Iraqi Journal of Science, 2026, Vol. 67, No. 2, pp: 613-628
DOI: 10.24996/ijs.2026.67.2.4

ISSN: 0067-2904

Design and Synthesis of several new developed Sulfa Drugs and screening of their Antimicrobial and Antifungal Activities

Sura S. Raoof1[1,2], Ahlam Marouf Al-Azzawi[1]
[1]*Department of Chemistry, College of Science, University of Baghdad, Baghdad, Ira*
[2]*Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq*

Received: 10/9/2024 Accepted: 24/2/2025 Published: 28/2/2026

Abstract

The objective of this study was to design and synthesize novel sulfa drugs by incorporating different cyclic imides into their structures. This goal was achieved in two steps. In the first step, four selected sulfa drugs, including sulfamerazine, sulfamethazine, sulfadiazine, and sulfamethoxazole, were reacted with different cyclic anhydrides, namely (maleic, phthalic, and succinic) anhydrides producing N-Drug amic acids (**1-6**). In the second step, the dehydration of compounds (**1-6**) was carried out through a fusion process to produce the target corresponding imides (N-Drug imides) (**7-12**). The results of the biological activity study indicated that the developed drugs (**7-12**) show very high antimicrobial.

Keywords: Sulfa Drugs, N-drug amic acid, N-drug cyclic imides, Dehydration, antibacterial and antifungal activities

تصميم وتحضير عدد من ادوية السلفا المطورة الجديدة وتقييم فعاليتها المضاد للبكتريا والفطريات

سرى صادق رؤوف[2,1], أحلام معروف العزاوي[1]
[1]قسم الكيمياء، كلية العلوم، جامعة بغداد، بغداد، العراق
[2]فرع الكيمياء الصيدلانية، كلية الصيدلة، الجامعة المستنصرية، بغداد،العراق

الخلاصة

الهدف من هذاه الدراسة هو تصميم وتحضير ادوية سلفا جديدة من خلال ادخال ايمايدات حلقية مختلفة في تراكيبها. وقد تم تحقيق هذا الهدف بخطوتين. في الخطوة الاولى ادخال اربعة من ادوية السلفا المختارة وهي (سلفاميرازين ,سلفاميثازين,سلفادايازين و سلفاميثاوكسازول) في تفاعل معد انهيدريدات حلقية مختلفة والتي هي انهيدريدات حلقية مختلفة والتي هي انهيدريدات (الماليك,الفثاليك والسكسنيك) مما اسفر عن تكوين مركبات N– دواء حوامض الاميك [1–6] . في الخطوة الثانية ,تم سحب الماء من المركبات [1–6] من خلال عملية الصهر مما انتج الايمايدات المقابلة الهدف (N–دواء ايمايدات) [7–12] . اوضحت نتائج دراسة الفعالية البايولوجية للمركبات الجديدة [7–12] تظهر نشاطا مضادا للمايكروبات بدرجة عالية جدا بانها ذات فعالية عالية جدا .

* Email : surasadiq752@gmail.com

1. Introduction

Sulfonamide, the active ingredient in prontosil, is crucial in medicine as the first substance that exhibits strong effects against systemic bacterial diseases[1, 2]. Generally, sulfonamides are used worldwide as antibacterial agents due to their low cost, minimal toxicity, and remarkable efficiency against prevalent bacterial infections[3, 4]. Additionally, sulfonamides have several pharmacological properties, including antihypertensive[5], antimalarial[6], antibacterial[7], anti-inflammatory[8], antiglaucoma[9], antitumor[10], antithyroid[11], anticancer effects[12], diuretic[13] and antibiotic[14].Moreover, sulfa medicines that are derived from the fundamental structure of the sulfonamide molecule are recognized as the initial pharmaceutical agents employed for both prophylactic and therapeutic purposes against different bacterial infections like influenza, eye infections, actinomyces infections, and urinary tract infections[15-17]. Cyclic imides are important organic compounds known for their diverse biological activities, such as anticonvulsant, antibacterial, anti-inflammatory, and anticancer therapeutic actions[18, 19]. Cyclic imides serve as fundamental building nuclei in the chemical structures of many drugs and different pharmaceutical compounds. Moreover, multi-drug-resistant (MDR) microorganisms are some of the important factors for the failure of chemotherapy in several infectious illnesses[21 ,20] . The increasing resistance to traditional antibiotics presents a novel problem for the pharmaceutical industry and healthcare practitioners, necessitating the development of new antibiotics[22]. Given these considerations, synthesizing modified or developed sulfa drugs by introducing imides cyclic in the chemical structures of some sulfa drugs[23]. This study aims to synthesise and develop new sulfa drugs. The resulting developed sulfa drugs are expected to possess high biological activity since they are built from two active segments (drug and cyclic imide), and this may lead to promising results that may help solve the problem of increasing resistance to old antibiotics.

2. Experimental part

2.1. Materials and instrumentation

All Chemical compounds in these studies were of analytical quality and were directly used without further purification. Sulfamethoxazole, sulfadiazine, sulfamerazine, and sulfamethazine were acquired from Sigma Aldrich, while other pure chemical substances and solvents were procured from Merck, BDH Alfa, and Fulka. The melting points were measured using the hot stage digital Stuart scientific SMP30 melting point apparatus manufactured in the UK. In addition, the 1H-NMR (300 MHz) and 13C NMR (76 MHz) spectra for all scaffolds were obtained using the Bruker 300MHZ in Iran using an instrument in DMSO-d6. The internal standard used was TMS. Infrared spectra (FT-IR) were recorded using the Shimadzu FT-IR-8400 spectrophotometers; all derivatives have been run in a KBr disc.

*2.1 Synthesis of N-(Sulfamerazine) maleamic acid **1***

The titled amic acid **1** was synthesized by reacting sulfamerazine drug (0.0018mol,0.47g) with maleic anhydride (0.0018mol,0.176g) and dissolved in acetone, stirring the mixture for two hours, at room temperature [24]. After cooling, the precipitate was filtered, washed with acetone, dried, and recrystallized in acetone. All physical properties are detailed in Table (1).

*2.2 Synthesis of N-(Sulfamethoxazole) maleamic acid **2***

The titled amic acid **2** was synthesized by reacting of sulfamethoxazole drug (0.0018mol,0.45g) with maleic anhydride (0.0018mol,0.176g) following the same steps that are used in the preparation for the compound **1**. The dry precipitate was recrystallization from acetone. All physical properties are detailed in Table (1).

*2.3 Synthesis of N-(Sulfamethazine) maleamic acid **3***

The titled amic acid **3** was synthesized by reacting of sulfamethazine drug (0.0018mol,0.5g) with maleic anhydride (0.0018mol,0.176g) using the same method employed for the synthesis of compound **1**. The dry precipitate was recrystallization from acetone. All physical properties are detailed in Table (1).

*2.4 Synthesis of N-(Sulfamethoxazole) phthalamic acid **4***

The titled amic acid **4** was synthesized via a reaction of sulfamethoxazole drug (0.0018mol,0.45g) with phthalic anhydride (0.0018mol,0.28g) following the same procedure used for the preparation for the compound **1**. The dry precipitate was recrystallization from acetone. All physical properties are detailed in Table (1).

*2.5 Synthesis of N-(Sulfamethazine) succinamic acid **5***

The titled amic acid **5** was synthesized via a reaction of sulfamethoxazole drug (0.0018mol,0.5g) with succinic anhydride (0.0018mol,0.18g) following the same procedure used for the preparation for the compound **1**. The dry precipitate was recrystallization from acetone. All physical properties are detailed in Table (1).

*2.6 Synthesis of N-(Sulfadiazine) succinamic acid **6***

The titled amic acid **6** was synthesized via a reaction of sulfadiazine drug (0.0018mol,0.45g) with succinic anhydride (0.0018mol,0.18g) following the same steps that are used in preparation for the compound **1**. The dry precipitate was recrystallization from acetone. All physical properties are detailed in Table (1).

2.7 Synthesis of N-(Sulfamerazine) maleimide 7

The titled compound **7** was synthesized through the dehydration of amic acid **1** by the thermal method by using the fusion method[25]. Specifically, 0.001 mol (0.344 g) of amic acid **1** was heated in a sand bath until it completely melted. The temperature was increased to a level above the melting point and maintained for one hour. After cooling to room temperature, the resulting solid product was collected and recrystallized by ethanol. All physical properties are presented in Table (2).

*2.8 Synthesis of N-(Sulfamethoxazole) maleimide **8***

The titled compound **8** was synthesized via dehydration of amic acid **2** (0.001mol, 0.333g) by the fusion method following the same method that is used in the synthesis of compound **7**. The resulting solid was recrystallization by ethanol. All physical properties are presented in Table (2).

*2.9 Synthesis of N-(Sulfamethazine) maleimide **9***

The titled compound **9** was synthesized through the dehydration of amic acid **3** (0.001mol, 0.358g) by the fusion method following the procedure employed for the synthesis of compound **7**. The resulting solid was purified by recrystallization with ethanol. All physical properties are detailed in Table (2).

*2.10 Synthesis of N-(Sulfamethoxazole) phthalimide **10***

The titled compound **10** was synthesized via dehydration of amic acid **4** (0.001mol, 0.383g) by the fusion method [26]following the same method that is used in the synthesis of compound **7**. The resulting solid was recrystallization by ethanol. All physical properties are detailed in Table (2).

*2.11 Synthesis of N-(Sulfamethazine) succinimide **11***

The titled compound **11** was synthesized via dehydration of amic acid **5** (0.001mol, 0.360g) by the fusion method following the same method that is used in the synthesis of compound **7**. The resulting solid was recrystallization by ethanol. All physical properties are detailed in Table (2).

*2.12 Synthesis of N-(Sulfamethoxazole) phthalimide **12]***

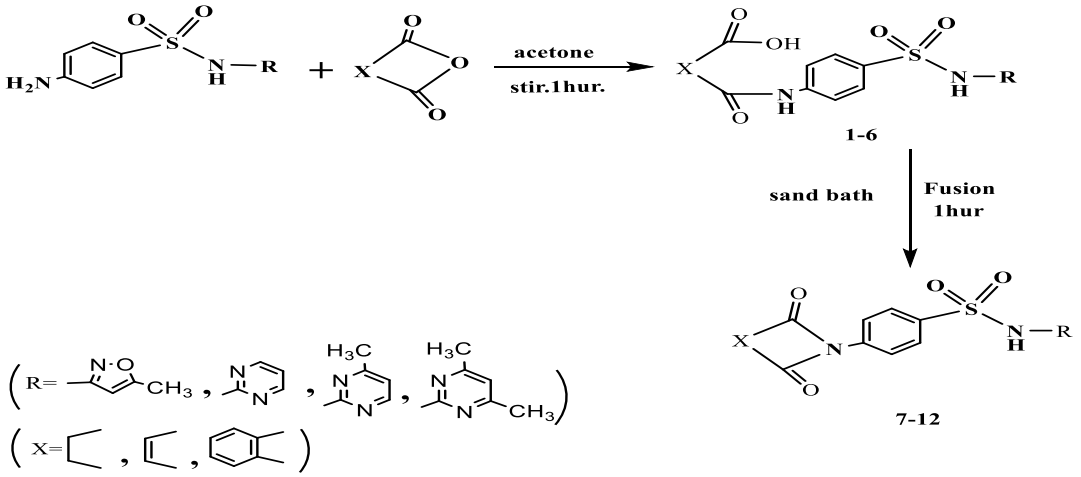
The titled compound **12** was synthesized via dehydration of amic acid **6** (0.001mol, 0.380g) by the fusion method following the same method that is used in the synthesis of compound **7**. The resulting solid was recrystallization from ethanol. All physical properties are detailed in Table (2).

2.13 Anti-bacterial and antifungal activity test

Antibacterial activity of newly synthesized (developed) N-Drug cyclic imides **7-12** was assessed using the disc diffusion method, employing a (5mm) filter paper disc saturated with the tested compounds solution. Dimethyl sulfoxide (DMSO) served as a negative control, while (sulfamerazine, sulfamethazine, sulfadiazine, and sulfamethoxazole) drugs (10µg/disc) were used as a positive control[27] . The plates were incubated at 37 °C for 24 hours. Compounds **7-12** were evaluated against three types of gram-positive bacteria, namely (*staphylococcus aureus, Streptococcus pneumonia, and Enterococci faecalis*) and one gram-negative bacteria (*pseudomonas aeruginosa*). Using the same techniques, the antifungal activity of the developed drugs **7-12** against (*Candida albicans*) fungi was evaluated, and inhibition zones were measured. The antibacterial and anti-fungal activity was listed in Tables (7).

3. Results and discussion

Infectious diseases remain a major contributor to mortality, largely driven by the rise of antibiotic-resistant microorganisms. Antibiotic resistance in bacteria and fungi is a significant factor contributing to the failure of chemotherapy in many infectious diseases. To address this issue, the increase in resistance to old antibiotics must be associated with the modification and development of new antibiotics. In this study, four sulfa drugs, including sulfamerazine, sulfamethazine, sulfadiazine, and sulfamethoxazole, were modified by introducing different cyclic imides in their structure, and this was performed through two steps as shown in scheme (1). In the first step, the mentioned sulfa drugs were introduced in reaction with different cyclic anhydrides, including (maleic, phthalic, and succinic) anhydride-producing N-Drug amic acid **1-6**. The reaction proceeds through a nucleophilic attack of the amino group present in the drug molecule on the carbonyl group in cyclic anhydride [28], leading to ring opening producing amic acids **1-6**. In the second step, amic acids **1-6** were dehydrated by the fusion process, and the reaction proceeded through an intramolecular nucleophilic attack between amide and carbonyl groups, leading to ring-closure producing N-Drug cyclic imides **7-12**. Physical properties of N-Drug amic acid **1-6** and the corresponding N-Drug cyclic imides **7-12** are shown in tables (1) and (2), respectively.



Scheme1: synthetic steps of target compounds

FTIR spectra of the prepared N-Drug amic acid **1-6** showed characteristic absorption bands at (3101-3481)$cm^{-1,}$ which are due to ν(O-H) carboxyl and ν(N-H) amide. Absorption bands due to ν (C=O) carboxyl and ν(C=O) amide appeared at (1689-1724) cm^{-1} and (1670-1704)cm^{-1} while absorption bands due to ν(C=N) and ν(C=C) appeared at (1600-1649)cm^{-1} and (1537-1595)cm^{-1} and finally absorption bands due to asym. ν (SO_2) and sym. N(SO_2) appeared at (1311-1367) cm^{-1} and (1128-1182) cm^{-1} respectively. FTIR spectra of the prepared N-Drug cyclic imides **7-12** showed the appearance of two clear absorption bands at (1770-1784) cm^{-1} and (1710-1720) $cm^{-1,}$ which are due to asym. ν (C=O) imide and sym. ν (C=O) imide and other absorption band at (1340-1392) cm^{-1} due to ν(C-N) imide. The presence of these clear absorption bands is an important proof of the success of imide formation. Absorption bands were observed in the ranges of (3244-3446) cm^{-1}, (1600-1649) cm^{-1}, and (1510-1596) cm^{-1}, corresponding to ν(N-H) of sulfonamide, ν(C=N), and ν(C=C), respectively, while additional bands were attributed to asymmetric vibrations. asym. ν (SO_2) and sym. ν (SO_2) appeared at (1317-1373) cm^{-1} and (1141-1174) cm^{-1}respectively. On the other hand, ^{1}H-NMR spectra of N-Drug amic acids **1,2,3,6** showed clear signals at (δ=2.07-2.52) ppm belonging to (CH_3) protons, the signal at (δ=6.08-6.58) ppm belong to vinylic protons and signal at (δ=6.0-7.97) ppm belong to aromatic protons. Other signals appeared at (δ=8.27-10.69) ppm, (δ=10.56-11.36) ppm, and (δ=12.16-13.15) ppm, which belong to (NH)proton, ($NHSO_2$) proton, and (OH) carboxyl proton respectively[29]. The ^{1}H-NMR spectrum of compound **6** shows a signal at (δ=2.70-2.85) ppm belonging to four protons (-CH_2-CH_2-). ^{13}C-NMR spectra of compounds **1,2,6** showed signals at (δ=12.52-23.82) ppm belonging to (CH_3) carbons, signal at (δ=95.82-143.87) ppm belong to vinylic and benzene and hetero ring carbons and signal at (δ= 156.98-164.35) ppm belong to (C=N) carbons. Signals belonging to (C=O) amide and (C=O) carboxyl carbons appeared at (δ=164.23-167.69) ppm and (δ=167.43-170.81) ppm, respectively. ^{13}C-NMR spectrum of compound **6** showed signal at (δ=31.0-36.25) ppm belong to (-CH_2-CH_2-) carbons. ^{1}H-NMR spectra of N-Drug cyclic imides **7,9** and**11** showed a signal at (δ=2.11-2.35) ppm belonging to (CH_3) protons, the signal at (δ=6.0-6.55) ppm belonging to vinylic protons, the signal at (6.0-7.9) ppm belong to aromatic protons and signal at (δ=8.13-10.64)ppm belong to (NH) protons. It is important to mention here that ^{1}H-NMR spectra of imides **7,9** and **11** showed the disappearance of signal that belongs to (OH) carboxyl proton, which is another proof of the success of imide formation. ^{1}H-NMR spectrum of compound **11** signal at (δ=2.69-2.85) ppm, which belongs to (-CH_2-CH_2-) protons present in the succinimide ring. On the other hand, ^{13}C-NMR spectra of compounds **7,9,11** showed a signal at (δ=23.30-26.94) ppm belong to (CH_3) carbons, signal at (δ=112.28-144.34) ppm belong to vinylic and aromatic carbons, signal at (δ=153.39-157.09) ppm belong to (C=N) carbons and signal at (δ=167.46-168.39) ppm belong to (C=O) imide carbons[30]. The 13C-NMR spectrum of compound 11 revealed a signal in the range of (δ=31.21-36.24) ppm, which is attributed to the (-CH2-CH2-) carbons.

All details of FTIR spectra data of compounds **1-6** and compounds **7-12** are listed in tables (3) and (4), while all details of ^{1}H-NMR and ^{13}C-NMR spectral data for some of the prepared compounds are listed in tables (5) and (6) respectively. Some of these compounds [S2, S6, S7, and S9) are shown in Fig (8-15).

Table 1: Physical properties of Amic Acids **1-6**

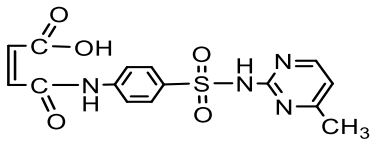
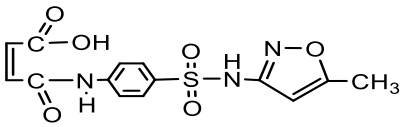
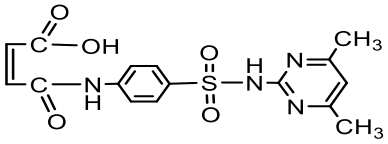
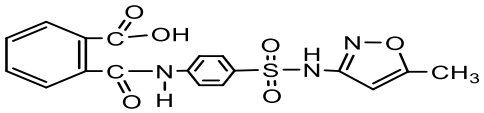
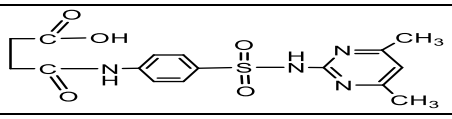
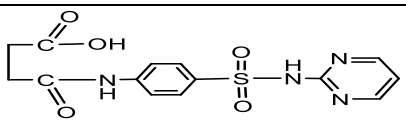
Comp. No	Compound structure	Melting Points ^{0}C	Color	Yield %	Recrystallization solvent
1		198-199	Yellow	91	Acetone
2		196-198	Light yellow	85	Acetone
3		214-216	Deep Yellow	77	Acetone
4		132-133	Deep brown	88	Acetone
5		187-189	Yellow	75	Acetone
6		191-193	Yellow	92	Acetone

Table 2: Physical properties of Imides **7-12**

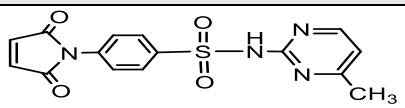
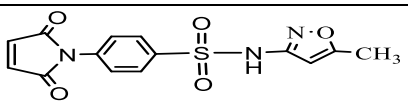
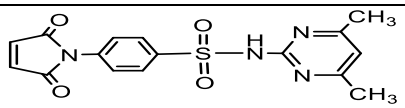
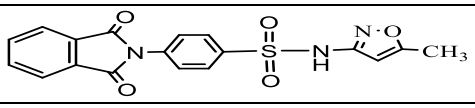
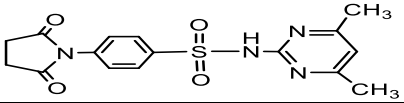
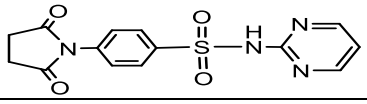
Comp. No	Compound structure	Melting Points ^{0}C	Color	Yield %	Recrystallization solvent
7		210-212	Deep brown	90	Ethanol
8		289-291	Deep brown	86	Ethanol
9		241-243	Black	72	Ethanol
10		232-233	Deep brown	92	Ethanol
11		200-203	Yellow	84	Ethanol
12		206-208	Off white	94	Ethanol

Table 3: FTIR spectral data (cm^{-1}) of Amic Acids **1-6**

Comp. No.	ν (O-H) ν (N-H)	ν (C-H) Aromatic	ν (C-H) Aliphatic	ν (C=O) Carboxyl	ν(C=O) Amide	ν(C=N)	ν(C=C)	asym. ν(SO_2)	sym. ν(SO_2)
1	3481 3379 3338	3049	2927 2856	1724	1680	1629	1593	1340 1321	1161
2	3286 3199 3101	3080	2995 2894 2844	1704	1704 (overlap)	1629 1614	1579	1344 1321	1164
3	3436 3261	3053	2925 2854	1689	1689 (overlap)	1629 1600	1537	1315	1128
4	3244 3174	3099	2939 2887	1718	1670	1649	1585	1361 1325	1182
5	3465 3386 3301 3232	3074 3001	2933 2837	1693	1693 (overlap)	1623	1595	1367 1311	1159
6	3442 3369 3240	3066	2923 2817	1710	1693	1639	1595	1332	1151

Table 4: FTIR spectral data (cm^{-1}) of Imides **7-12**

Comp. No.	ν (N-H)	ν (C-H) Aromatic	ν (C-H) Aliphatic	ν (C=O) Imide	ν(C=N)	ν(C=C)	ν(C-N) Imide	asym. ν(SO_2)	sym. ν(SO_2)
7	3421 3382	3020	2972 2925 2869	1776 1714	1629	1593	1382	1350	1141
8	3417 3245	3076	2970 2906 2821	1774 1718	1629	1596	1392	1371 1344	1166
9	3446 3382	3076	2923 2802	1780 1714	1627	1595	1380	1325	1159
10	3380	3056	2937 2880	1784 1714	1600	1510	1373	1373 (overlap)	1174
11	3375 3244	3099 3002	2979 2941 2850	1776 1710	1618	1595	1392	1317	1163
12	3355 3282	3078 3035	2939 2871 2812	1770 1720	1649 1633	1581	1340	1340 (overlap)	1164

Table 5: ^{1}H-NMR spectral data(ppm) of compounds **1,2,3,6,7,9, and 11**

Comp. No	^{1}H-NMR spectral data (δ) ppm
1	(δ=2.07) ppm (3H, CH_3), (δ=6.22-6.56) ppm (2H, vinylic protons), (δ=6.84-7.95) ppm (6H, aromatic protons), (δ=8.27-8.3) ppm (1H, NH), (δ=10.56) ppm (1H, NH-SO_2), (δ=12.16) ppm(1H, OH).
2	(δ=2.25-2.27) ppm (3H, CH_3), (δ=6.08-6.58) ppm (2H, -vinylic protons), (δ=7.45-7.79) ppm (5H, aromatic and hetero ring protons), (δ=10.69) ppm (1H, NH), (δ=11.36) ppm (1H, NH-SO2), (δ=12.85) ppm (1H, OH).
3	(δ=2.27-2.52) ppm (6H, 2CH_3), (δ=6.08-6.58) ppm (2H, -vinylic protons), (δ=7.44-7.96) ppm (5H, aromatic protons), (δ=10.69) ppm (2H, NH), (δ=13.15) ppm(1H, OH).
6	(δ=2.70-2.85) ppm (4H, CH_2-CH_2-), (δ=6.0-7.79) ppm (7 H, aromatic protons), (δ=8.45-8.50) ppm (1H, NH), (δ=10.75) ppm (1H, NH-SO_2), (δ=12.25) ppm (1 H, OH).
7	(δ=2. 24)ppm (3H, CH_3), (δ a=6.0-6.48) ppm (2H, vinylic protons), (δ=6.85-7.93) ppm (6H, aromatic protons), (δ=8.31) ppm (1H, NH)
9	(δ=2.11-2.22) ppm (6H, 2CH_3), (δ=6.19-6.55) ppm (2H, vinylic protons), (δ=6.71-7.95) ppm (5H, aromatic protons), (δ=10.64) ppm (1H, NH).
11	(δ =2.24-2.35) ppm (6H,2CH_3), (δ=2.69-2.85) ppm (4H, CH_2-CH_2-), (δ=6.0-7.97) ppm (5H,aromatic protons), (δ=8.13) ppm (1H, NH)

Table 6: ^{13}C-NMR spectral data(ppm) of compounds **1,2,6,7,9, and 11**

Comp. No	^{13}C-NMR spectral data (δ, ppm)
1	(δ=23.71-23.82) ppm (CH_3), (δ=112.45-142.95) ppm (vinylic and aromatic protons), (δ=156.98-157.99) ppm (C=N carbons), (δ=164.23) ppm (C=O amide), (δ =167.43-168.71)ppm (C=O) carboxylic
2	(δ=12.52) ppm (CH_3), (δ=95.82-143.47) ppm (vinylic and aromatic protons), (δ=157.99) ppm (C-O in oxazole ring), (δ=164.35) ppm (C=N), (δ=167.37) ppm (C=O) amide, (δ=170.81) ppm (C=O carboxyl
6	(δ=31.0-36.25) ppm (-CH_2-CH_2-) carbons, (δ=112.60-143.87) ppm (aromatic carbons), (δ=157.4-158.86) ppm (C=N), (δ=167.69) ppm (C=O amide) , (δ=168.49) ppm (C=O) carboxyl
7	(δ=26.94) ppm (CH_3), (δ=112.90-144.34) ppm (vinylic and aromatic carbons), (δ=153.77) ppm (C=N), (δ=167.77-168.39) ppm (C=O imide)
9	(δ=23.31-23.56) ppm (two CH_3), (δ=112.28-142.75) ppm (vinylic and aromatic carbons), (δ=156-61-157.09) ppm (C=N), (δ=167.46-167.77) ppm (C=O imide)
11	(δ=23.30-23.56) ppm (two CH_3), (δ=31.21-36.24) ppm(-CH_2-CH_2-) carbons, (δ a=153.39-157.09) ppm (C=N), ((δ=167.77)ppm (C=O imide)

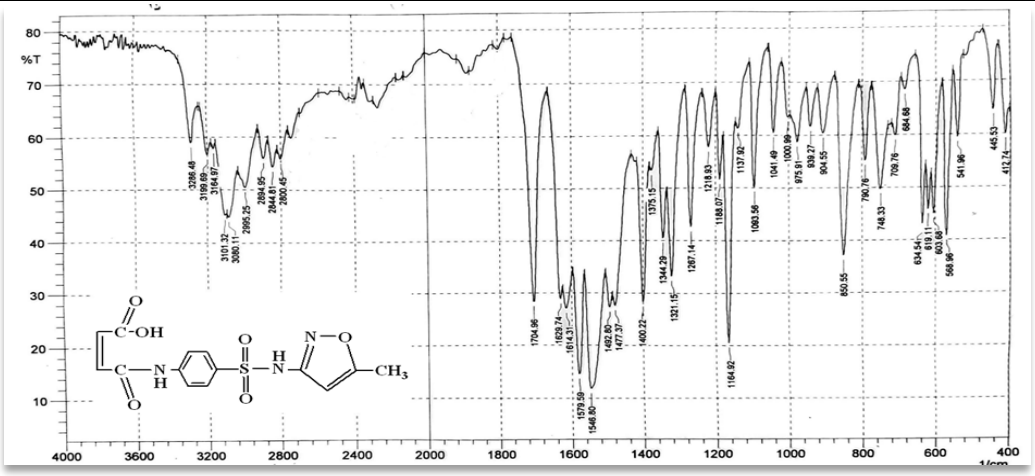


Figure 4: FT-IR spectrum of compound **2**

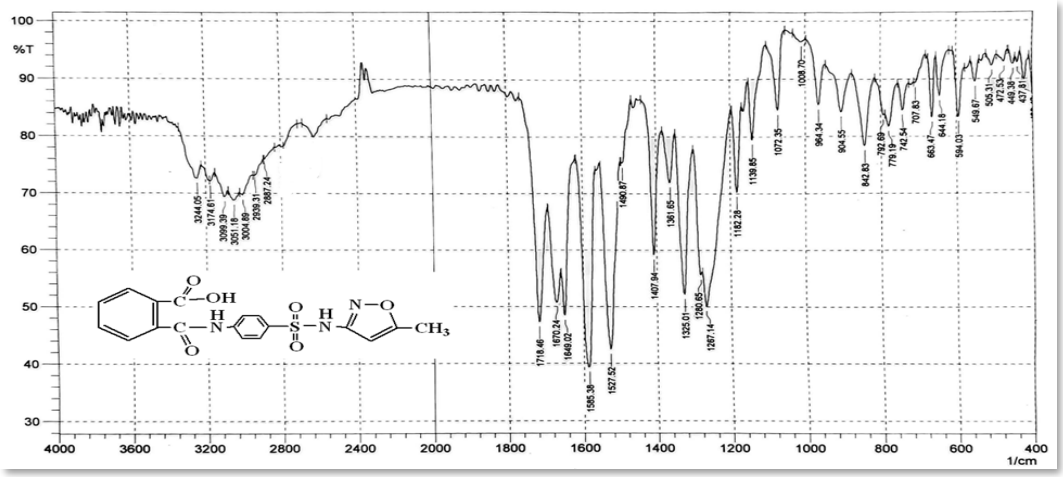


Figure 5: FT-IR spectrum of compound **4**

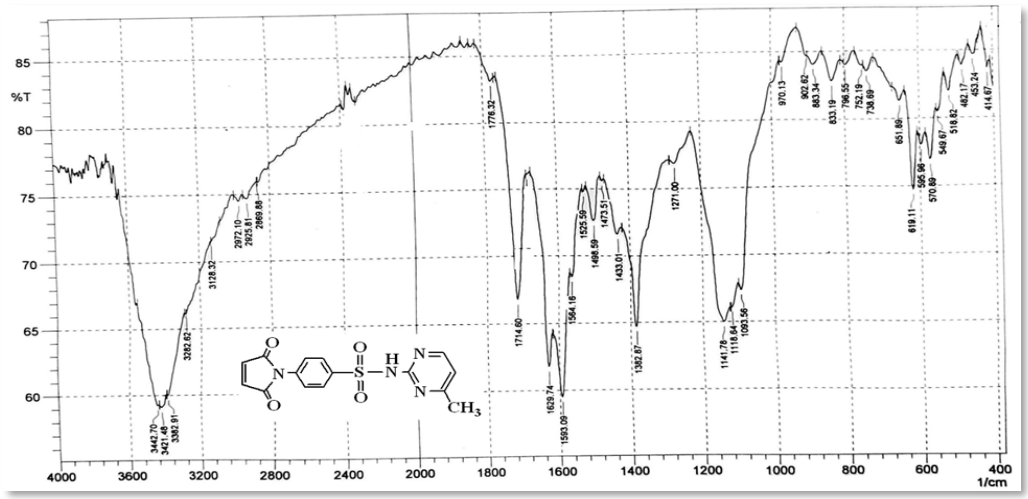


Figure 6: FT-IR spectrum of compound **7**

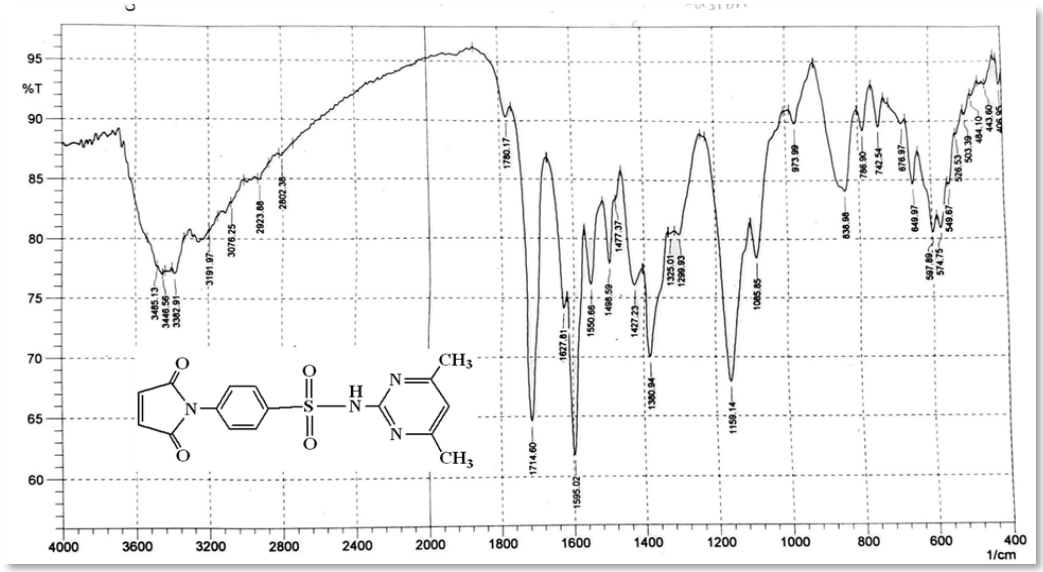


Figure7: FT-IR spectrum of compound **9**

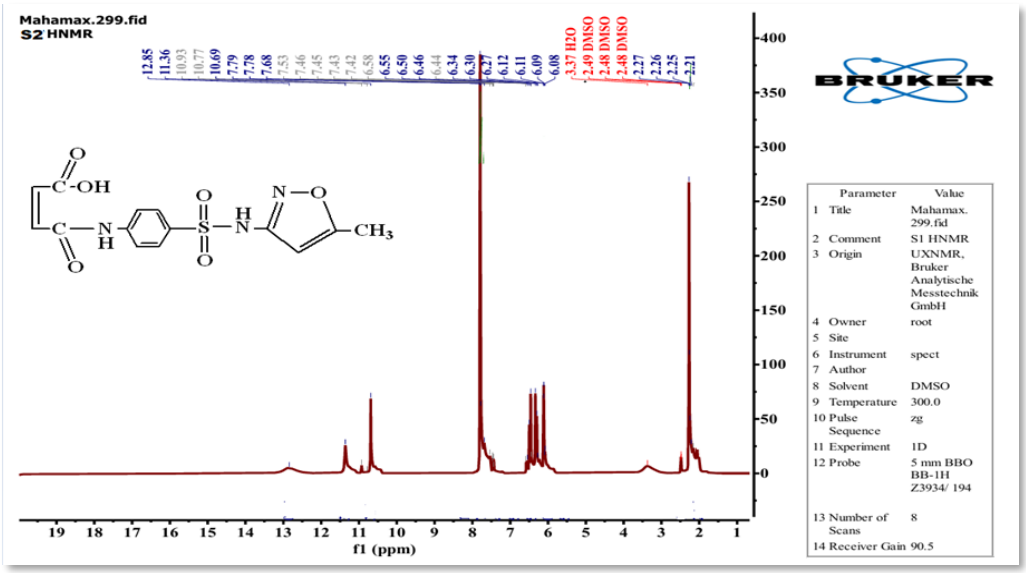


Figure 8: [1]H-NMR spectrum of compound **2**

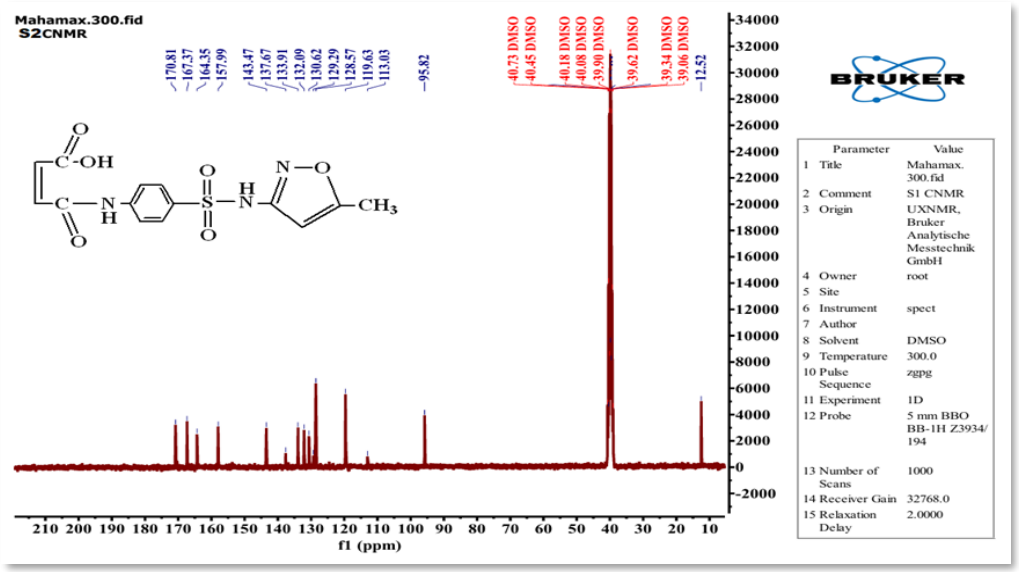


Figure 9: [13]C-NMR spectrum of compound **2**

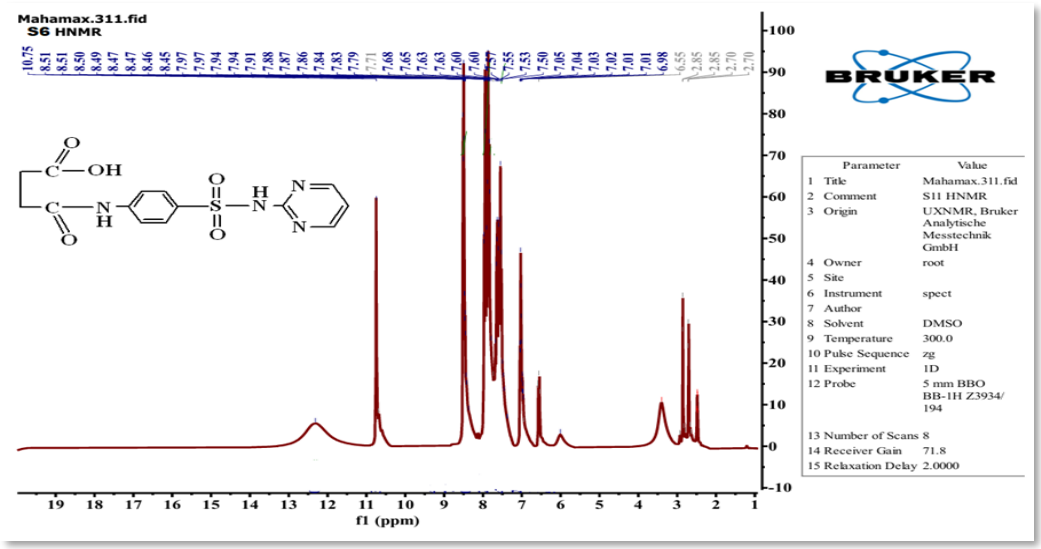


Figure 10:[1]H-NMR spectrum of compound **6**

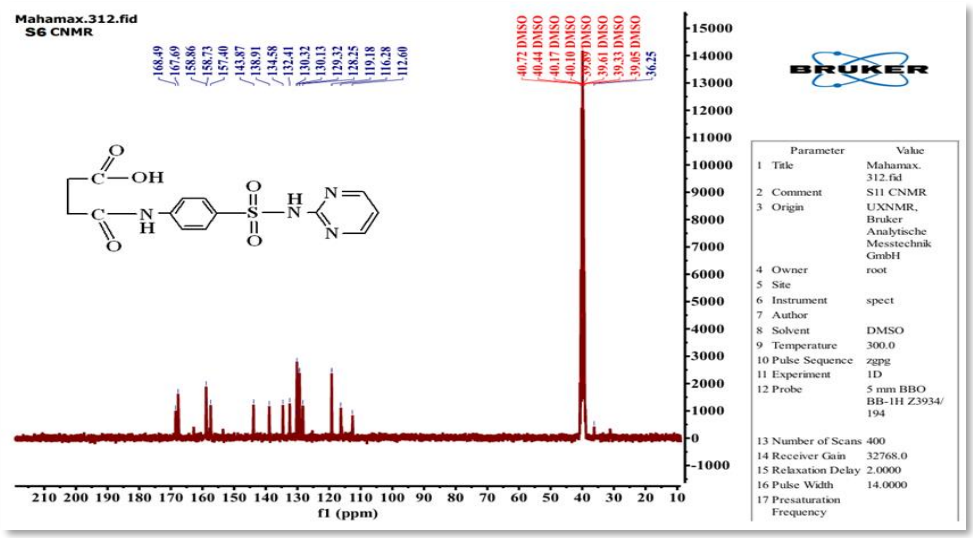


Figure 11: ^{13}C-NMR spectrum of compound **6**

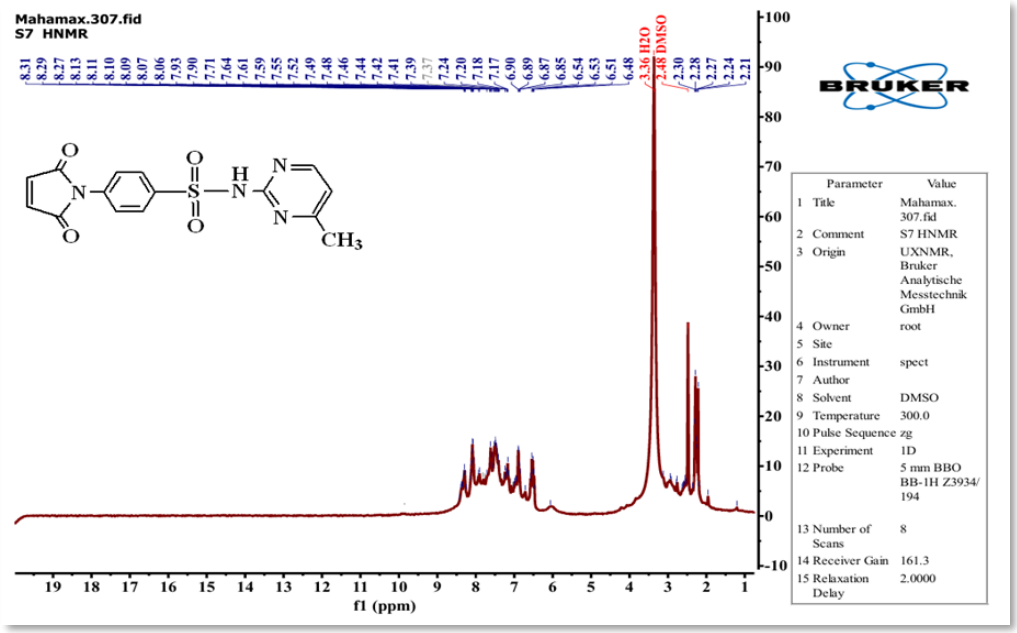


Figure 12: ^{1}H-NMR spectrum of compound **7**

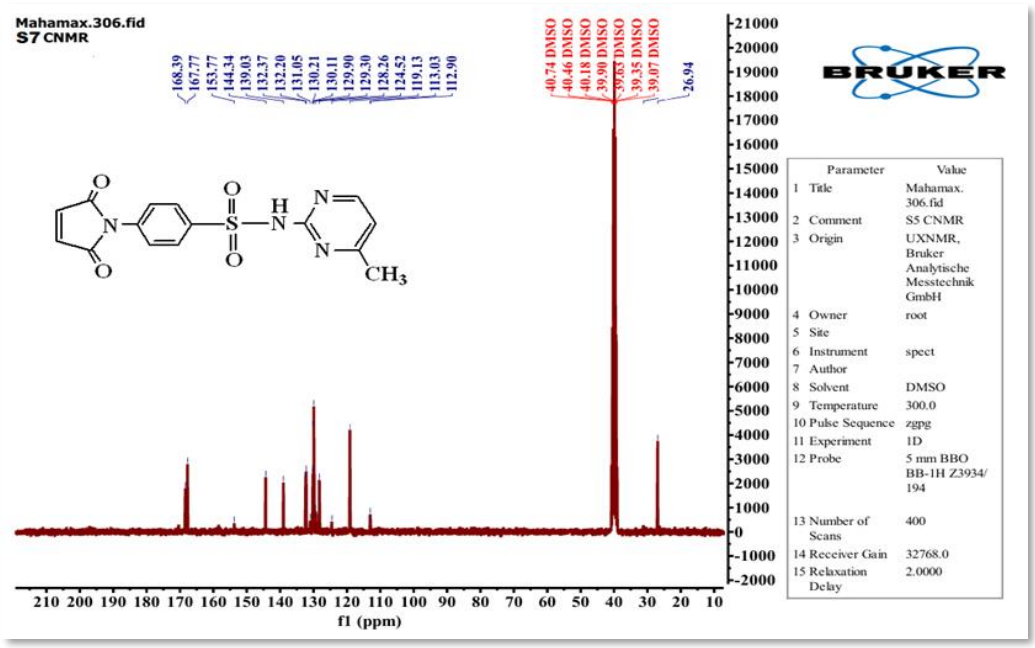


Figure 13: ^{13}C-NMR spectrum of compound **7**

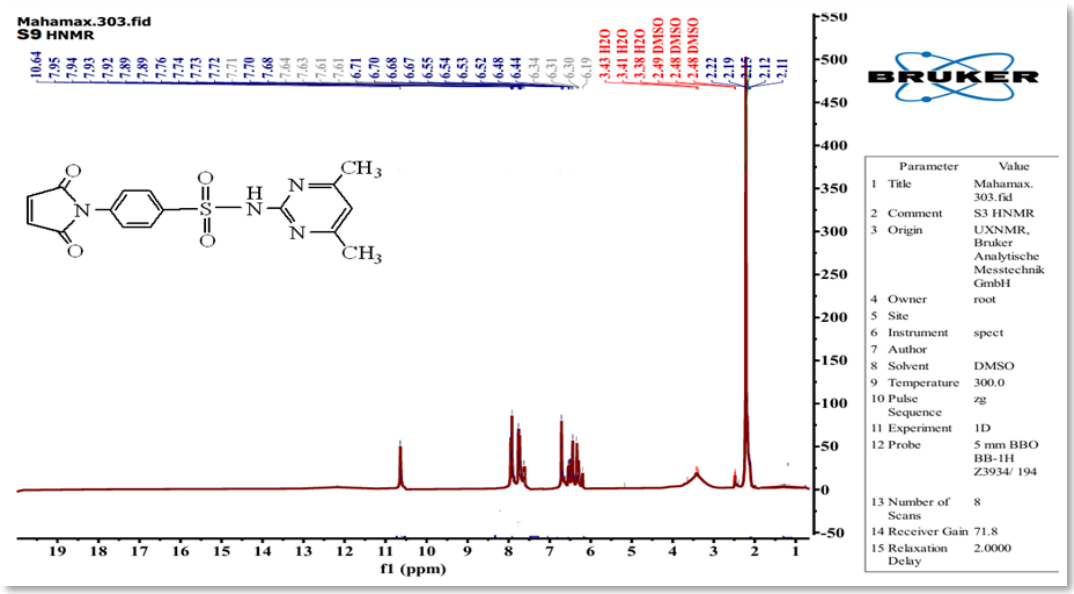


Figure 14: ^{1}H-NMR spectrum of compound **9**

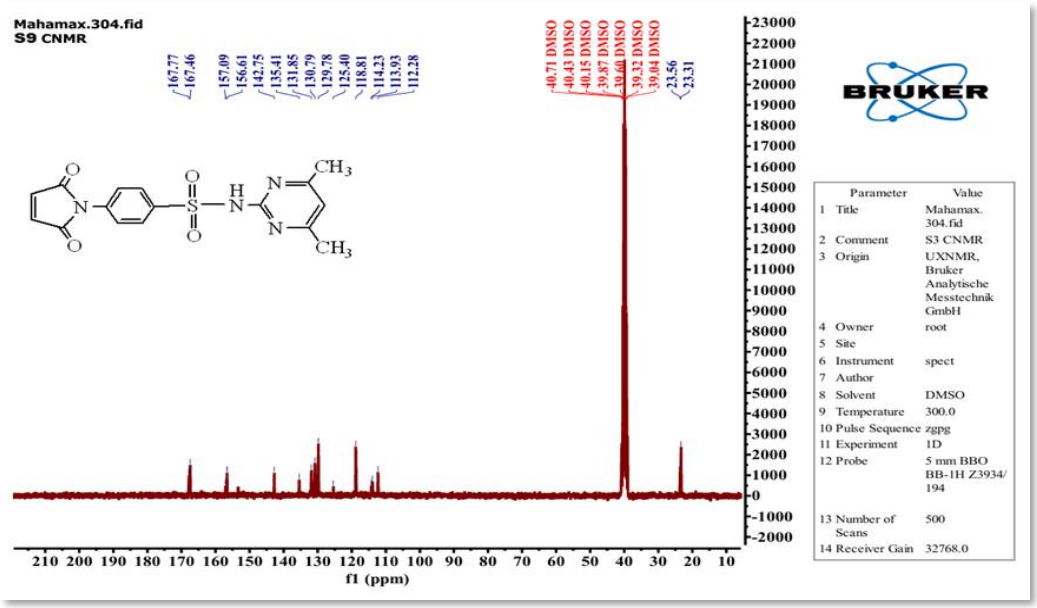
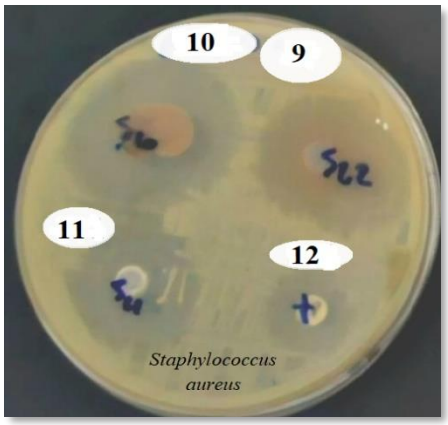


Figure 15: ^{13}C-NMR spectrum of compound **9**

4. Biological activity

Antimicrobial activity of the developed N-drug cyclic imides 7-12 was assessed against three types of gram-positive bacteria, namely (*staphylococcus aureus, Streptococcus pneumonia,* and *Enterococci faecalis*) and one gram-negative bacteria (*pseudomonas aeruginosa*). This evaluation was conducted using the disc diffusion method and diffusion method and (5mm) filter paper disc saturated with tested compounds solution. In these tests, DMSO is the negative control, while the positive control consists of the drugs (sulfamerazine, sulfamethazine, sulfadiazine, and sulfamethoxazole). Subsequently, the plates were incubated at a temperature of (37 °C) for (24) hrs.[31]. The inhibition zones of the developed drugs **7-12** against different types of bacteria were measured, and the results are presented in Table 7 and illustrated in Figures 1 and 2. Using the same techniques, the antifungal activity of the developed drugs **7-12** against (*Candida albicans*) fungi was evaluated, and inhibition zones were measured, the results are also listed in Tables (7) and depicted in Figure 3. Overall, the results of antibacterial activity indicated that the developed drugs **7-12** exhibited significantly higher antibacterial activity compared to the original drugs, with inhibition zone values for the developed drugs **7-12** being two times or three times higher than those of the starting drugs. Also, the inhibition zones of antifungal activity of the developed drugs are higher than those of the starting drugs. The listed in Table (7) showed that compound **10** possesses the highest antibacterial activity against (*staphylococcus aureus)*, compound **11** showed the highest antibacterial activity against (*Streptococcus pneumonia*), compound **9** showed the highest antibacterial activity against (*Enterococci faecalis*), and compound **7** showed the highest antibacterial activity against (*pseudomonas aeruginosa*).On the other hand, compound **11** showed the highest antibacterial activity against (*Candida albicans*) fungi. It is important to mention here that the type of imide ring present in developed drugs plays a vital role in the biological activity of drugs containing the same drug compound. Thus, compounds **8** and **10** have the same drug component (sulfamethoxazole). This drug component is linked to the maleimide ring in compound 8 and linked to the phthalimide ring in compound **10**. A comparison of the results of both the antibacterial and antifungal activities of these two compounds **8** and **10** indicated that the presence of a phthalimide ring in compound **10** exhibits this drug's higher antibacterial activity than compound [8] against all types of bacteria and fungi. Also, compounds **9** and **11** contain the same drug compound (sulfamethazine), which is

linked to the maleimide ring in compound **9** and linked to the succinimide ring in compound **11**. A comparison the result of the antibacterial and antifungal activities of these two compounds **9** and **11** showed that the presence of a succinimide ring in compound **11** exhibits this drug's higher antibacterial activity than compound **9** against (*Streptococcus pneumonia*) and (*pseudomonas aeruginosa*) beside higher antifungal activity against (*Candida albicans*) fungi while the presence of maleimide ring in compound **9** exhibit this drug higher antibacterial activity than compound **11** against (*Enterococci faecalis*).



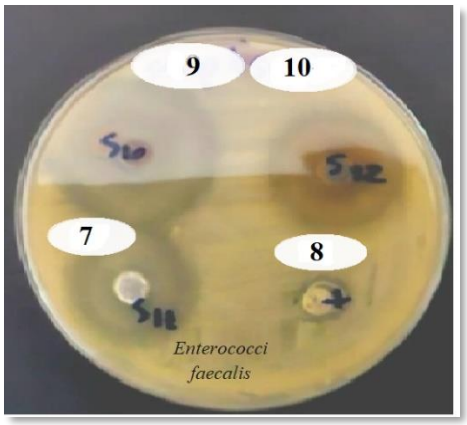


Figure.1: Inhibition zone of compounds **[9-12]** **Figure.2:**Inhibition zone of compounds **[7-10]** **(Gram-positive bacterial)**

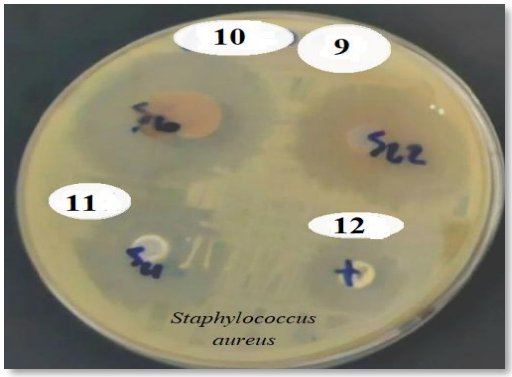


Figure3: Inhibition zone of compounds **8-11** (fungal)

Table7: Inhibition zones of antimicrobial and anti-fungal activity of compounds **7-12** in mm

Comp. No	Gram-positive bacteria			Gram-negative bacteria	Fungi
	Staphylococcus aureus	*Streptococcus pneumonia*	*Enterococci faecalis*	*Pseudomonas aeruginosa*	*Candida albicans*
7	33	26	27	37	20
8	30	25	25	16	20
9	35	28	44	20	17
10	40	30	30	18	38
11	35	40	30	29	40
12	27	38	30	17	16
S1	15	18	10	14	19
S2	14	10	12	16	13
S3	15	11	11	15	14
S4	10	11	12	13	12
DMSO	0	0	0	0	0
S1=sulfamethoxazole, S2= sulfadiazine, S3= sulfamerazine, S4= sulfamethazine					

4. Conclusions

In conclusion, the results of the antimicrobial activity of the developed drugs are highly promising. The incorporation of cyclic imides into drug molecules significantly enhances their antimicrobial activity. These findings align with our expectations and this study will contribute to addressing the issue of resistance to traditional antibiotics.

Acknowledgements

Special thanks to Senior Chemist Minera Khalid Ahmed Al-Mashhdani and Ruqia Fawzi Alwan for doing FT-IR spectra at the University of Baghdad

References

[1] M. Paumelle, F. Donnadieu, M. Joly, P. Besse-Hoggan, and J. Artigas, "Effects of sulfonamide antibiotics on aquatic microbial community composition and functions," *Environment International,* vol. 146, p. 106198, 2021.

[2] O. C. Nunes, C. M. Manaia, B. A. Kolvenbach, and P. F.-X. Corvini, "Living with sulfonamides: a diverse range of mechanisms observed in bacteria," *Applied microbiology and biotechnology,* vol. 104, no. 24, pp. 10389-10408, 2020.

[3] N. Mallikarjuna and J. Keshavayya, "Synthesis, spectroscopic characterization and pharmacological studies on novel sulfamethaxazole based azo dyes," *Journal of King Saud University-Science,* vol. 32, no. 1, pp. 251-259, 2020.

[4] D. I. Ugwu *et al.*, "Anti-hypertensive properties of 2-[N-(4-methylbenzenesulfonyl)-1-phenylformamido]-n-(4-nitrophenyl)-3-phenylpropenamide: experimental and theoretical studies," *Chemical Physics Impact,* vol. 6, p. 100158, 2023.

[5] M. Chalkha *et al.*, "Crystallographic study, biological assessment and POM/Docking studies of pyrazoles-sulfonamide hybrids (PSH): Identification of a combined Antibacterial/Antiviral pharmacophore sites leading to in-silico screening the anti-Covid-19 activity," *Journal of Molecular Structure,* vol. 1267, p. 133605, 2022.

[6] C. Yamali *et al.*, "Synthesis, biological evaluation and in silico modelling studies of 1, 3, 5-trisubstituted pyrazoles carrying benzenesulfonamide as potential anticancer agents and selective cancer-associated hCA IX isoenzyme inhibitors," *Bioorganic chemistry,* vol. 92, p. 103222, 2019.

[7] M. Ferraroni, A. Angeli, M. Pinteala, and C. T. Supuran, "Sulfonamide diuretic azosemide as an efficient carbonic anhydrase inhibitor," *Journal of Molecular Structure,* vol. 1268, p. 133672, 2022.

[8] E. Masini, F. Carta, A. Scozzafava, and C. T. Supuran, "Antiglaucoma carbonic anhydrase inhibitors: a patent review," *Expert opinion on therapeutic patents,* vol. 23, no. 6, pp. 705-716, 2013.

[9] A. Ahmed *et al.*, "Acyl pyrazole sulfonamides as new antidiabetic agents: synthesis, glucosidase inhibition studies, and molecular docking analysis," *Frontiers in Chemistry,* vol. 12, p. 1380523, 2024.

[10] F. Carta, A. Scozzafava, and C. T. Supuran, "Sulfonamides: a patent review (2008–2012)," *Expert opinion on therapeutic patents,* vol. 22, no. 7, pp. 747-758, 2012.

[11] N. M. Abdelazeem, W. M. Aboulthana, A. S. Hassan, A. A. Almehizia, A. M. Naglah, and H. M. Alkahtani, "Synthesis, in silico ADMET prediction analysis, and pharmacological evaluation of sulfonamide derivatives tethered with pyrazole or pyridine as anti-diabetic and anti-Alzheimer's agents," *Saudi Pharmaceutical Journal,* vol. 32, no. 5, p. 102025, 2024.

[12] I. T. Babalola and G. Suleiman, "Design, synthesis, and molecular docking studies of N-substituted sulfonamides as potential anticancer therapeutics," *Journal of Taibah University Medical Sciences,* vol. 19, no. 1, pp. 175-183, 2024.

[13] S. Kumar, P. Sekar, and S. K. Raju, "Synthetic methodologies and pharmacological applications of sulphonamide containing Schiff bases and their metal complexes: A comprehensive review."

[14] S. Mondal and S. Malakar, "Synthesis of sulfonamide and their synthetic and therapeutic applications: Recent advances," *Tetrahedron,* vol. 76, no. 48, p. 131662, 2020.

[15] H. Ebrahimi, J. Hadi, and H. Al-Ansari, "A new series of Schiff bases derived from sulfa drugs and indole-3-carboxaldehyde: Synthesis, characterization, spectral and DFT computational studies," *Journal of molecular structure,* vol. 1039, pp. 37-45, 2013.

[16] H. A. G. Al-Halfi, W. A. Al-Masoudi, and A. A. Alrekabi, "Synthesis and physiological study of Schiff base derived from sulfanilamide and vaniline," *Basrah Journal of Veterinary Research,* vol. 19, no. 2, pp. 281-290, 2020.

[17] A. Tačić, V. Nikolić, L. Nikolić, and I. Savić, "Antimicrobial sulfonamide drugs," *Advanced technologies,* vol. 6, no. 1, pp. 58-71, 2017.

[18] E. Jafari, A. Jahanian-Najafabadi, S. Poorirani, F. Hassanzadeh, and S. Sadeghian-Rizi, "Synthesis and evaluation of antimicrobial activity of cyclic imides derived from phthalic and succinic anhydrides," *Research in pharmaceutical sciences,* vol. 12, no. 6, pp. 526-534, 2017.

[19] N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu, and S. B. Jonnalagadda, "A review on recent advances in nitrogen-containing molecules and their biological applications," *Molecules,* vol. 25, no. 8, p. 1909, 2020.

[20] E. Tacconelli *et al.*, "Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis," *The Lancet infectious diseases,* vol. 18, no. 3, pp. 318-327, 2018.

[21] M. S. Butler, M. A. Blaskovich, and M. A. Cooper, "Antibiotics in the clinical pipeline at the end of 2015," *The Journal of antibiotics,* vol. 70, no. 1, pp. 3-24, 2017.

[22] C. Bougheloum, S. Alioua, S. Meliani, R. Belghiche, A. Djahoudi, and A. Messalhi, "Environmentally benign synthesis, molecular docking study, and ADME prediction of some novel aryl sulfones containing cyclic imide moiety as antimicrobial agents," *Phosphorus, Sulfur, and Silicon and the Related Elements,* vol. 198, no. 11, pp. 955-966, 2023.

[23] D. Nasser Binjawhar *et al.*, "Powerful Approach for New Drugs as Antibacterial Agents via Molecular Docking and In Vitro Studies of Some New Cyclic Imides and Quinazoline-2, 5-diones," *ACS omega,* vol. 9, no. 16, pp. 18566-18575, 2024.

[24] M. I. Kalaf and O. S. Hashim, "Synthesis & characterization of some 1, 3, 4-oxadiazolederivatives & new cyclic imides from creatinine," *Iraqi Journal of Science,* vol. 56, no. 2A, pp. 921-941, 2015.

[25] T. M. Yassen and A. M. AL-Azzawi, "Synthesis and characterization of new bis-schiff bases linked to various imide cycles," *Iraqi Journal of Science,* pp. 1062-1070, 2023.

[26] M. S. Hasan and A. M. AL-Azzawi, "Synthesis, Modification and Characterization of New Phenolic Resins linked to Tetrabromophthalimide," *Iraqi Journal of Science,* pp. 2681-2695, 2023.

[27] R. A. Ali, E. O. Al-Tamimi, and S. A. Wadood, "Synthesis, Identification, and Study of the Antimicrobial and Antioxidant Activities of Some New 2, 5-Disubstituted-1, 3, 4-Oxadiazole Derivatives," *Iraqi Journal of Science,* pp. 4837-4844, 2024.

[28] S. V. Patil, K. A. Mahale, K. S. Gosavi, G. B. Deshmukh, and N. S. Patil, "Solvent-mediated one-pot synthesis of cyclic N-substituted imides," *Organic Preparations and Procedures International,* vol. 45, no. 4, pp. 314-320, 2013.

[29] A. Shamaya, O. Al-Jeilawi, and N. A. Khudhair, "Novel Synthesis of Some N-Hydroxy Phthalimide Derivatives with Investigation of Its Corrosion Inhibition for Carbon Steel in HCl Solution, Chem. Methodol. 5(2021) 331-340," ed, 2021.

[30] S. E. M. Reda and S. M. Abed, "Imidazole-Cyclic Derivatives (Preparation, Spectral Studies, Microbial Studies)," *European Chemical Bulletin,* vol. 11, no. 11, pp. 27-35, 2022.

[31] [31] M. Krátký *et al.*, "Sulfadiazine salicylaldehyde-based Schiff bases: Synthesis, antimicrobial activity and cytotoxicity," *Molecules,* vol. 22, no. 9, p. 1573, 2017.