solvent, 3.4 for 3-carboxylate pyridine ring(CH_3OC=O), and 3.8 ppm for methoxy group (CH_3O-), respectively. The two types of protons of the 5-carboxylate group on the pyridine ring (CH_3CH_2OC=O) have appeared as a triplet and quartet at chemical shifts (1.1,4) ppm, the signals at δ 3.35 and 3.95 ppm as two triplets are assigned to the protons bound to the carbon atoms next to an oxygen atom and nitrogen atom (-O-CH_2CH_2-N=CH). The H_2 close to the nitrogen atom shifted from 2.7 ppm to 3.95 ppm which indicated the formation of the desired Schiff bases compounds, also the third type of CH_2close to the oxygen atom and pyridine ring of -CH_2- O-CH_2-CH_2N=CH groups appeared as two doublets for two geminal protons at δ(4.6) ppm and one proton of 4-dihydropyridine was observed as a singlet at δ 5.3 ppm, and the aromatic protons were observed as a multiplet at chemical shift 7-8 ppm for eight protons[16] as shown in Figure 2 and Table 3.

^{13}C-NMR spectrum compound 6g showed 26 signals related to different types of carbon atoms at a different chemical shift.

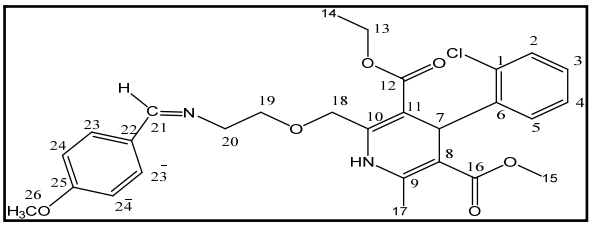

Figure 5 Compound 6g

The methyl carbon atoms of CH_3 (C_{14}), CH_3 (C_{17}), CH_3OC=O (C_{15}), and CH_3O (C_{26}) produced signals at δ 13.80, 17.98, 50, and 55 ppm. The ^{13}C-NMR spectrum of the amine showed a methylene carbon atom (CH_2) (C_{20}) at a chemical shift of 41.38 ppm, while this group in the spectrum of compound 6g was observed at 59.69 ppm, after the formation of the desired compound. Other methylene groups (CH_2) were found at δ 59.10 (C_{13}), 66.10 (C_{18}), and70 (C_{19}) ppm, and the CH (C_7) at 34.55 ppm. The most significant characteristic signal was the line of C_{21} related to the (C=N) bond, which was found at 160 ppm[14-15], followed by the two (C=O) carbon atoms, C_{12} and C_{16}, at 166 and 166.85 ppm, respectively, and C_{25} at 161.39 ppm. 13 signals from 113–145 ppm belonged to aromatic carbon atoms.[14]as shown in Figure 2.

The ^{1}H-NMR spectrum (DMSO-d_6), δ in ppm of compound 6d showed signals due to the presence of butyloxy group at 0.96 (t, 3H, for CH_3), 1.46 (h, 2H, CH_2-), 1.7 (p,2H, CH_2), 4 (t, CH_2O-), 7.7.67 (m, 8H aromatic H), 8.29 (s,1H,CH=N), 8.44 (s, 1H, N-H). The ^{1}H-NMR spectrum of compound 6a indicated the formation of the desired compound through the appearance of signals attributed to the presence of benzyloxy group at δ 5.2 ppm (s,2H, CH_2-O), 8.3 ppm (s, 1H, CH=N), and 7–7.8 ppm (m,12H for aromatic H). The signal belonging to CH_2—Owas seen at 69 ppm, and the signal related to C=N carbon was found at 162 ppm in the^{13}C-NMR spectrum, as shown in Table 3, and Figure 3.

The synthesized derivatives of amlodipine (6a-k) were tested for antibacterial activity using two pathogenic strains of Gram-negative and Gram-positive bacteria, such as *E.coli* and *Staphylococcus aureus*, that inhibit many steps in cell wall synthesis or act through inhibition of enzymes. The antibacterial studies of some of the newly synthesized compounds were assessed by measuring the minimum inhibitory zone using the disc agar diffusion method at a concentration of 50 µg per disc, and the results are represented in Table 4.

The synthesized compounds showed more activity against *E.coli* than *S-aureus*, this result indicates the effect of substituent on the activity of the derivatives against both kinds of bacteria. The synthesized

compounds 6a to 6d and 6g showed excellent activity against *Ecoli,* which may be due to the presence of the ether group CH_2-O-C,aliphatic and aromatic groups (phenyl ring), which increase the lipophilicity of the compounds. In addition, the heteroatom of the pyridine moiety also contributes to microbial growth inhibition. Ciprofloxacin and amoxicillin were chosen as positive controls as standard drugs, and KBr was chosen as a negative control because it has no antibacterial activity. The compounds 6a to 6c, and 6j also showed moderate activity against *S. aureus*. They exhibit similar activity to the standard drug amoxicillin against both types of bacteria, which has a wide effect on gram-positive bacteria. However, the synthesized compounds showed less activity than the antibiotic ciprofloxacin.

Bacterial cell walls contain peptidoglycan, lipopolysaccharide, lipoprotein phospholipid, and protein. These compounds tend to be highly bound to proteins or peptidoglycan. The potency of 6h to 6k against both types of bacterial pathogens was discovered to be less effective.

Conclusion

New Schiff bases were synthesized via the condensation reaction of equimolar amounts of both amine and aldehyde compounds, and the yield of the products was good. The compounds were tested for antibacterial activity against two types of bacteria, gram-negative *E. coli* and gram -positive *S. aureus*, and showed moderate to good activity, with the ether group CH_2–O–C being more active than the others (6h to k). This may be due to the ability of these compounds to attack the peptidoglycan cell wall to prevent bacterial cell wall synthesis or simply inhibit cell growth.

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Competing interests

The author declares that she has no competing interests.

References

1. Abu –Dief AM, Muhamed IMA. A review on versatile applications of transition metal complexes incorporating Schiff bases. Beni-Suef J Basic Appl Sci 2015; 4:119–33. doi: 10.1016/j.bjbas.2015.05.004
2. Qin W, Long S, Panunzio M, Biondi S. Schiff Bases: A Short Survey on an Evergreen Chemistry Tool. Molecules 2013; 18(10):12264–89. doi: 10.3390/molecules181012264
3. Kajal A, Bala S, Kamboj S, Sharma N, Sain V. Schiff Bases: A Versatile Pharmacophore. Journal of Catalysts 2013; 2013. doi: 10.1155/2013/893512
4. Farhan MA, Ali WB, Nief OA. Synthesis, Characterization and Biological Activity of Schiff Bases Derived from Heterocyclic Compounds. Teikyo Medical Journal 2022; 45(1):4781–90.
5. Iacopita D, CeramellaJ,Catalona A, Saturnino C, Bonomo MJ, Franchini C et al. Schiff Bases: Interesting Scaffolds with Promising Antitumoral Properties. Appl Sci 2021; 11(4):1877. doi: 10.3390/app11041877
6. Brodowska K, Lodyga-Chruscinska E. ChemInform Abstract:Schiff bases—interesting range of applications in various fields of science. ChemInform 2014; 68(2):129–34. doi: 10.1002/chin.201511346
7. Azab ME, Rizk SA, Amr A El-G E. Synthesis of some novel heterocyclic and Schiff base derivatives as antimicrobial agents. Molecules 2015; 20(10):18201–18. doi: 10.3390/molecules201018201
8. da Silva CM, da Silva DL, Modolo LV, Alves RB, de Resende MA, Martins CVB, et al. Schiff bases: A short review of their antimicrobial activities. J Adv Res 2011; 2:1–8. doi: 10.1016/j.jare.2010.05.004
9. Kumar J, Rai A, Raj V. comprehensive review on the pharmacological activity of Schiff base containing derivatives. Organic and Medicinal Chemistry International Journal 2017; 1(3):88–102. doi: 10.19080/OMCIJ.2017.01.555564
10. Hawaiz FE, Hussein AJ, Samad MK, One- pot three-component synthesis of some new azopyrazoline derivatives. Eur J Chem 2014; 5(2):233–6. doi: 10.5155/eurjchem.5.2.233-236.979
11. Hawaiz FE, Shekh Omer DA. Ultrasound-assisted Synthesis of Some New Curcumin Analogues and Their Corresponding Pyrazoline Derivatives. ARO Sci J KU 2017; 5(1):30–5 doi: https://doi.org/10.14500/aro.10149
12. Ahmed SM,Salih KM, Ahmad HO, Jawhar ZH, Hamad DH. Synthesis, spectroscopic characterization and antibacterial activity of

new series of Schiff base derived from 4-aminoantipyrine and 2-amino benzimidazole. Zanco J Med Sci 2019; 23(2):206–12. doi: 10.15218/zjms.2019.026
13. Samad MK, Hawaiz FM. Synthesis, characterization, antioxidant power and acute toxicity of some new azo-benzamide and azo-imidazolone derivatives with in vivo and in vitro antimicrobial evaluation. Bioorg Chem 2019; 85: 431–44. doi: 10.1016/j.bioorg.2019.01.014.
14. Ziauddin HM, Markandewar R, Baseer MA. Novel Heterocyclic Schiff Base Synthesis and Antimicrobial Studies. J Chem Chem Sci 2016; 6(10):919–25.
15. Sweaha Z J, Auribieb M A.Synthesis and Antibacterial Activity of Schiff Base Compounds Derived from Glyoxal, Vanillin with Their Complexes with Iron (ш). Egypt J Chem 2020; 63(10):3985–94. doi: 10.21608/EJCHEM.2020.31555.2699
16. Jiang Y, LuanY, Qin F, Zhao L, Li Z. 2012. Catanionic Vesicles from an Amphiphilic Prodrug Molecule: a New Concept of Drug Delivery System. RSC Adv 2012; 2:6905–12. doi: 10.1039/C2RA20653F