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Synthesis, Characterization, and Antibacterial Activity of someAmino Acid Derivatives

Jawad Kadhum Shneine*[1], Dina Ziad Qassem[1], Suhad Saad Mahmoud[2]

[1]Department of Chemistry, College of Science, Al-Nahrain University Baghdad – Iraq.[2]Department of Biotechnology, College of Science, Baghdad University Baghdad – Iraq.

Abstract : The present work includes the synthesis of glycine and L-amino acid derivatives**6-10 (A,B)**via Schiff`s bases**3(A,B)**, which were obtained from the reaction of 2-aminopyridine**2**with benzaldehyde**1A** or 4-chlorobenzaldehyde**1B**.The reaction of **3(A,B)** with benzoyl chlorideyielded benzamide derivatives**5(A,B)**. The synthesis of **6-10 (A,B)**has been performed by the reaction of **5(A,B)**with (glycine, L-alanine, L-phenylalanine, L-aspartic acid and L-asparagine). Infrared and nuclear magnetic spectroscopic techniques FT-IR, ^{1}H NMR, and ^{13}C NMR were used to characterize the newly synthesized compounds. The antibacterial activity of final products has been evaluated against two kinds of Gram positive and Gram negative bacteria(*Staphylococcus aureus* and *Klebsiella pneumonia*).Overall, results indicatea lower and moderate antibacterial activity in comparison with Meropenem as a reference against both bacteria. The highest activity was obtained using the compound**7B** for both kinds of bacteria and **6A** for only *Klebsiella pneumonia.*

Keywords : Schiff's bases, 2-Aminopyridine, L-Amino acids, Antibacterial activity, Benzamide

Introduction

In the last decade, Schiff's bases have been indicated as anti-proliferative[(1)], anti-inflammatory[(2)],antimicrobial[(3)], antiviral[(4)], antimalarial[(5)], anticancer[(6)], antibacterial[(7)],antifungal[(8)] and anti-tubercular[(9)]active compounds. Schiff's bases can be considered as wide used intermediates in the pharmaceutical chemistry to synthesize many biological active compounds. Ring fusion and addition reactions to their double bonds are a member of the most important reactions for Schiff s bases. In this respect, it is intended in this work to benefit these opportunities in order to make compounds containing amino acids in their structure. Amino acids as natural products play a central role both as building blocks of proteins and as intermediates in metabolism. As main elements of proteins, the 20 essential amino acids expand anenormous diversity of chemical functionality[(11)]. Amino acid derivatives have been also indicated as essential component of drugs and exhibit antibacterial [(11)], antifungal [(12)], anticancer [(13)], and antibodies [(14)]. For example, the best known penicillin and cephalosporin comprise in their structures L-2-Aminoadipic acid, L-cysteine, and L-valine[(15)]. Therefore, the aimed compounds are expected to be potent antibacterial active compounds.

The aim of present work is to synthesize L-amino acid derivatives via Schiff's bases which are derived from 2-aminopyridine,benzaldehydeor 4-chlorobenzaldehyde.Moreover, the antibacterial activity of the final compounds has to be evaluated against a Gram positive and a Gram negative bacteria (*Staphylococcus aureus*) and (*Klebsiella pneumonia)* respectively.

Experimental

Analytical Instruments

Melting points were determined with Chachan, MLP-01melting point apparatus. FT-IR spectra were recorded with FTIR-8300Schimadzu, by KBr disk technique.^{1}HNMR and ^{13}CNMR spectrawere recorded with Spectrometer 400 MHz, Avance III 400, Bruker, Germany in DMSO-d6 as a solvent.

Synthetic Methods

1 Synthesis of N-(4-monosubstitutedbenzylidene) pyridin-2-amine 3(A,B)[16]

(0.01mol) of benzaldehyde 1Aor 4-chlorobenzaldehyde 1B and (0,01 mol, 0.94 g) of 2-aminopyridine 2 were dissolved in 15mL absolute ethanol containing a drop of glacial acetic acid and refluxed for 10 hrs. The reaction mixture was then allowed to cool to room temperature; the formed solid was filtered, washed with (2%) HCl solution, then with water. The product was recrystallized from ethanol and dried.

N- benzylidene pyridin-2-amine(3A):

Color = pale yellow, yield = 67%, m.p. = 91 ^{o}C.FT-IR(cm^{-1}): υ(C=N) =1678, υ(C=C) arom. = 1597, υ (N=C–H) arom. =3209,υ(C–H) arom. = 3082, υ(C–H) aliph =2970 and 2950.

N-(4-Chlorobenzylidene) pyridin-2-amine (3B):

Color= pale yellow,yield = 64%,m.p. =80^{o}C.FT-IR (cm^{-1}): υ(C=N) = 1678, υ(C=C) arom. =1585, υ (N=C–H) arom. = 3147, υ(C–H) arom. = 3086, υ(C–H) aliph = 2962 and 2931.

2 Synthesis of N-[α-chloro (4-monosubstitutedbenzyl)]-N-pyrid-2-yl benzamide5(A,B) [16]

(0.005 mol) of **3(A,B)**was dissolved in 10 mL dry benzene and placed in a three necked round bottom flask. (0.005mol, 0.6 mL) of benzoyl chloride was dissolved in 6 mL dry benzene and poured in a dropping funnel. Benzoyl chloride solution was added dropwise to the reaction mixture at 60^{o}C with continuous stirring within 1 hr. Then the solvent was removed and the solid residue was filtered, washed with (2%) solution of sodium carbonate, then with water, recrystallized from ethanol and dried.

N-(α-chlorobenzyl) -N-pyrid-2-yl benzamide (5A):

Color = white, yield = 63%, m.p. = 101 ^{o}C.FT-IR(cm^{-1}):υ(C=O) amide = 1685,υ (C=C) arom. =1600,υ(C–H) arom. = 3062,υ (N=C–H) arom. =3240, υ(C–H) aliph. =2927 and 2843, υ(C–Cl) = 775.

N-[α-chloro (4-Chlorobenzyl)]-N-pyrid-2-yl benzamide (5B):

Color = white, yield = 74%, m.p. = 117^{o}C.FT-IR (cm^{-1}): υ(C=O) amide = 1685,υ(C=C) arom. = 1593,υ(C–H) arom. =3070,υ (N=C–H) arom. = 3200, υ(C–H) aliph. = 2987 and 2885,υ(C–Cl) = 779.

3 Synthesis of (2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-(4-monosubstituted-phenyl)-methyl]-L-amino acid 6-10 (A,B)[17]

(0.005 mol) of **5(A,B)** and (0.005 mol) amino acid were dissolved in 10 mL (2:1) 1,4-dioxane-waterand refluxed for 4 hrs. The resulting mixture was cooled and few drops of water were added, crystals were separated out, filtered, and washed with water. The product was then recrystallized from (2:1) 1, 4-dioxane-water and dried.

N- [(benzoyl-pyridin-2-yl-amino)-phenyl-methyl]-Glycine (6A):

Color= pale white, yield = 72%, m.p. = 75^{o}C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid,υ (OH) = 3294, υ (NH) = 3275, υ(C=C) arom. = 1608,υ(C–H) arom. =3074, υ (N=C–H) arom. = 3213, υ(C–H) aliph. = 2927 and 2850.

^{1}HNMR (ppm): δ = 1.2 (1H, *s*, NH), δ =3.4(2H, *s*, CH_2), δ =4.1 (1H, *s*, CH), δ =7.2-8.4 (14H, *m*, =CH of three aromatic rings), δ =11 (1H, *s*, OH).

N-[(benzoyl-pyridin-2-yl-amino)-(4-Chloro-phenyl)-methyl]-glycine (6B):

Color =white, yield = 72%, m.p. = 77°C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid, υ (OH) = 3298, υ (NH) = 3275, υ(C=C) arom. = 1608,υ(C–H) arom. =3062, υ (N =C–H) arom. = 3209,υ(C–H) aliph. = 2927 and 2850.^{1}HNMR (ppm): δ =1.1 (1H, *s*,NH), δ = 3.4 (2H, *s*, CH_2), δ =4.6(1H, *s*, CH),δ =7.14-8.395 (13H, *m*, =CH of three aromatic rings), δ =11 (1H, *s*, OH). ^{13}CNMR (ppm):δ =60.1 (1C, CH_2), δ =72.3 (1C, CH), δ= 114.7-152.1 (17C, 3 aromatic rings), δ =165.9 (1C, C=Oamide), δ =167.3 (1C, C=Oacid).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-phenyl-methyl]-L-alanine (7A):

Color = pale white, yield = 72%, m.p. = 76°C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid, υ (OH) = 3294, υ (NH) = 3275,υ(C=C) arom. = 1608, υ(C–H) arom. = 3062, υ (N=C–H) arom. = 3213, υ(C–H) aliph. = 2935 and 2850.^{1}HNMR (ppm): δ =1.1 (1H, *s*, NH), δ = 1.4(3H, *d*, CH_3), δ =3.5 (1H, *q*, CH), δ =4.0 (1H, *s*, CH), δ =7.1-8.3 (14H, *m*, =CH of three aromatic rings),δ = 10.7 (1H, *s*, OH).^{13}CNMR (ppm): δ = 60.1(1C, CH), δ =72.4 (1C, CH), δ =114.6-152.1 (17C, 3 aromatic rings), δ =165.9 (1C, C=Oamide),δ =167.3 (1C, C=Oacid).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-(4-Chloro-phenyl)-methyl]-L-alanine (7B):

Color =pale white, yield = 72%, m.p. = 73°C. FT-IR (cm^{-1}): υ(C=O) =1678 overlap between C=O amide and C=O acid, υ (OH) = 3298, υ (NH) = 3275, υ(C=C) arom. =1608, υ(C–H) arom. = 3062, υ (N=C–H) arom. = 3209, υ(C–H) aliph. = 2931 and 2858. ^{1}HNMR (ppm): δ = 1.1 (1H, *s*, NH), δ = 3.5 (1H, *q*, CH), δ= 4.0 (1H, *s*, CH), δ = 7.1-8.3 (13H, *m*, =CH of three aromatic rings), δ = 10.7 (1H, *s*, OH).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-phenyl-methyl]-L-phenylalanine (8A):

Color = pale white, yield = 68%, m.p. = 71°C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid, υ (OH) = 3294, υ (NH) = 3275, υ(C=C) arom. = 1608, υ(C–H) arom. =3074, υ (N=C–H) arom. = 3209, υ(C–H) aliph. = 2931 and 2843.^{1}HNMR (ppm): δ = 1.2 (1H, *s*, NH), δ = 3.1 (2H, *d*, CH_2), δ =3.5 (1H, *trp*, CH), δ =4.0 (1H, *s*, CH), δ =7.1-8.3(19H, *m*, CH of four aromatic rings), δ =10.7 (H, *s*, OH).^{13}C NMR (ppm): δ= 36.3 (1C, =CH_2), δ =54.3 (1C, CH), δ =114.7-166.2 (23C, 4 aromatic rings), δ =167.3 (1C, C =Oamide), δ =173.2 (1C, C=Oacid).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-(4-Chloro-phenyl)-methyl]-L-phenylalanine(8B):

color = pale yellow, yield = 71%, m.p. =74°C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid,υ (OH) = 3298, υ (NH) = 3275, υ(C=C) arom. = 1608, υ(C–H) arom. =3074, υ (N=C–H) arom. = 3209, υ(C–H) aliph. = 2927 and 2854. ^{1}HNMR (ppm): δ =1.2 (1H, *s*, NH), δ = 3.2 (2H, *d*, CH_2), δ =3.5 (1H, *trp*, CH), δ =4.0 (1H, *s*, CH),δ =7.1-8.3 (18H, *m*, =CH of three aromatic rings), δ =10.7 (1H, *s*, OH).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-phenyl-methyl]-L-asparatic acid (9A):

Color = pale white, yield =78%, m.p. = 78°C.FT-IR (cm^{-1}):υ(C=O) = 1678 overlap between C=O amide and C=O acid,υ (OH) = 3294, υ (NH) = 3275, υ(C=C) arom. = 1608, υ(C–H) arom. = 3070, υ (N=C–H) arom. = 3213, υ(C–H) aliph. =asym 2950 and sym 2870.^{1}H NMR(ppm): δ = 1.1 (1H, *s*, NH), δ =3.4 (1H, *trp*, CH), δ =3.5 (2H, *d*, CH_2), δ =3.5 (1H, *s*, CH), δ =7.0 (1H, *d*, CH), δ =7.1-8.3 (14H, *m*, =CH of three aromatic rings), δ =10.789 (2H, *s*, OH).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-(4-Chloro-phenyl)-methyl]-L-asparatic acid (9B):

Color =pale white, yield =72%, m.p. = 77°C.FT-IR (cm^{-1}): υ(C=O) =1678 overlap between C=O amide and C=O acid,υ (OH) = 3298, υ (NH) = 3275, υ(C=C) arom. = 1608, υ(C–H) arom. = 3062, υ (N=C–H) arom. = 3209, υ(C–H) aliph. = 2927 and 2854. ^{1}HNMR (ppm): δ= 1.1 (1H, *s*, NH), δ =3.3-3.4 (1H, *trp*, CH), δ =3.5 (2H, *d*, CH_2), δ =4.0 (1H, *s*, CH), δ =7.1-8.3 (13H, *m*, =CH of three aromatic rings), δ =11 (2H, *s*, OH).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino) - phenyl-methyl]-L-asparagein (10A):

Color = pale white, yield = 78%, m.p. =77°C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid, υ (OH) = 3294, υ (NH) = 3275, υ(C=C) arom. = 1608, υ(C–H) arom. = 3074, υ (N=C–H)arom. = 3213, υ(C–H) aliph. =asym 2931 and sym 2858. ^{1}HNMR (ppm): δ = 0.9-1.0 (3H, *s*, NH), δ =3.3 (1H, *trp*, CH), δ =3.5 (2H, *d*, CH_2), δ =4.0 (1H, *s*, CH), δ =7.0-8.2 (14H, *m*, =CH of three aromatic rings), δ =10.645 (1H, *s*, OH).^{13}CNMR (ppm): δ =36.3 (1C, CH_2), δ =54.3 (1C, CH), δ =114.7-166.2 (17C, 3 aromatic rings), δ =167.3 (2C, C=Oamide), δ =173.2 (1C, C=Oacid).

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-(4-Chloro-phenyl)-methyl]-L-asparagein (10B):

Color =pale white, yield = 75%, m.p. = 72°C.FT-IR (cm^{-1}):υ(C=O) =1678 overlap between C=O amide and C=O acid,υ (OH) = 3298, υ (NH) = 3275, υ(C=C) arom. = 1608, υ(C–H) arom. =3074, υ (N=C–H) arom. =3213, υ(C–H) aliph. = 2927 and 2873.^{1}HNMR (ppm): δ = 1.1 (3H, *s*, NH), δ =3.3 (H, *trp*, CH_2), δ =3.5 (2H, *d*, CH_2), δ =4.0 (1H, *s*, CH), δ =7.1-8.3 (13H, *m*, =CH of three aromatic rings), δ = 10.7 (1H, *s*, OH).

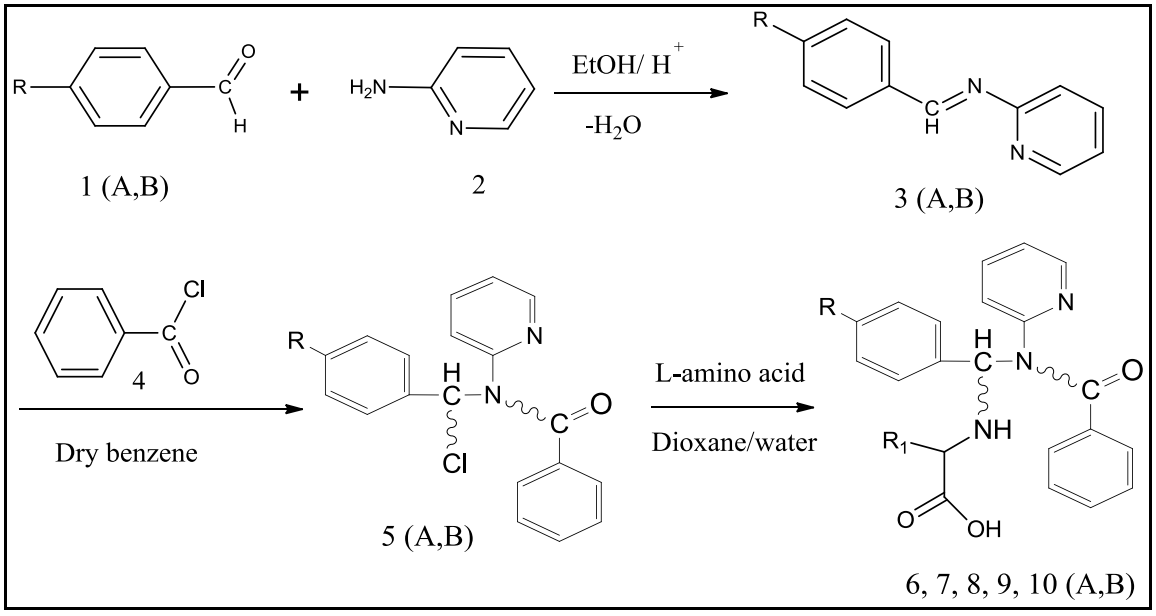
Antibacterial activity

The antibacterial activity was performed according to the disc diffusion method [19].Here bythe prepared agar and Petri dishes were sterilized by autoclaving at 121°C for 15 min. The agar was inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium, suitably spaced apart holes were made (6 mm in diameter). These holes were filled with (5, 10, 25, and 50) µg/mL of the synthesized compounds dissolved in DMSO as a solvent. The plates were incubated at 37 °C for 24 hours.

Results and Discussion

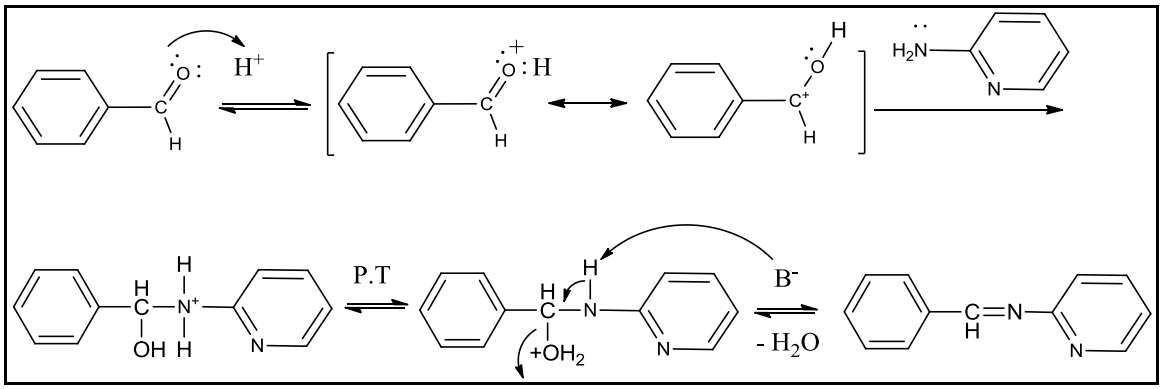
1Chemistry

Scheme1shows the synthetic route starting from 2-aminopyridine 2 and benzaldehyde1A or 4-chlorobenzaldehyde1Btowards aimed compounds 6-10 (A,B).



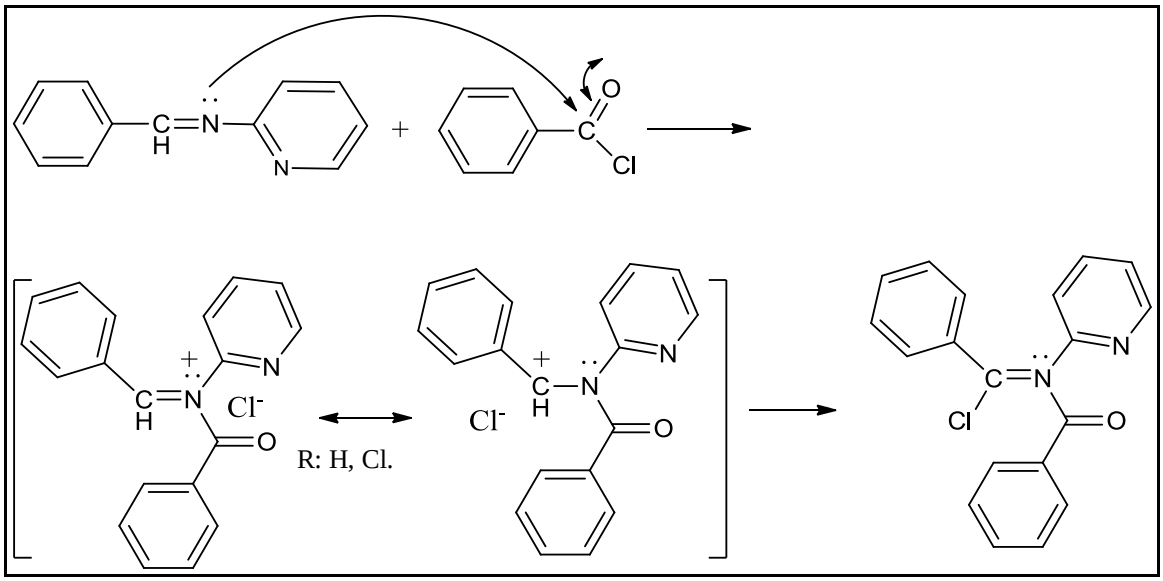
Scheme 1: Synthetic route of aimed compounds 6, 7, 8, 9, 10 (A,B), R = H for 3A or Cl for 3B; R_1 = H for 6(A,B), CH_3 for 7(A,B), $C_6H_5CH_2$ for 8(A,B), COOH for 9(A,B), and $CONH_2$ for 10(A,B) respectively.

Schiff`s bases 3(A,B) were prepared through acid catalyzed condensation reaction of 2-aminopyridine 2 with benzaldehyde 1Aor 4-chlorobenzaldehyde 1Bin ethanol[16]. The formed Schiff`s bases may be a mixture of E/Z diastereomers. The condensation reaction follows an addition-elimination mechanism described below[18].



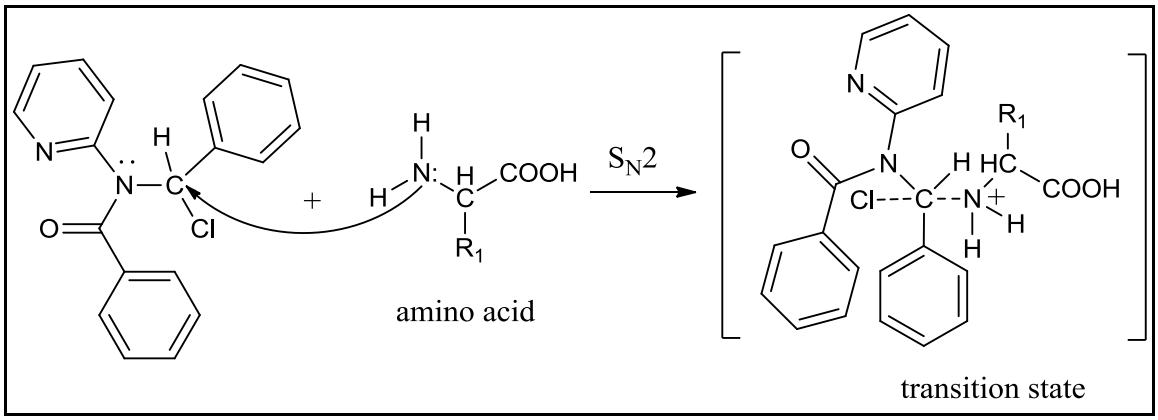
In the FT-IR spectrum the formation of 3(A,B) compounds are indicated by appearance of C=N absorption band at 1678 cm^{-1}, disappearance of carbonyl group absorption band at 1689 &1699 cm^{-1}, and disappearance of the NH_2 absorption band at 3300 cm^{-1} for symmetric and 3443 $cm^{-1}$for asymmetric bands, respectively.

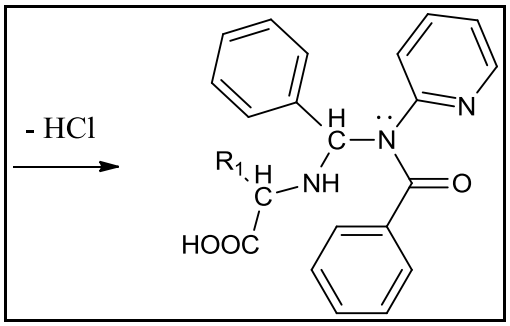
Schiff `s bases are nucleophiles and weak bases, so they do not react with simple allyl, alkyl or benzyl halides, but they react smoothly with the relatively more reactive acid halides such as benzoylchloride[16]. The reaction of N-(4-monosubstitutedbenzylidene) pyridin-2-amine with benzoyl chlorideyieldedN-[chloro-(4-monosubstituted-phenyl)-methyl]-N-pyridin-2-yl-benzamide 5(A,B). The saturation of the double bond produced a new asymmetric carbon atom (stereogenic center) and therefore the product might be a racemic mixture of the two enantiomers. The reaction may follow a nucleophilic addition mechanism as follows [18].



In the FT-IR spectrum, the formation of compounds5(A,B) are indicated by appearance of C–Cl absorption band 775 and 759cm^{-1}, appearance of carbonyl group absorption band at 1685 $cm^{-1}$and 1681 cm^{1}, and disappearance of C=N absorption band at 1678cm^{-1}.

(2S)-2-N-[(benzoyl-pyridin-2-yl-amino)-(4-monosubstituted-phenyl)-methyl]-L- amino acid 6-10(A,B) have been synthesized by reaction of amino acid with N-[chloro-(4-monosubstituted-phenyl)-methyl]-N-pyridin-2-yl-benzamide in 2:1 of 1, 4-dioxane-water as a solvent [17].The product now contains two chiral centers, the original carbon and the new generated carbon atom resulted from amino acids. That means the product is a mixture of diasteriomers. The reaction mechanism may follow a S_N2 mechanism described below [18]:





FT-IR spectra of compounds 6-10 (A,B) show an appearance of a band at 1678 cm^{-1}, a band at 3275 cm^{-1}, and a band in the range of (3294-3302) cm^{-1},which refer to the carbonyl amide, overlapped with the carbonyl carboxylic acid, NH-, and OH- groups, respectively. Also the disappearance of the absorption band at the range of (659-705) $cm^{-1}$for chloride confirms the displacement of chloride with the amino acid.

In ^{1}HNMR spectra of 6-10 (A,B) compounds the following proton assignments are noticed:a singlet signal at δ =0.9-1.2 ppm forNH proton, a singlet signal at δ =10.6-11.0ppm for hydroxylproton and multiplet signals at δ = 7.0-8.2ppm for benzene, benzoyl and pyridine protons.

In ^{13}CNMR spectra of 6-10 (A,B) compounds the following carbon assignments are detected:a signal at δ =114.7-166.2 ppm for benzene, benzoyl and pyridine aromatic rings, a signal atδ = 165.9-167.3 ppm for carbonyl group amide and a signal at δ = 167.2-173.2 ppm for acidic carbonyl group.

2 Antibacterial activities

The antibacterial activities were determined by measuring the diameter of the empty region around the wall (Inhibition zone). Results of preliminary screening tests are visualized in Fig. 1 and Fig. 2. Generally, The synthesized compounds 6-10 (A,B) showed a lower antibacterial and moderate activity in comparison with Meropenem as a reference against both *S.aureus* and *K. pneumonia*. From the obtained data in Fig. 1 and 2, it is found that L-alanine compound 7Bcaused the highest activity against both types of the studied bacteria, but onlywhen the concentration reaches 50 µg/mL. The glycine compound 6A caused a higher activity against *K. pneumonia* and moderate activity against *S. aureus*, when the concentration reaches 50 µg/mL. In principle, some compounds exhibited no activity, when the concentration was very low (5 and 10 µg/mL), as seen in compounds6B, 7A, 7B,8A, 9A, and 10A.Tested compounds could kill bacteria by destroying the cell wall. This can be explained by covalently binding to penicillin-binding proteins (PBPs) involved in the biosynthesis of mucopeptides in bacterial cell walls and this lead to rapid bacterial cell death. Bactericidal effects result through inhibition of cellular growth, division and the loss of cell wall integrity, which might cause cell wall lysis[(20)].

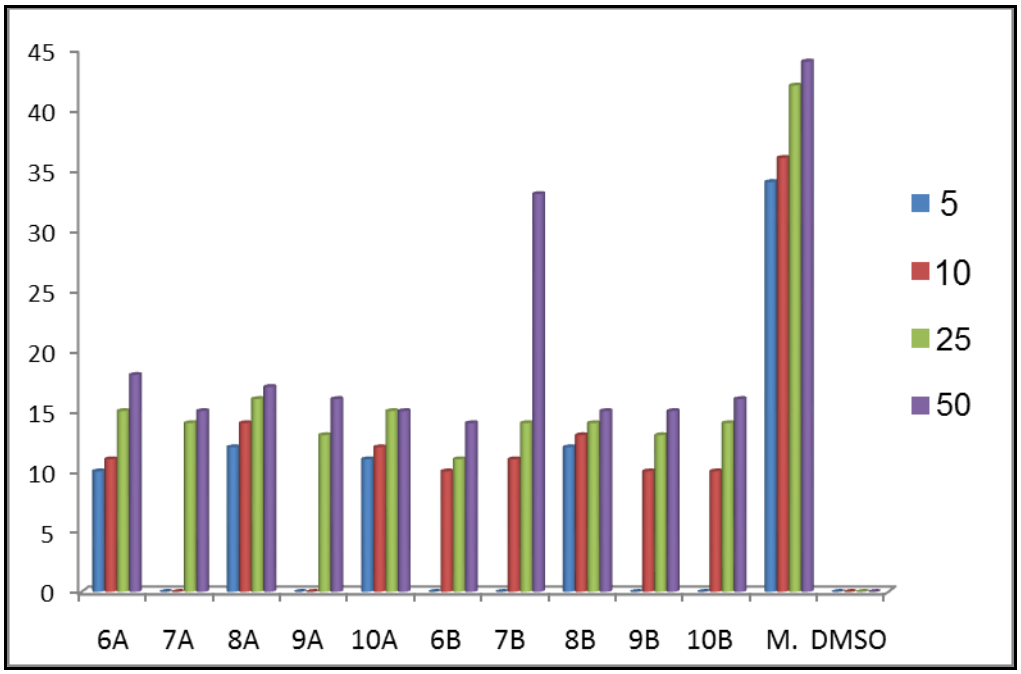


Fig. 1:Antibacterial effect of compounds 6-10 (A,B)on *S.aureus*, compound concentration = 5, 10, 25, 50 (µg/mL) dissolved in DMSO at 37 °C for 24 hrs.M=Meropenem as reference

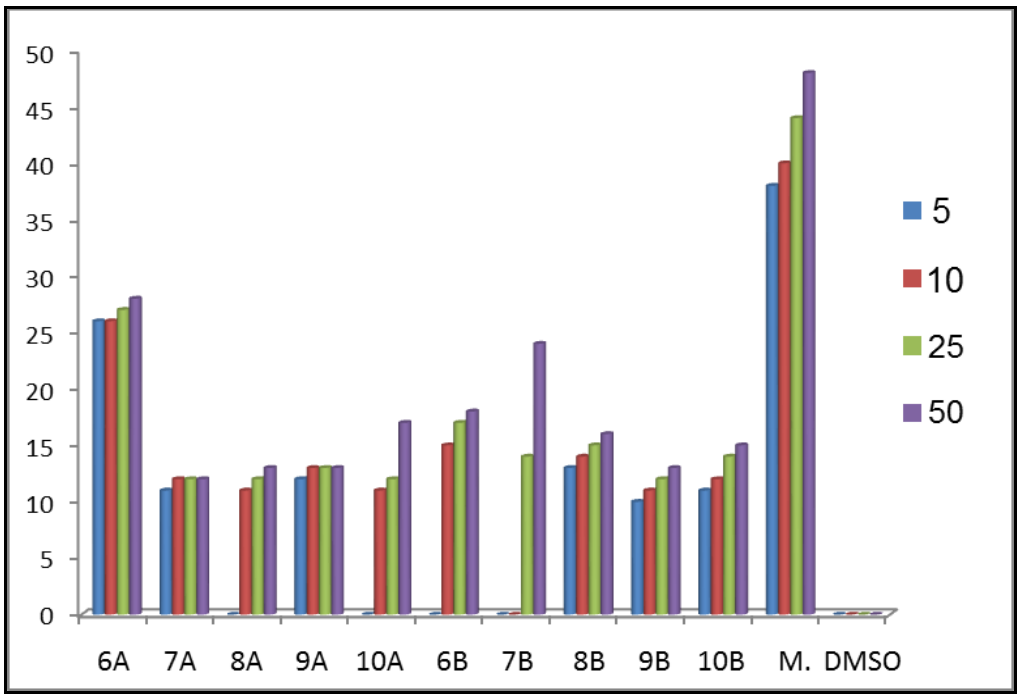


Fig. 2: Antibacterial effect of compounds 6-10 (A,B) on *K.pneumonia*, compound concentration = 5, 10, 25, 50 (µg/mL) dissolved in DMSO at 37 °C for 24 hrs. M=Meropenem as reference

Conclusion

Glycine- 6B and L-alanine-7B derivatives were the best candidates among the synthesized compounds, in which 4-chlorobenzaldehyde was used as starting material. Fundamentally, structural variation and substitution were important factors to be effective on weather Gram positive or negative tested bacteria. Furthermore, it is clear, that more structural substitution and variation willbe investigated and experimented to reach more favorable results.

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