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Synthesis, Identification, Theoretical Study, and Effect of the New Heterocyclic System from Ciprofloxacin Derivatives on the Activity of Some Liver Enzymes

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Abstract:

The target of this study was to synthesize several new Ciprofloxacin drug analogs by providing a nucleophilic substitution procedure that provides new functionality at the carboxylic group location. The analogs were synthesized, designed, and characterized by ^{1}HNMR, and FTIR. The synthetic path began from the reaction of ciprofloxacin drug with morpholine to give compound[B], ciprofloxacin derivative was linked with a variety of primary and secondary amines to give compounds[B1-B9]. The above-mentioned prepared compounds [B3 and B5] were applied to liver enzymes, and the increase in the activity of these enzymes was observed. In addition, a theoretical study was conducted to study the energies and properties of the prepared compounds.

Keywords: Ciprofloxacin, Liver enzymes, Mannich reactions, Spectrum, Synthesis

Introduction:

Ciprofloxacin (CP, Fig. 1), is a broad-spectrum fluoroquinolone (FQ)[1] antibiotic with few adverse effects, it is widely used and has been found to inhibit cancer cell proliferation and induce apoptosis in a variety of cancer cell lines [2-3]. FQ is also employed in clinical trials as second-line medicine to treat tuberculosis because it has favorable pharmacokinetic profiles of good adsorptionand , efficient penetration into host macrophages [4]. It is one of the most commonly given antibacterial medications, according to the World Health Organization [5]. Ciprofloxacin is approved for the treatment of a wide range of Gram-positive and Gram-negative bacterial illnesses [6,7]. Ciprofloxacin's COOH group was transformed into amide and ester derivatives, which have different antibacterial properties [8]. Ciprofloxacin was integrated into a new series of Schiff bases of 1,2,4-triazole via the Mannich process, and the antibacterial results were comparable to ciprofloxacin[9]. When compared to ciprofloxacin, NH-derivatives of ciprofloxacin demonstrated improved activity against Gram-negative bacteria [10]. Metal complexes are still a valuable resource for developing anticancer and antibacterial drugs in pharmaceutical chemistry, and they can be used to treat drug-resistant bacteria and a variety of viral illnesses [11-13]. As a result, fluoroquinolones are used to treat a variety of illnesses, including infections of the urinary system, respiratory tract, skin, gastrointestinal tract, and bones [14,15]. In this research ciprofloxacin has been incorporated into morphilene via Mannich reaction to give a new compound, then synthesis of several levofloxacin analogs by providing novel functionality at the carboxylic group position. For this reason, the carboxylic group at C-6 was reacted at the carbonyl carbon novel structural hybrids of ciprofloxacin with different amines to check the effectiveness of newly introduced remains on the activity of some liver enzymes.

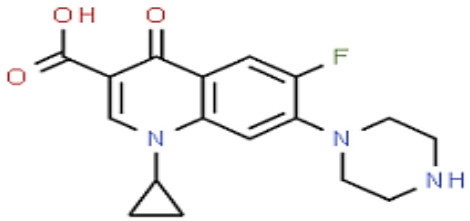


Figure 1: Ciprofloxacin drug

Material and Methods:

Materials and Physical Measurements:

All melting points were recorded, uncorrected, using a Gallen Kamp capillary melting point equipment. Infrared (IR) spectra were registered using KBr disk on [Shimadzu model (FTIR-8400S)] spectrometer.^{1}H NMR spectra in DMSO-d6 were acquired using an internal standard for the Varian Mercury-400 spectrometer, the reference used was tetramethylsilane (TMS). The purity of compounds was checked by TLC on aluminum-coated plates of 60 F245 (E. Merck), using) ethyl acetate and hexane, 2:1v:v) as the mobile phase and iodine was used as a visualizing agent. Fluka and Sigma-Aldrich provided all starting ingredients and solvents, which were used without further purification.

Synthesis of the Organic Compounds:

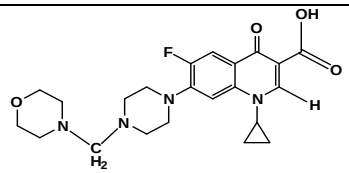
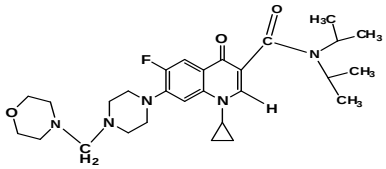
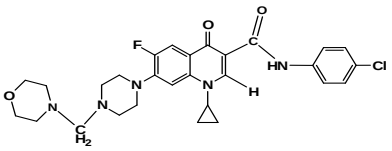
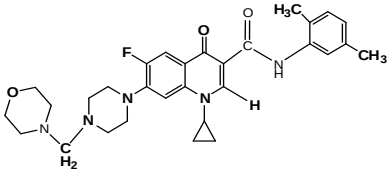
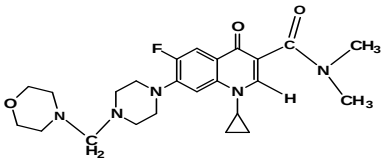
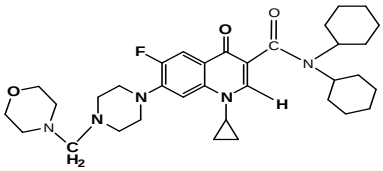
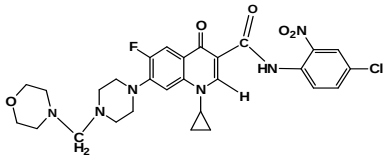
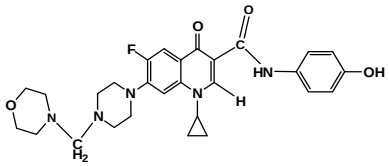
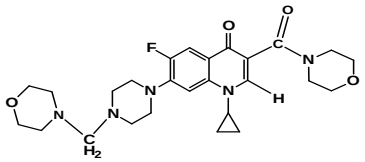
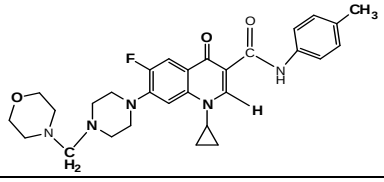
Synthesis of Compound [B] [16]:

Stirred the blend of ciprofloxacin (0.01mol, 3.31g) and morpholine (0.01 mol,1.5 g) in 25 ml ethanol, and formaldehyde (37%CH_2O) excess was added dropwise and heated to reflux for 4 hours at 70-75°C and allowed to cool to ambient temperature before freezing overnight to form crystals to make the title compound. The precipitate was filtered and recrystallized from [Ethanol with Water 2:8], the physical properties of synthesized compounds are shown in table.1.

Synthesis of Compounds [B_1- B_9] [17]:

Various ciprofloxacin derivatives were synthesized using aromatic or aliphatic amines (Diisopropylamine, 4-Chloroaniline, 2,5-Dimethylaniline, Dimethylamine, Dicyclohexylamine, 4-Chloro-2-nitroaniline, 4-Hydroxyaniline, Morphline, 4- Methylaniline). Ciprofloxacin (0.001 moles) was added to 20 mL of ethanol in a round-bottomed flask. After a few drops of sulphuric acid were added to the flask, the reaction was refluxed for 5 to 8 hours. Following the exhaustion of ciprofloxacin, 0.001 molar solutions of aromatic or aliphatic amines in ethanol were added one at a time. The reaction was refluxed for other 2 to 3 hours with constant stirring until complete. Evaporation was used to lower the reaction mixture's volume. The precipitates were filtered and recrystallized from the filtrate (DMF), the physical properties of synthesized compounds shown in table.1.

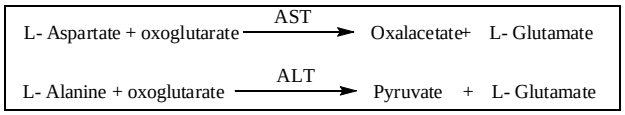
Table 1. The physical properties of synthesized compounds (B- B9)

Comp. No.	structure	Chemical Formula	Molecular Weight	Color	M. P. °C	Yield %
B		$C_{22}H_{27}FN_4O_4$	430.47	yellow	218-220	89
B1		$C_{28}H_{40}FN_5O_3$	513.65	Deep yellow	270-272	60
B2		$C_{28}H_{31}ClFN_5O_3$	540.03	light brown	220-222	62
B3		$C_{30}H_{36}FN_5O_3$	533.64	brown	278-280	70
B4		$C_{24}H_{32}FN_5O_3$	457.54	light yellow	262-264	75
B5		$C_{34}H_{48}FN_5O_3$	593.78	Brown	202-204	70
B6		$C_{28}H_{30}ClFN_6O_5$	585.03	orange	293-295	54
B7		$C_{28}H_{32}FN_5O_4$	521.58	Dark red	280-282	62
B8		$C_{26}H_{34}FN_5O_4$	499.58	Deep yellow	232-234	68
B9		$C_{29}H_{34}FN_5O_3$	519.61	Brown	272-274	46

Materials and Methods of Biological Activity Section

Compounds (B3 and B5) have an effect on the activities of SGOT and SGPT. The following

processes are used to colorimetrically determine the activity of SGOT or SGPT.



The pyruvate or oxaloacetate formed was measured in its derived from 2,4-dinitrophenylhydrazine, which was absorbed at wave length 546 nm (SYRBIO kit).

A Compound [(Stock Solution , 0.01 M) (B3 and B5)]

By dissolving the compounds (B3 and B5) in distilled water, a stock solution (0.01 M) was created, and the following concentrations [(10-2, 10-3, 10-4, 10-5 M)] were created by diluting with distilled water. The activity of the enzymes SGOT and SGPT were determined in human serum using the same procedures as these enzymes, but with 100 µl of buffer replaced with 100 l of substances (B3 and B5). The activation % was estimated by comparing efficiency under identical conditions with and without chemicals (B3 and B5), using the equation:

% Activation
=100× the activity in the presence of activator/the activity in the absence of activator – 100. The activation constant (K_a) was calculated according to the following equation:

$V_{max} + A = V_{max} - A/ (1+ [A]/ K_a)$

where A is activation constant.
+A is with activator
-A is without activator
[A] is an activator concentration

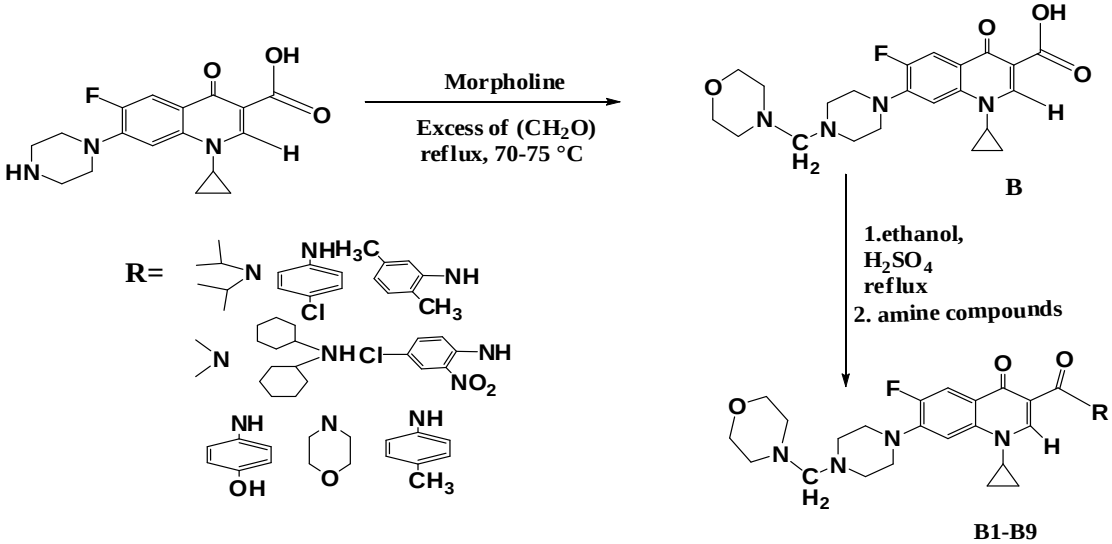
3.3. A Constant Concentration of Compounds (B3 and B5) (10^{-2} M)

To investigate the kind of activation, a constant concentration of chemicals (B3 and B5) (10-2 M) was employed with varying substrate concentrations of [(40, 80, 120, 160, 200)] mmol/L for SGOT and SGPT. Different substrate concentrations of these enzymes SGOT and SGPT were produced using buffers [(phosphate buffer pH = 7.40, 100 mmol/L)]. The enzyme velocity was estimated using the Burke and Linweaver equation and plotting 1/v versus 1/[s] were evaluated values; Ka, apparent Vmax (Vmapp), apparent Km (Kmapp), kind of inhibition or activation [18,19].

Result and Discussion:

Synthesis:

The synthetic approach ,detailed in Scheme 1 ,was used to produce derivatives (B-B9) in modest yields. FTIR and ^{1}H NMR spectrum data was used to determine the structures of the produced compounds.



Scheme1. The chemical proceedings for the synthesis of compounds (B-B9)

FT-IR Spectra

FTIR spectrum of compound (B) offered significant characteristic stretching vibration bands corresponding to the 3446 cm^{-1}(of -OH), 3060cm^{-1}(of -CH aromatic), 2960, 2837cm^{-1}(CH of aliphatic), 1722 cm^{-1}(C=O of acid), 1629 cm^{-1}(C=O of ketone), 1573,1496 cm^{-1}(of C=C aromatic). The FTIR spectra of compounds B1-B9 are demonstrated in Table. 2 and (Figs.9, 10, 11).

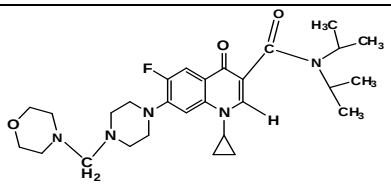
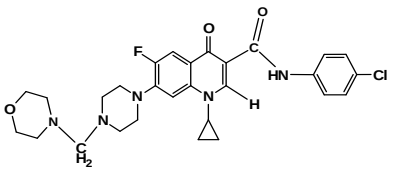
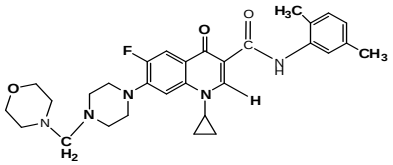
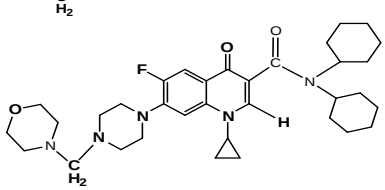
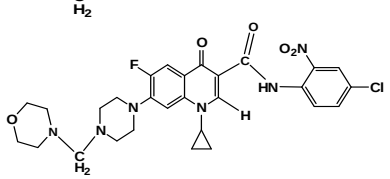
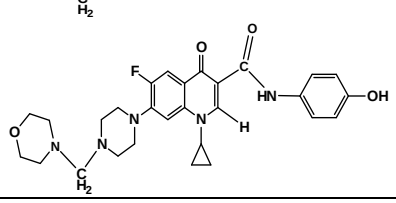
Table 2. FT-IR Spectral data of synthesized compounds (B1-B9) in cm^{-1}

Comp. No.	υN-H	υC-H Aromatic	υC-H Aliphatic	υC=O of amide	υC=O of ketone	υC=C aromatic	Others
B1	3372	3080	2970,2873	1672	1623	1558	1143 υ (C-O)
B2	3382	3070	2964,2839	1679	1625	1573,1494	1095 υ(C-Cl)
B3	3390	3060	2978,2921	1674	1620	1566,1483	1153 υ (C-O)
B4	3365	3066	2972,2864	1670	1622	1575,1584	1182 υ (C-O)
B5	3367	3083	2933,2860	1670	1625	1575,1494	1145 υ (C-O)
B6	3276	3054	2932,2862	1668	1623	1573,1476	1504,1340 υ(NO_2), 1159 υ (C-O)
B7	3255	3047	2966,2873	1664	1623	1580,1481	3382 υ(O-H), 1151 υ (C-O)
B8	3375	3068	2970,2871	1662	1627	1554	1183υ (C-O)
B9	3396	3029	2962,2860	1670	1627	1575,1483	1172υ (C-O)

^{1}HNMR Spectra:

The ^{1}HNMR spectra of some compounds (B1, B2, B3, B5, B6, B7) are listed in Table. 3 and (Figs. 12,13and 14).

Table 3. ^{1}HNMR data for compounds (B1, B2, B3, B5, B6, B7) in ppm.

Comp. No.	Compounds structure	^{1}HNMR data of (δ-H) in ppm
B1		1.22(3H, d,CH_3), 1.11-1.29(4H, m,CH_2-CH_2),2.56-2.83, (12H, m, N-CH_2-CH_2-N), 2.90-2.97 (1H, m, CH-N), 3.16-3.28 (4CH_2, m, CH_2-O), 3.77 (2H, s, N-CH_2-N), 7.85-7.97 (2H, m, CH aromatic), 8.37(1H, s, CH=C)
B2		1.00-1.31 (4H, m, CH_2-CH_2), 2.07-2.69 (12H, m, N-CH_2-CH_2-N), 2.86-3.23(1H, m, CH-N), 3.39-3.73(4CH_2, m, CH_2-O), 4.22 (2H, s, N-CH2-N), 6.94-7.98 (6H, m, CH aromatic), 8.67(1H, s, CH=C), 9.52(1H, s, NH)
B3		1.05-1.26 (4H, m, CH_2-CH_2), 1.92 (3H, s, CH_3), 2.13 (3H, s, CH_3), 2.34-2.97 (12H, m, N-CH_2-CH_2-N), 3.32-3.78 (4CH_2, m, CH_2-O), 3.93-3.98(1H, m, CH-N), 3.20 (2H, s, N-CH_2-N), 6.37-8.30 (5H, m, CH aromatic), 8.73(1H, s, CH=C), 9.70(1H, s, NH)
B5		1.03-1.32(20H, m, CH_2cyclohexane), 1.50-1.85(4H, m, CH_2-CH_2 cyclopropane), 2.08-2.18(1H, m, CH-N), 2.28-2.76 (8H, m, N-CH_2-CH_2-N), 3.28-3.59 (4CH_2, m, CH_2-O), 4.90 (2H, s, N-CH_2-N), 7.52-8.11(2H, m, CH aromatic), 8.65(1H, s, CH=C)
B6		0.96-1.29 (4H, m, CH_2-CH_2), 2.66-2.98 (12H, m, N-CH_2-CH_2-N), 3.23-3.45(1H, m, CH-N), 3.25-3.53(4CH_2, m, CH_2-O), 3.86 (2H, s, N-CH_2-N), 7.14-8.10 (5H, m, CH aromatic), 8.71(1H, s, CH=C), 9.61(1H, s, NH)
B7		1.00-1.29 (4H, m, CH_2-CH_2), 2.60-2.98(12H, m, N-CH_2-CH_2-N), 3.23-3.83(1H, m, CH-N), 3.32-3.78 (4CH_2, m, CH_2-O), 4.60 (2H, s, N-CH_2-N), 6.71(1H, s, OH), 6.86-8.25 (6H, m, CH aromatic), 8.66(1H, s, CH=C), 9.61(1H, s, NH)

Biological Activity of Transferase Enzymes (SGOT and SGPT).

The objective of this study is to look into the effects of SGOT and SGPT enzyme compounds (B3 and B5). The biochemical assays demonstrated that these substances stimulated the activity of the SGOT and SGPT enzymes. The impact of various chemical concentrations (B3 and B5) on the activity of SGOT and SGPT enzymes in human serum is shown in Table. 4. This study aims to look into the effects of SGOT and SGPT enzyme compounds (B3 and B5). The biochemical experiments demonstrated that these substances had an activating effect on the activity of the SGOT and SGPT enzymes. In compound(B3) and compound(B5), the SGOT and SGPT enzyme activity were (11 and 14 U/L) correspondingly. Figs 2 and 3 show the association between chemical concentrations (B3 and B5) and enzyme activity (1 and 2). According to these findings, the proportion of enzyme activation increased with each rise in compound concentration.

Table 4. The impact of different concentration of compounds (B3 and B5) on the activity of SGOT and SGPT enzymes in human serum.

Concentration (M)	GOT activity (U/L)	Activation (%)	GPT activity (U/L)	Activation(%)
Sample				
0	11	0.000	14	0.000
Compound (B3)				
10^{-2}	357	3,245	82	571
10^{-3}	167	1,521	48	342
10^{-4}	129	1,172	33	238
10^{-5}	83	751	24	171
Compound (B5)				
10^{-2}	384	3,492	94	671
10^{-3}	188	1,708	64	454
10^{-4}	76	694	37	264
10^{-5}	42	378	18	129

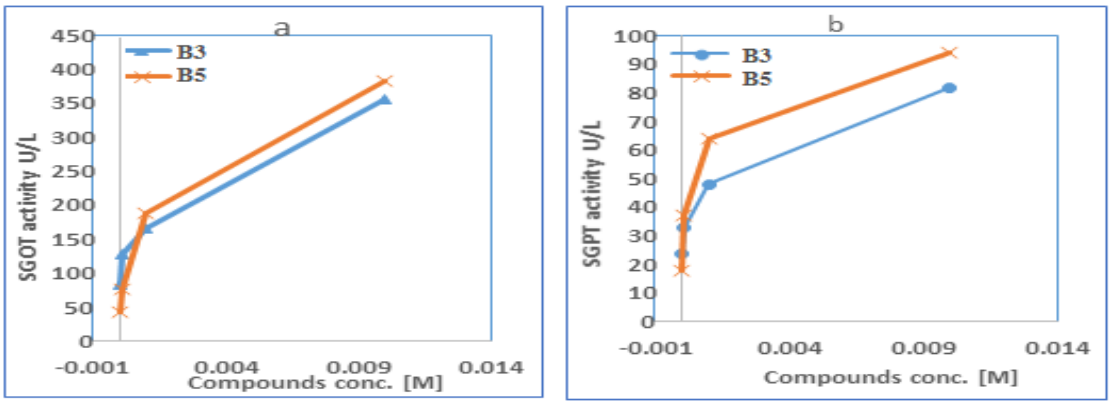


Figure 2. (a) The connection between the concentration of compounds (B3 and B5) and SGOT enzyme action. (b) Therelationship between the concentration of compound (B3 and B5) and SGPT enzyme action.

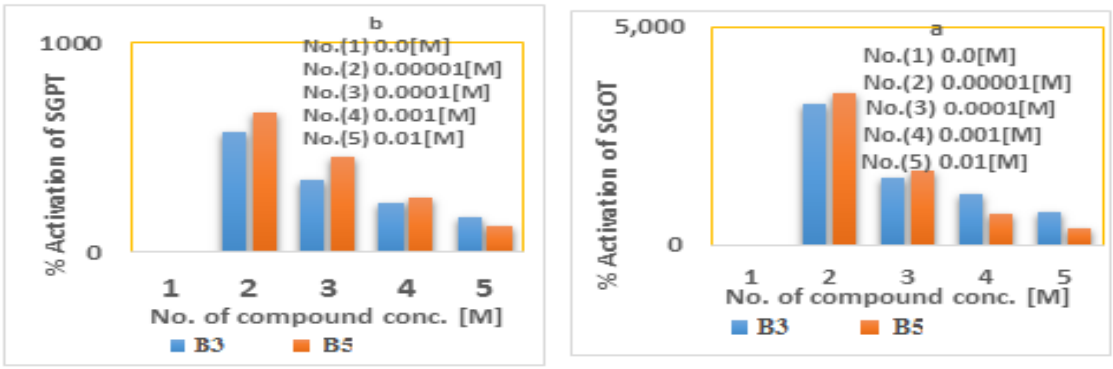


Figure 3. (a) The percentage of SGOT enzyme activation and the concentration of compounds (B3 and B5). (b) The percentage of SGPT enzyme activation and the concentration of compounds (B3 and B5).

Competitive, non-competitive and uncompetitive activators can easily be distinguished by using the Lineweaver–Burk plot's double reciprocal plot. The concentration of enzymes was kept constant during both groups of rate determinations. The speed of the inactivated enzyme was calculated in the first experiment, and a constant amount of activator was inserted in each enzyme test in the second experiment. Various substances are capable of reducing or eliminating the catalytic activity of a particular enzyme [20].

Table. 5 with Figs. 4 and 5 display the kind of enzyme activation using Line weaver–Burk plot for compounds (B3 and B5) on SGOT and SGPT activity. The Km values and Vmax were determined with (10^{-2} M) of compounds (B3 and B5) and without it. Vmax without compounds (B3 and B5) was greater than Vmax in the presence of compounds (B3 and B5). A liquate 10^{-2} M of compounds (B3 and B5) were non-competitive activation for enzymes activity. Non-competitive activation altered the enzyme's Vmax but not its Km. The Ka values of enzymes for compounds investigated at various concentrations were calculated using the Lineweaver– Burk equation.

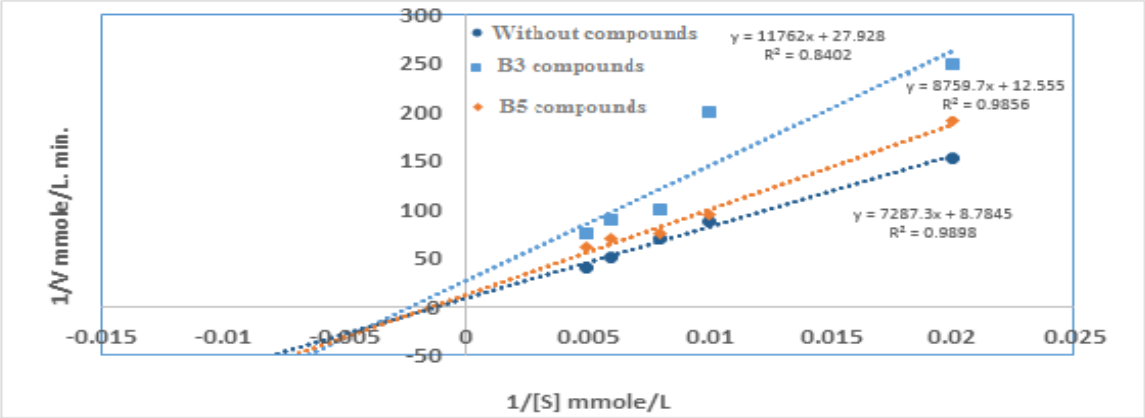


Figure 4. Lineweaver-Burk plots for compounds (B3 and B5) effects on SGOT.

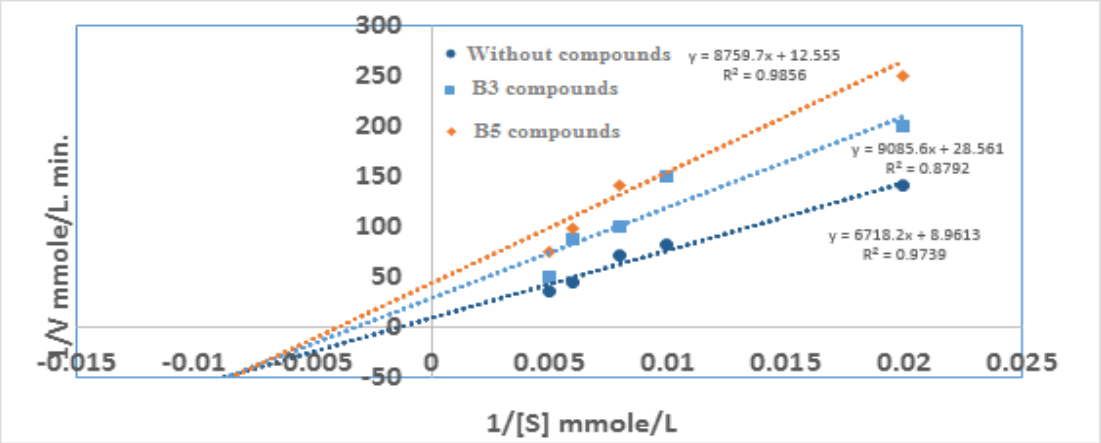


Figure 5. Lineweaver-Burk plots for compounds (B3 and B5) effects on SGPT.

Table 5. The kinetic properties of SGOT and SGPT with compounds (B3 and B5).

Enzymes	K_m (mmole/L)	V_{max} (mmole/ L). min.	K_a(mmole/L)	Type of effect
SGOT				
Without compound	200	0.114	------	------
Compound (B3)	200	0.036	0.0046	Noncompetitive
Compound (B5)	200	0.079	0.022	Noncompetitive
SGPT				
Without compound	200	0.112	------	-------
Compound (B3)	200	0.035	0.0045	Noncompetitive
Compound (B5)	200	0.022	0.0024	Noncompetitive

Amino acid metabolism, as well as the urea and tricarboxylic acid cycles, rely heavily on enzymes. We hypothesized that compounds (B3 and B5) include (-NH, =C, and =O) groups, which activate the active sides of amino acids in SGOT and SGPT enzymes by boosting their alliance for substrate reaction.

Theoretical Study

The optimize geometry and HOMO and LUMO energies for the compounds (B3 and B5) were calculated by using the semi-empirical (PM3) method. Figs 6 and 7 respectively show the shapes and contain the energy values for all bonding molecular orbitals [including the highest occupied molecular orbital HOMO, plus the lowest unoccupied molecular orbital LUMO] for (B3 and B5) compounds. They also demonstrated the symmetry assignment for each molecular orbital. Both HOMO and LUMO are the main orbitals in chemical stability. According to the semi-empirical, the reactive ability of the above compounds is related to the molecular orbitals (MO) that are the HOMO and the LUMO [21]

Table. 6, shows (E_{HOMO}) which represents the capacity to donate an electron, [22]. While (E_{LUMO}) indicates the capacity to obtain electron. The energy variation between HOMO and LOMO explains the ability of compounds (B3 and B5) to donate electrons and thus stimulate the ends of amino acids present in the enzyme, and this is consistent with the practical results that showed that these compounds (B3 and A5) are enzymes activator.

Table 6. Some energies and physical properties for compounds (B3 and B5)

Property	PM3 method
Compound B3	**Compound B5**
E_{tot} (kcal/mole) = -143898.6266	E_{tot} (kcal/mole) = -159149.5978
E_b (kcal/mole) = -7812.4140	E_b (kcal/mole) =-9185.3676
ΔH^o_f (kcal/mole) = -47.4750	ΔH^o_f (kcal/mole) = -111.6446
E_{HOMO} (ev.) = -8.679	E_{HOMO} (ev.) = -8.705
E_{LOMO} (ev.) =- 0.340	E_{LOMO} (ev.) =-0.705
$\Delta E_{HOMO-LUMO}$(ev.) = 8.339	$\Delta E_{HOMO-LUMO}$(ev.) = 8.000

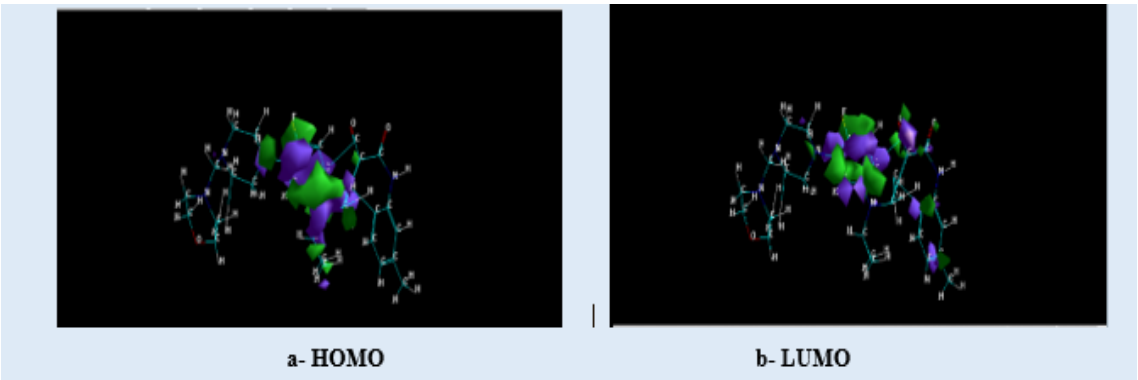


Figure 6. The calculated a- HOMO, b- LUMO for the compound (B3)

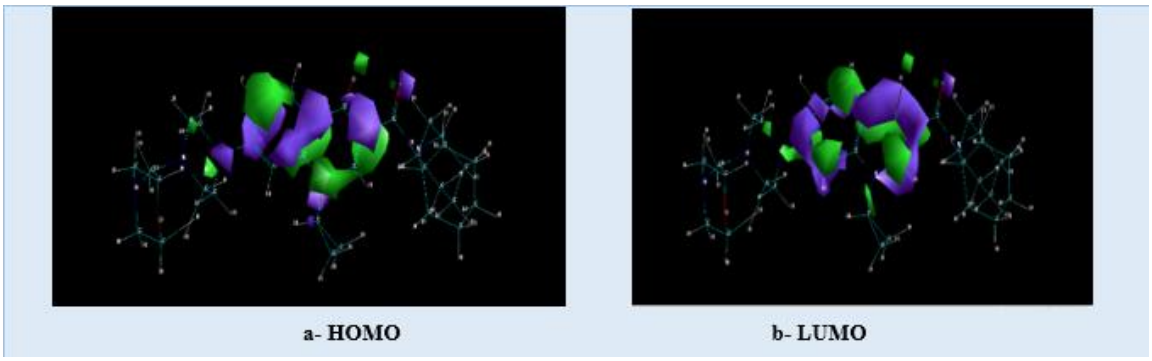


Figure 7. The calculated a- HOMO, b- LUMO for the compound (B5)

The electrostatic potential of the molecules is governed by the electron distribution seen in Fig. 8. The electrostatic potential (E.P.) describes how a molecular system's energy interacts with a positive point charge. The electrostatic potential (E.P.) is critical for locating reaction sites in a molecule;

positively charged organisms are more likely to attack a molecule with high electrostatic potential [23].

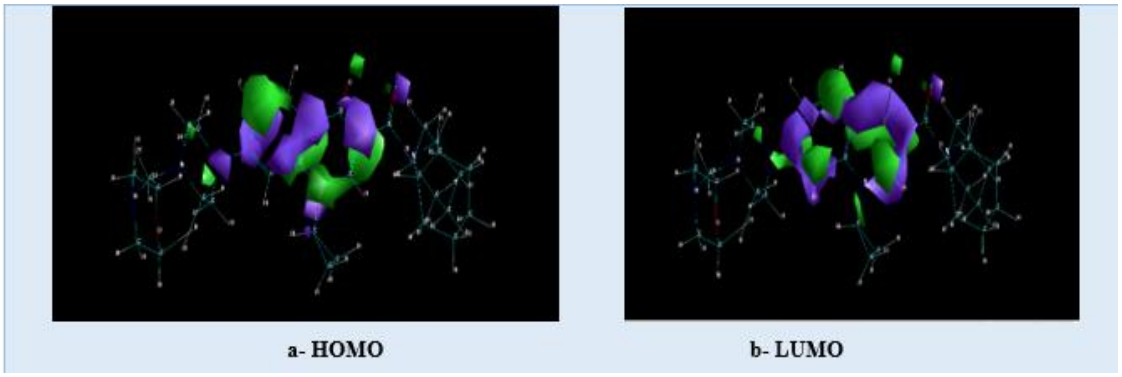


Figure 8. The calculated electrostatic potential a- B3, b- B5 compounds

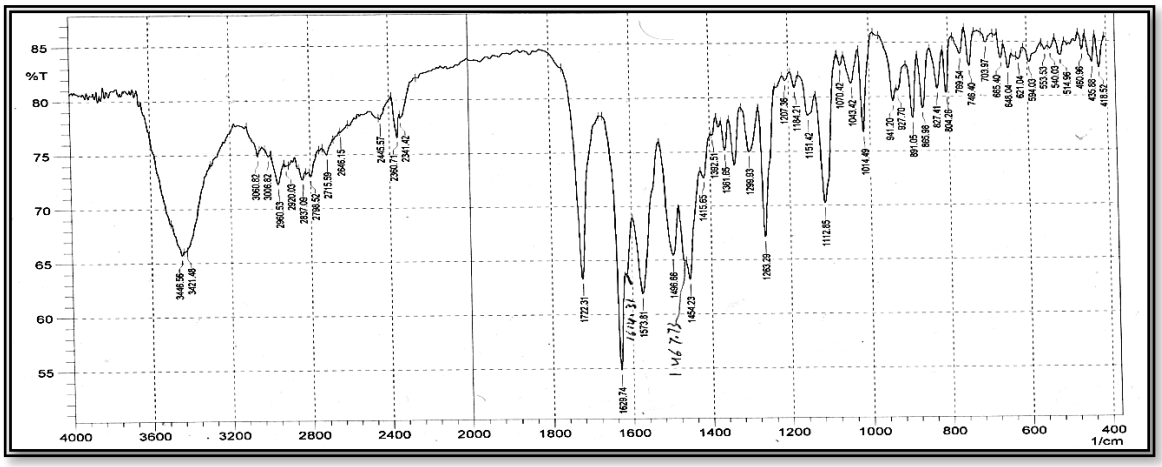


Figure 9. FT-IR, spectrum of compound (B)

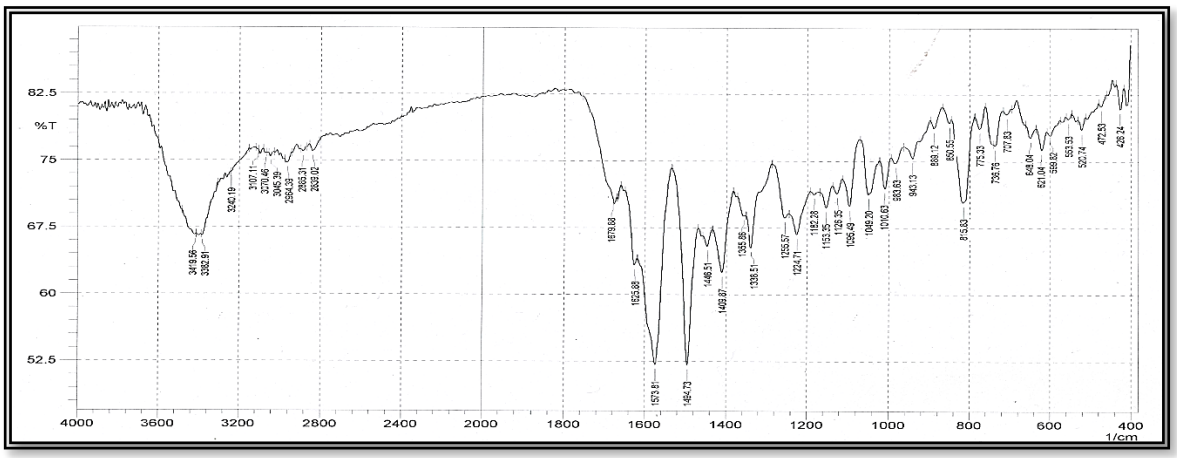


Figure 10. FT-IR, spectrum of compound (B2)

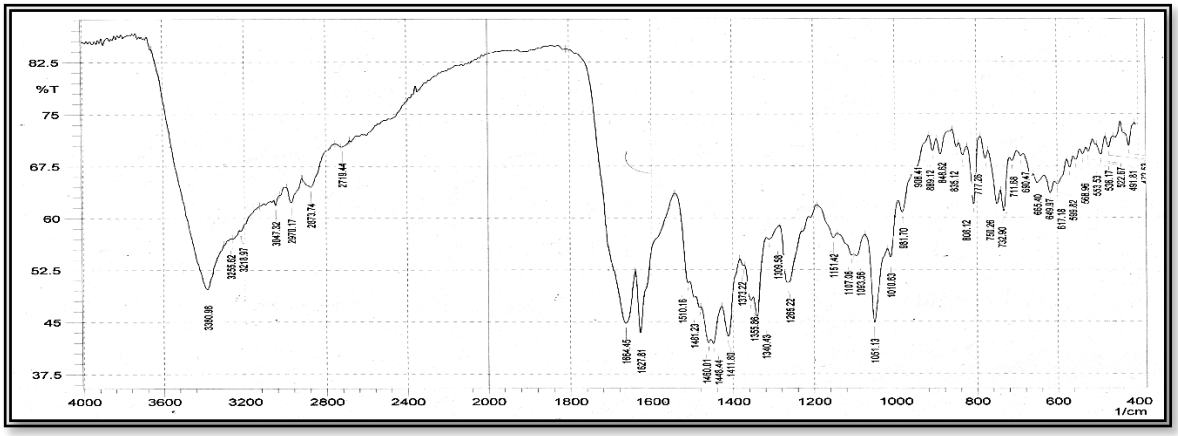


Figure 11. FT-IR, spectrum of compound (B 7)

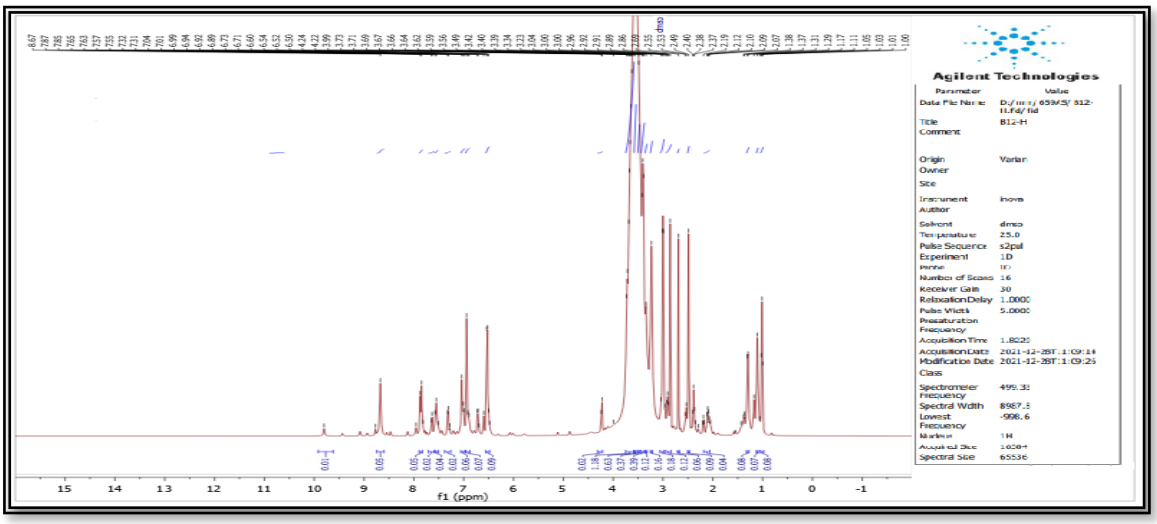


Figure 12. [1]HNMR spectrum of compound (B 2)

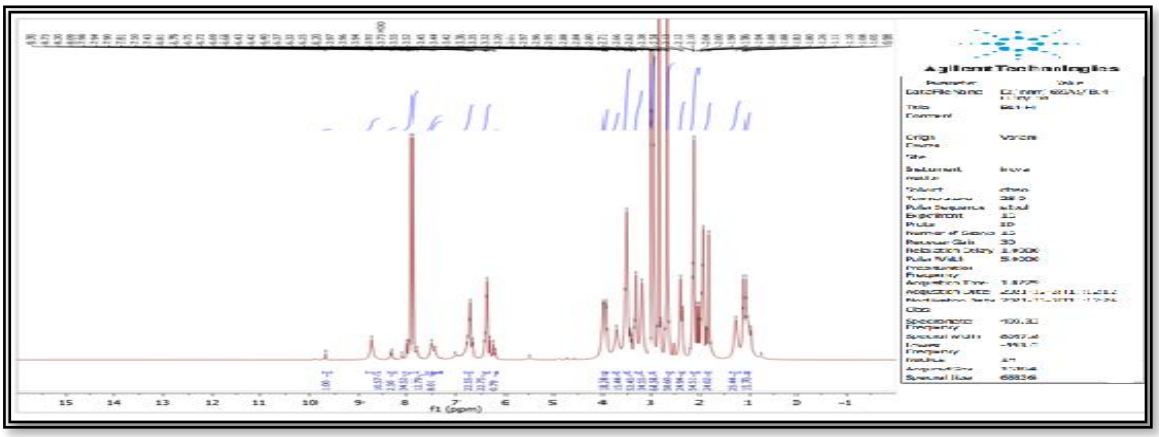


Figure 13. [1]HNMR spectrum of compound (B 3)

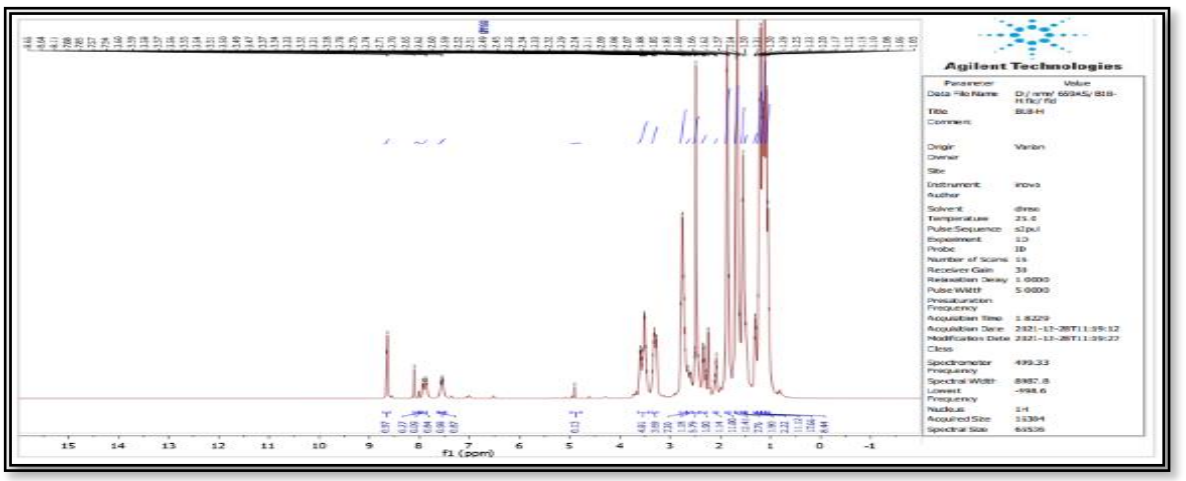


Figure 14. ^{1}HNMR spectrum of compound (B 5)

Conclusion:

Various methodology involving structural modifications have been attempted for the synthesis of new ciprofloxacin derivatives featuring amide functional groups at carbon C-3 of the fluoroquinolone scaffold. As detailed above, ten carboxamide analogues have been synthesized and characterized. B3 and B5 compounds were studied evaluated for their activity on some liver enzymes (GOT and GPT). The ciprofloxacin derivatives were found to have activating effects on the GOT and GPT enzymes in biochemical experiments. Also, we worked on a theoretical study in order to compare the findings to those of the experiment results. Our theoretical results are in a good agreement with the experimental ones.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' contributions statement:

A. S. S. conceived the idea of the article and worked on the practical side. Z. T. Kh. worked on the application of the compounds and made the theoretical and practical calculations. S. A. Y. and W. A. R. M. wrote the manuscript and proofread it. All the author discussed the final results.

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تحضير وتشخيص والدراسة النظرية للنظام الحلقي غير المتجانس الجديد المشتق من عقار السيبروفلوكساسين على نشاط بعض إنزيمات الكبد

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الخلاصة:

الهدف من هذه الدراسة هو تصنيع عدة نظائر جديدة لعقار سيبروفلوكساسين من خلال توفير إجراء بديل محب للنواة يوفر وظائف جديدة في موقع المجموعة الكربوكسيلية .تم تصنيعها وتصميمها والتأكد من المركبات الكيميائية المحضرة باستعمال طيف الرنين النووي المغناطيسي البروتوني (NMR-H وطيف االاشعة تحت الحمراء (FTIR) يبدأ المسار التخليقي من تفاعل عقار سيبروفلوكساسين مع المورفولين لإعطاء المركب [B] ، وتم ربط مشتق سيبروفلوكساسين بمجموعة متنوعة من الأمين الأولي والثانوي لإعطاء المركبات [B1-B9] ، وتم تطبيق المركبات المحضرة المذكورة أعلاه على انزيمات الكبد ، كما لوحظ زيادة في نشاط هذه الانزيمات .بالإضافة إلى دراسة نظرية لدراسة طاقات وخصائص المركبات المحضرة.

الكلمات المفتاحية: سيبروفلوكساسين، انزيمات الكبد، تفاعل مانخ، الاطياف، التحضير.