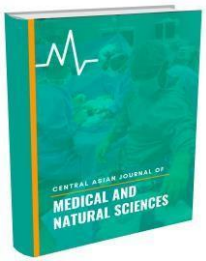


CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
https://cajmns.centralasianstudies.org/index.php/CAJMNS
Volume: 05 Issue: 03 | July 2024 ISSN: 2660-4159

.

Article

Novel Bioactive 1,4-Dihydroquinazoline Derivatives from Ciprofloxacin

Marwan Hasan Ali[1*], Farah Muthanna Muhammad[2], Shaima Hatem Abdullah[2], Ghazwan Hassan Abdel Wahab[2]

1. Nineveh Education Directorate, Nineveh, Iraq[1].
2. Department of Chemistry, College of Education for Pure Sciences, Tikrit University, Tikrit, Iraq[2].

* Correspondence: marwanchem1986@gmail.com

Abstract: This study focused on the synthesis and characterization of various cyclic compounds derived from the ciprofloxacin core, employing a series of chemical reactions. Ethanol acted as both solvent and reactant, facilitating the reversible transformation into an ester, subsequently reacting with hydrazine to form hydrazides under sulfuric acid catalysis. These hydrazides further reacted with benzaldehyde replacements to form hydrazones, which then reacted with 2-aminobenzoic acid to yield quinazolins. The synthesized compounds were thoroughly characterized using spectroscopic methods, including 13C NMR, 1H NMR, and IR. The biological activity of the compounds was evaluated using the agar-well diffusion technique against Gram-positive Staphylococcus aureus and Gram-negative E. coli. The results demonstrated the efficacy of the synthesized compounds as antibacterial agents. This study fills a gap in the literature by providing a novel approach to the synthesis of biologically active compounds derived from ciprofloxacin, with implications for the development of new antimicrobial agents.

Keywords: Ciprofloxacin, Hydrazones, Quinazoline, Heterocyclic Rings.

Citation: Marwan Hasan Ali, Farah Muthanna Muhammad, Shaima Hatem Abdullah, Ghazwan Hassan Abdel Wahab. Novel Bioactive 1,4-Dihydroquinazoline Derivivates from Ciprofloxacin Central Asian Journal of Medical and Natural Science 2024, 5(3), 351-365.

Received: 3th April 2024
Revised: 3th May 2024
Accepted: 10th May 2024
Published: 17th May 2024

1. Introduction

Quinazoline is a heterocyclic compound composed of two hexagonal rings(1,2), one of which is a pyrimidine ring containing a nitrogen atom(3) and a carbonyl group in the position(4), and the other is a benzene ring. Reagents looking for the nucleus(4). Heterocyclic compounds are found in many life compounds, such as proteins, enzymes, and nucleic acids(5). It is also found in alkaloids in plants and many antibiotics, such as penicillin(6). It is also characterized by having important uses as medicines, insecticides, dyes, polymers and other uses(7).

2. Materials and Methods

2.1. Chemicals used: Chemicals prepared from Aldrich, BDH Thomas, Fluka, Merck, were used.

2.2. Equipment used: The prepared compounds were diagnosed using the following spectrophotometers:

1. Infrared spectroscopy using the FT.IR (400s) device, supplied by SaHIMADZU company in the form of KBr discs.
2. Nuclear magnetic resonance spectroscopy 1H.N.M.R and 13C.N.M.R.

2.3. Preparation: Ethyl -1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1- yl)-1,4 dihydroquinoline-3-carboxylate(8).The compound was prepared from the reaction of ciprofloxacin (0.015 mol, 5 g) dissolved in (30) ml of ethanol in the presence of (3) ml of sulfuric acid. (60-62)°C and in percentage (43) %.

2.4. Preparation:-1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide: The compound was prepared by mixing compound (1) (0.008 mol, 3 g) with hydrazine (1) ml in the presence of ethanol as a solvent. The mixture rose for (6) hours, the mixture was filtered and gave a white precipitate with a melting point (270-273)°C and a percentage (68). %.

2.5. Preparation:1-cyclopropyl-6-fluoro-N'-(4-Sub.benzylidene)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carbohydrazide(9): The preparation involved dissolving the chemical (2) (0.0015) mol in 25 ml of 100% ethanol, 0.0015 mol of each dissolved benzaldehyde replacement, and glacial acetic acid as a catalyst. The mixture was then allowed to rise for eight hours. As displayed in the subsequent table:

Table 1. The mixture was then allowed to rise for eight hours

.Comp .No	R	Molecular formula	M.P (C)⁰	Yield %	Color
H_3	OH -4	$C_{24}H_{24}FN_5O_3$	200-202	76	White
H_4	Cl -4	$C_{24}H_{23}ClFN_5O_2$	218-220	83	Yellow
H_5	Br -4	$C_{24}H_{23}BrFN_5O_2$	224-226	85	White
H_6	-4 $N(CH_3)_2$	$C_{26}H_{29}FN_6O_2$	174-176	77	Orange

2.6. Preparations:1-cyclopropyl-6-fluoro-N-(2-(4-Sub.phenyl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxamide: The compounds were made by dissolving (0.0001) mol of 2 aminobenzoic acid in the following compounds: H3, H4, H5, and H6. The mixture was then ascended for seven hours, filtered, and washed with 10% sodium bicarbonate, distilled water, and ethanol before recrystallization. The precipitates were dehydrated. as seen in the table below:

Table 2. The precipitates were dehydrated.

.Comp .No	R	Molecular Formula	M.P (C)^0	Yield %	Color
H_7	OH -4	$C_{31}H_{29}FN_6O_4$	265-267	65	Orange
H_8	Cl -4	$C_{31}H_{28}ClFN_6O_3$	236-238	57	Yellow
H_9	Br -4	$C_{31}H_{28}BrFN_6O_3$	254-256	67	Orange
H_{10}	-4 $N(CH_3)_2$	$C_{33}H_{34}FN_7O_3$	225-227	52	Orange

2.7. Measurement of biological activity: The biological activity was measured using the agar-well di?usion technique, following guidelines from (Balouiri et al., 2012) and (Gonelimali et al., 2013). This technique involves dispersing the bacterial inoculum across the whole culture medium using a glass di?user. Then, a single dish in which a single bacterial sample was grown independently was loaded with solutions containing 100 microliters of each concentration by drilling sterile holes with a 6 mm diameter into the middle of the agar. This procedure was performed for every bacterial model utilized in the study, all of the solutions that Hadrat gathered, and their concentrations.Gram-positive Staphylococcus aureus and Gram-negative E. coli were the two types of bacteria used to assess the compounds' biological activity (antibacterial activity test). The isolates mentioned above were selected and then cultivated in a liquid medium called Nutrient Broth to activate them. After that, they were kept in a lab incubator for a whole day at 37 °C to prepare for the bacterial vaccination. By comparing the vaccination to the McFarland standard at a degree of 0.5, the concentration of 1.5 x 108 bacterial cells per milliliter of the physiological solution was determined.

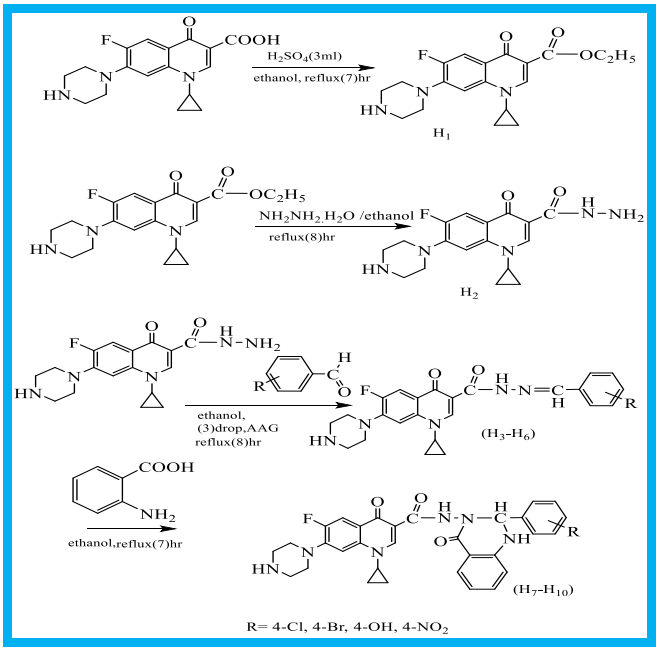


Figure 1. The concentration of 1.5 x 108 bacterial cells per milliliter of the physiological solution was determined.

3. Results

3.1. Characterization of the compound (10) (H1) : The diagnosis process was carried out by some physical properties, in the form of (color and melting point) and using the infrared spectrum (IR), where the infrared spectrum shows a beam at the location (3429)cm-1, back to stretching (N-H) of the piperazine ring, beam at position (3033) cm-1, back to stretching (Ar-H) cm-1, bundle at position (1718) cm-1, back to stretching (C= O) cm-1 ester, beam at site (1629) cm-1, back to stretch (C=O) cm-1 pyridine ring, and beam at site (1541) cm-1 back to (C=C) aromatic and beam at The position (1272) cm-1, refers to the stretch (C- O), and the beam at the position (892) cm-1, refers to (C-F), and Figure (1) shows the IR spectrum of compound [H1].

3.2. Characterization of the compound (H2): The diagnosis process was carried out by some physical properties, in the form of (color and melting point) and using the infrared spectrum (IR), where the infrared spectrum shows two beams at the site (3411-3242) cm-1, back to stretch (NH2), beam at position (3037) cm-1, back to stretch (Ar-H) cm-1, beam at position (1714) cm-1, back to stretch (C=O) cm-1 pyridine ring, beam at site (1620) cm-1, back to stretch (C=O) cm-1, beam at site (1585) cm-1, back to (C=C) aromatic, and beam at site (1280)) cm-1, due to stretching (C-O), and a beam at the position (966) cm-1, returning to (C- F), and Fig. (2) shows the IR spectrum of compound [H2].

3.3. Characterization of the compounds: (H6-H3). The IR spectrum of the compounds showed the disappearance of the group beams at the site (3411-3242) cm-1, back to the stretching (NH2), and the appearance of bands at the frequency (1627-1604) cm-1dating back to (N=CH), beams at position (3055-3037) cm-1, back to stretching (Ar-H), bundles at location (1736-1714) cm-1, back to stretching (C=O) cm-1 ring pyridine, bundles at site (1517-1498) cm-1 back to (C=C) aromatic and bundles at position (1272) cm-1, back to stretching (C-O), bundle at position (810-804) cm-1, It goes back to (C-F), and figures (6,5,4,3) show the infrared spectrum (IR)) of the compounds [H3, H4, H5, H6].

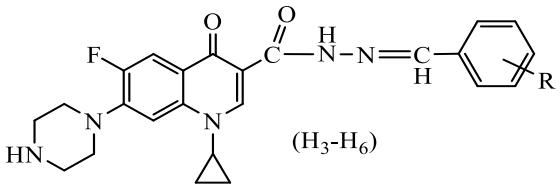


Figure 2. The infrared spectrum (IR)) of the compounds [H3, H4, H5, H6].

Table 3. The infrared spectrum (IR)) of the compounds [H3, H4, H5, H6].

.Comp No	R	ν N-H	ν Ar -H	ν C=O	ν C=N	ν C=C	ν Ar	ν C-N	Others
H_3	OH-4	3402	3051	1716	1627	1498,1456		1272	νOH 3423
H_4	Cl-4	3394	3053	1735	1625	1475,1452		1272	ν C-Cl 825
H_5	Br-4	3390	3043	1733	1625	1479,1464		1272	ν C-Br 619
H_6	-4	3390	3055	1735	1604	1517,1473		1272	νCH3 sy
	$N(CH_3)_2$								2884 asy 2925

3.4. Characterization of the compounds: (H7-H10) : The obtained imines (H3-H6) were reacted with 2-aminobenzoic acid (antranlic acid) to get the quinazoline-4-un compounds (H7-H10). This kind of reaction works by the suggested mechanism listed below (11):

And Figures (7,8,9,10) show the IR spectrum of the compounds [H7, H8, H9, H10].

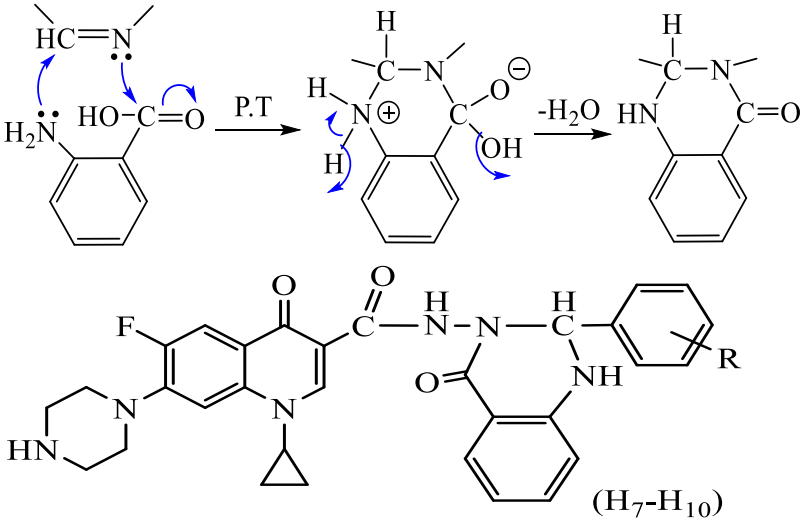


Figure 3. This kind of reaction works by the suggested mechanism listed below.

Table 4. The IR spectrum of the compounds [H7, H8, H9, H10].

.Comp No	R	N-H	Ar -H	C=O	C=C Ar	C-N	Others
H_7	OH-4	3378	3053	1672	1504 ,1546	1272	□OH 3382 N-CH_2-S 2885
H_8	Cl-4	3346	3030	1666	1476,1523	1267	□ C-Cl 864 N-CH_2-S 2977
H_9	Br-4	3363	3062	1672	1475,1623	1282	□C-Br 773 N-CH_2-S 2958
H_{10}	-4 $N(CH_3)_2$	3340	3043	1673	1445,1593	1263	□CH_3 sy 2862 asy 2968 N-CH_2-S 2925

The proton nuclear magnetic resonance (1H-NMR) spectrum of the compound (H3) showed a high single signal at displacement(2.51) δ of the protons of the solvent (DMSO), and signals at chemical displacement(2.17,1.17) δ of the tuberidine ring protons, and a signal at The chemical shift (1.30) δ refers to the cyclopropane proton, in addition to the appearance of a multiple signal within the displacement (7.63,6.72) δ belonging to the protons of the aromatic rings, and also a single single signal appeared at the displacement 8.69) δ belonging to the imine group protons (N = CH) addition to the appearance of a single single signal at the displacement δ (8.70) due to (OH), as in Figure

(11) which shows the nuclear magnetic resonance spectrum (1H.NMR) for the compound (H3).

The proton nuclear magnetic resonance (1H-NMR) spectrum of the compound (H4) showed a high single signal at displacement (2.51) δ of the protons of the solvent (DMSO), and signals at chemical displacement (3.87,1.21) δ of the piperazine ring protons, and a signal at The chemical shift (1.35) δ refers to the cyclopropane proton, as well as the appearance of a multiple signal within the displacement (7.73- 7.37) δ belonging to the protons of the aromatic rings, and also a single single signal appeared at the displacement(8.74) δ belonging to the imine group protons (N = CH), as in Figure (12) which shows the spectrum of nuclear magnetic resonance (1H.NMR) for compound (H4).

The proton nuclear magnetic resonance (1H-NMR) spectrum of the compound (H7) revealed a strong single signal at the solvent's protons' displacement (2.51) δ (DMSO) and signals at the piperazine ring protons' chemical displacement (2.48-1.15) δ, and an indication at In chemical shift (1.34), δ denotes the proton of cyclopropane. In addition to the numerous signal that shows up inside the displacement (7.89-7.28) δ of the aromatic ring protons, moreover, a solitary signal from the (OH) proton occurred at displacement 8.66) δ., as shown I Figure (13) The compound (H8) exhibited a proton nuclear magnetic resonance (1H-NMR) spectrum with a high single signal at displacement (2.51) δ of the solvent (DMSO) protons, signals at chemical displacement (3.85,2.94, 1.20) δ of the tube riding ring protons, and a signal at the chemical shift (1.34) corresponding to the cyclopropane proton, as well as the appearance of multiple signals within the displacement (8.66-7.55) corresponding to the protons of the aromatic rings, as depicted in Figure. (14) As illustrated in Figure (15), the nuclear magnetic resonance spectrum (1H NMR) for compound (H9) revealed a high single signal at displacement (2.52) δ of the solvent (DMSO) protons, signals at chemical displacement (3.84,2.95, 1.05) δ of the piperazine ring protons, and a signal at the chemical shift (3.43,1.34) refers to the cyclopropane proton. Additionally, there appeared to be multiple signals within the displacement (8.73-7.54) pertaining to the aromatic rings' protons.

As seen in Figure (16), the compound (H10)'s proton nuclear magnetic resonance (1H-NMR) spectrum revealed a high single signal at displacement (2.53) δ of the solvent (DMSO) protons, signals at chemical displacement (3.01) δ of the piperazine ring proton, and the appearance of multiple signals within displacement (8.52-6.80) δ belong to the protons of the aromatic rings.

As demonstrated in Figure (17), the (13C-NMR) spectrum of the prepared compound (H4) revealed the following: signals at (39.38) δ back to carbon in cyclopropane and at (40.86) δ back to carbon in the piperazine ring, signals at (130.52,129.39) δ back to carbon (C = C) aromatic, and a signal at (161.07) δ refers to the carbon atom (C = O).

As seen in Figure (16), the compound (H10)'s proton nuclear magnetic resonance (1H-NMR) spectrum revealed a high single signal at displacement (2.53) δ of the solvent (DMSO) protons, signals at chemical displacement (3.01) of the piperazine ring proton, and the appearance of multiple signals within displacement (8.52-6.80) δ belong to the protons of the aromatic rings.

A signal was observed at frequency (39.38) δ back to carbon in cyclopropane, at (40.86) δ back to carbon in the piperazine ring, at (130.52,129.39) δ back to carbon (C = C) aromatic, and at (161.07) δ refers to the carbon atom (C = O) when examining the (13C-NMR) spectrum for the prepared compound (H4), as illustrated in Figure 17. The (13C-NMR) spectrum of the prepared compound (H7) was examined, and it was found that, as shown in Figure (18), signals appeared at frequency 36.31) back to carbon in cyclopropane, at (51.04,45.78) δ back to carbon in the piperazine ring, at (148.33- 106.54) δ back to carbon (C = C) aromatic, and at (166.46) δ refers to the carbon atom (C = O). The generated molecule (H8)'s (13C-NMR) spectra were examined, and it was discovered that a signal at (50.49,45.69) δ and a signal at (36.33,8.04) δ, which correspond to the carbon in

cyclopropane, occurred. In the piperazine ring, δ reverts to carbon and signals at (161-106.59). As seen in Figure (19), which displays the NMR spectrum of carbon (13C.MNR) for the molecule (H8), δ refers to the aromatic carbon (C = C), with a signal at 176.85). δ refers to the carbon atom (C = O). When studying the spectrum of (13C-NMR) for the prepared compound (H9), it was noticed that a signal appeared at frequency (36.33,8.04) δ back to carbon in cyclopropane and a signal at(50.96,45.68) δ back to carbon in the piperazine ring, and signals at 106.60-148.40)) δ belongs to the aromatic carbon (C = C), and a signal at (176.70) δ belongs to the carbon atom (C = O), as shown in Figure (20), which shows the nuclear magnetic resonance spectrum of carbon (13C.MNR) for compound (H9).

3.5. Evaluation of Biological activity:(14,15) We tested the solutions against two distinct types of bacteria, S. aureus and E. coli, and the results are displayed in the tables. These tests were done to determine the efficiency of the solutions against various bacterial species. The table shows that the testing showed the selected solutions to be highly effective. The compounds' efficacy against the two types of selected bacterial genera varied noticeably across the solutions, suggesting that the compounds were efficient against the antibacterial activity towards these species. The microbial inhibitory zones' total diameter varied from 9 mm to 40 mm.

Significantly, the inhibitory decrease of the secondary dilutions showed efficacy similar to that of the concentrated solutions, suggesting that low concentrations have low-concentration antibacterial activity (LCAA) or that inhibiting bacteria at low concentrations may be accomplished more affordably (LEC). Very little

A table around the agar pit filled with the created chemical compounds, indicating the biological activity of some of the compounds against the microorganisms Staphylococcus aureus and E. coli, measured in millimeters.

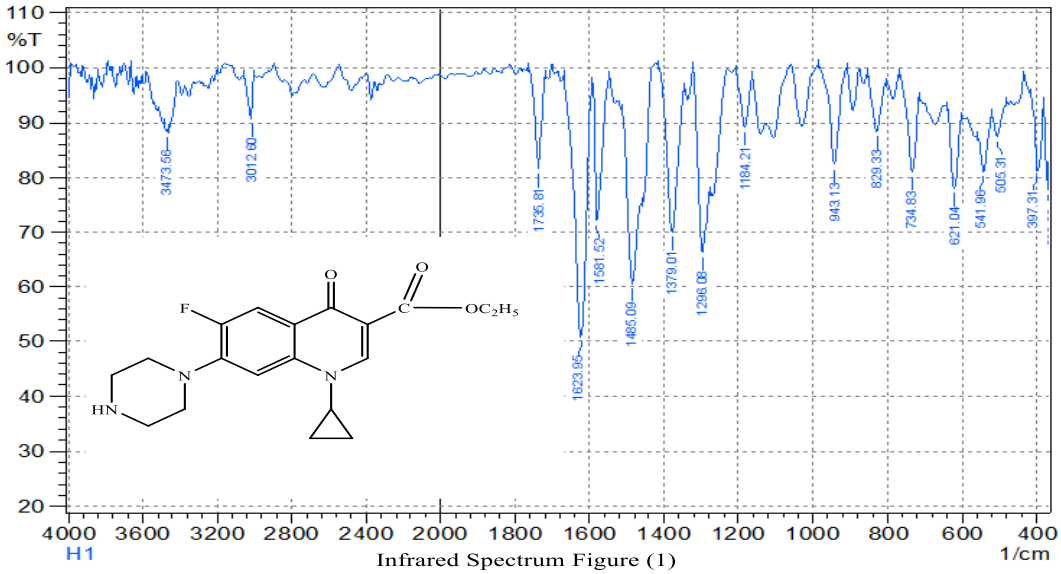
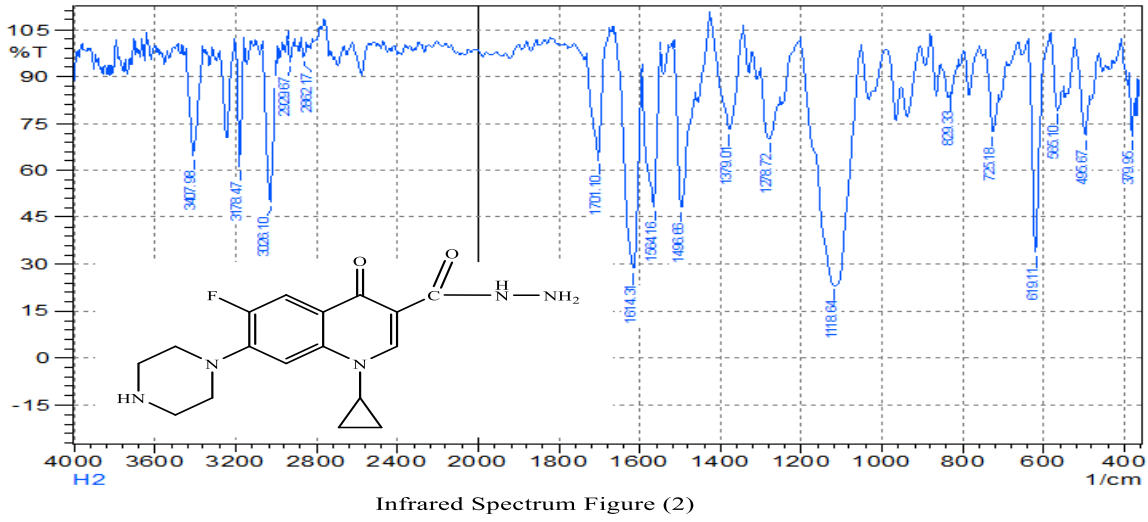
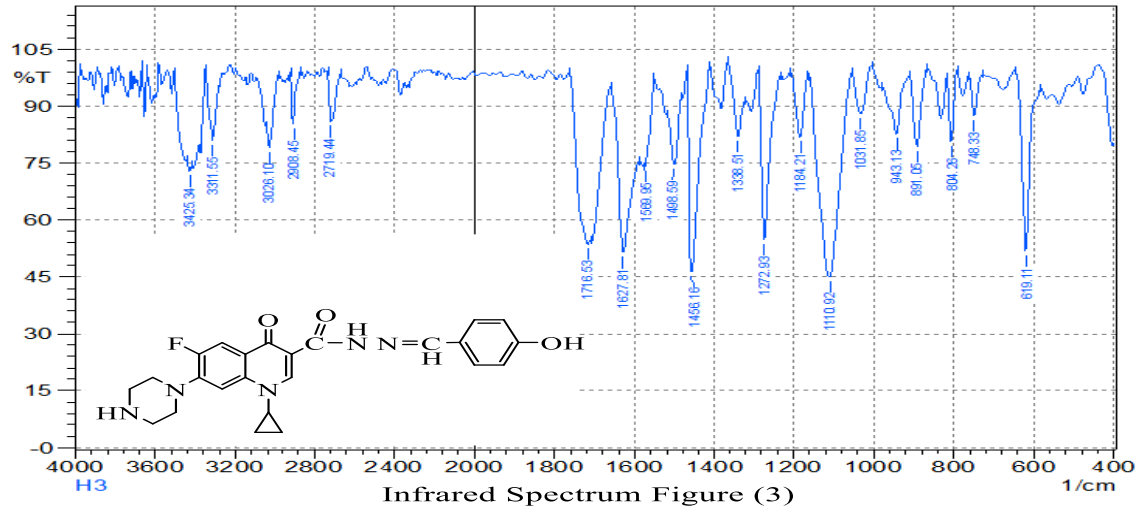


Figure 4. Infrared Spectrum (1)



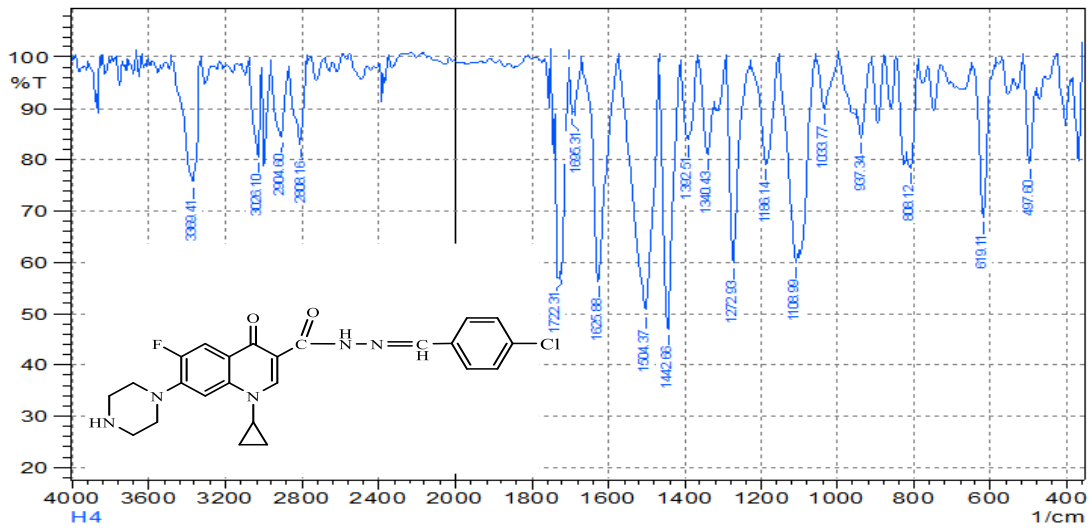
Infrared Spectrum Figure (2)

Figure 5. Infrared Spectrum (2)



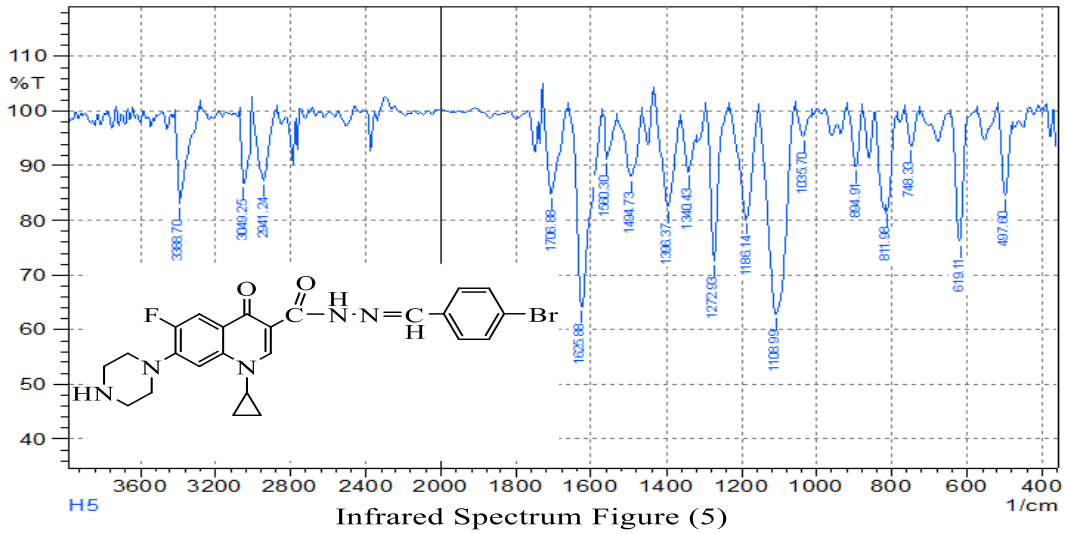
Infrared Spectrum Figure (3)

Figure 6. Infrared Spectrum (3)



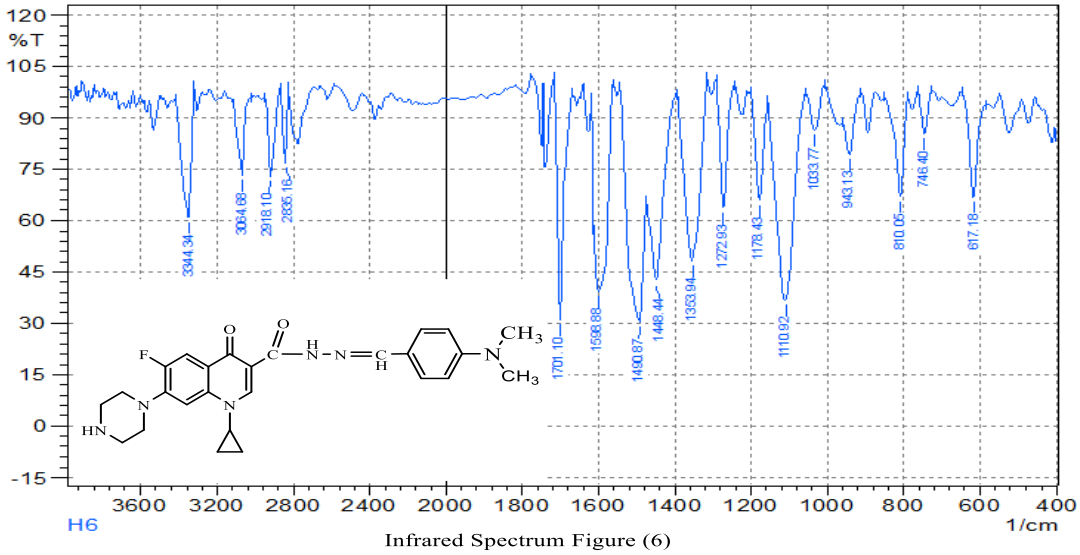
Infrared Spectrum Figure (4)

Figure 7. Infrared Spectrum (4)



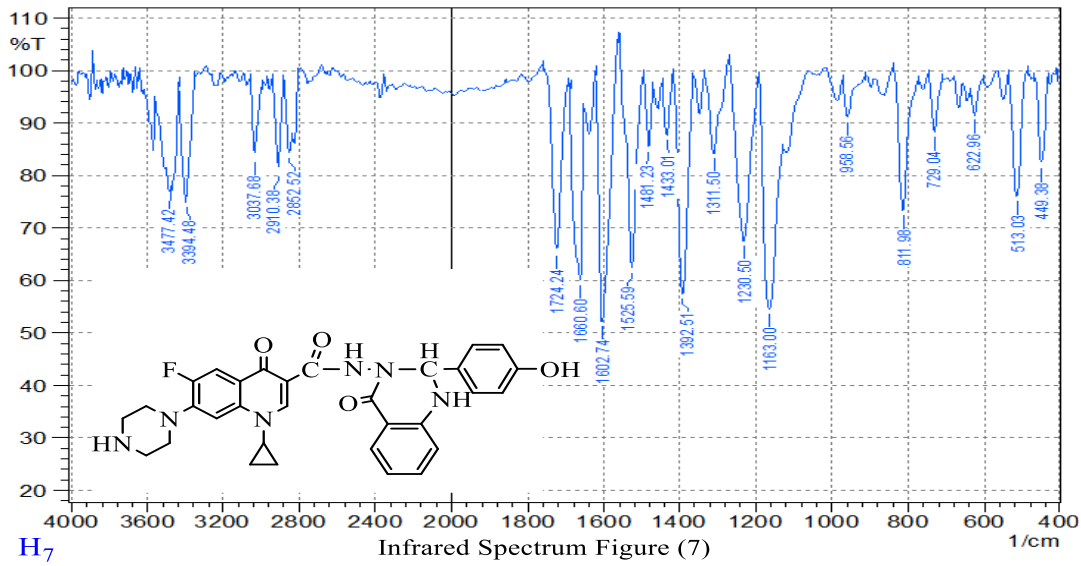
Infrared Spectrum Figure (5)

Figure 8. Infrared Spectrum (5)



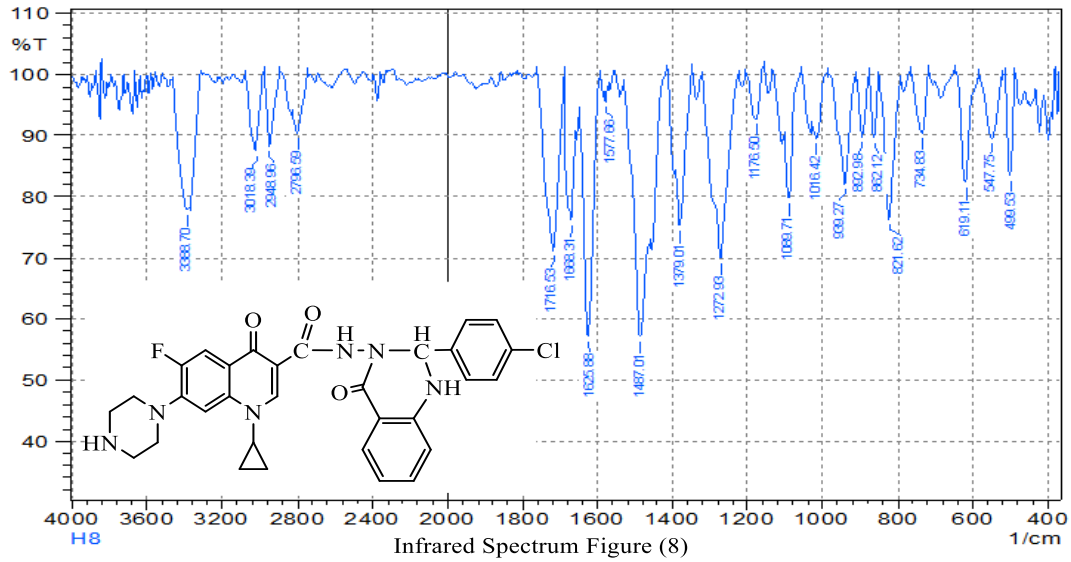
Infrared Spectrum Figure (6)

Figure 9. Infrared Spectrum (6)



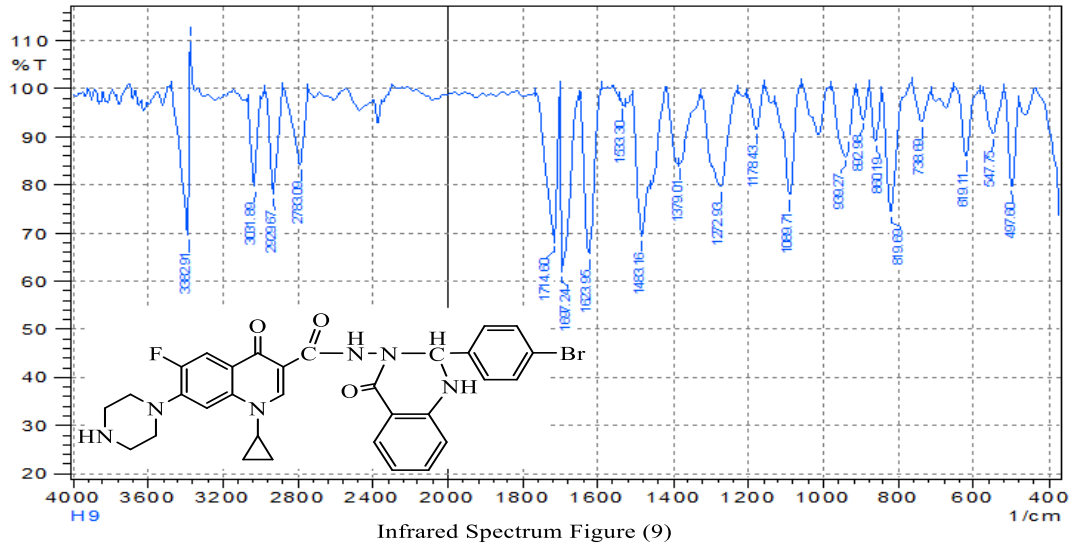
Infrared Spectrum Figure (7)

Figure 10. Infrared Spectrum (7)



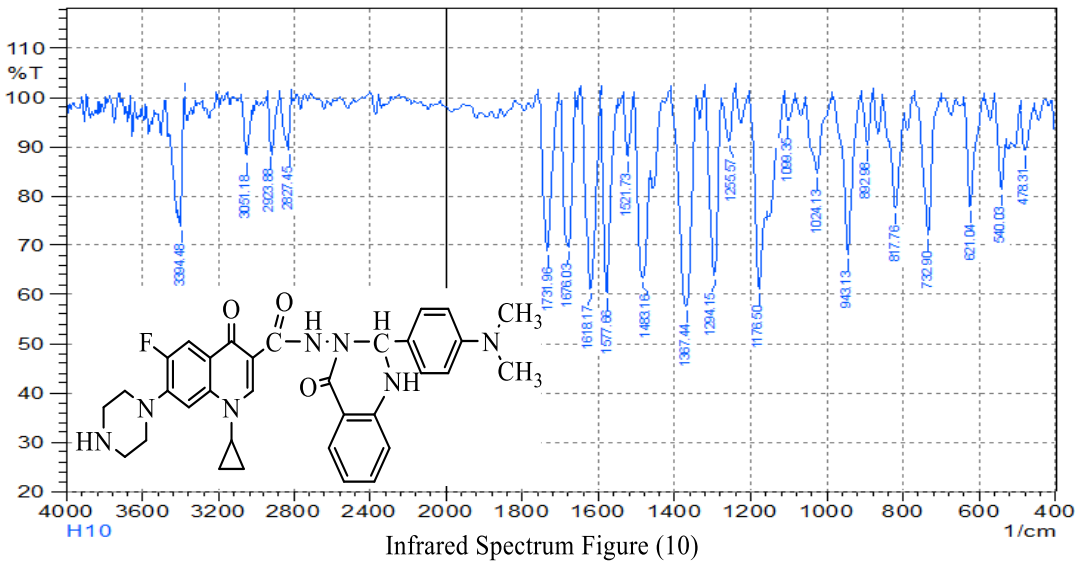
Infrared Spectrum Figure (8)

Figure 11. Infrared Spectrum (8)



Infrared Spectrum Figure (9)

Figure 12. Infrared Spectrum (9)



Infrared Spectrum Figure (10)

Figure 13. Infrared Spectrum (10)

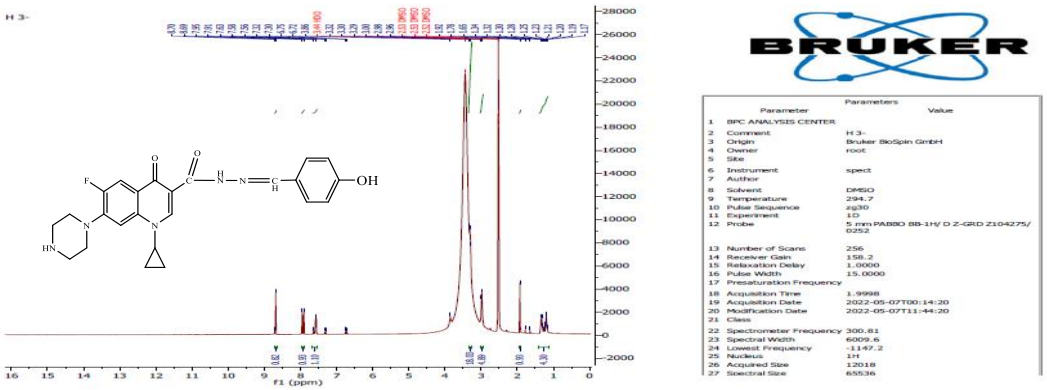


Figure 14. The nuclear magnetic resonance (1H.NMR) spectrum of the compound (H3).

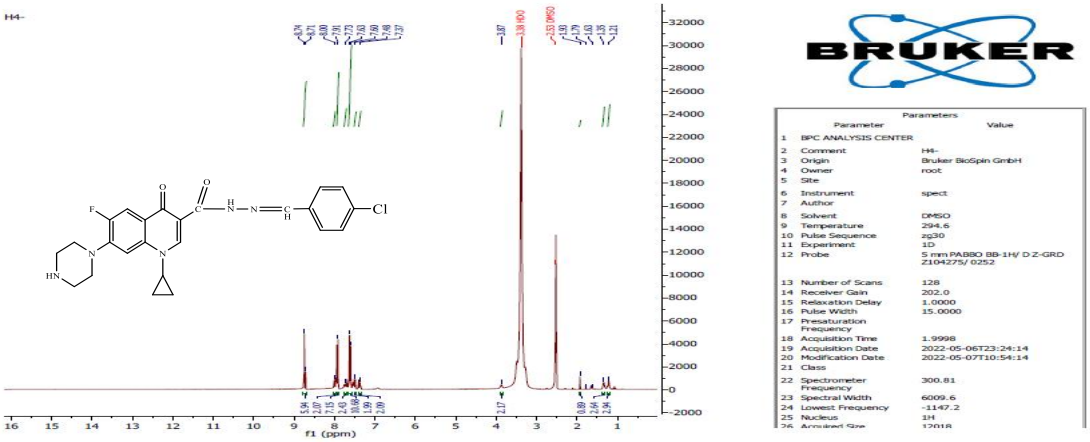


Figure 15. The nuclear magnetic resonance (1H.NMR) spectrum of the compound (H4).

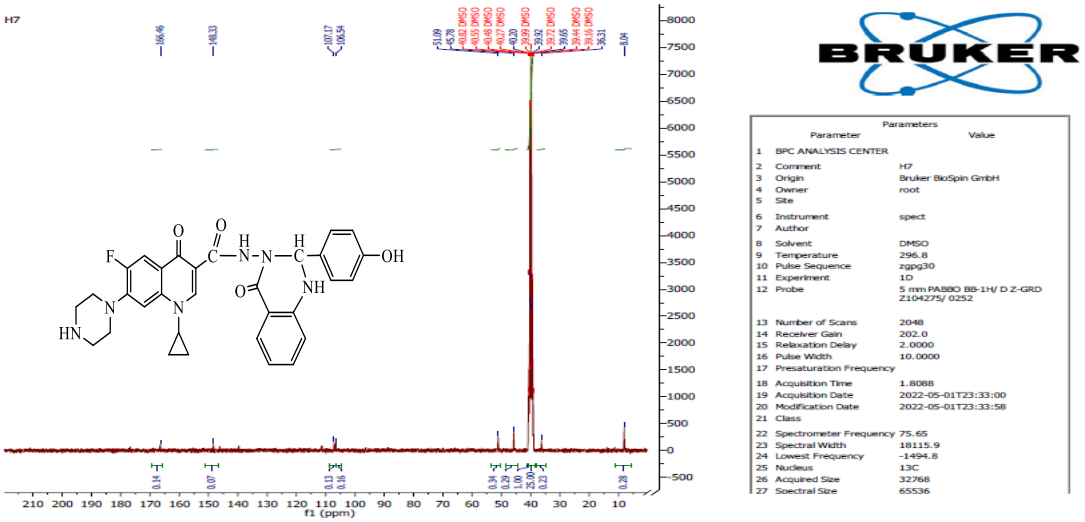


Figure 16. The nuclear magnetic resonance (1H.NMR) spectrum of the compound (H7).

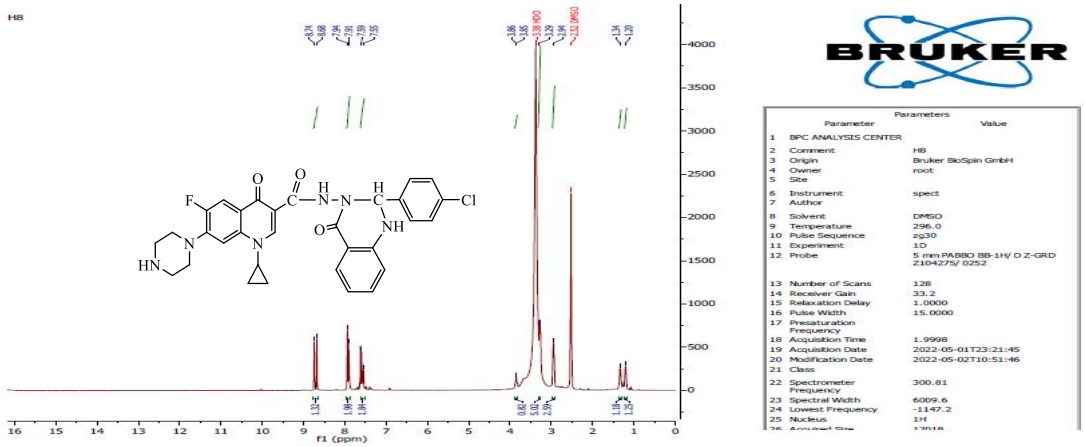


Figure 17. The nuclear magnetic resonance (1H.NMR) spectrum of the compound (H8).

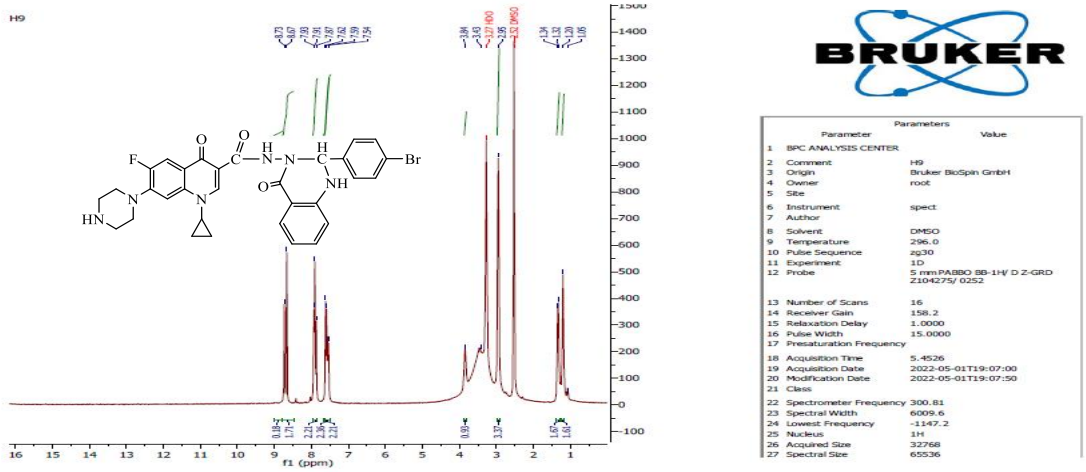


Figure 18. The nuclear magnetic resonance (1H.NMR) spectrum of the compound (H9).

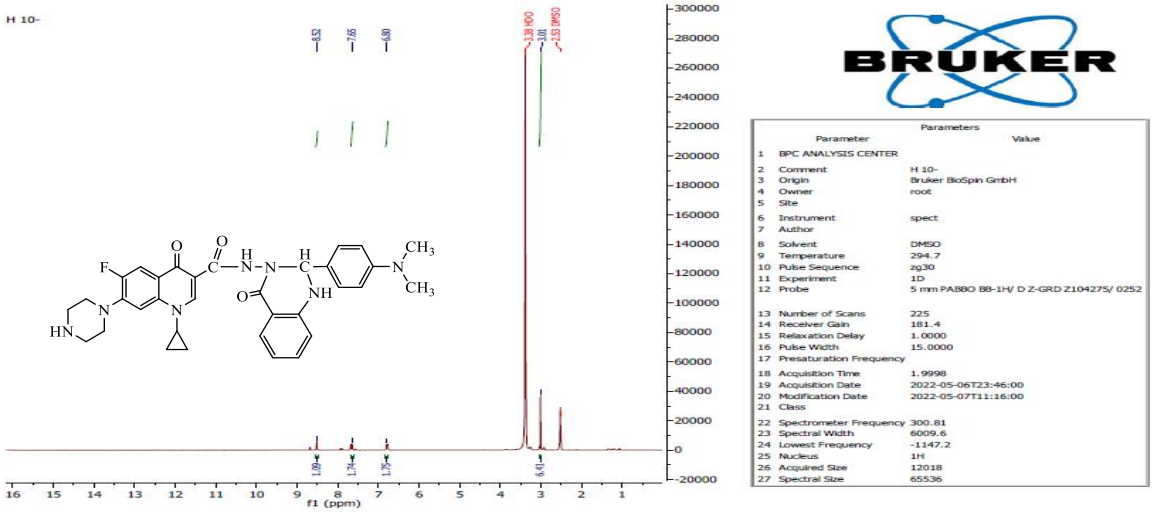


Figure 19. The nuclear magnetic resonance (1H.NMR) spectrum of the compound (H10).

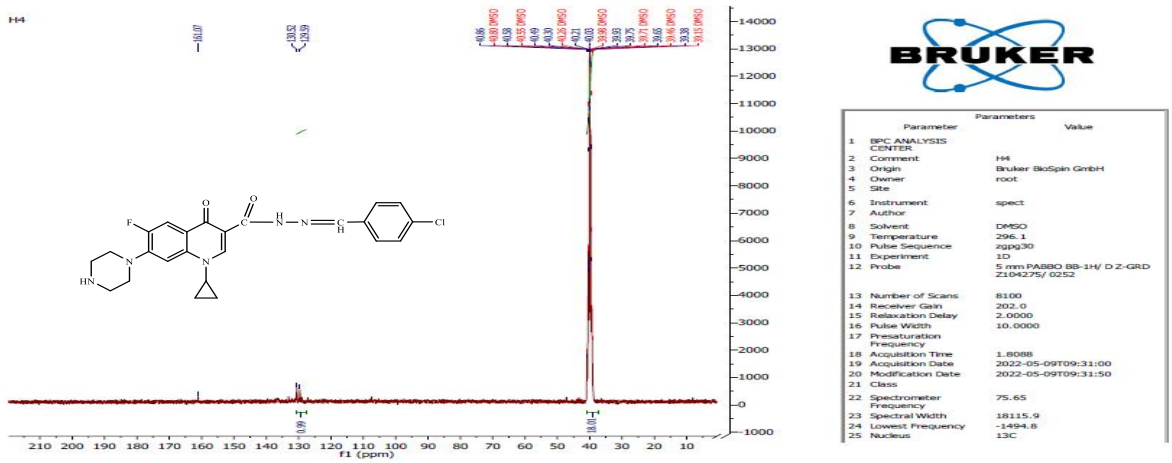


Figure 20. The nuclear magnetic resonance spectrum of carbon (13C.MNR) for the compound (H4).

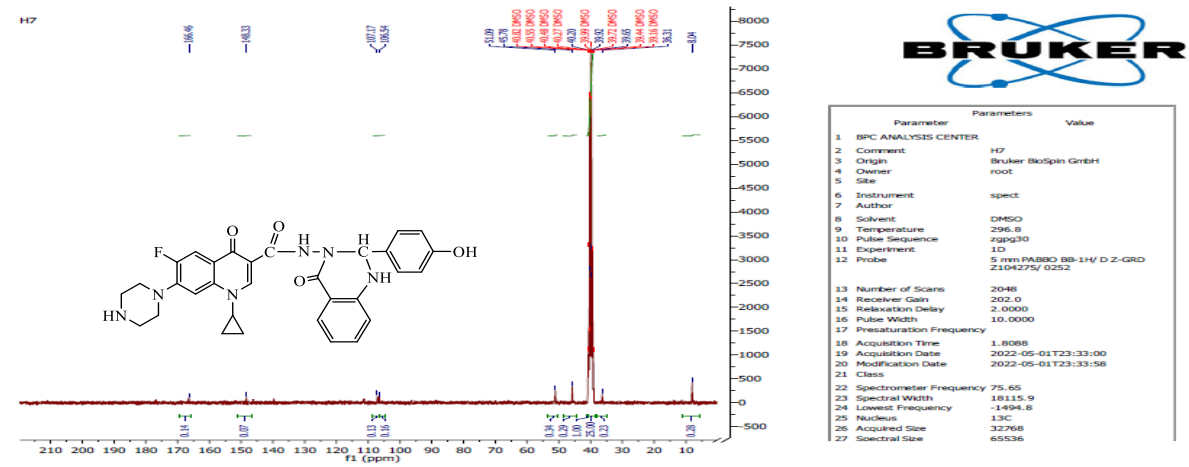


Figure 21. The nuclear magnetic resonance spectrum of carbon (13C.MNR) for the compound (H7).

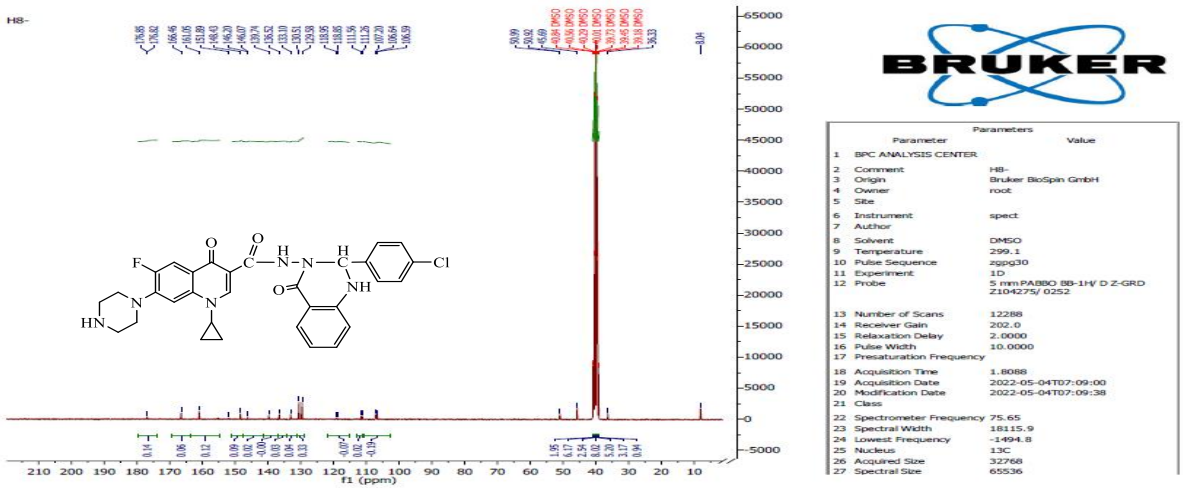


Figure 22. The nuclear magnetic resonance spectrum of carbon (13C.MNR) for the compound (H8).

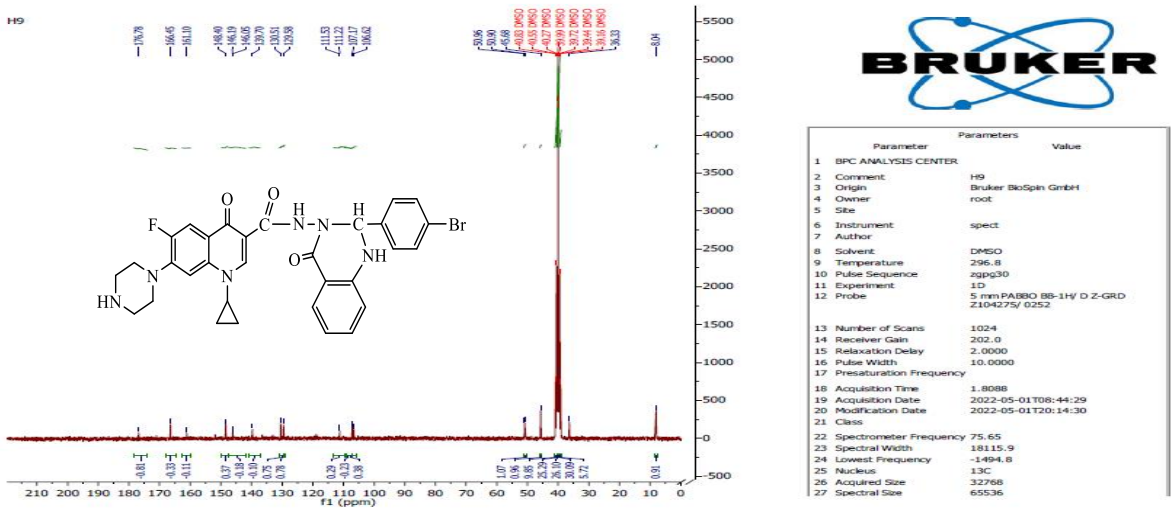


Figure 23. The nuclear magnetic resonance spectrum of carbon (13C.MNR) for the compound (H9).

Table 5. Inhibition Zone (mm)

Inhibition zone (mm)						
E. coli			*Staphylococcus aureus*			
0.0001	0.001	0.1	0.0001	0.001	0.1	sample code
11	21	25	25	40	40	H8
0	17	23	20	30	30	H9
0	18	24	20	22	32	H10

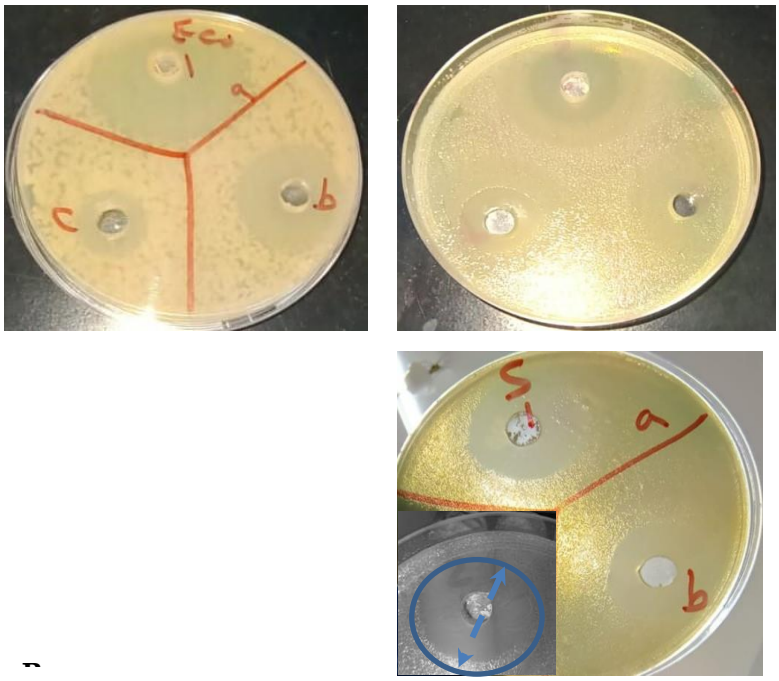


Figure 24. Inhibition Zone

4. Conclusion

During the diagnosis of these compounds, it was proved that the chemical composition was correct, and that these compounds were of high product, stable, as well as easy to prepare.

REFERENCES

[1] A. M. Alafeefy, A. A. Kadi, A. S. El-Azab, S. G. Abdel-Hamide, and M. H. Daba, "Arch . Pharm," vol. 341, no. 6, pp. 377-385, 2008.

[2] P. P. Kung, M. D. Casper, K. L. Cook, L. W. Lingardo, L. M. Risen, T. A. Vickers, R. Ranken, L. B. Blyn, J. R. Wyatt, P. D. Cook, and D. J. Ecker, "J. Med. Chem," vol. 42, pp. 4705-4713, 1999.

[3] A. Pinner, "Ber. Dtsch. Chem. Ges," vol. 18, pp. 759-763, 1885.

[4] M. Schlesis et al., "Antiviral Research," vol. 79, no. 1, pp. 49-61, 2008.

[5] A. R. Katritzky and C. W. Reez, "Comprehensive Heterocyclic Chemistry Synthesis and Uses of Heterocyclic Compounds," Pergamon Press Ltd., p. 434, 1984.

[6] J. S. Fruton and S. Simmonds, "General Biochemistry," 2nd ed., John Wiley and Sons Inc., p. 45, 1963.

[7] F. S. Kammuna and I. S. Al Shaibani, "Introduction to the Chemistry of Heterocyclic Compounds," Basra University Press, p. 15, 1986.

[8] H. M. Hassan, "Synthesis and identification of some heterocyclic compounds derived from-2,6-Dipicolinic acid and study of biological activity," M.S. thesis, University of Tikret, 2019.

[9] A.-A. J. S. Abed-Alsatar, "Synthesis and characterization of some new heterocyclic compounds with studying the biological activity for some of them," Karbala J. Pharm. Sci., vol. 9, no. 14, pp. 50–64, 2018.

[10] R. M. S. Robert, F. X. W. Francis, and D. J. K. David, "Spectrometric Identification of Organic Compounds," Wiley, 2005.

[11] I. G. Ibrahem, "Synthesis and identification of heterocyclic compounds fourth, fifth and sixth," M.S. thesis, University of Tikret, 2018.

[12] M. Balouiri, M. Sadiki, and S. K. Ibnsouda, "Methods for in vitro evaluating antimicrobial activity: A review," J. Pharm. Anal., vol. 6, no. 2, pp. 71–79, 2016.

[13] F. D. Gonelimali et al., "Antimicrobial properties and mechanism of action of some plant extracts against food pathogens and spoilage microorganisms," Front. Microbiol., vol. 9, 2018.

[14] J. N. Saleh and A. Khalid, "Synthesis, characterization and biological activity evaluation of some new pyrimidine derivatives by solid base catalyst AL2O3- OBa," Cent. Asian J. Med. Nat. Sci., vol. 4, no. 4, pp. 231-239, 2023.

[15] M. J. Saleh and K. A. Al-Badrany, "Preparation, characterization of new 2-oxo pyran derivatives by AL2O3- OK solid base catalyst and biological activity evaluation," Cent. Asian J. Med. Nat. Sci., vol. 4, no. 4, pp. 222-230, 2023.