In Silico Molecular Docking, Synthesis and Preliminary Evaluation of Antibacterial Activity of Levofloxacin Carboxamides with Certain Amino Acids

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Abstract:

Levofloxacin carboxamides with certain amino acids were prepared through an amide linkage to the amino acid (glycine, histidine, or serine). These carboxamides were subjected to an in silico molecular docking evaluation on DNA gyrase to predict their antibacterial activity using the GOLD suite. The binding affinities were very significant and encouraged the synthesis of the suggested carboxamides for intensive evaluation. These carboxamides were also subjected to Swiss ADME software to predict their ADME parameters. Levofloxacin carboxamides were prepared in high yield, and their chemical structures were confirmed by spectral analysis, such as 1H-NMR, 13C-NMR and FT-IR spectroscopy.

Antibacterial activities were evaluated for the new carboxamides against two G-ve (Klebsiella and P. aeruginosa) and one G+ve (Streptococcus pneumonia) bacteria. When compared to levofloxacin, all of the synthesized carboxamides 1-3 demonstrated good activity against three types of bacteria. These carboxamides showed significant antibacterial activities against S. pneumoniae and lower activities against Klebsiella.

Key words: Levofloxacin, Glycine, Serine, Histidine, DNA gyrase, Molecular Docking, ADME Studies.

تصميم ونمذجة جزيئية وتخليق وتقييم الفعالية المضادة للبكتريا لمشتقات الليفوفلوكساسين كربوكسامايد مرتبطة بأحماض امينية محددة.

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الخلاصة:

مشتقات كاربروكسيلية لليفوفلوكساسين مرتبطة باحماض امينية (كلايسن,هستدين وسيرين) عبر الصرة الامايدية.هذه طريقة جديدة تم دراستها نظريا عن طريق برنامج الدوكنك مع انزيم الدي ان أي كايريس للتحقق من كفائتها كمضادات حيوية.هذه المشتقات تم انتاجها بكميات عالية وتم فحص تركيبها الكيميائي عبرطيف الرنين المغناطيسي للهيدروجين والكاربون وطيف الاشعة تحت الحمراء .

تم قياس الفعالية الحيوية ضد اثنان من البكتريا السالبة لصبغة غرام(الكلبسيلة الرئوية والزائفة الزنجارية) وبكتريا واحدة موجبة لصبغة غرام(العقدية الرئوية).أظهرت جميع المركبات المصنعة فعالية جيدة مقارنة بالليفوفلوكساسين,افضل فعالية كانت ضد بكتريا العقدية الرئوية واقل فعالية كانت ضد الكلبسيلة الرئوية.

الكلمات المفتاحية: ليفوفلوكساسين, كلايسين, هستدين, سيرين,انزيم الدي ان أي كايريس, الالتحام الجزيئي,فحص خصائص حركية الدواء.

Introduction

Chemical substances known as antimicrobial agents are used to treat bacterial, viral, fungal, and microorganism infections (1). In the previous decades, numerous antimicrobial drugs were employed to treat various infections (2). Penicillins and sulfonamides, were often employed in therapeutic settings (3). Quinolones and fluoroquinolones, a class of synthetic antibiotics with broad-spectrum activity and powerful bactericidal agents, were later developed (4).

Levofloxacin is an FDA-approved antibiotic of the third-generation fluoroquinolones, and is particularly effective against penicillin-resistant strains of Chlamydia pneumonia, Mycoplasma pneumoniae, and S. pneumoniae (5). Levofloxacin act by inhibiting DNA gyrase, an enzyme necessary for DNA replication (6).

Levofloxacin has many uses in medicinal chemistry, including the treatment of urinary and respiratory tract infections (7).

The fundamental action of fluoroquinolones as anticancer agents is their capacity to obstruct the topoisomerase II enzyme (8). These also induce the apoptotic pathway, stopping colony formation, telomerase activity reduction, metastasis, invasion, and migration, as well as arresting the S/G2 stage of the cell cycle (9). Furthermore, multiple studies on fluoroquinolone combination medicines showed that some of them can enhance the efficacy of recognized anticancer medications (10).

The structural activity relationship of levofloxacin has proven that C7-piperazine, C6-F, C4-carbonyl, and C3-carboxylic acid or its isostere were significantly important for antibacterial activity(11).

The C-3 carboxyl group was modified in several ways to create a new derivative that acts as an antibacterial or anticancer agent(12).

In this work, we will introduce L-amino acids to the C3 carboxylic group of levofloxacin to produce new carboxamides that may have better antimicrobial and anticancer activity than levofloxacin.

Experimental work

Materials

Levofloxacin was purchased from Hyperchem (China). Ethyl chloroformate (ECF) was purchased from Sigma Aldrich (Germany), and amino acids were from Alpha-Chemika (India).

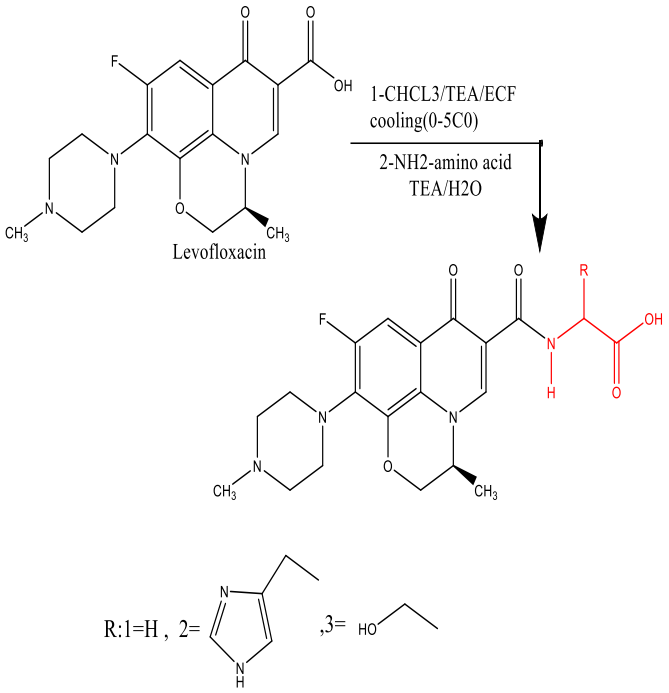
General methods

Melting points were recorded using the Stuart Electrical melting point apparatus (Germany).

FT-IR spectra were recorded on a Shimadzu FT-IR spectrophotometer using KBr discs. TMS was used as the internal standard. The 1H NMR and 13C-NMR were acquired using a Bruker AC-400 (400 MHz) apparatus in DMSO-d6. Coupling constants J and chemical shifts (d) are reported in Hz and ppm, respectively.

Chemical synthesis

The procedure indicated in Scheme 1 was used to synthesize the target compound



Scheme (1): Synthesis of the target compounds (1-3)

Procedure for Synthesis of the target compounds (1-3)

Levofloxacin (10 mmol) was dissolved in dry chloroform (50ml), triethylamine (10mmol) was added, and the mixture was placed in an ice bath at (-5 to -10 oC) and stirred by a mechanical stirrer. 10 mmol of Ethyl chloroformate was added dropwise during 20 min to the mixture with continuous stirring for 1hr. A cold solution of amino acids (10mmol) in distilled water (20ml) containing TEA (20mmol) was added at once to the initial mixture and stirred vigorously for two hrs in an ice bath and for another two hrs at room temperature (13).

A separatory funnel was used to separate the chloroform layer from the aqueous layer, which contained unreacted levofloxacin. While, the aqueous layer contained TEA-HCl, unreacted amino acids, and possibly the product. The volume of the aqueous layer was reduced, and THF was added to remove TEA. HCl, which is insoluble in THF, was flittered. Hot dry ethanol (50 ml) was added to dissolve and extract the product. To the ethanolic solution, a small amount of charcoal was added with stirring and warming and then filtered. Ethanol was evaporated and the product was collected and dried in an oven at 50 oC for one hr.

Levofloxacin carboxamide with glycine

(S)-(9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7H-[1,4]-oxazino[2,3,4-ij] quinoline-6-carbonyl) glycine (1).

Yellow powder, yield, 73.2%, m.p. 190-192 oC . IR (KBr) characteristic bands (v, cm-1);

3433.06 (O-H stretching vibration), 3286.84(NH amide stretching vibration), 2977 (stretching vibration of CH3 Alkane), 2941(stretching vibration (symmetric) of CH3 Alkane), 1708 (C=O carbonyl of carboxylic acid), 1643 (C=O carbonyl of secondary amide, 1622 (C=O carbonyl group of dihydropyridine ring), 1294 (C-N stretching vibration), 1083 (C-F stretching).

1H-NMR (DMSO-d6, 500MHz, δ); 10.13 (s,1H, OH of carboxylic acid), 8.97(s, 1H, CH alpha to nitrogen of quinoline ring), δ8.76(s,1H, NH of secondary amide), 7.34(s,1H, CH of quinoline ring), 4.83-4.94 (dd, 2H, CH2 alpha to oxygen atom in oxazine ring), 3.98(d,2H, CH2 alpha to carboxylic acid and secondary amide),

2.90-3.07(m,5H,2CH2 in piperazine ring and CH alpha to methyl group in oxazine ring), 2.58 (t,4H,2CH2 of piperazine ring), 1.43(s,3H, CH3 next to piperazine ring), 1.19(d,3H, CH3 next to oxazinane ring).
13C-NMR (DMSO-d6, 400MHz): 176.83 (1C, carbonyl carbon of quinoline ring), 172.23 (1C, carbonyl carbon of carboxylic acid) 166.50 (1C, carbonyl carbon of secondary amide) ,157.05 -103.56 (8C, carbon of quinoline ring), 68.66-60.33 (2C, carbon of oxazine ring), 55.31-54.34 (4C, carbon of piperazine ring), 45.70 (1C, carbon of CH3 next to piperazine ring), 42.63(1C, carbon alpha to secondary amide), 18.39 (1C, carbon of CH3 next to oxazine ring).

Levofloxacin carboxamide with L-Histidine

(9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7H-[1,4]-oxazino[2,3,4-ij] quinoline-6-carbonyl) histidine (2):
Light yellow powder (yield, 75. 1%). m. p 195-197 oC. IR characteristic bands; (v, cm-1):3450(NH stretching of imidazole ring), 3433(O-H stretching of carboxylic acid), 3294(NH stretching of secondary amide), 2977 (stretching vibration (asymmetric) of CH3 Alkane, 2939(stretching vibration (symmetric) of CH3 Alkane), 1718(C=O carbonyl group of carboxylic acid),1639(C=O carbonyl group of secondary amides),1622(C=O carbonyl group of quinoline ring), 1242(C-O-C stretching vibration), 1089(C-F stretching).
1H-NMR (DMSO-d6,400MHz, δ): 10.30 (s,1H,NH of imidazole ring), 10.14(s,1H ,OH of carboxylic acid), 8.96(s, 1H, CH alpha to nitrogen of quinoline ring), 8.73 (d,1H,CH of imidazole ring), 8.59(s,1H,NH of secondary amide), 7.56(s,1H,CH of quinoline ring), 7.39(d,1H,CH of imidazole ring), 4.49-4.61(m,1H,CH alpha to carboxylic acid), 4.21-4.23(dd,2H,CH2 alpha to oxygen atom in oxazine ring), 3.98(d,2H,CH2 alpha to carboxylic acid and secondary amide), 3.24-3.77 (m,5H,2CH2 in piperazine ring and CH alpha to methyl group in oxazine ring), 2.99-3.04 (m,2H,CH2 next to imidazole ring), 2.49 (t,4H,2CH2 of piperazine ring), 2.27 (s,3H,CH3 next to piperazine ring), 1.46 (d,3H,CH3 next to oxazine ring).
13C-NMR (DMSO-d6, 400MHz):176.83 (1C,carbonyl carbon of quinoline ring) 166.52(1C,carbonyl carbon of carboxylic acid) 164.97(1C,carbonyl carbon of secondary amide), 157.12-103.60(8C,carbon of quinoline ring),132.48-107.08 (3C,carbon of imidazole ring),68.51-60.18- (2C,carbon of oxazine ring), 55.59-50.34(4C,carbon of piperazine ring), 46.27(1C,carbon of CH3 next to piperazine ring), 42.63 (1C,carbon alpha to 20 amide),18.39 (2C,CH2 carbon next to imidazole ring),18.22 (1C,carbon of CH3 next to oxazine ring).

Levofloxacin carboxamide with L-Serine

(9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7H-[1,4] oxazino[2,3,4-ij]quinoline-6-carbonyl) serine (3):
Red powder, yield =77.4%, m.p. 215-217 oC, IR (KBr) (v,cm-1): 3433 (O-H stretching vibration of carboxylic acid), 3427(O-H stretching vibration of serine),3288 (NH amide stretching vibration) 2972 (stretching vibration (asymmetric) of CH3 Alkane, 2881 (stretching vibration (symmetric) of CH3 Alkane) 1704(C=O carbonyl group of carboxylic acid),1687(C=O amide carbonyl group),1639(C=O carbonyl of quinoline ring),1558(C=C of aromatic ring),1236(C-O-C, stretching vibration) , 1091(C-F stretching).
1H-NMR (DMSO-d6, 500MHz,): 10.38 (s,1H, OH of carboxylic acid), 8.96(s, 1H, CH alpha to nitrogen of quinoline ring), 8.59(s,1H,NH of secondary amide), 7.56(s,1H,CH of benzene ring), 4.58(s,1H, OH of serine), 4.34-4.53(m,1H,CH alpha to carboxylic acid), 4.21-4.23(dd,2H,CH2 alpha to oxygen atom in oxazine ring),3.98

(d,2H,CH2 alpha to carboxylic acid and secondary amide), 3.31-3.38(m,5H,2CH2 in piperazine ring and CH alpha to methyl group in oxazine ring), 3.02-3.08(m,2H,CH2 alpha to hydroxyl group), δ2.59(t,4H,2CH2 of piperazine ring), 2.34(s,3H,CH3 next to piperazine ring), 1.45(d,3H,CH3 next to oxazine ring).
13C-NMR (DMSO-d6, 400MHz): 176.82 (1C,carbonyl carbon of quinoline ring) 171.89(1C,carbonyl carbon of carboxylic acid) 164.64(1C,carbonyl carbon of secondary amide),157.10 -103.82 (6C,carbon of benzene ring) 146.64-110.39 (2C,carbon of quinoline ring), 68.54-60.20 (2C,carbon of oxazine ring) 62.20(1C,carbon alpha to hydroxyl group), 58.20(1C,carbon alpha to secondary amide),55.33-50.04- (4C,carbon of piperazine ring), 45.85 (1C,carbon of CH3 next to piperazine ring), 18.38(1C,carbon of CH3 next to oxazine ring).

Computational Methods:

Application of ADME.

The free online program the Swiss ADME, the pharmacokinetics (absorption, distribution, metabolism, and excretion), and other physicochemical aspects of our produced drugs are evaluated (14).

The newly created compound's structure was depicted using ChemAxon's Marvin JS, which eventually transformed into the SMILE name.

Molecular Docking

Using the Genetic Optimization for Ligand Docking (GOLD) program of the CCDC (Cambridge Crystallographic Data Center) (v.5.7.1), a molecular docking analysis for the designed compounds was conducted. The Hermes visualizer program (v.1.10.1) was utilized to show the active sites, ligands, receptors, interaction modes (hydrogen connections or short contacts), pose estimation, bond length estimation, and develop photos.

Preparation of the ligand and receptor.

First, ChemDraw Professional (v.16.0) software was used to draw the chemical structures of the suggested ligands. The Chem3D (v.16.0) was used to minimize the energy for the molecules by using the MM2 force field.

Second, the three-dimensional structures of the two active targets were used to dock the recently created ligands; the crystal structure of DNA gyrase protein (PDB code: 4DUH) complexes with levofloxacin. The receptors were then downloaded from the protein data bank into the GOLD Hermes module (PDB). The co-crystallized ligands were re-docked to confirm the docking procedure. Finally, in order to assure proper tautomeric states and the ionization of amino acid (AA) residues, the polar hydrogen atoms were added. Then, the crystallographic water molecules that are not a part of the active site are removed to prepare the structures of the DNA gyrase receptors and 4DUH proteins.

Molecular Docking:

The receptor was set up for docking using the CCDC GOLD suite's Hermes visualizer tool. To determine the active site of the target enzyme, the initial ligand interaction site was used (15). The docking approach made use of all of the protein residues with the protein binding site identified within the (10 A°) of the reference ligand. Each parameter that is used during docking is set to its default value. The early termination option was turned off, and the top-ranked solution was kept as the default. The number of generated poses was set to 10. Chemscore kinase was utilized as a configuration template. while the piecewise linear potential (ChemPLP) is utilized as a scoring function.

Finally, the output was saved in mol.2 file form. The outcomes of docking would offer valuable information on the optimum binding mode, binding free energy, and docked positions. The ideal interaction

between our recently created ligands and the receptor's amino acids (DNA gyrase) was determined.

Antibacterial screening of the synthesized target compounds 1-3:

The preliminary antibacterial activity of the target compounds was evaluated using the Well Diffusion Method (16). Three bacterial species were used in vitro test subjects to determine the antibacterial activity of the new compounds: two types of gram-negative bacteria (K. pneumonia and P.aeruginosa) and one type of gram-positive bacteria (S. pneumoniae). Levofloxacin was used as an antibacterial positive control.

Results and Discussion:

Explanation of ADME Results.

For the prediction of the ADME and physicochemical properties of synthesized compounds, the Swiss ADME server was utilized. Before synthesis and biological testing, it is a helpful and affordable way to identify the ADME features and rule out ligands that are insufficient and have an unsatisfactory pharmacokinetic profile (17).

The "rule of five" (RO5) of Lipinski states that compounds must have a molecular mass of 500 Daltons or less, five or fewer H-bond donors, ten or fewer H-bond acceptors, and a log p of five or less (the octanol-water partition coefficient) for oral absorption. Compounds that do not meet these requirements will have poor bioavailability and permeability. (18).

Our findings demonstrated that every synthetic chemical satisfies the RO5. For substances that are passively absorbed, limited oral bioavailability is anticipated. with a TPSA >140 oA. As indicated in the table, all of the compounds we synthesized had a TPSA of less than 140 oA (between 114.45 and 135.89 0A) and a bioavailability of 0.55, indicating that all of the derivatives reached the systemic circulation.

Table (1): The ADME results target compounds

Compound	H-bond donor	H- bond acceptor	MR (m3/mol)	TPSA (0A2)	G.I.T absorption	BBB permeability	Bioavailability score	Lipinski violation
1	2	7	114.45	104.11	high	NO	0.55	0
2	3	8	135.89	132.79	high	NO	0.55	1
3	3	8	120.42	124.34	high	NO	0.55	0

Interpretation of Docking Results.

Flexible ligands are docked with protein binding sites using the genetic algorithm GOLD (Genetic Optimization for Ligand Docking)(19).

In general, GOLD has the potential to anticipate the pose and offers the excellent outcomes for virtual screening. The GOLD suite, which also contains Hermes, Mercury, ConQuest, GOLD, Mogul, and other software, includes this program.

By altering the geometry of the structure, energy optimization techniques were created to identify the stable and lowest energy conformation.

By analyzing the molecular interaction between the designed chemical compounds and the active binding sites of the proteins, such as DNA gyrase, docking experiments determine the binding energies and specificities of the designed compounds to proteins. According to their PLP fitness associated with the complex formation at the active sites, the developed compounds, levofloxacin were characterized in terms of their ability to inhibit DNA gyrase.

The GOLD program also displays the length of all bonds and the hydrogen bonding distance between our designed ligands and a certain protein as being ≤3Aº(20).

The docked molecules' PLP fitness on the target DNA gyrase enzyme was found to be between (80.72-87.53). Table 2 shows

the amino acids discovered through the docking process.

The connection through short interactions with our ligands and hydrogen bonds. The brief connections also contain additional holding forces, such as van der Waals, electrostatic, steric, pi-pi stacking, dipole-dipole, and others.

Table (2): Molecular docking of levofloxacin and the target compounds with DNA gyrase

Compound	DNA gyrase binding energy (PLP fitness)	Amino acids involved in interaction H-bonding	Amino acids involved in short contact
1	87.53	GLY 102	GLY 102, GLY 101, ARG 76, LYS 103, ILE 94, ILE 78 ASN 46 (4), ASP 73 (2) THR 165,2 HOH Bridge with ARG 73 & GLY 77 & THR 165
2	80.72	ARG 136 (2)	ARG 136 (2), GLY 101 (2), LYS 103, SP 73, ILE 78 (3), ILE 94
3	85.46	GLY 102, GLY 101 (2)	GLY 102 (2), GLY 101 (3) LYS 103, VAL 43 THR 165, ILE 78 (6) HOH Bridge with ASP 73 & THR 165 & GLY 77
levofloxacin	76.85	HOH Bridge with ARG 73 & GLY 77 & THR 165	LYS 103 (3), PRO 79 (3) VAL 120, ILE 94, ARG 76 HOH Bridge with ARG 73 & GLY 77 & THR 165

Molecular binding pattern of levofloxacin with the DNA gyrase enzyme. The produced ligands **1-3** demonstrated positive docking findings with the DNA gyrase enzyme complex when compared to levofloxacin, with compound **1** demonstrating the greatest outcomes. PLP fitness, which was 87.53, was docked. Finally, the experimental data and our docking analysis have a strong correlation. The following

figures illustrate the hydrogen bond in the DNA gyrase (PDB ID: 4DUH) in figure (1) represent levofloxacin across through HOH Bridge with ARG 73 & GLY 77 & THR 165amino acids, figure (2) the compound 1a binding with GLY 102 amino acids, figure 3 shows the interaction of chemical 1b with amino acids in ARG 136 (2).

Figure 4 shows the chemical 1c's binding to amino acids GLY 102 and GLY 101.

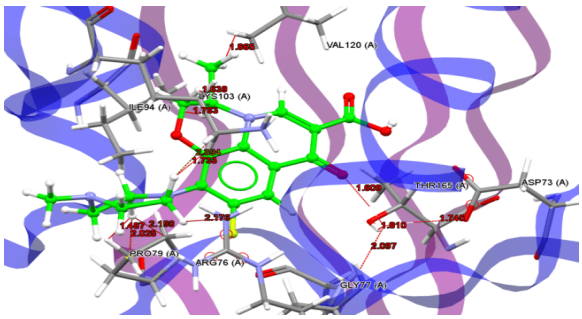


Figure (1): Levofloxacin interacts with the DNA gyrase enzyme through H-bonds and short contacts (PDB code: 4DUH). Levofloxacin interaction with amino acid residues via an H-bond [HOH Bridge with ARG 73 & GLY 77 & THR 165] is shown in green, whereas short contact is displayed in red.

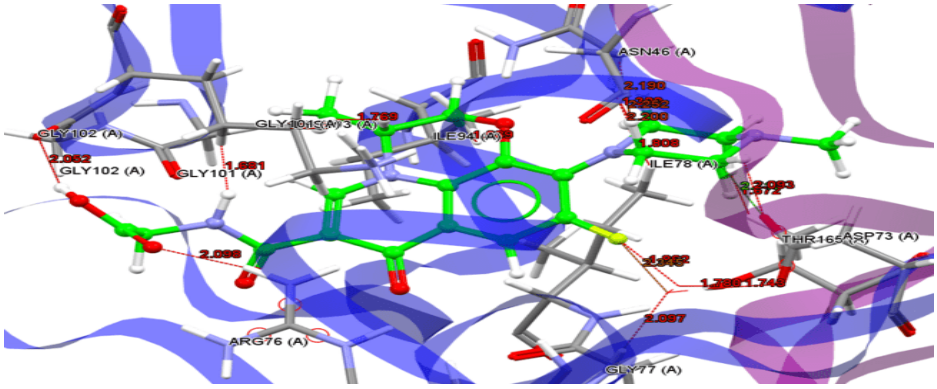


Figure (2): The compound 1, interacts with the DNA gyrase enzyme through H-bonds and short contacts (PDB code: 4DUH). 1a interaction with amino acid residues via an H-bond [GLY 102] is shown in green, whereas short contact is displayed in red

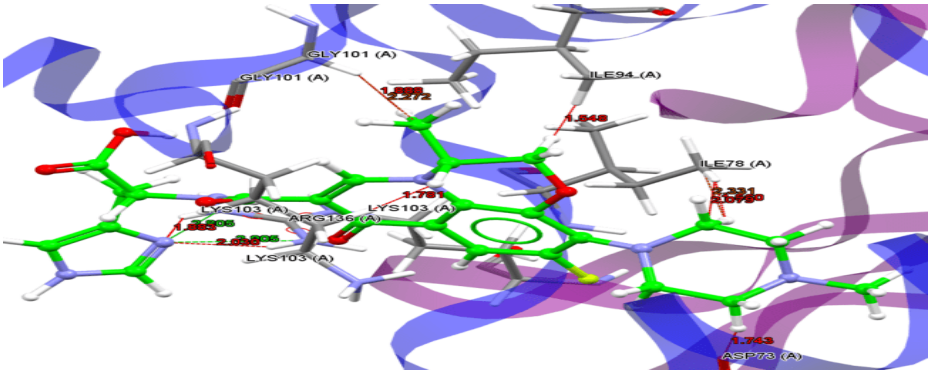


Figure (3): The compound 2 interacts with the DNA gyrase enzyme through H-bonds and short contacts (PDB code: 4DUH). 1b interaction with amino acid residues via an H-bond [ARG 136 (2)] is shown in green, whereas short contact is displayed in red.

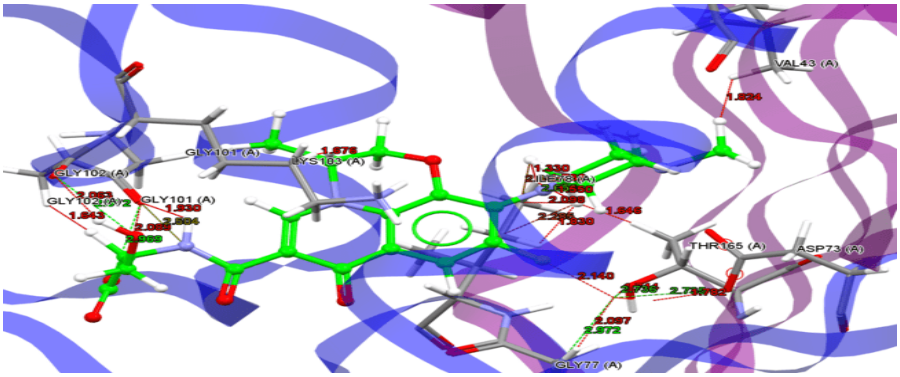


Figure (4) The compound 3 interacts with the DNA gyrase enzyme through H-bonds and short contacts (PDB code: 4DUH). 1b interaction with amino acid residues via an H-bond [GLY 102, GLY 101 (2)] is shown in green, whereas short contact is displayed in red.

Results of anti-bacterial evaluation:
Levofloxacin served as a reference drug in this investigation for the newly synthesized compounds 1-3, while dimethyl sulfoxide served as a pure control. These compounds tested against three types of bacteria, two types of gram-negative bacteria (*K. pneumonia* and *P. aeruginosa*) and one type of gram-positive bacteria concentrations (500, 250, 125, 62.5, 31.25, and 15 µg/mL). The results revealed that the greater activity was against *S. pneumonia and* moderate activity was against *P. aeruginosa and Klebsiella pneumonia* (Table3). It can be assumed that the antibacterial activity of levofloxacin was largely retained. The synthesized levofloxacin carboxamides recorded potential and significant results of antibacterial activities.

Table (3): The antibacterial activity of the investigated compounds on tested bacteria

Compounds	Concentration (µg/mL)	Inhibition zone(mm)		
		Gram negative		Gram positive
		Klebsiella Pneumonia	***P. aeruginosa***	***S. pneumonia***
levofloxacin	500	20	20	18
	250	18	20	16
	125	13	15	15
	62.5	10	10	10
	31.25	3	5	7
	15.625	-	4	-
DMSO	pure	-	-	-
1a	500	20	20	30
	250	20	20	25
	125	15	15	24
	62.5	10	10	20
	31.25	7	10	13
	15.625	-	-	10
1b	500	12	25	27
	250	10	20	25
	125	8	20	15
	62.5	5	15	10
	31.25	3	10	8
	15.625	-	5	4
1c	500	20	20	20
	250	18	20	17
	125	15	15	12
	62.5	13	8	10
	31.25	10	4	5
	15.625	-	-	3

Conclusion
Levofloxacin carboxamides (**1-3**) has been synthesized, successfully in reasonable yields, and their chemical structures were confirmed using spectral analysis (FT-IR and ^{1}H-NMR and ^{13}C-NMR) and elemental microanalysis. All the synthesized compounds **1-3** exhibited good activities on three types of bacteria, when compared with the activity of standard drug (levofloxacin). Moreover, the greatest activities of these compounds occur on S. *pneumonia* and their lowest activities occur on *K. pneumonia*. According to the

ADME investigations, compounds (**1-3**) comply with the Lipinski rule. Docking studies recorded better results for binding affinities on the DNA gyrase enzyme, when compared with levofloxacin.

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