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Modification, Characterization of New Thiazolidinone and Oxazolidinone Derived from Levofloxacin and Evaluation of Anti-oxidant

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Abstract

The research study included the synthesis of a new series of heterocyclic derivatives containing the antibiotic Levofloxacin. The first way provides for the reaction of Levofloxacin with thionyl chloride in benzene as a solvent to give an acid chloride derivative. A new class of acid hydrazide synthesized from Levofloxacin was studied. Schiff bases were produced via the reaction of acid hydrazide with substituted aromatic ketones in methanol. The next stage involved the response of Schiff bases with thioglycolic acid and mono chloroacetic acid in DMF to produce derivatives of the antibiotic levofloxacin that have five heterocyclic members, including the derivatives thiazolidine-4-one and oxazolidine-5-one. The FTIR, ^{1}HNMR, and ^{13}CNMR spectra methods were used to confirm the structures of newly synthesized compounds. Also, the antioxidant properties of the synthetic compounds were evaluated in vitro. According to this study, levofloxacin-derived compounds have higher antioxidant capacities than ascorbic acid (vitamin C), and the medication also acts as an anti-inflammatory for respiratory infections.

Keywords: Levofloxacin, Thiazolidin-4-one, Oxazolidinone, Schiff bases, Anti-oxidant activity.

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1. Introduction

Levofloxacin is a fluoroquinolone antibiotic used to treat various conditions, including allergies, prostatitis, and urinary tract infections. Studies show that the antibiotic Levofloxacin kills bacteria quickly while protecting human DNA by acting as a DNA synthesis inhibitor in bacterial cells. Levofloxacin has demonstrated anticancer action against various cancer cells, including breast and lung cancer cells, with cell cycle arrest occurring most frequently in the S and G2 phases of progression [1,2].

As a result, many anticancer fluoroquinolones differ from clinical antibacterial fluoroquinolone in that they have nitrogen-containing rings on the 7-position and the 2-position, like piperazine. Additionally, alterations for the carboxylic group at the 3-position were not documented [2,3]. This group was modified with heterocyclic derivatives and showed higher antioxidants than vitamin C. The most frequent heteroatoms are (N, O, and sulfur S) [4,15]. Heterocyclic compounds are organic compounds with at least one hetero atom and are cyclic. Heterocyclic compounds are among the most influential families of organic chemicals used in various biological disciplines because of their activity in multiple diseases. It has been used to create anticancer pharmaceuticals [5], anti-fungal [6], antioxidants [7] and anti-microbial [8]. Hugo Schiff was the first to report Schiff's bases in 1864. In principle, it is produced when an aldehyde or ketone is combined with the primary amine [9].

These compounds are also known as imine and azomethine; numerous heterocyclic compounds have been investigated to develop drug-like molecules. Thiazolidin-4-one and Oxazolidin-4-one [10,18] derivatives, among others, have been playing a significant role in pharmaceutical chemistry.

2. Materials and Methods

The melting points of the prepared compounds were obtained using open glass capillaries by SMP10 digital. Shimadzu FTIR-8400 Fourier Transform Infrared (FTIR) Spectrophotometer was used to record the FTIR spectra as a KBr disc, and Bruker Bio Spin instrument was used to record the ^{1}H-NMR MHz and 13C-NMR spectra at the University of Basra in Iraq.

2.1 Synthesis of acid chloride derivative (1) [11]

Levofloxacin (0.5 g,1.3 mmol) was taken with (0.5 mL) of thionyl chloride in the presence of dry benzene (15 mL) and was refluxed for 4 hours evaporated the solvent and washed with diethyl ether. The products were collected as crystals. Physiochemical properties are shown in **Table 1**.

2.2 Synthesis of acid hydrazide derivative (2) [12,19]

In a round bottom flask, Acid chloride derivative (1) (0.5 g,1.3 mmol) was dissolved in 10 mL of methanol as a solvent. An excess of hydrazine hydrate (1.5 mL, 99%) was added to the reaction mixture and refluxed for 8 hours. The solvent was evaporated, and the product was washed with Diethyl ether and collected as crystals. Physiochemical properties as shown in **Table 1**.

2.3 Synthesis of Schiff bases derivatives (3-5) [13,20-22]

A mixture of acid hydrazide (0.5 g, 0.0013 mmol) and various aromatic ketones [p-bromo Acetophenone, *p*-Chloro Acetophenone, p-amino Acetophenone] (0.0013 mol) in methanol (20 mL) and few drops of GAA was refluxed for 8 hours; the precipitate was filtered, washed with diethyl ether to give the final product. The physical properties are listed in **Table 1**.

2.4 Synthesis of oxazolidine-4-one derivatives (6-8) [10,23]

To a well-stirred mixture of chloroacetic acid (0.0013 mmol) and drops of Et_3N as a catalyst, Schiff bases [3-5] (0.0013 mmol) in DMF (10 mL) were added. After 35 hours of refluxing, the mixture was put into freezing water to produce the final result. The physical properties are listed in **Table 2.**

2.5 Synthesis of thiazolidine-4-one derivatives (9-11) [10,17,24]

A mixture of Schiff bases [3-5] (0.0013 mmol) and an excess of 2-mercapto acetic acid (0.0026 mmol) in DMF was refluxed for 35 hours. The solvent was evaporated, and the residue was neutralized with 5% Na_2CO_3 solution to remove excess 2-mercapto acetic acid. The reaction mixture was poured into ice water to give the final product. The physical properties are listed in **Table 3**.

Table 1. The physical characteristics and FT-IR data of the compounds 1-5

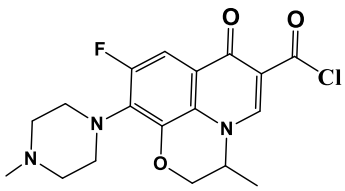
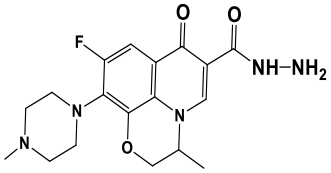
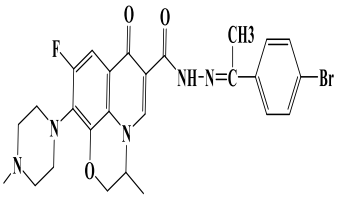
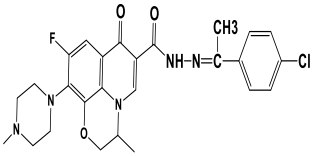
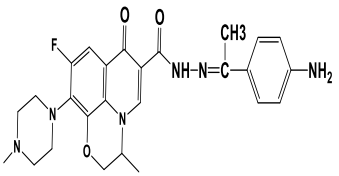
No.	Physical properties				Major FTIR Absorption cm^{-1}					
	Structure	M.P	Yield %	Color	(N-H)	(C-H) Arom.	(C-H) Aliph	(C=O)	(C=N) (C=C)	Other bands
1		236-238	76	Yellow	_	3041	2975 2856	1768 1718	_ 1590	(C-O) 1294
2		280-282	66	Green	3280	3080	2977 2839	1701 1683	_ 1556	(NH_2) 3434 3298
3		250-252	81	Yellow	3155	3050	2960 2856	1704 1662	1639 1560	
/										
4		298-300	88	Off-white	3280	3160	2977 2962	1710 1689	1640 1575	
5		295-296	80	Pale Yellow	3218	3043	2948 2902	1697 1658	1641 1542	(NH_2) 3431 3325

Table 2. The physical characteristics and FT-IR data of the compounds 6-8

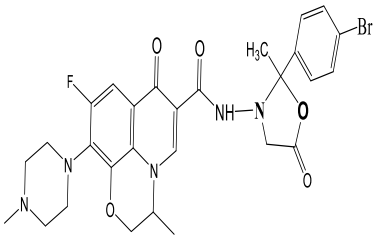
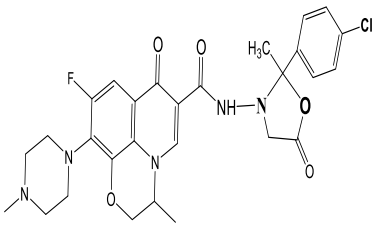
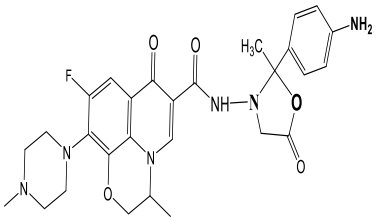
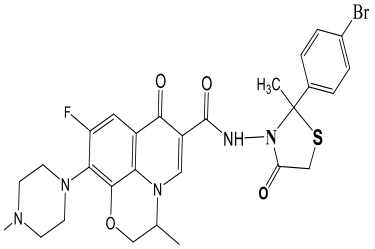
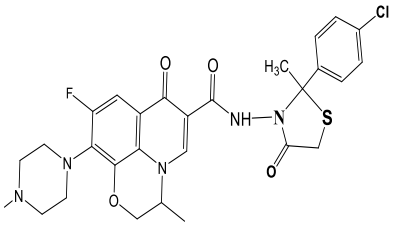
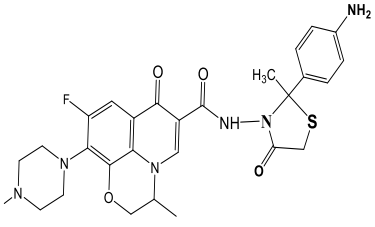
No.	Physical properties				Major FTIR Absorption cm^{-1}					
	Structure	M.P	Yield %	Color	(N-H)	(C-H) Arom	(C-H) Aliph	(C=O)	(C=C) (C-O)	Other bands
6		213-215	66	White	3170	3099	2972 2845	1620 1749	1580 1245	
7		246-248	65	White	3113	3083	2952 2866	1697 1710	1588 1230	
8		233-235	68	Off-White	3201	3037	2983 2833	1670 1716	1600 1280	(NH_2) 3390 3444

Table 3. The physical characteristics and FT-IR spectrum of the compounds 9-11

No.	Physical properties				Major FTIR Absorption cm^{-1}					
	Structure	M.P	Yield %	Color	(N-H)	(C-H) Arom	(C-H) Aliph	(C=O)	(C=C) (C-S)	Other bands
9		287-289	65	Brown	3112	3058	2954 2896	1620 1733	1566 655	
10		257-259	63	Dark Brown	3180	3089	2981 2846	1683 1703	1590 713	
11		277-278	70	Dark Yellow	3150	3037	2989 2813	1672 1712	1602 690	(NH_2) 3425 3375

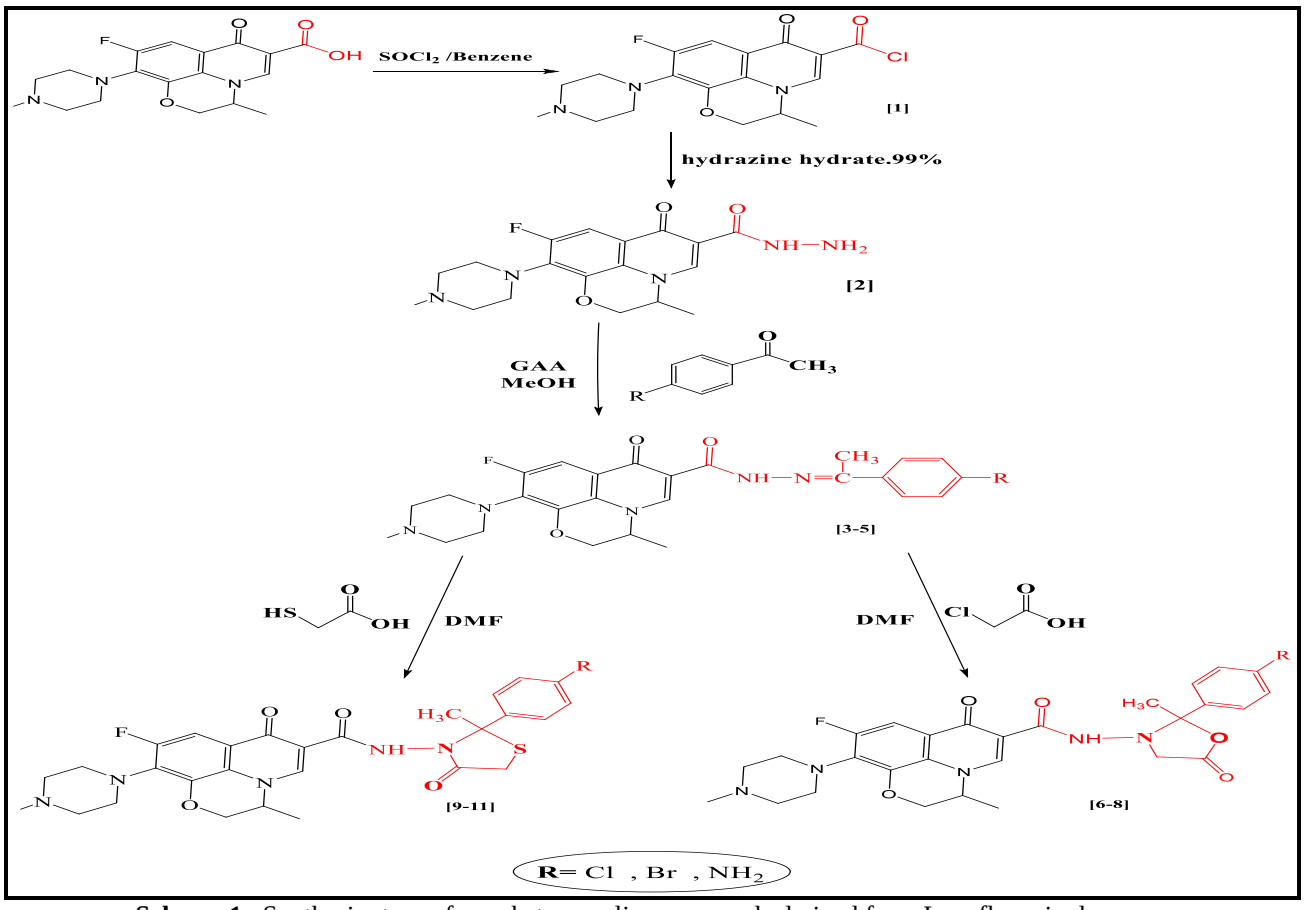
Anti-oxidant: [14,25-26]

2.6 Preparation of the solutions of DPPH and the samples

For each prepared compound, a stock solution was produced by dissolving 1 mg of the compound in 10 mL of methanol to create (100) ppm. This stock solution was diluted to make the other concentrations (100, 50, 25) ppm. The (2,2-diphenyl-1-picrylhydrazyl) (2 mg) was dissolved in 50 mL of methanol, and the solution was kept shielded from light by covering the test tubes with aluminum foil. Additionally, identical vitamin C concentrations (ascorbic acid) were generated.

3. Results and Discussion [27,28]

Thiazolidin-4-one and Oxazolidin-5-one derivatives were synthesized from Schiff bases derived from Levofloxacin, including new five-member heterocyclic rings. The synthesis steps are summarized in **Scheme 1**.



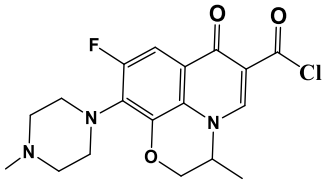
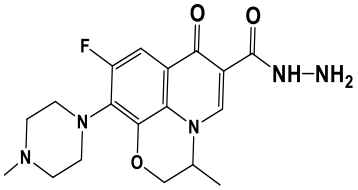
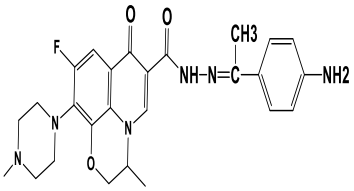
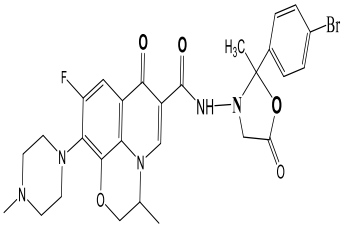
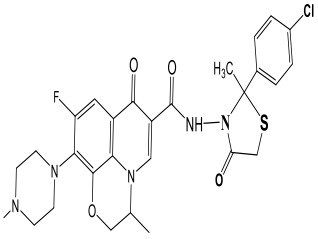
Scheme 1. Synthesis steps of new heterocyclic compounds derived from Levofloxacin drug

Levofloxacin reaction with thionyl chloride ($SOCl_2$) in Benzene as solvent. The FT-IR spectrum showed the appearance of ν(C=O) acid chloride and ketone at (1768) cm^{-1} and (1718) cm^{-1}. It showed ν(C=C) at (1590) cm^{-1}, FT-IR spectrum of this compound (2) indicates that (CO-Cl) at (1768) cm^{-1} was disappeared from the spectrum while the appearance of the asymmetric and symmetric stretching bands of (NH_2) absorption bands at (3434) cm^{-1} asym., (3298) cm^{-1} sym., also the presence of a sharp band of υ (N-H) at (3280) cm^{-1}, υ (C-H) aromatic at (3080) cm^{-1}, υ (C-H) aliphatic at (2977, 2839) cm^{-1} and υ(C=O) at (1701, 1683) cm^{-1},1H-NMR and ^{13}C-NMR are shown in **Table 4** and **5**. **Figure 2-5**.

Schiff bases derivatives [3-5] are synthesized by the reaction of acid hydrazide derived from levofloxacin with substituted aromatic ketones in Me-OH as a solvent. The FT-IR spectra of

compounds [3-5] shown disappearance of amine absorption bands of acid hydrazide, while appearance of new bands of azomethine (C=N) at (1639-1641) cm^{-1}, FTIR spectral data showed absorption at (C-H) aromatic bands at (3160-3043) cm^{-1}, ν (C=O) amide absorption bands at (1689-1658) cm^{-1} and (C=C) aromatic bands at (1575-1542) cm^{-1} spectrum. While the ^{1}H-NMR spectral data for compound [5] appeared doublet signal at δ= 1.22 ppm (3H, -CH3-CH, CH3 in oxazine ring); singlet signal at δ= 2.23 ppm (3H, -CH_3-N-); triplet signal at δ= 2.50-3.11 ppm (2H,-N-CH_2-CH_2-N-, 2CH_2 in piperazine ring); multiplet signal at δ= 4.38 ppm (1H, -O-CH_2-CH-); singlet signal at δ= 4.94 ppm (1H, -NH_2); while appeared multiplet signal at δ= 6.51-7.59 ppm (m, 5H, Ar-H); singlet signal at δ=8.92 ppm (1H, -CO-NH); at δ= 9.11 ppm (s, 1H, -N-CH=C$(CO)_2$ and ^{13}C-NMR spectral data are listed in **Table 5** and **Figure 6,7**.

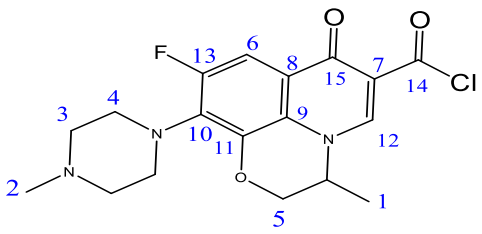
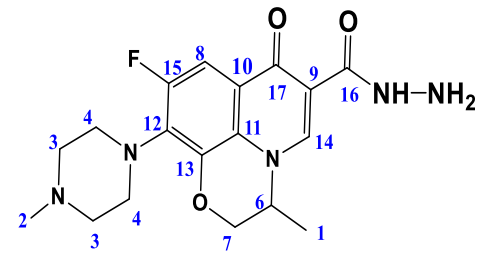
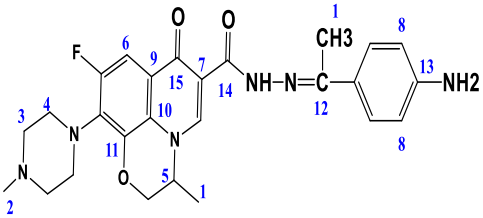
Table 4. Compounds were characterized by ^{1}H-NMR

No.	Structures	Spectral data (^{1}H-NMR) (δppm)
1		1.39 (d, 3H, -C**H**$_3$-CH- , CH_3 in oxazine ring) ; 2.51 (s, 3H, C**H**$_3$_N) ; 3-4(t, 2H, -NC**H**$_2$C**H**$_2$-N- , 2CH_2 in piperazine ring) ; 4.42 (d, 2H, -C**H**$_2$-O) ; 7.60 (s, 1H, Ar-**H**) ; 9:00 (s, 1H, -N-C**H**=C$(CO)_2$)
2		1.42 (d, 3H, -C**H**$_3$-CH-, CH_3 in oxazine ring) ; 2.21 (s, 3H, C**H**$_3$_N) ; 3.27-3.56(t, 2H, -NC**H**$_2$C**H**$_2$N- , 2CH_2 in piperazine ring) 4.42 (d, 2H, -C**H**$_2$-O) ; 4.90 (s, 1H, -N**H**$_2$) ; 7.49 (s, 1H, Ar-**H**) ; 8:91 (s, 1H, -N-C**H**=C$(CO)_2$) ; 10.61 (s, 1H, -CO-N**H**)
5		1.22 (d, 3H, -C**H**$_3$-CH, CH_3 in oxazine ring) ; 2.23 (s, 3H, -C**H**$_3$-N-) ; 2.50-3.11 (t, 2H, -N-C**H**$_2$-C**H**$_2$-N- , 2CH_2 in piperazine ring) ; 4.38 (m, 1H, -O-CH_2-C**H**-) ; 4.94 (s, 1H, -N**H**$_2$) ; 6.51_7.59 (m, 5H, Ar-**H**) ; 8.92 (s, 1H, -CO-N**H**) ; 9.11 (s, 1H, -N-C**H**=C$(CO)_2$)
6		1.14 (d, 3H, -C**H**$_3$-CH, CH_3 in oxazine ring) ; 2.83 (s, 3H, -C**H**$_3$-N-) ; 3.13-3.26 (t, 2H, -N-C**H**$_2$-C**H**$_2$-N- , 2CH_2 in piperazine ring) ; 4.11 (s , 2H ,oxazolidin-4-one ring) ; 4.11-4.45 (m, 1H, -O-CH_2-C**H**-) ;7.09-8.34 (m, 5H, Ar-**H**) ; 8.40 (s, 1H, -N-C**H**=C$(CO)_2$) ; 9.61 (s, 1H, -CO-N**H**)
10		1.44 (d, 3H, -C**H**$_3$-CH, CH_3 in oxazine ring) ; 2.27 (s, 3H, -C**H**$_3$-N-) ; 3.37-3.44 (t, 2H, -N-C**H**$_2$-C**H**$_2$-N-, 2CH_2 in piperazine ring) ; 4.13 (s , 2H ,thiazolidin-4-one ring) ; 4.37-4.60 (m, 1H, -O-CH_2-C**H**-) ; 7.45-7.96 (m, 5H, Ar-**H**) ; 8.80 (s, 1H, -N-C**H**=C$(CO)_2$) ; 8.99 (s, 1H, -CO-N**H**)

The Thiazolidin-4-one derivative was synthesized by cyclization reaction of Schiff base [3-5] with thioglycolic acid in DMF as a solvent, as shown in **Scheme (1)**, to produce compounds [9-11]. These compounds' FTIR spectra showed the disappearance of azomethine group absorption bands at range (1639-1641) cm^{-1}, show the bands of (C-S) thiazolidine ring absorption at range (655-

713) cm^{-1}, while showed absorption band for (C-H) aromatic at (3037-3089) cm^{-1}, *ν* (CO-NH) at (1620-1680) cm^{-1} and *ν* (C=O) at (1703-1733) cm^{-1} for thiazolidine ring, and ν (C=C) at (1566-1602) cm^{-1} for aromatic bands. The ^{1}H-NMR spectrum data for compound [10] as shown in fig-8, appeared doublet signal at δ= 1.44 ppm (3H, CH_3-CH, CH_3 in oxazine ring); singlet signal at δ= 2.27 ppm (3H, -CH_3-N-); triplet signal at δ= 3.37-3.44 ppm (2H, -N-CH_2- CH_2-N-, 2CH_2 in piperazine ring); singlet signal at δ= 4.13 ppm (2H, thiazolidin-4-one ring); while appeared multiplet signal at δ= 7.45-7.96 ppm (5H, Ar-H); singlet signal at δ= 8.80 ppm (1H,-N-CH=C$(CO)_2$); 8.99 ppm (s, 1H, -CO-NH). Schiff bases [3-5] were reacted with Chloroacetic acid to synthesize the oxazolidin-5-one derivatives [6-8]. These compounds' FTIR spectra showed the disappearance of azomethine group absorption bands at (1639-1641) cm^{-1}, with bands of (C=O oxazolidinone ring) at range (1230-1280) cm^{-1}, absorption bands for (C-H Arom.) at (3037-3099) cm^{-1}, *ν* (CO-NH) absorption bands at (1620-1680) cm^{-1} and *ν* (C=C Arom.) bands at (1566-1602) cm^{-1} spectrum. The ^{1}H-NMR spectral data for compound [6] as shown in **Figure 9**, appeared doublet signal at δ= 1.44 ppm (3H, -C**H**$_3$-CH , CH_3 in oxazine ring); at singlet signal δ= 2.27 ppm (3H,-C**H**$_3$-N-); triplet signal at δ= 3.37-3.44 ppm (2H, -N-C**H**$_2$-C**H**$_2$-N-, 2CH_2 in piperazine ring); singlet signal at δ= 4.13 ppm (2H ,oxazolidin-4-one ring); while appeared multiplet signal at δ= 7.45-7.96 ppm (5H, Ar-**H**); at δ= 8.80 ppm (1H, -N-C**H**=C$(CO)_2$) and signals at δ= 8.99 ppm (1H, -CO-N**H**).

Table 5. Compounds were characterized by ^{13}C-NMR [29,30]

No.	Structures	Spectral data (^{13}C-NMR) (ᵟppm)
1		**C**$_1$/18.42 **C**$_2$/40.35 **C**$_3$/51.75 **C**$_4$/55.75 **C**$_5$/68.75 **C**$_6$/103.79 **C**$_7$/107.28 **C**$_8$/120.92 **C**$_9$/125.22 **C**$_{10}$/130.99 **C**$_{11}$/141.06 **C**$_{12}$/146.58 **C**$_{13}$/157.00 **C**$_{14}$/176.85 **C**$_{15}$/166.44
2		**C**$_1$/20.37 **C**$_2$/39.88 **C**$_3$/46.49 **C**$_4$/50.52 **C**$_6$/55.20 **C**$_7$/68.49 **C**$_8$/103.59 **C**$_9$/109.95 **C**$_{10}$/120.09 **C**$_{11}$/124.69 **C**$_{12}$/131.24 **C**$_{13}$/140.51 **C**$_{14}$/144.80 **C**$_{15}$/154.38 **C**$_{16}$/166.69 **C**$_{17}$/174.68
5		**C**$_1$/18.37 **C**$_2$/39.29 **C**$_3$/48.10 **C**$_4$/54.01 **C**$_5$/55.33 **C**$_6$/107.30 **C**$_7$/113.64 **C**$_8$/125.24 **C**$_9$/128.12 **C**$_{10}$/140.00 **C**$_{11}$/146.84 **C**$_{12}$/150.51 **C**$_{13}$/160.78 **C**$_{14}$/166.50 **C**$_{15}$/176.89

In vitro antioxidant activity (DPPH. 2,2-diphenyl-1-picrylhydrazyl) [14,16]

The activity of all the compounds [3–10] and the beginning drug levofloxacin was comparable to or slightly higher than the standard (ascorbic acid). The DPPH (2,2-diphenyl-1-picrylhydrazyl) assay method predestines it at different concentrations (25, 50 and 100) g/mL. The outcome is

determined by the reaction of and is defined by change. The amount of electrons caught determines the stoichiometry of the deep violet color (DPPH) or decolorization. Among all chemicals,compounds [3,4,5,6,9,10] showed the most outstanding performance. When compared to some compounds that include amino groups, some compounds [4,7,10] bearing a Chloro group (electron-withdrawing group) at the para position demonstrated high antioxidant activity (electron donating group). Intense antioxidant action is shown by compounds [5,8,10] modified with halogen groups -Cl (electron-withdrawing group). As shown in **Table 6** and **Figure 1**.

Table 6. Antioxidant for compounds (3-10)

Comp No.	25(mg/ml)	50(mg/ml)	100(mg/ml)
3	96.03	90.19	89.07
4	93.03	98.19	91.07
5	92.78	87.82	95.17
6	88.13	99.15	94.57
7	75.53	87.82	95.53
8	88.31	86.93	80.89
9	92.11	82.13	92.50
10	81.44	88.38	91.11
Ascorbic acid	80.95	86.25	90.54

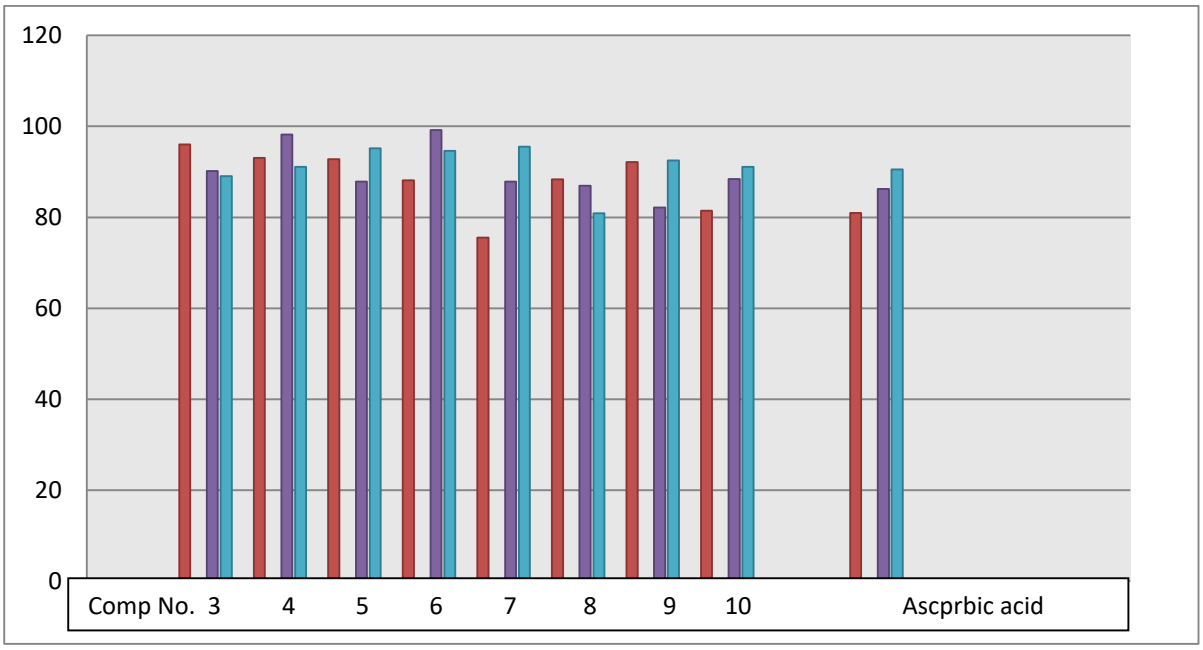


Figure 1. The compounds and their effectiveness with ascorbic acid

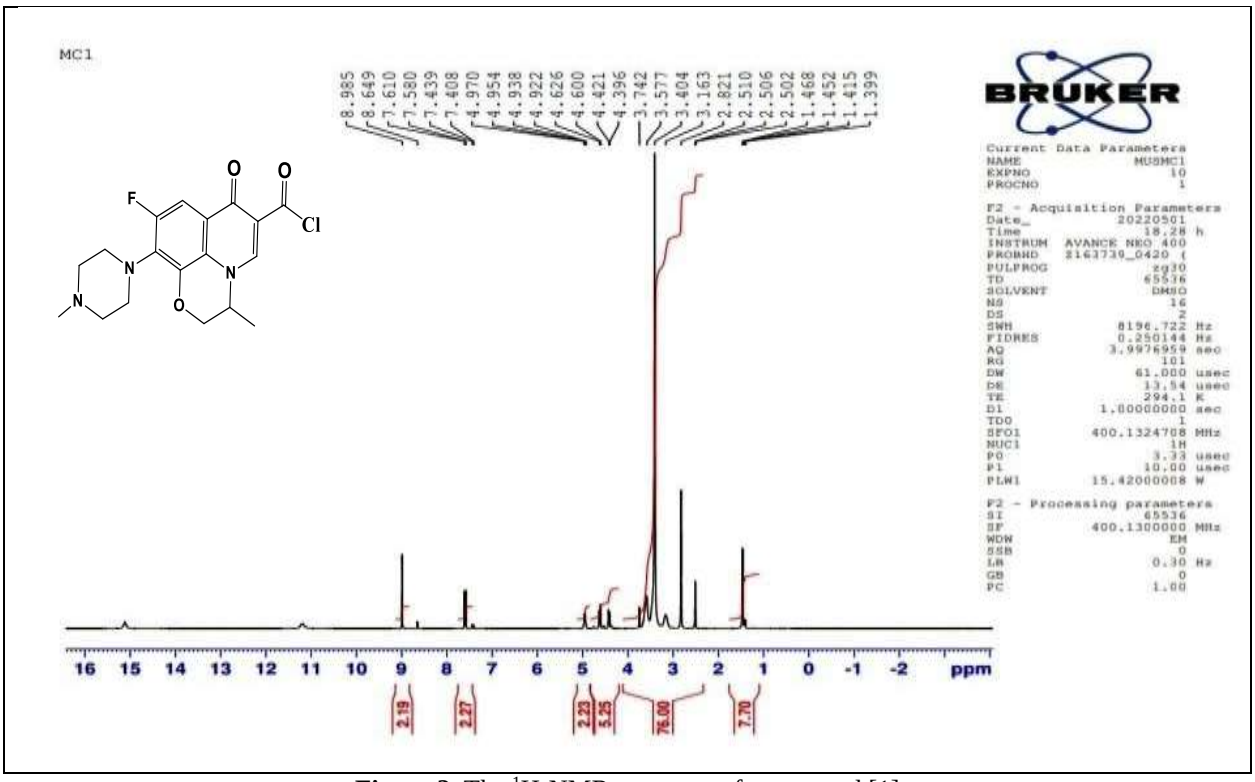


Figure 2. The ^{1}H-NMR spectrum of compound [1]

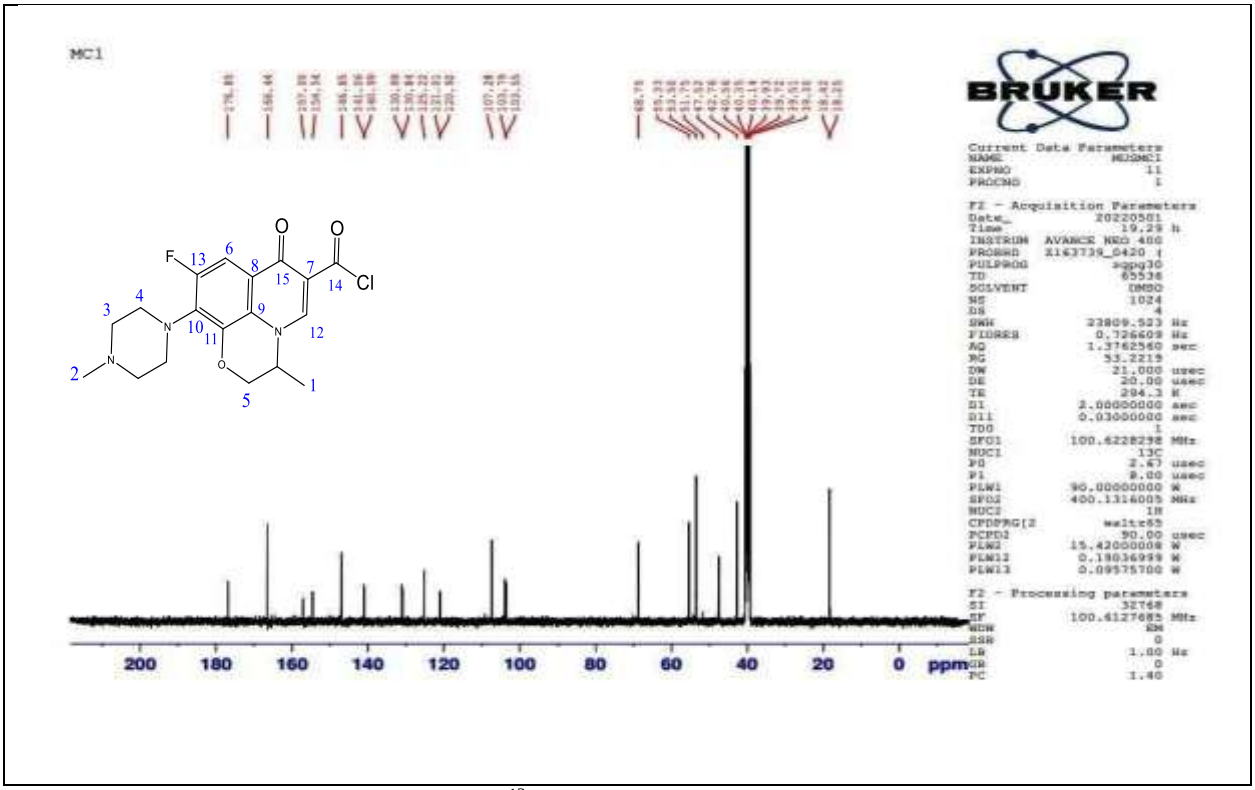


Figure 3. The ^{13}C-NMR spectrum of compound [1]

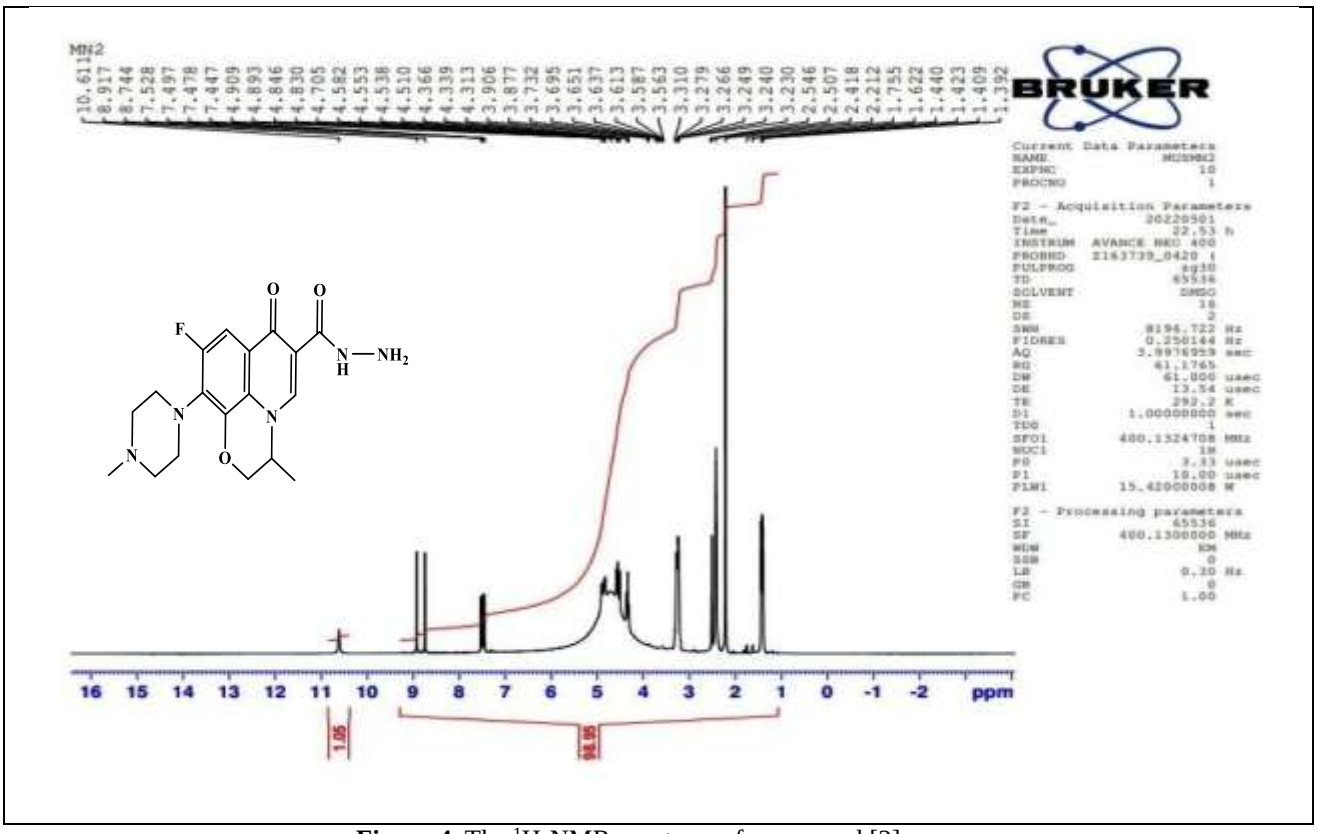


Figure 4. The ^{1}H-NMR spectrum of compound [2]

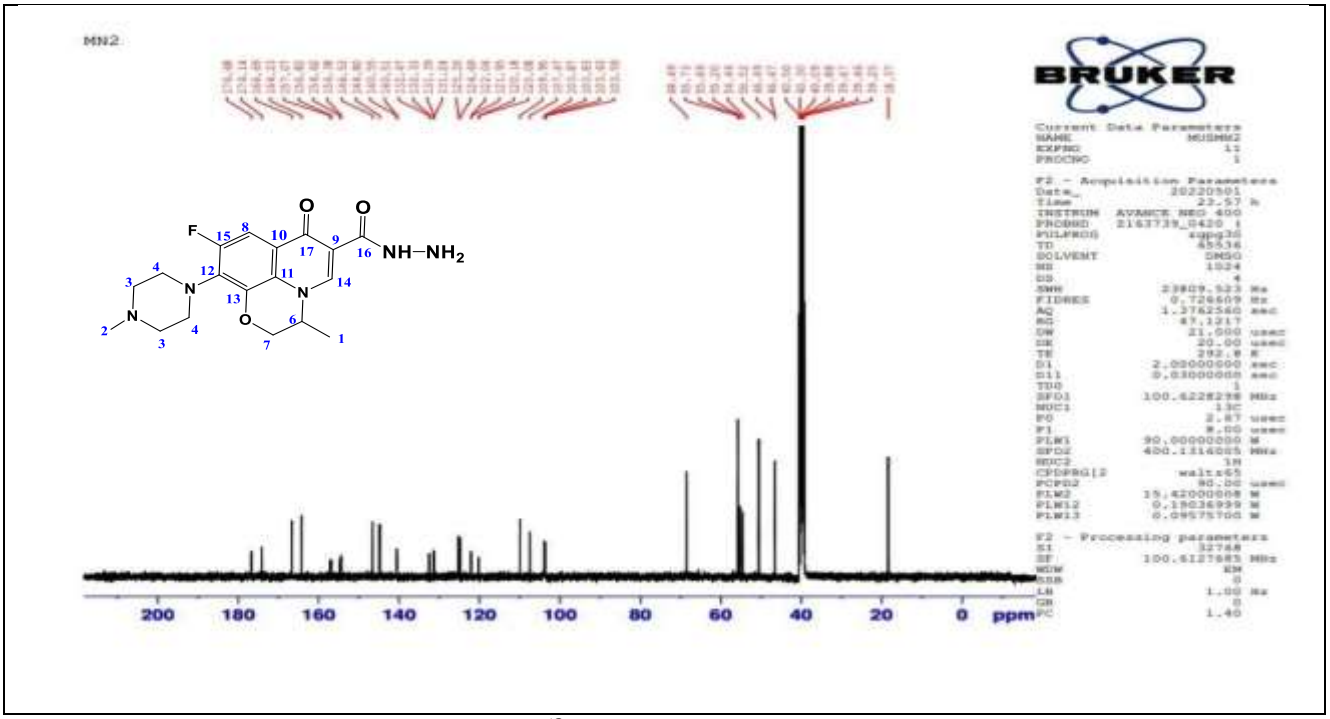


Figure 5. The ^{13}C-NMR spectrum of compound [2]

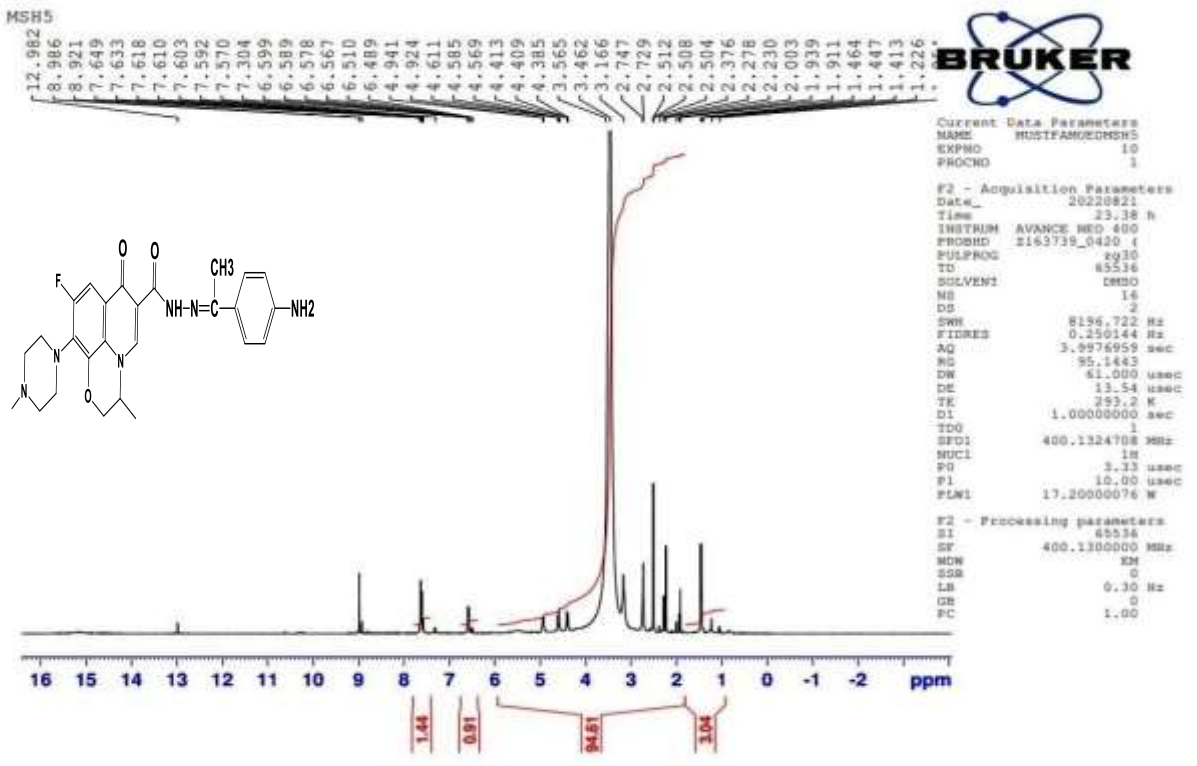


Figure 6. The ^{1}H-NMR spectrum of compound [5]

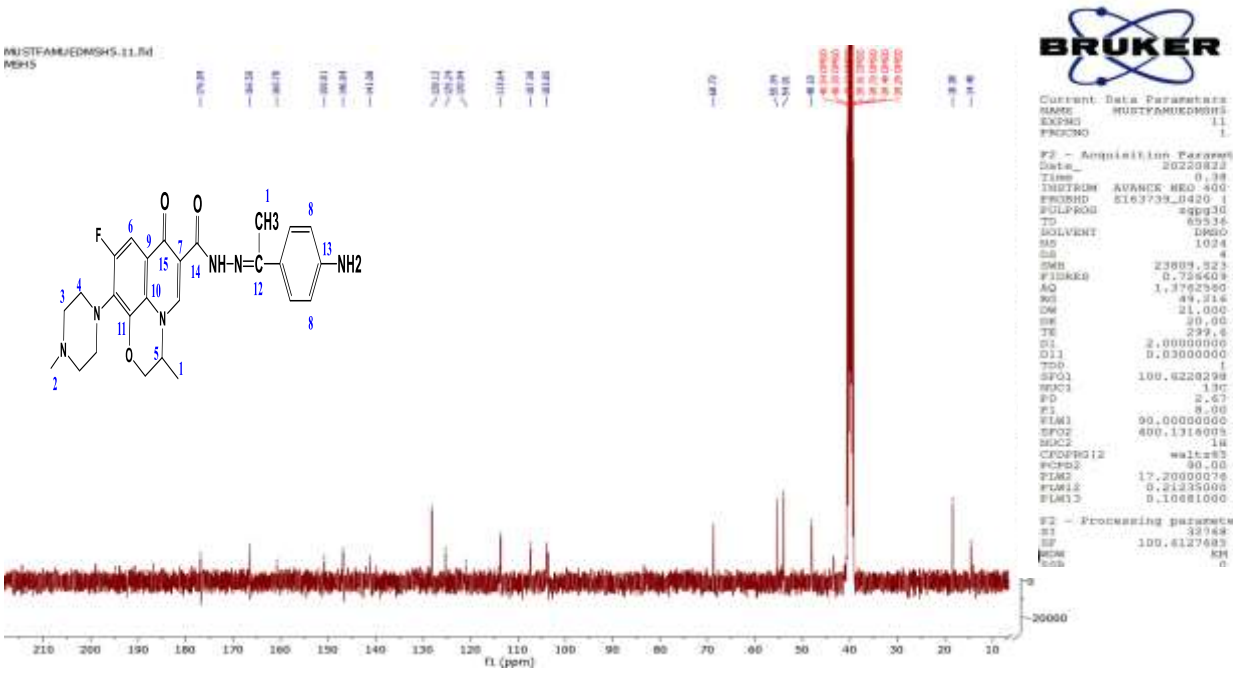


Figure 7. The ^{13}C-NMR spectrum of compound [5]

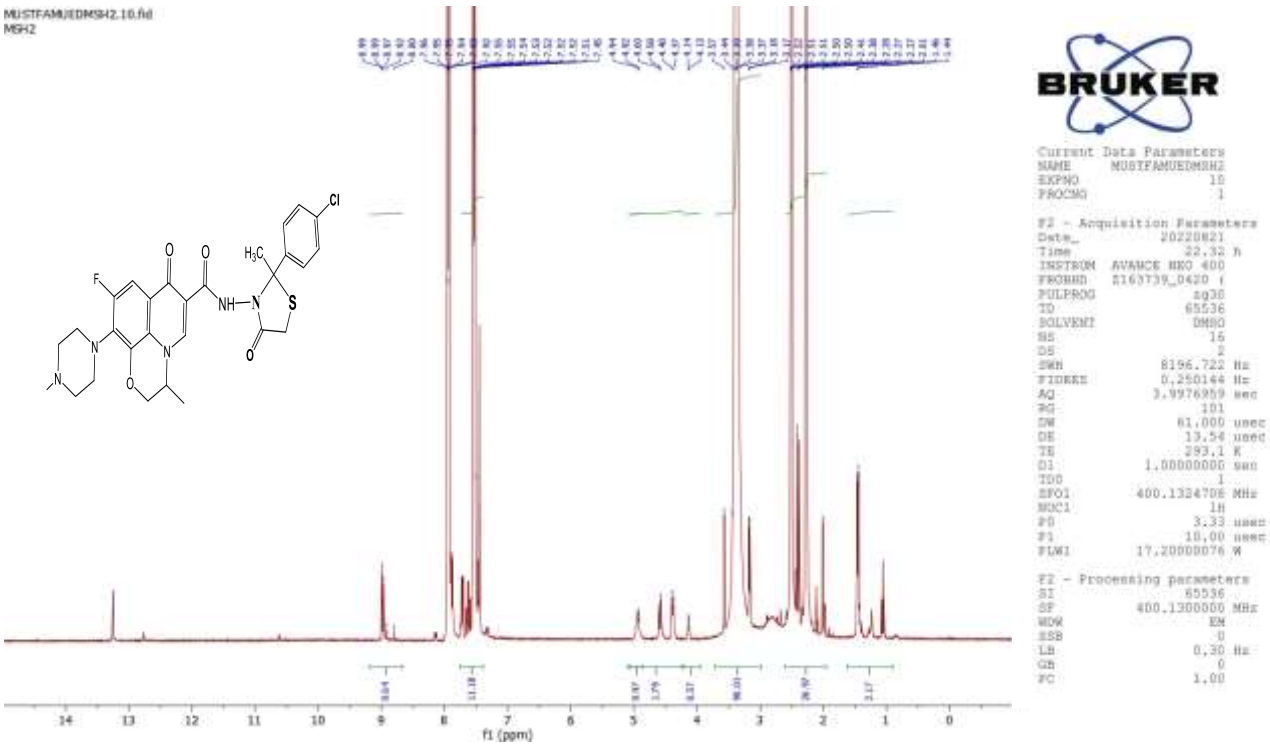


Figure 8. The [1]H-NMR spectrum of compound Thiazolidinone derivative

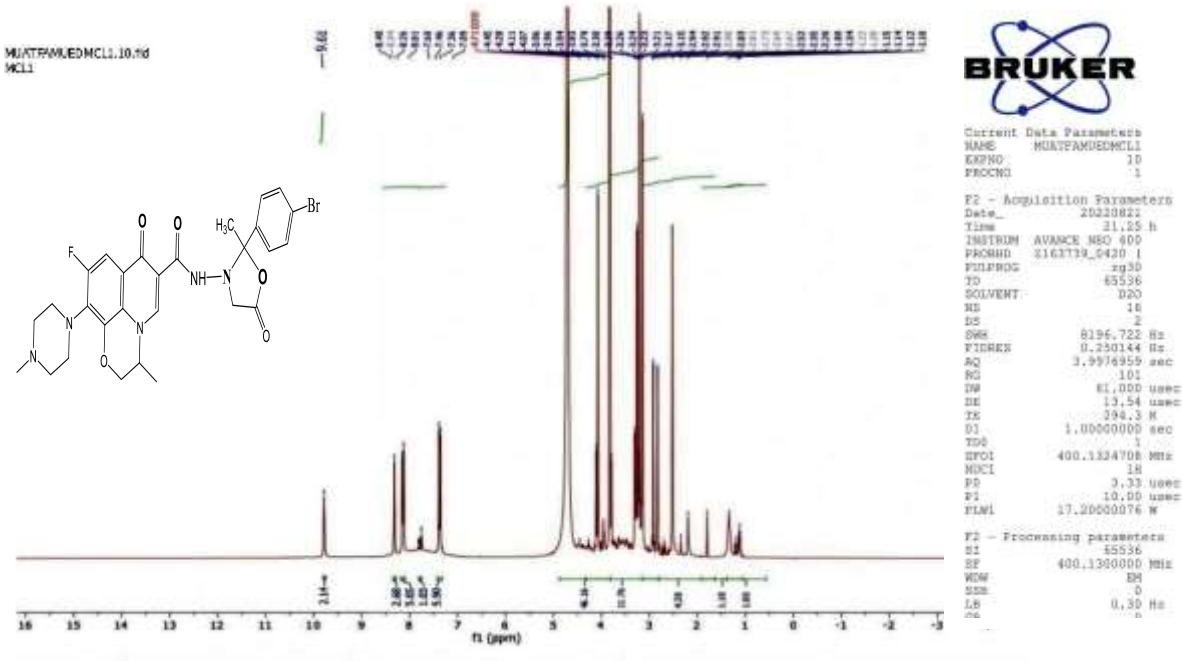


Figure 9. The [1]H-NMR spectrum of compound Oxazolidinone derivative

4. Conclusion

The levofloxacin drug was fused to new five-membered rings of oxazolidinone and thiazolidinone. Several novel derivatives were found by using the FTIR, [1]H-NMR, and [13]CNMR spectra. The antioxidant activity of compounds 3 through 10 was then assessed. These substances have heterocyclic derivative modifications and more robust antioxidant capacities than vitamin C.

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Conflict of Interest

The authors declare that they do not have any competing interests.

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Ethical Clearance

This work has been approved by the Scientific Committee at the University of Baghdad/ College of Science.

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