

Synthesis and Characterization of some new derivatives of thiadiazoles derived from ciprofloxacin Drug and Study of Their Biological Activity words

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Abstract

The first Schiff bases were designed in this study by reacting various aldehydes or ketones with thiadiazole derived from ciprofloxacin drug. A glacial acetic acid role is a catalyst and causes the reaction to proceed faster (A1-A4). Subsequently, the Schiff bases react with Sodium azide in tetrahydrofuran as a solvent to prepare new derivatives (A5-A8). Diazonium salt (A9) is produced via diazotization with Acetyl acetone and Na₂CO₃ to product (A10). Mannich reaction was performed to produce (A11-A16) via reaction of thiadiazole (A) with selected aldehyde and secondary amine. The prepared derivatives have been identified by FT-IR, ¹HNMR Gram-positive (*Staphylococcus*), Gram-negative (*Pseudomonas aeruginosa*), and Fungi (*Candida albicans*) bacteria and fungi were successfully scanned by the antibacterial and antifungal action.

Introduction:

Heterocyclic molecules are the most diverse family of organic compounds. Many heterocyclic compounds are currently known because of intensive synthetic research and their use in organic synthesis. This number is constantly increasing [1]. Schiff bases contain the functional group (-C=N). Hugo Schiff first compressed the azomethine group. Schiff bases are widely used in chemical reactions, such as pure organic, bioorganic, and inorganic chemistry. [2]. Numerous Schiff compounds have been synthesized, and their complexes have been investigated as a result of their structural features [3]. They are heterocyclic organic molecules, which have four nitrogen atoms and one carbon atom, with powerful biological activity. These species have important biological activities and are attractive for the study of medicinal applications. [4,5]. These heterocyclic molecules are most effective since they have four free pairs of electrons for each of the four nitrogen atoms in the electron molecular framework [7]. Heterocyclic azo dyes have many excellent properties and are an essential

class for polyester fiber dyes, as well as nontextile industries such as nonlinear optical systems, phototherapy, and lasers [8]. In addition, they have important biological activities such as anticancer, cytotoxicity, antimicrobial, anti-tuberculosis, antifungal, and agricultural pesticides [9, 10]. Besides the chemical utility of selenium compounds, they have broad pharmacological and biological activities, for instance, antifungal activity such as *Aspergillus niger*, *Aspergillus*, and *Candida albicans*, antibacterial such as *Staphylococcus aureus* as gram-positive bacteria, and *Escherichia coli* as gram-negative bacteria, antiviral, anti-inflammatory, and antioxidant effects. On the other hand, the biological activity of azo dye compounds is elevated when they contain organ selenium moiety [11, 12].

Also, mannich bases are the end products formed from the Mannich reaction, i.e., nucleophilic addition reaction of non-enolizable aldehyde and any primary or secondary amine to produce stabilized imine. Mannich bases have gained importance due to their application in antibacterial activity and other applications are in agrochemicals such as plant growth regulators. Prodrugs of Mannich bases of various active compounds have been prepared to overcome the limitations [13].

Materials and Methods

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

1 Preparation of Ciprofloxacin (3-(5-amino-1,3,4-thiadiazol-2-yl)) A [14]

Ciprofloxacin (0,01 mole), thiosemicarbazide (0,02 mole), and phosphorous oxychloride (15 ml) in DMF were combined and refluxed for three hours. After completion of the reaction (by TLC (10 mL) of ice water was added dropwisely to the mixture. After cooling, ice water (50 mL) was added to portions by stirring. The yellow precipitate was filtered, washed with hot water (15) . Next, the mixture was neutralized with sodium hydroxide to obtain a deep yellow. Put a full stop the mixture filtered, dried, and recrystallized from (DMF), m.p (250-252) °C, yielding (80%) Table (1).

2 Synthesis of Schiff bases (A1-A4) [15]

A reaction of A (0.01 mole) with various aldehydes or ketones (0.01moles), in 25 ml of absolute ethanol and few drops of glacial acetic acid. The solution was refluxed on water-bath for (6-8) hrs. at 80 °C, producing a series of Schiff bases. and the precipitate was filtered. It was recrystallized with ethanol. The physical properties are shown in Table (1).

3 Synthesis of Tetrazole (A5-A8) [16]

0.002 mole of the produced Schiff bases (A1-A4) was mixed with sodium azide (0.004 mol) in 20 ml of THF. The solution was refluxed for 6 to 8 hours at (40-60) °C and the precipitate was filtered. It was recrystallized with ethanol. The physical properties are shown in Table (1).

4 Synthesis of Diazonium salt (A9) [17]

Compound (A) (0.02) was dissolved in of (2.5 mL concentrated HCl dissolved in (3 mL water) and cooled in an ice bath. The temperature was kept between (0-5) °C. and a second aqueous solution made from (0.018 mole) NaNO₂ in (3 mL H₂O was then gradually added while stirring the mixture in the ice bath until precipitate The product. Filtered, dried, and purified using DMF. Table (1)

5 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) [18]

Acetyl acetone (0.02 mole) was dissolved in(20 mL) of absolute ethanol and added to the mixture along with 0.01 mole of sodium carbonate while stirring for around 10 minutes. The mixture then refluxed for seven hours. The finished product. The obtained product was filtered, dried, and purified from pure ethanol. Table (1)

6 Synthesis of (A11-A16) General method (Mannich Reaction) [18]

A mixture of aromatic aldehyde (0.001 mole) in absolute ethanol (10 ml) and selected secondary aminen(0.015 mole) were fefluxed (0.015 mole) until a clear solution was formed. (0.004 mole) of compound A dissolved in (10 mL) of absolute ethanol was heated, added to the initial reaction mixture, and refluxed for five hours. The Mixture was concentrated by heating, and a resulting separated product was filtered. and recrystallized from chloroform to produce the required compounds (A11-A16). Table (1)

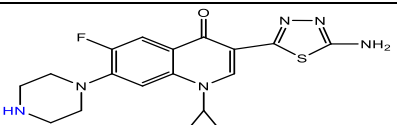
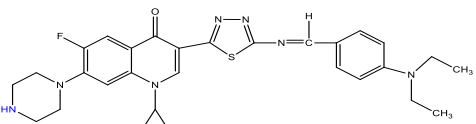
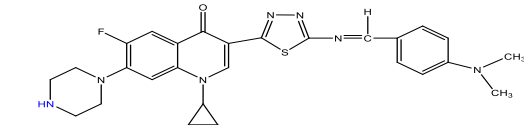
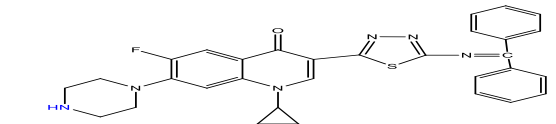
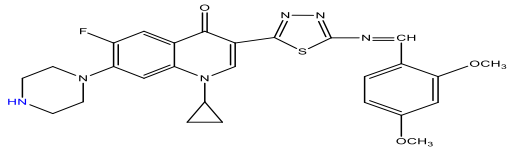
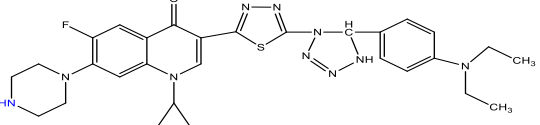
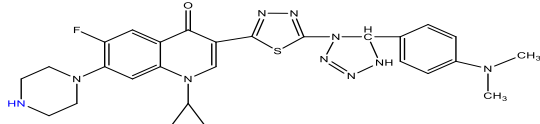
Results and Discussions:

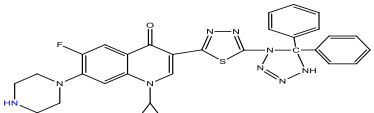
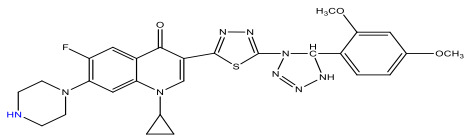
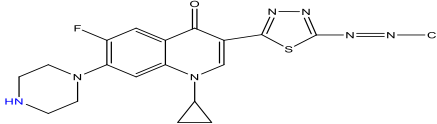
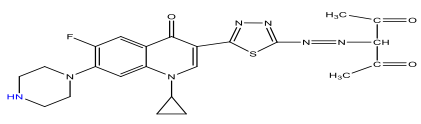
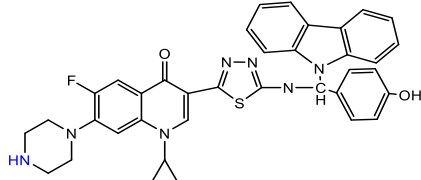
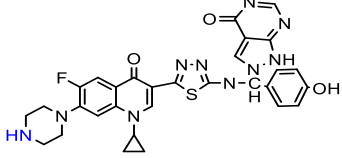
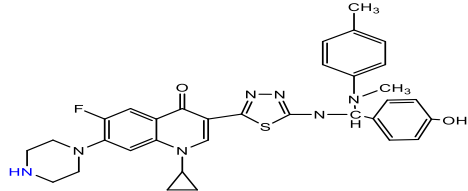
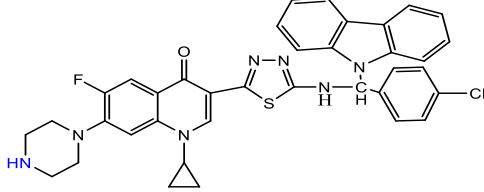
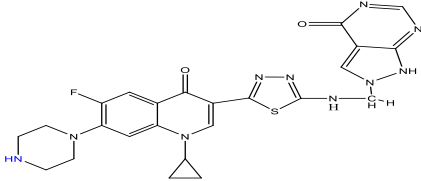
The reactions in (Scheme 1) were used to prepare 1 mole of Ciprofloxacin compound from 0,02 mole) thiosemicarbazide, and phosphorous oxychloride (15 ml) in DMF were combined and refluxed for three hours., which was refluxed for 10 hours to produce yellow precipitates of compound (A). reaction with the different aldehydes or ketones to prepare (A1-A4) compounds [15]. Then, the Schiff bases reaction with sodium azide gives new derivative compounds (A5-A8) [16]. Also, the compound (A10) synthesized from the reaction of thiadiazol (A) with diazonium salt (A9) [17] and then reacted with Acetylacetone to prepare (A10).in the other series (A11-A16) compounds have been synthesized by reaction of thiadiazol (A) with aldehyde and selected secondary amine using Mannich Reaction. The Physical Properties of all compounds are shown in Table 1. The compounds would also be characterized by FT-IR spectra. The FT-IR spectra of the compound shown (A6) C=N group at 1629 cm⁻¹ showed a stretching vibrations band, 1510 cm⁻¹ absorption bands to the C-N group, 1455 cm⁻¹, and absorption bands to the N=N group. As seen in the compound (A10)'s FT-IR spectra, at 1720 cm⁻¹ stretching vibrations bands to the C=O group were seen and absorption bands to the C-H group were seen at 2946 cm⁻¹. In the FT-IR spectra of compound (A16), stretching vibrations bands to the N-H group were seen at 3211 cm⁻¹, and at 1730 cm⁻¹absorption bands to the C=O group were seen. Compound (A6) ¹HNMR spectra also revealed the distinctive chemical alterations (DMSO-d₆, ppm) ¹H-NMR data of compound A6 in Fig.4 6.98 (s, H, NH); 6.93 (s, CH tetrazole); 9.67 (s, 2H,CH); Preparation of (A10),thiadiazol compound data of compound in Fig.5 ,2.70 (q,2H,CH₂N) , 7.57 (d,2H,CH aromatic) ,9.1(s,¹H,NH), 3.2(s,1H,CH), 2.2(s;3H,CH₃C=O) The (A16) compound was characterized by 1HNMR shown in the Fig.6 1.21 (4H,m,CH₂-CH₂), 2,15(3H,s,CH₃) 3.67 (8H,m,N-CH₂CH₂-N), 3.83 (1H,s, S-CH₂-N) 6.8 (9H,m,CH_{aromatic}) 8.6 (1H,s, CH=C) The biological activity of compounds (A6, A10, A16) will be better than all prepared compounds as shown in table 2.

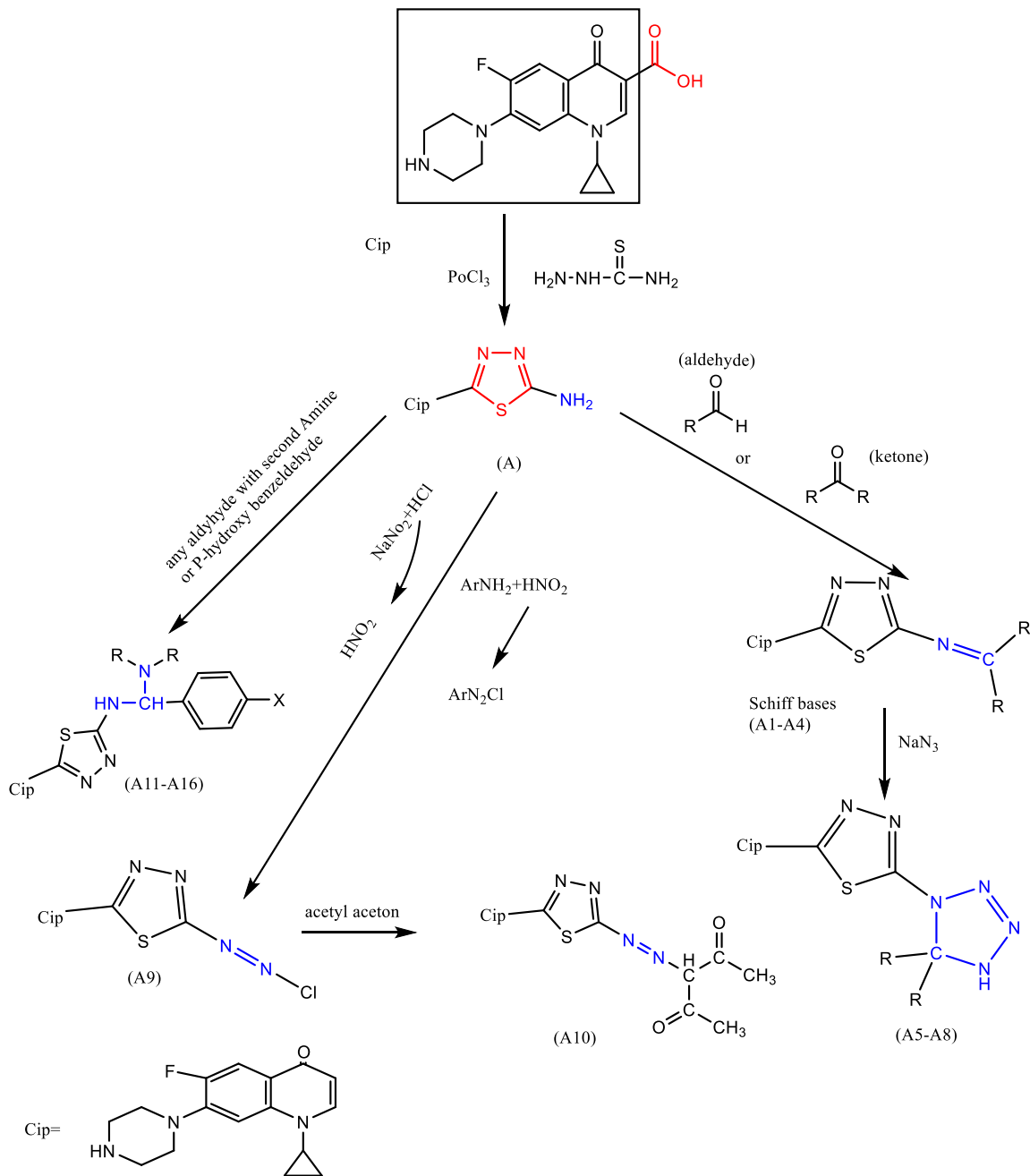
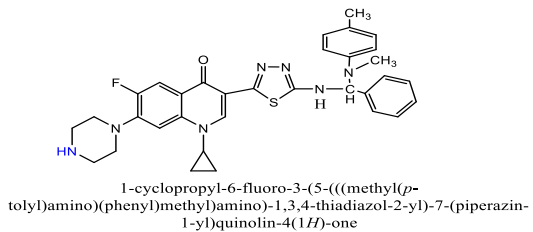
Biological activates

The biological activity of some generated compounds (A6, A10, and A16) against various bacterial strains was tested. *Candida albicans*, *Staphylococcus aureus*, and *pseudomonas aeruginosa* were isolated using the agar well diffusion method. According to Mahdi, (2017)10, the agar well diffusion method was employed to identify the antibacterial activity of (A6-A10-A16) against harmful bacteria and fungus at the concentration (100-50-25-10) mg/ml. Table 2 lists the antibacterial outcomes.

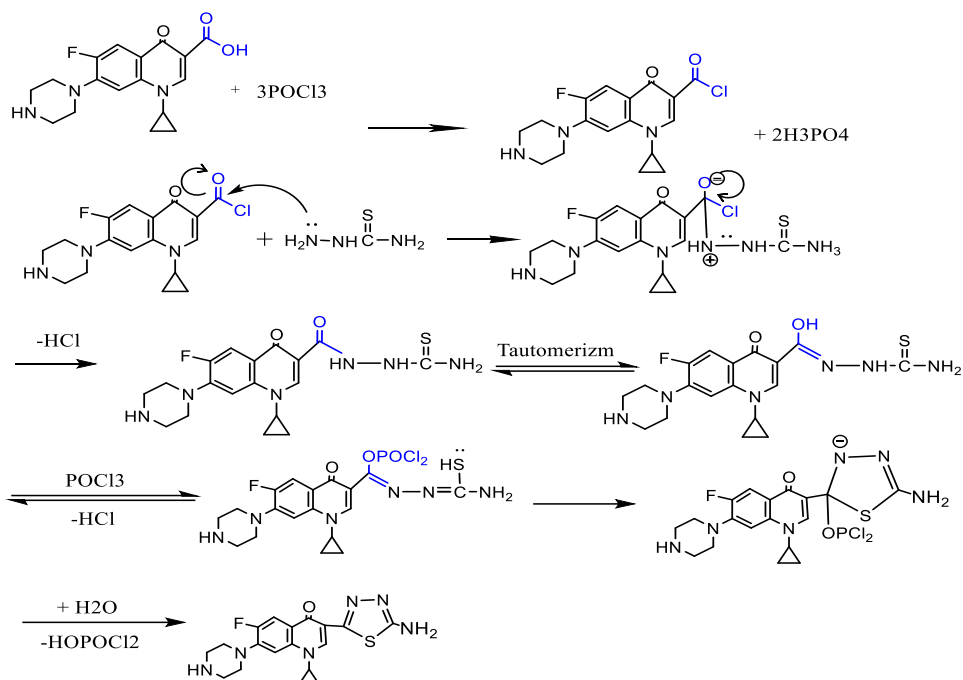
Table 1: Some of the Physical Properties of the Compounds (A-A16)

Comp. no	Name and structure	Yield %	Color	M.P °C
A	 3-(5-amino-1,3,4-thiadiazol-2-yl)-1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	42	Yellow	180-182
A1	 1-cyclopropyl-3-(5-((4-(diethylamino)benzylidene)amino)-1,3,4-thiadiazol-2-yl)-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	70	Maroon	210-212
A2	 1-cyclopropyl-3-(5-((4-(dimethylamino)benzylidene)amino)-1,3,4-thiadiazol-2-yl)-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	75	Barn red	208-210
A3	 1-cyclopropyl-3-(5-((diphenylmethylene)amino)-1,3,4-thiadiazol-2-yl)-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	78	Maroon	198-200
A4	 1-cyclopropyl-3-(5-((2,4-dimethoxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	65	Dark red	212-214
A5	 1-cyclopropyl-3-(5-(5-(4-(diethylamino)phenyl)-4,5-dihydro-1H-tetrazol-1-yl)-1,3,4-thiadiazol-2-yl)-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	92	Gray	128-130
A6	 1-cyclopropyl-3-(5-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-tetrazol-1-yl)-1,3,4-thiadiazol-2-yl)-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one	90	Dark brown	124-126

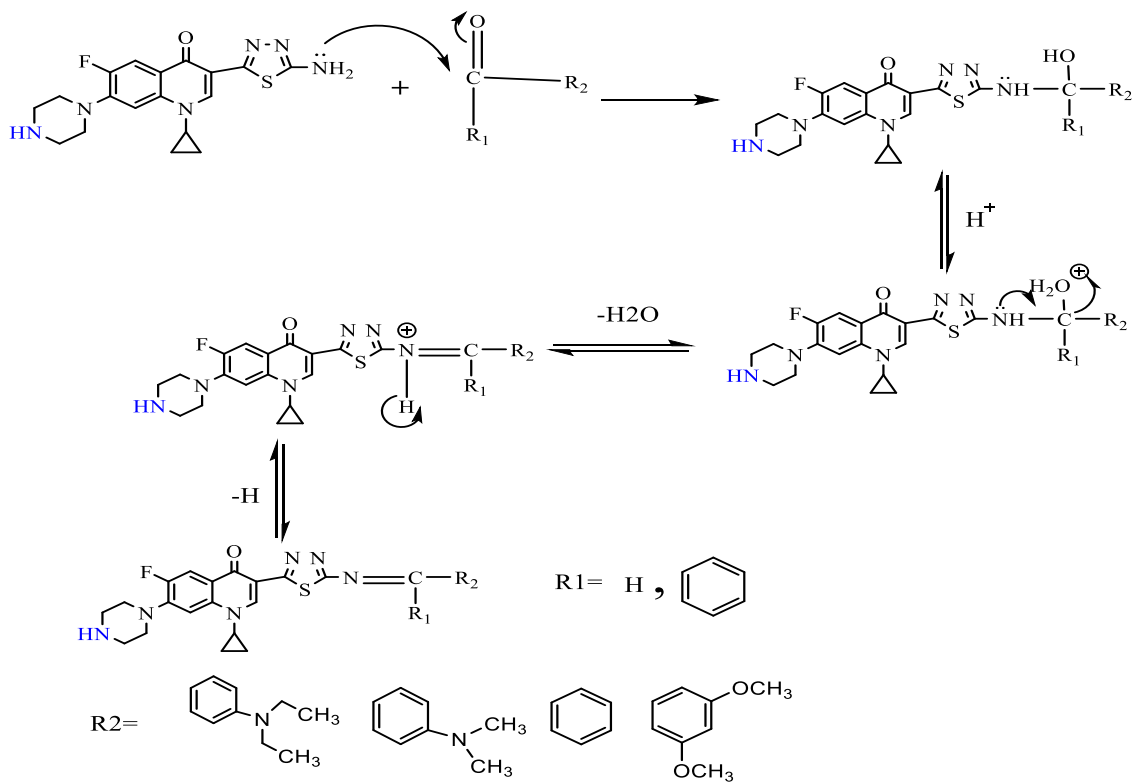
A7		90	Light brown	118-120
A8		95	Black	130-132
A9		75	Brown	180-182
A10		85	Black	200-202
A11		53	White	140-142
A12		50	Off white	196 198
A13		60	Brown	98-100
A14		78	White	157-159
A15		62	Peggy	180-182



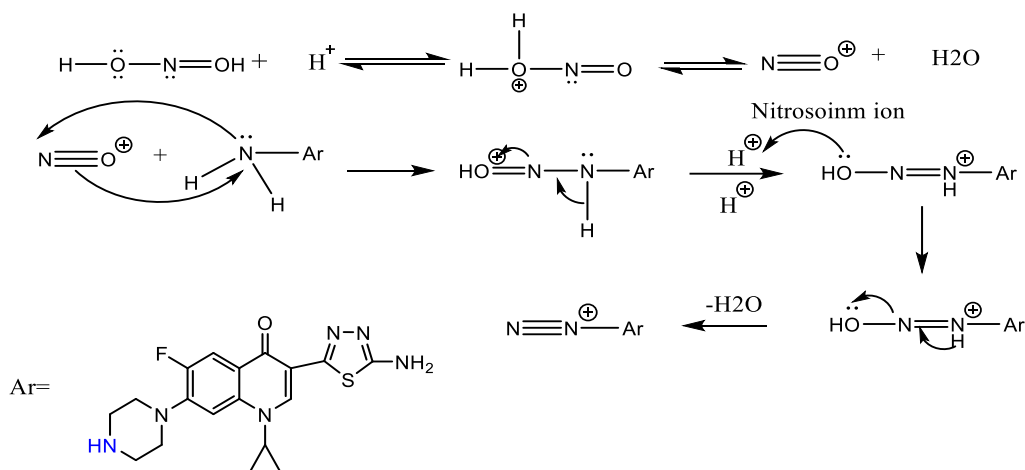
Scheme 1



Scheme 2: Mechanism steps for synthesis of compound A



Scheme 3: Mechanism steps for synthesis of compound (A1-A4)



Scheme 4: Mechanism steps for synthesis of compound A9

Table 2. Biological activity for some synthesized compounds

Isolates	A			
	100 mg/ mL	50 mg/ mL	25 mg/ mL	10 mg/ mL
Pseudomonas aeruginosa	7.8±1.5	6.8 ± 1.5	5.6 ± 1.5	0.0±0.0
Candida Albicans	23.3±0.5	20.5±0.5	18.3±0.5	15.3±0.5
Staphylococcus aureus	12.3±0.5	10.5±0.5	8.3±0.5	4.3±0.5
Isolates	A6			
	100 mg/ mL	50 mg/ mL	25 mg/ mL	10 mg/ mL
Pseudomonas aeruginosa	7.6±1.5	6.5 ± 1.5	5.5 ± 1.5	0 ± 0
Candida Albicans	39.3 ± 1.5	35.3±1.15	25.3±1.0	23.3±0.5
Staphylococcus aureus	12.3 ± 0.5	10.3± 0.5	7.6 ± 1.5	0 ± 0
Isolates	A10			
	100 mg/ml	50 mg/ml	25 mg/ml	10 mg/ml
Pseudomonas aeruginosa	39.8 ±1.5	35.5 ± 1.5	0 ± 0	0 ± 0
Candida Albicans	6.6 ± 0.5	4.5 ± 0.5	0 ± 0	0 ± 0
Staphylococcus aureus	20 ±1	15 ± 1	14 ± 1	0 ± 0
Isolates	A16			
	100 mg/ml	50 mg/ml	25 mg/ml	10 mg/ml
Pseudomonas aeruginosa	7.6 ± 1.5	0 ± 0	0 ± 0	0 ± 0
Candida Albicans	28.3±0.5	25.3±1.5	23.3 ± 1.5	18 ± 1
Staphylococcus aureus	15.3±0.5	10.3 ± 0.5	9.6 ± 1.5	0 ± 0

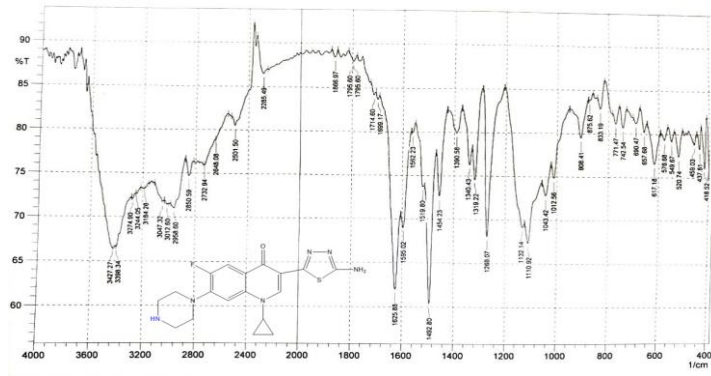


Fig. 1. FT-IR spectrum for compound (A)

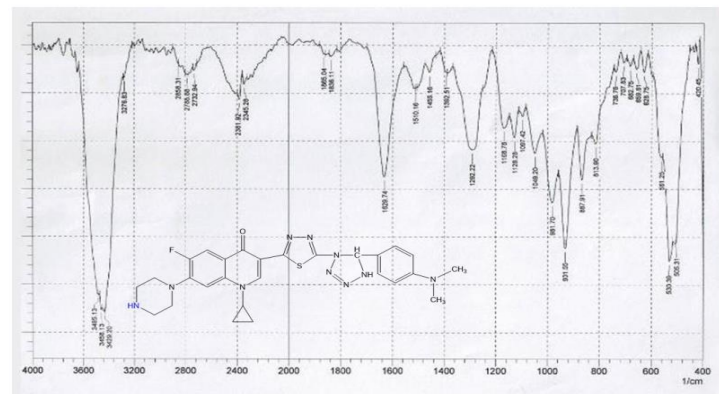


Fig. 2. FT-IR spectrum for compound (A6)

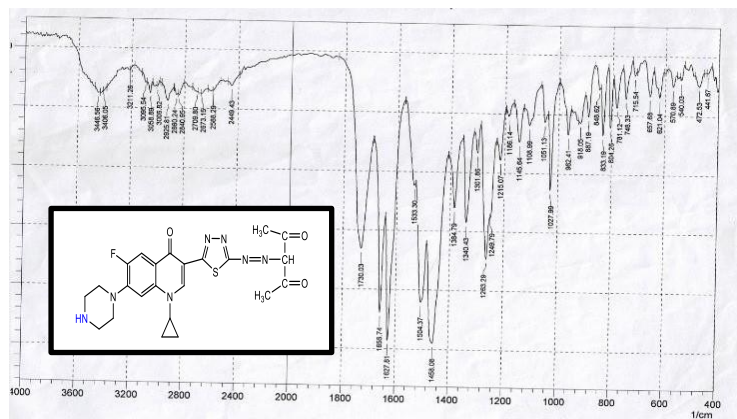


Fig. 3. FT-IR spectrum for compound (A10)

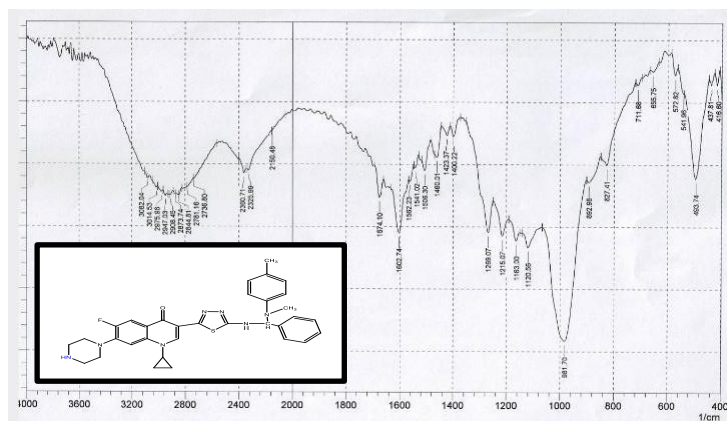


Fig. 4. FT-IR spectrum for compound (A16)

Comp.no H-NMR spectra

A (1.0)(t,3H,CH3-CH₂),(2.58)(q,2H,CH₂N),(2.19)(s,3H,CH₃N),(2.4)(t,2H,CH₂CH₂),(3.5-3.6)(m,2H,CH₂NH),(3.3)(s,3H,CH₃O),(7.7)(d,2H,CH_{aromatic}),(10.01)(s,1H,NH),(5.98)(s,1H,OH),(1.35)(s,2H,CH₂)

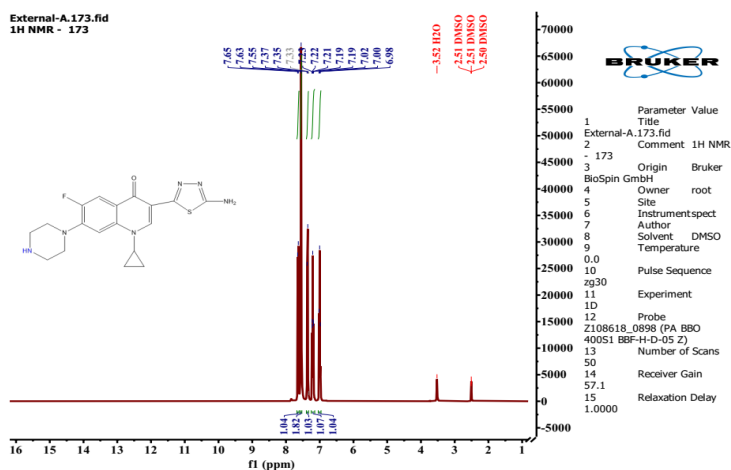


Fig. 5 FT-IR spectrum for compound (A)

The ¹HNMR spectrum (DMSO as a solvent) of compound (A6) Figure (6) displays the signal at δ 1.05ppm (t, 2H, CH₂) for (cyclopropan), δ 1.06 (t, 2H, CH₂) for (cyclopropan), δ 1.6ppm (s,1H,NH) (cyclopiyrdine), 3.2 ppm(t, 6H, CH₃) δ 2.19 ppm (d,2H,2CH₂) (cyclopiyrdine), δ 3.3ppm (d,2H,2CH₂) (cyclopiyrdine), and δ 6.98-7.64 ppm (m, 7H, aromatic).

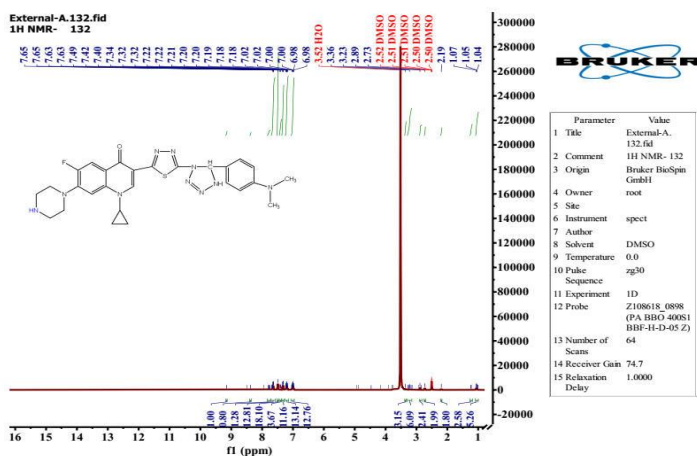


Fig. 6. ¹H-NMR spectrum for compound (A6)

Comp.no H-NMR spectra

A10 (1.0)(t,3H,CH3-CH₂),(2.58)(q,2H,CH₂N),(2.19)(s,3H,CH₃N),(2.4)(t,2H,CH₂CH₂),(3.5-3.6)(m,2H,CH₂NH),(3.3)(s,3H,CH₃O),(7.7)(d,2H,CH_{aromatic}),(10.01)(s,1H,NH),(5.98)(s,1H,OH),(1.35)(s,2H,CH₂)

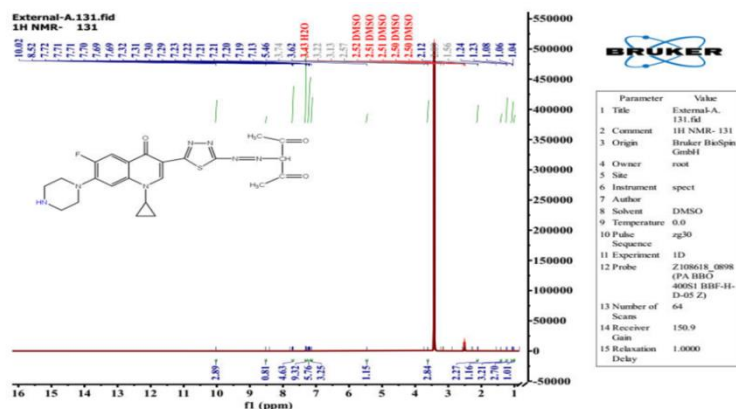


Fig. 7. ¹H-NMR spectrum for compound (A10)

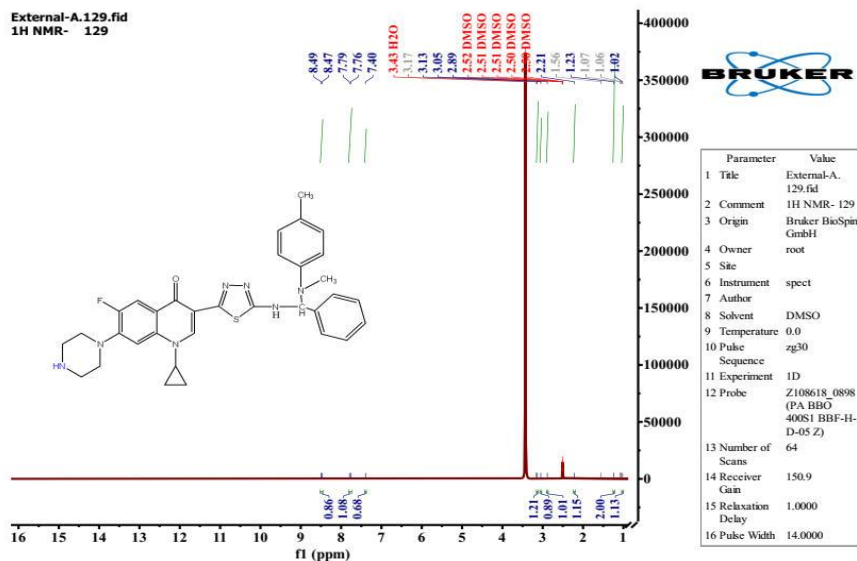


Fig. 8. ¹H-NMR spectrum for compound (A16)

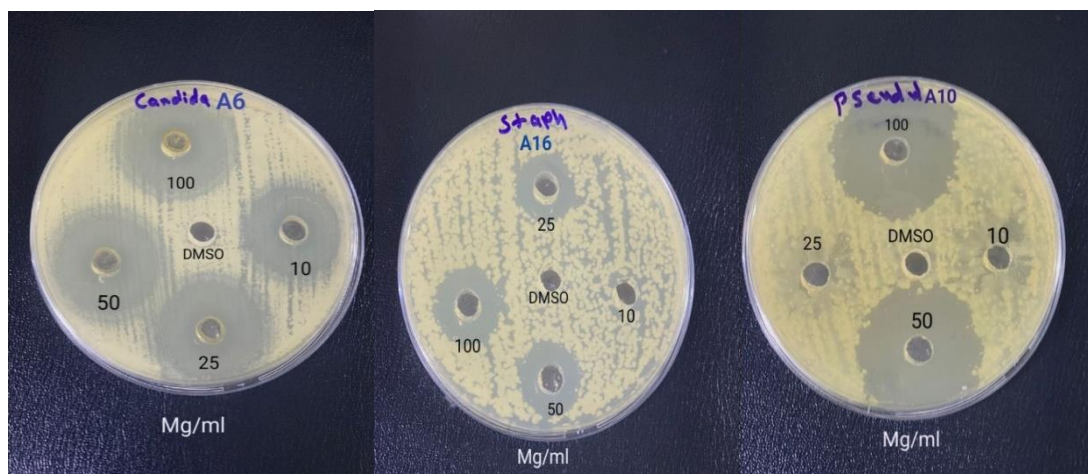


Fig. 9. The efficiency of compounds for inhibit bacteria p.aeruginosa(Staphylococcus aureus), and fungi(Candida albicans)

Conclusions

By using FT-IR and ^1H NMR, numerous novel synthetic compounds synthesized from the drug 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. While A6's biological activity outperformed all other synthesized compounds.

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تحضير وتشخيص بعض مشتقات الجديدة للثايدوزول المشتقة من عقار سيبروفلوكساسين ودراسة الفعالية البيولوجية لها

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الخلاصة:

في البداية تم تصنيع قواعد شف بواسطة تفاعل انواع مختلفة من الاديهايدات والكيوتونات مع الثيادايازول بوجود حامض الخليك الثلجي كعامل مساعد، ومن تفاعل قواعد شيف مع ازيد الصوديوم حضرت مشتقات جديدة. و تم تحضير املاح الدايزونيوم من تفاعل اسينل اسيتون مع بيكاربونات الصوديوم. واخيرا حضرت قواعد مانخ من تفاعل الثايدوزول مع الاديهايدات وامينات ثانوية كما موضح في الجدول الاول إذ تم قياس درجات الانصهار وتشخيص المركبات المحضرة بطيف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي للبروتون وكذلك تم اختبار الفعالية الحيوية لبعضها.

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