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المجلة العراقية لبحوث السوق
وحماية المستهلك

THE ECONOMIC IMPORTANCE IN LOCAL PRODUCTION OF CIPROFLOXACIN DERIVATIVES

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ABSTRACT

Marketing are not just for business specialists alone, but rather it touches the life of every human being, as each of us is a member of the marketing movement. Most importantly, marketing medicines due to their importance in the health aspect. Our research aims to manufacture pharmaceuticals derived from ciprofloxacin locally and also improvement from antibiotic on the marktes, rather than relying on imports from outside Iraq. Undoubtedly, this initiative has the potential to benefit individuals and the community both economically and qualitatively. Among the key advantages of these derivatives is their effectiveness in treating urinary tract infections and certain fungal infections. The primary goal is to support individuals and the community, enabling them to compete with pharmaceutical companies outside Iraq. Ciprofloxacin derivatives has been successfully synthesized through series reactions of Ciprofloxacin compound derivatives were produced (A-B8).

The research is aimed at the development and evaluation of a formulation for ciprofloxacin. This endeavor to treat various bacterial infections and fungi, while also focusing on the creation of new heterocyclic derivatives.

our research has demonstrated promising antibacterial and antifungal properties, successfully eradicating Gram-positive bacteria *(Staphylococcus)*, Gram-negative bacteria *(Pseudomonas aeruginosa)*, and fungi *(Candida albicans)*.

Keywords: biological activity, Ciprofloxacin, 2-aminobenzothiazole derivatives, Diazonium salt, Synthesis.

الاهمية الاقتصادية في الأنتاج المحلي لمشتقات دواء السيبروفلوكساسين

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الخلاصة

التسويق لا يقتصر على متخصصي الأعمال فقط، بل إنه يمس حياة كل إنسان، فكل منا عضو في الحركة التسويقية. والأهم من ذلك تسويق الأدوية لأهميتها في الجانب الصحي. يهدف بحثنا إلى تصنيع الأدوية المشتقة من السيبروفلوكساسين محليا وكذلك تحسين المضادات الحيوية في الأسواق بدلا من الاعتماد على الاستيراد من خارج العراق. ومما لا شك فيه أن هذه المبادرة لديها القدرة على إفادة الأفراد والمجتمع اقتصاديا ونوعيا. ومن المزايا الرئيسية لهذه المشتقات فعاليتها في علاج التهابات المسالك البولية وبعض الالتهابات الفطرية. الهدف الأساسي هو دعم الأفراد والمجتمع وتمكينهم من المنافسة مع شركات الأدوية خارج العراق. تم تصنيع مشتقات السيبروفلوكساسين بنجاح من خلال التفاعلات المتسلسلة لمشتقات مركب السيبروفلوكساسين.(A-B8)

ويهدف البحث إلى تطوير وتقييم تركيبة للسيبروفلوكساسين. يهدف هذا المسعى إلى علاج العديد من الالتهابات البكتيرية والفطريات، مع التركيز أيضًا على إنشاء مشتقات حلقية غير متجانسة جديدة. لقد أظهر بحثنا خصائص واعدة

* **The article is taken from the master's thesis of the first researcher.**

مضادة للبكتيريا والفطريات، ونجح في القضاء على البكتيريا إيجابية الجرام *(Staphylococcus)*، والبكتيريا سالبة الجرام *(Pseudomonas aeruginosa)*، و الفطريات *(Candida albicans)*.

الكلمات المفتاحية: الفعالية البايلوجية، السيبروفلوكساسين، مشتقات2- امينوبنزوثايزول، املاح الدايزونيوم، التصنيع.

INTRODUCTION

The history of heterocyclic chemistry began in 1800, connecting to the development of organic chemistry. Heterocyclic chemistry is an essential branch of organic chemistry that accounts for nearly one-third of recent publications (**Hosseinzadeh *et al.*, 2018)** In our everyday lives, heterocyclic compounds containing one or more heteroatoms are used in veterinary, agrochemicals, and medicinal products **(Ahmed *et al.*, 2019; Khurshed *et al.*, 2022).** Ciprofloxacin is a broad-spectrum fluoroquinolone (FQ) that is a member of the bicyclic heterocyclic compound (CP, Fig. 1) family. (**Rabbani & Islam, 2020)**. It is a commonly used antibiotic with little side effects that has been shown to stop the growth of cancer cells and cause apoptosis in a range of cancer cell lines. **(Kassab & Gedawy, 2018)**. Additionally, benzothiazole is a member of the family of bicyclic heterocyclic compounds, which are composed of nitrogen and sulfur atoms fused together with a benzene nucleus (**Al-Mokaram *et al.*, 2022)**.Benzothiazole, substitute a heterocyclic molecule, is used in research as a building block to synthesize larger typically bioactive compounds. Despite having reactive sites that enable functionalization as a heterocycle, its aromaticity makes it reasonably stable **(Patrick 2003)**. Benzothiazoles are also used to treat antimicrobial **(Mahmood *et al.*, 2022; Khammas & Hamood 2019)**, antifungal **(Jamel *et al.*, 2019; Nebras *et al.*, 2019)**, anticancer **(Patil & Rajput 2014; Razzaq *et al.*, 2022)** and anti-inflammatory **(Mohan & Naser, 2023; Awad *et al.*, 2019)** activity. These biologicali data prompted us to synthesize some new benzothiazole derivatives as showing in equation (1). **(Patrick 2003; Hamdia & Sundus, 2023)**. In general, acetylenic compounds were discovered to be highly relevant in the field of medicine because triple-bond medicinal compounds have better activity and lower toxicity (**Canseco, *et al.*, 2023)**.. Also more easily absorbed by living organisms than alkenes (**Mousa *et al.*, 2022)**. Some acetylenic compounds were employed as antispasmodics **(Saran *et al.*, 2022)**. hypertensive **(Raghad, 2023)**. Anticholinergic**,** anticancer **(Akhtar *et al.*, 2016)**. and antibacterial agents.

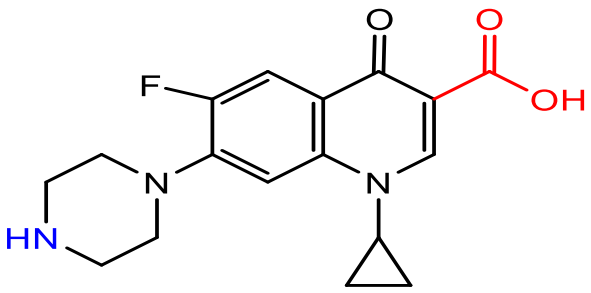
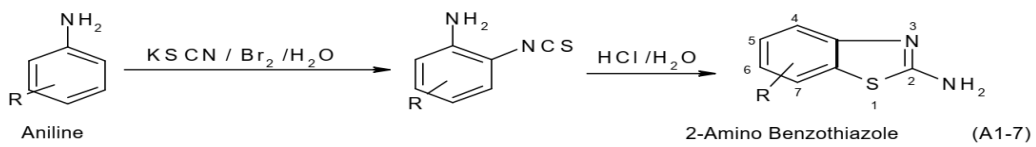


Figure (1): Ciprofloxacin structure with marked fragments that were modified.



Equation (1)

MATERIALS AND METHODS

Fluka and Sigma-Aldrich were the sources for all components and solvents. Melting points were measured using the Gallen Kamp capillary melting point device. Additionally, FT-IR measurements were taken using a Shimadzu model FT-IR-8400S camera. 1H-NMR spectra were acquired in DMSO-d6 solvent by employing TMS as an internal standard and a Bruker spectrophotometer ultra-shield at 300 MHz.

Synthesis of (thiadiazol Ciprofloxacin) (A) (Tomma, 2011; Yaseen *et al.*, 2021).

Ciprofloxacin (0,01 mole), thiosemecarbazide(0,02 mole), and phosphorus oxychloride (15 ml) were mixed and refluxed for three h . After was complete the reaction (by TLC confirmed the eleuant was EtOAc and Hexane 1/2), added dropwise (10 ml) ice water to the mixture was cooled and refluxed once more for one h. The mixture was cooled and neutralized with sodium hydroxide to obtain a deep yellow precipitate which was filtered and dried before recrystallization. The melting point was (250-252) °C, with a yield of 80% for compound (A). Table (1) contains a list of structure and physical properties of preperd compounds.

Synthesis of Diazonium salt (A9) (Narren *et al.*, 2022).

Compound (A) (0.02) was dissolved in (2.5 mL concentrated HCl in 3 mL water) and cooled in an ice bath. The temperature was kept between 0 and 5^{o}C, and a second aqueous solution made from (0.018 mole) NaNO2 in (3 mL) H_2O was then gradually added while stirring the mixture in the ice bath until precipitate appeared. The precipitate was filtered, dried, and recrystallized using DMF.

Synthesis of compounds 3-((5-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinolin-3-yl)-1,3,4-thiadiazol-2-yl)diazenyl) pentane-2,4-dione (A10) (Narren *et al.*, 2022).

In order to make compound (A10), in a round bottom flask, add (0.02 moles) of A9 acetyl acetone which was dissolved in (20 mL) of absolute ethanol. Then add the mixture to the flask along with 0.01 mole of sodium carbonate while stirring for around 10 minutes. The mixture was refluxed for seven hours. The precipitate was filtering, drying, and purified with pure ethanol. to obtend compound (A10).

Synthesis of (4-(2-chloroacetyl) Ciprofloxacin (B) (Al-zubiady *et al.*, 2016).

In a round-bottom flask, combine (0.002 moles) of ciprofloxacin, (10 ml) of DMF, and (0.025 moles) of trimethylamine. the mixture was stirred for 8 h., leave this reaction mixture at room temperature stirrer for 1 day, then pour it over crushed ice. The detached substance was dried and recrystallized using absolute ethanol and water in a 1:1 ratio.

Synthesis of Substituted-2-aminobenzothiazole (B1-B4) (Zhilitskaya *et al.*, 2021).

Dissolved in a round bottom flask with a dropping funnel, (0.03 moles) of substituted aromatic primary amine and (0.01 moles) of ammonium thiocyanate were added dropwise while stirring and chilling to a solution of (1.2 ml) of bromine in (10 ml) of glacial acetic acid. There was more stirring for two hours. Then, after vigorous stirring, the produced solution was added to iced water. It was filtered, rinsed, dehydrated, and recrystallized from (1:1) absolute ethanol and water. The final product is a solid.

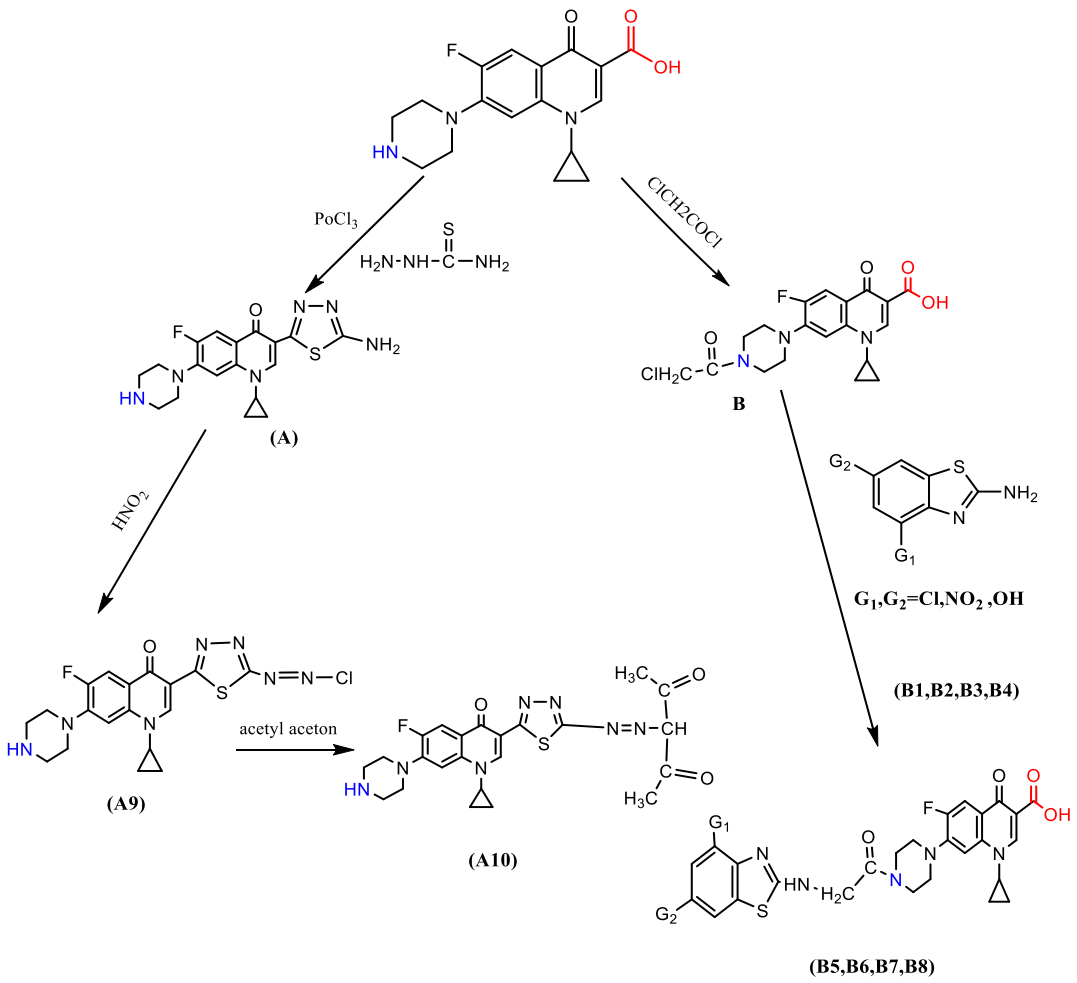
Synthesis of N-(2-aminoacetyl substituted benzothiazole) (B5-B8) (Sulthana & Pandian, 2019).

A solution of substituted-2-amino benzothiazole (1-5) (0.001 moles) in (10 ml) of absolute ethanol was added drop by drop to the reaction mixture, which was then refluxed for ten hours. The reaction mixture also contained (0.005 moles) of anhydrous potassium

carbonate. After cooling, ethanol was used as a solvent, and the precipitate was then separated, filtered, and recrystallized.

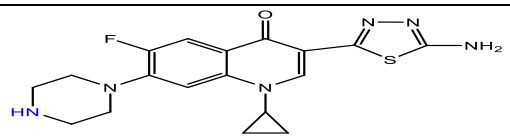
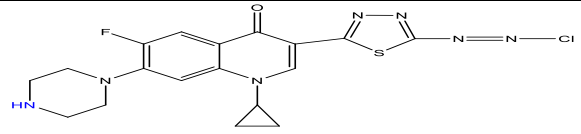
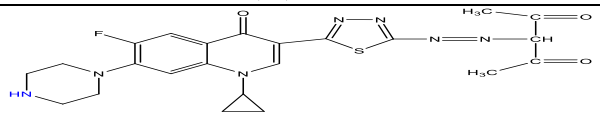
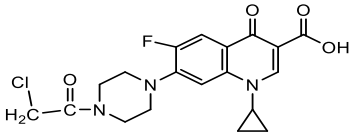
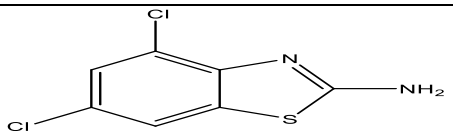
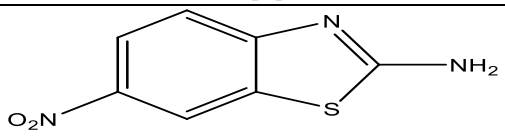
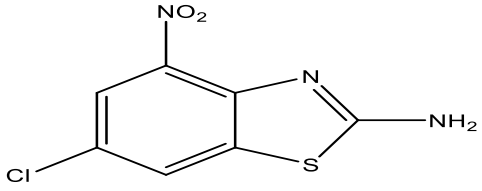
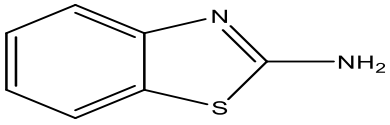
RESALT AND DISCUSSIONS

The reactions in (Scheme 1) were used 1 moles of Ciprofloxacin compound with 2 moles of ethyl acetoacetate, which was refluxed for 10 hours to prepare yellow precipitates of compound (A). Additionally, compound (A10) was synthesized by reacting thiadiazol (A) with nitrous acid to prepare diazonium salt (A9) and then reacting it with acetylacetone to produce compound (A10). The physical properties of all compounds are shown in Table 1. The compounds will also be characterized by FTIR spectrum, and the results show the FT-IR spectra of compound (A10), where stretching vibrations bands to the C=O group were seen at 1720 cm^{-1}, and absorption bands to the C-H group were seen at 2946 cm^{-1}. The preparation of compound (A10), thiadiazol compound data is as follows: 2.70 ppm (q, 2H, CH2N), 7.57 ppm (d, 2H, CH aromatic), 9.1 ppm (s, 1H, NH), 3.2 ppm (s, 1H, CH), 2.2 ppm (s; 3H, CH3C=O). Compound B was prepared by a nucleophilic substitution reaction of Ciprofloxacin with chloroacetyl chloride and trimethylamine as a catalyst at a temperature of (5-10°C). The compound B was characterized by FTIR (3500-2500) cm^{-1} (O-H stretch, of -COOH) and (1720, 1710) cm^{-1} (C=O stretch, -COOH). Compound B's 1HNMR spectra also revealed distinctive chemical alterations (DMSO-d6, ppm) listed below: Double peak (3.56, 3.29), Singlet signal of CH2Cl protons (4.24). The spectrum is shown in the (Fig 4). The compounds (B5, B6, B7, and B8) were prepared by the reaction of compound B with substituted 2-aminobenzothiazole derivatives. Compound (B-B8) was prepared as shown in scheme (1). The FTIR spectrum shown in (Fig 6) has (2500-3500) cm^{-1} (O-H stretch, -COOH), 1720 cm^{-1} (C=O stretch, -COOH), and 1643 cm^{-1} (-CON- Amide, C=O stretching). The biological activity of compounds (A, A10, B8) will be better than all the prepared compounds as shown in table 2. The prepared compounds are depicted in the Schemes **shown in table (2).**


PoCl3
H2N-NH-C(=S)-NH2
ClCH2COCl
HNO2
acetyl aceton
(A)
B
(A9)
(A10)
G1,G2=Cl,NO2,OH
(B1,B2,B3,B4)
(B5,B6,B7,B8)

Scheme 1

Table (1): Physical Properties and Structures of the Compounds (A-B8).

Compo .und no	Structures	Yiel d %	Color	M.P °C
A	 3-(5-amino-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one	42	Yellow	180-182
A9	 3-(5-(chlorodiazenyl)-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one	75	Brown	178-181
A10	 3-((5-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinolin-3-yl)-1,3,4-thiadiazol-2-yl)diazenyl)pentane-2,4-dione	85	Black	200-202
B	 7-(4-(2-chloroacetyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	92	white	230-232
B1	 4,6-dichlorobenzo[*d*]thiazol-2-amine	98	Beige	58-60
B2	 6-nitrobenzo[*d*]thiazol-2-amine	90	Yellow	190-192
B3	 6-chloro-4-nitrobenzo[*d*]thiazol-2-amine	66	orange	120-122
B4	 benzo[*d*]thiazol-2-amine	85	Off white	186-188

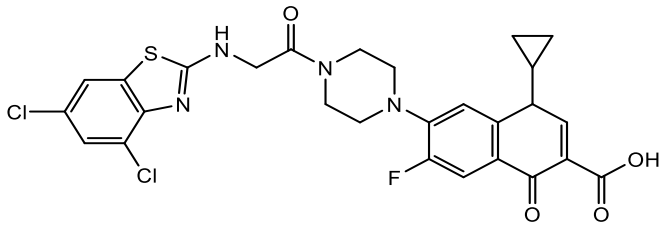
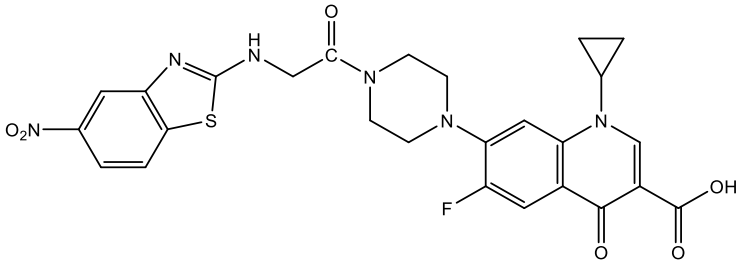
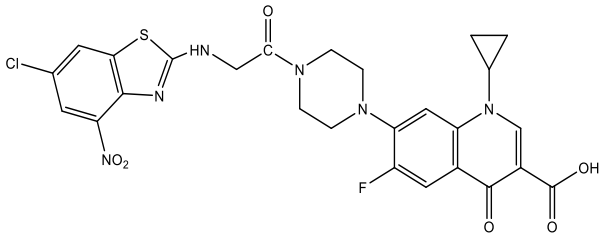
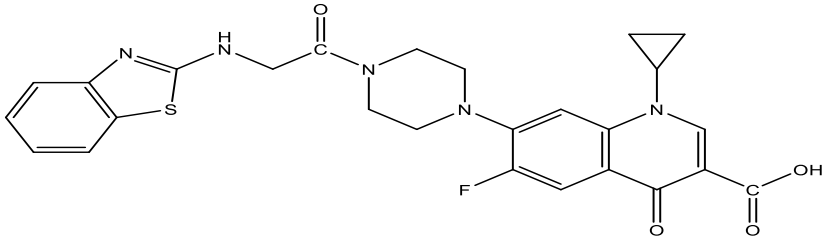
B5	 4-cyclopropyl-6-(4-((4,6-dichlorobenzo[*d*]thiazol-2-yl)glycyl)piperazin-1-yl)-7-fluoro-1-oxo-1,4-dihydronaphthalene-2-carboxylic acid	70	Beige	174-176
B6	 1-cyclopropyl-6-fluoro-7-(4-((5-nitrobenzo[*d*]thiazol-2-yl)glycyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	60	Light Yellow	208-210
B7	 7-(4-((6-chloro-4-nitrobenzo[*d*]thiazol-2-yl)glycyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	98	orange	260-262
B8	 7-(4-(benzo[*d*]thiazol-2-ylglycyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	80	white	262-264

Table (2): FT-IR Spectral data of synthesized compounds (A-B8) in cm^{-1}

Comp. No.	υN-H	υC-H Aromatic	υC-H Aliphatic.	υC=N	of υC=O ketone	υC=C aromatic	Others
A	3298	3047	2958,2850	1699	1625	1595	1269 υ (C-O) in COOH
A9	3233	3033	2931,2839	1700	1625	1552,1494	1271 υ(C-N)
A10	3292	3061	2978,2921	1675	1620	1566,1483	1153 υ (C-O)
B	3246	3095	2925,2860	1656	1627	1504,1458	1186 υ (C-O)
B5	3225	3201	2997,2951	1678	1612	1585,1427	1138 υ (C-O)
B6	3271	3082	2924,2854	1797	1739	1500,1476	1504,1388 υ(NO2), 1159 υ (C-O)
B7	3275	3056	2966,2873	1664	1624	1562,1504	3382 υ(O-H), 1130 υ (C-O)
B8	3259	3068	2970,2871	1643	1627	1554	1100υ (C-O)

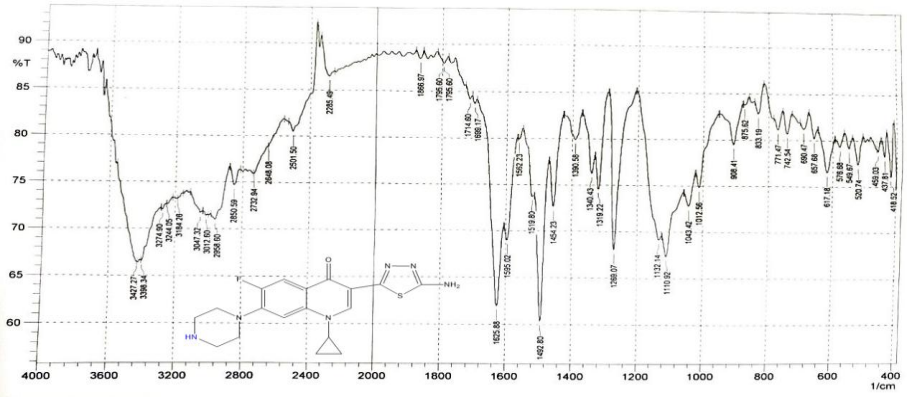


Figure (2): Compound FT-IR spectrum (A).

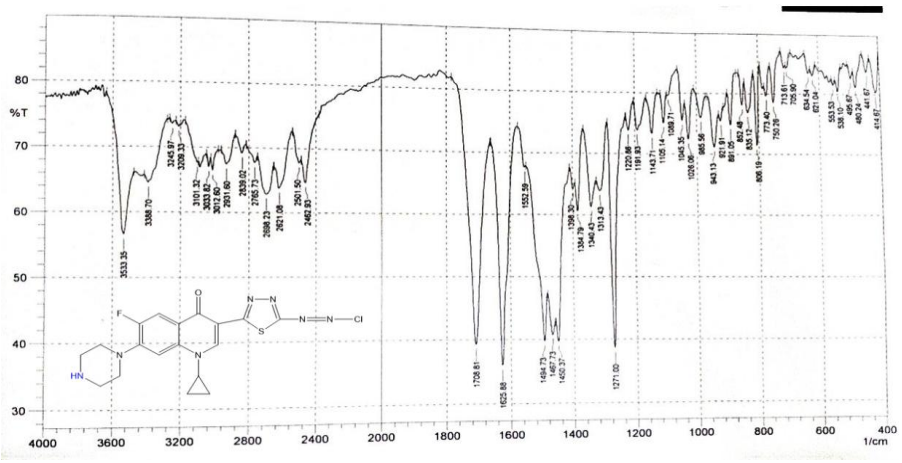


Figure (3): Compound FT-IR spectrum (A9).

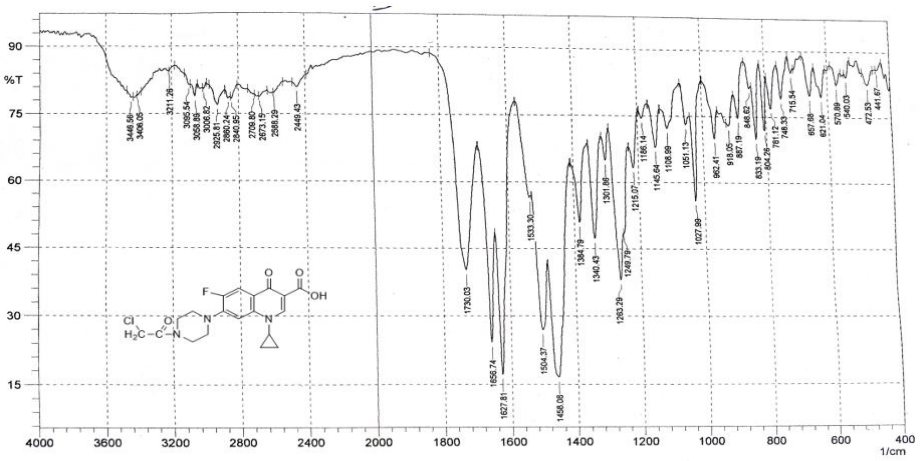


Figure (4): Compound FT-IR spectrum (B).

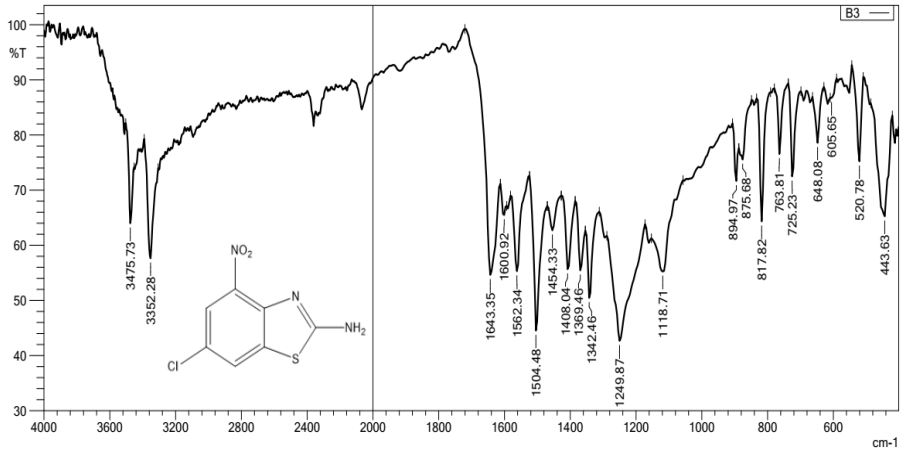


Figure (5): Compound FT-IR spectrum (B3).

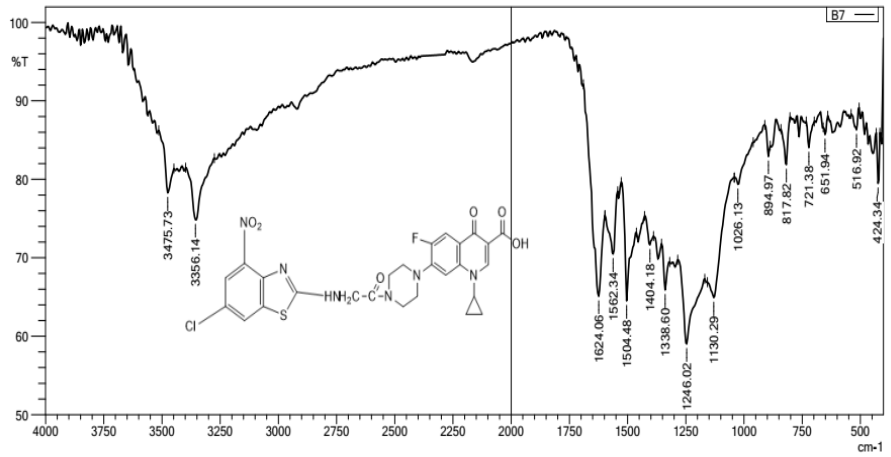


Figure (6): Compound FT-IR spectrum (B7).

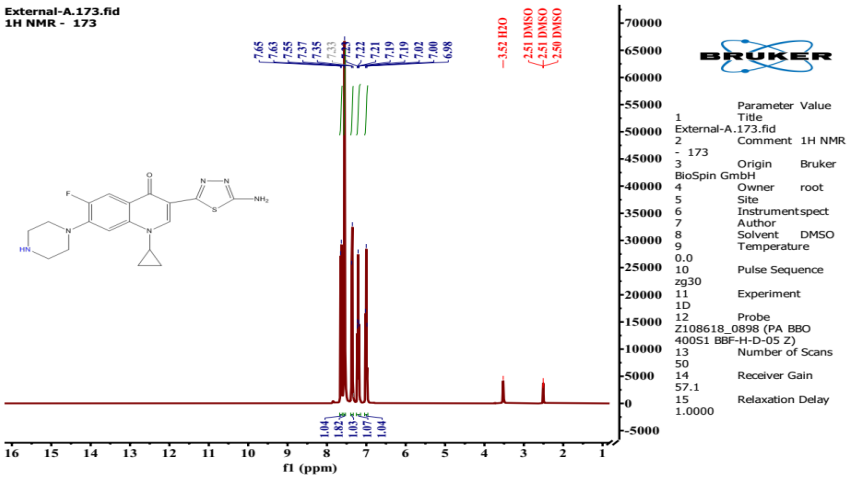


Figure (7): ^{1}H-NMR compound spectral A.

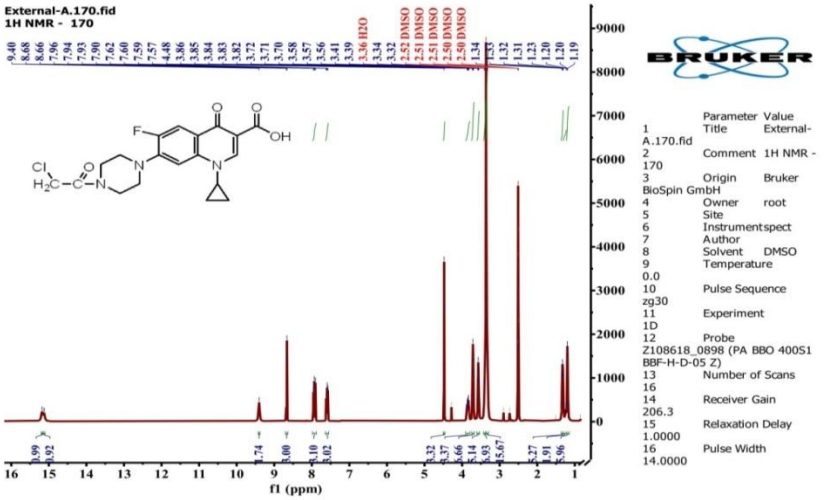


Figure (8): ^{1}H-NMR compound spectral B.

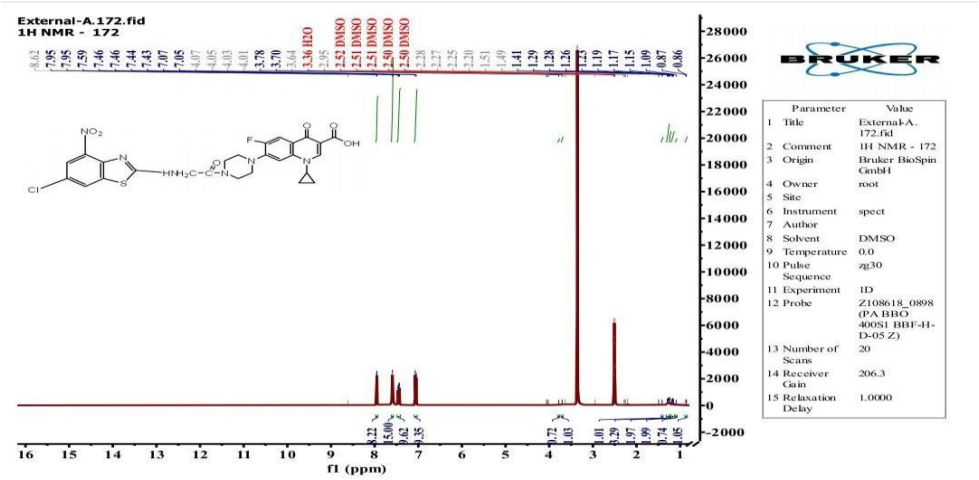


Figure (9): ^{1}H-NMR compound spectral B7.

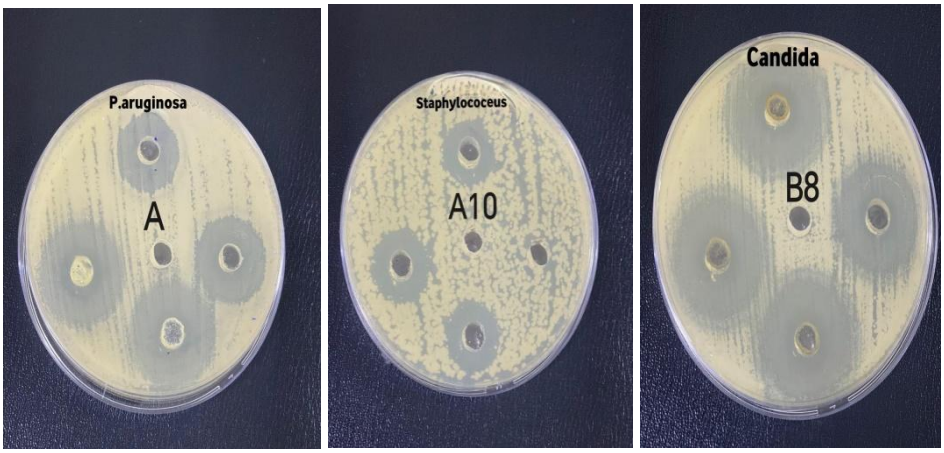


Figure (10): The effectiveness of compounds(A,A10and B8) for inhibit bacteria p.aeruginosa (*Staphylococcus aureus*), and fungi (*Candida albicans*)

Biological activates

Studies on the In Vitro Antibacterial Activity The antibacterial potency of the obtained compounds was investigated. First, their minimal inhibitory concentrations were determined for each of them (0.02, 0.01, 0.005, 0.002) mg/ml. The biological activity of some generated compounds (A, A10, and B8) against various bacterial strains was tested. *Candida albicans*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were isolated using the agar well diffusion method **(Mahdi *et al.*, 2017)**. The antibacterial activity of (A-A10-B8) against harmful bacteria and fungus was identified using the agar well diffusion method. Table 3 lists the antibacterial outcomes.

As a fungicide drugs

Examples of fungicides in the benzimidazole class are benomyl, carbendazim, and chlorphenazole. Benzothiazoles are a systemic fungicide that can be used both to prevent and treat fungal infections. The plant takes it up via its roots and its green tissues. It stops the production of beta-tubulin, stops the creation of germ tubes, and stops myceliagrowth. It is suitable for use alongside the majority of pesticides. This substance is applied topicaly to prevent diseases such as blasts, sheath blight, brown spots, powdery mildew, scab, anthracnose, and leaf spot from spreading in various crops **(Saini *et al.*, 2023)**.

As antimicrobial drugs

Ciprofloxacin: Ciprofloxacin is an antibiotic that belongs to the class of medicines known as quinolon. It is applied to infections brought on by specific microorganisms. Most often, it is utilized. Treat infections of the skin, sinuses, bones, and lungs. bladder, kidney, prostate, stomach, and ears. **(Walia *et al.*, 2011; Alzhrani *et al.*, 2022**).

Antibacterial Activity. Together with the patented medicine, Table 3 highlights the in vitro bactericidal activity of 3-substituted carboxylic acids against drug-sensitive Gram-positive ***(Staphylococcus aureus)*** and Gram-negative ***(Pseudomonas aeruginosa)*** bacteria. Our goal was to create analogs that exhibited similar efficacy against all tested strains of ciprofloxacin. The results suggest that compound A exhibited strong activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, whereas compound B8's phenyl ring containing an electron-donating group also demonstrated action against the same bacteria. Thiadiazol A10 was introduced and demonstrated reasonable efficacy against *Pseudomonas*

aeruginosa. In terms of the structure-activity relationship, the results indicate that the antibacterial activity profile against all types of bacteria was changed by the addition of the amino group in the ciprofloxacin molecule. However, changing the substitution in the amino ring also produced notable differences in activity. The expansion of activity appears to be due to better interaction of the molecule with target enzymes or to penetration by these bacteria.

Table (3): Biological activity for some synthesized compounds.

Isol. No.	Compound No.	0.02mg/ml	0.01mg/ml	0.005mg/ml	0.002mg/ml
P.aeruginosa	A	24	20	15	10
Candida Albicans	A	33	30	23	21
Staphylococcus aureus	A	11	0	0	0
P.aeruginosa	A10	32	27	20	18
Candida Albicans	A10	33	28	24	20
Staphylococcus aureus	A10	20	15	0	0
P.aeruginosa	B8	25	20	15	0
Candida Albicans	B8	25	24	21	20
Staphylococcus aureus	B8	18	16	15	0

CONCLUSION

By using FT-IR and ^{1}H NMR, numerous novel synthetic compounds made from Ciprofloxacin have been described. Some of these compounds have also been tested for their antibacterial and antifungal properties. The outcomes indicated that they were biologically active. **B8**'s biological activity outperformed that of all other synthesized compounds.

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