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Design and Synthesis of New Cyclic Imides Derived from 4-[N-(2-Amino Thiazole-4-Yl]) Sulfamethexazole with Evaluation of their Antimicrobial Activity

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Abstract

This study introduces a series of novel cyclic imides, which incorporate two biologically significant components - the thiazole ring and sulfonamide. These target imides were developed using a method of multistep synthesis. The chosen starting material was the compound sulfamethoxazole, which is known to contain a biologically active sulfonamide. In the first step, sulfamethoxazole was reacted with chloroacetyl chloride, yielding compound [1] (4-N-(2-chloro acetamido) sulfamethoxazole) followed by reaction of compound [1] with thiourea provided a cure [2]. (4-(sulfamethoxazole-].4-y1)-2-aminothiazole) was obtained. Compound [2] played a major role and was successfully included in the third stage of the reaction with various cyclic anhydrides including succinic, phthalic, maleic, glutaric anhydride etc. This reaction led to the synthesis of the corresponding aromatic acids [3-6]. The fourth step of amic acid dehydration using the fusion method [3-6] successfully achieved the goal, resulting in the synthesis of new imides [7-10]. Additionally, the study involved the synthesis of a new cyclic imide [11] (sulfamethoxazole thiazole tetrachloro phthalimide) through a one-step process. This process involved the fusion of compound [2] and tetrachlorophthalic anhydride. Finally, the newly synthesized imides were screened for their antimicrobial activities, and the obtained results were promising.

Keywords: Sulfamethoxazole, Amic acids, Cyclic imides, Dehydration, Biologically active moieties.

تصميم وتحضير ايمايدات حلقية جديدة مشتقة من4 -[N-(2- امينوثايازول -4- يل) سلفاميثاوكسازول مع تقدير فعاليتها المضادة للمايكروبات

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الخلاصة

تقدم هذه الدراسة سلسلة من الأيمايدات الحلقية الجديدة والتي تتضمن مكونين مهمين بيولوجيًا (حلقة الثايازول والسلفون امايد)., تم تطوير هذه الإيمايدات المستهدفة باستخدام طريقة تخليق متعدد الخطوات. وكانت المادة الأولية المختارة هي مركب السلفاميثاوكسازول، المعروف باحتوائه على السلفوناميد الفعال بيولوجيًا .

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في الخطوة الأولى، تم تفاعل سلفاميثاوكسازول مع كلورو كلوريد الأستيل مما نتج عنه المركب [1] (4-ن-(2-كلورو أسيتاميدو) سلفاميثاوكسازول) ثم تفاعل المركب [1] مع الثايويوريا مما كون المركب [2].وهو وهو 4 -(سلفاميثاوكسازول -4- يل) -2- أمينوثايازول. لعب المركب [2] دورًا رئيسيًا حيث تم إدراجه بنجاح في المرحلة الثالثة من التفاعل مع الأنهيدريدات الحلقية المختلفة بما في ذلك أنهيدريد السكسنيك ، الفثاليك ، الماليك وكلوتاريك وغيرها. أدى هذا التفاعل إلى تخليق الأحماض العطرية المقابلة [3-6]. وقد نجحت الخطوة الرابعة في تجفيف حمض الأميك باستخدام طريقة الصهر [3-6] لتحقيق الهدف، مما أدى إلى تخليق أحماض الأياميدات الجديدة [7-10]. بالإضافة إلى ذلك، تضمنت الدراسة تخليق إيمايد حلقي جديد [11] (سلفاميثاوكسازول ثيازول رباعي كلورو فثال ايمايد) من خلال خطوة واحدة. حيث تضمنت هذه العملية مزج المركب [2] مع رباعي كلورو أنهيدريد الفثاليك .و أخيرًا، تم فحص مركبات الإياميدات المصنعة حديثًا لمعرفة نشاطها المضاد للميكروبات، وكانت النتائج التي تم الحصول عليها واعدة.

1-Introduction:

Molecules containing the thiazole ring system are highly significant aza-heterocycles present in pharmaceuticals and natural products. Due to their physicochemical properties and wide range of biological properties they are recognized as important components in medicine. These applications include analgesic, anti-inflammatory, anti-tuberculous, carcinogenic, fungal and antibacterial properties [1-5]. Sulfonamides also represent an interesting scaffold that carry awide range of biological activities which include anti-inflammatory, antimicrobial. anthelmintic and anticancer activities [6-9]. Furthermore, sulfonamides remain the most important core unit in building a wide variety of drugs such as chlorpropamide, sulfamethoxy pyridazine sulfafurazole and sulfamethoxazole [6]. On the other hand, much attention has been paid to cyclic imides due to their various activities and their using as important segments in the synthesis of bioactive compounds such as hypoglycemic, antitumor, antimicrobial synthesis and anti-inflammatory [10-12]. Moreover, structures of many drugs, resins and polymers are based on cyclic imides [13-15]. According to the above findings we thought it is so worthy to design and synthesize new molecules via combination of these three scaffolds (cyclic imide, sulfonamide, thiazole) in a single molecular frame work. Thus, the aim of the present work was directed towards design and synthesis of new cyclic imides carrying both thiazole ring and sulfamethoxazole drug component together in the same molecule followed by investigation their antimicrobial activity.

2-Experimental

The melting points of the synthesized compounds were determined using a Gallenkamp capillary melting point apparatus. The Fourier Transform Infrared (FTIR) spectra of the compounds were recorded on a Shimadzu FTIR-8400 Spectrophotometer. The 1H-NMR and 13C-NMR spectra were acquired using a Bruker Ultrashield 400 MHz instrument. Tetramethylsilane was employed as the internal standard, and DMSO-d6 was utilized as the solvent.

[1] 2-1 Synthesis of 4-N-(2-Chloro acetamido) Sulfamethoxazole

Sulfamethoxazole (0.005 mol, 1.26g) was dissolved in 20 mL of chloroform. Separately, chloroacetyl chloride (0.005 mol, 0.56g) was added dropwise to the solution under cooling and stirring [16]. Potassium carbonate (0.005mol, 0.69g) was also present in the mixture to act as a base. The reaction mixture was then heated to reflux for 12 hours. After refluxing, the mixture was allowed to cool back to room temperature. After the evaporation of almost all of the solvent, the remaining substance was added to 20 mL of ice water while stirring. The resulting solid was then filtered, rinsed with a 5% solution of $NaHCO_3$, followed by distilled water. After drying, the substance was recrystallized from dioxane.

2-2 Synthesis of 4-(sulfamethoxazole-4-y1)-2-amino thiazole [2]

Thiourea (0.01 mol, 0.76 g) was added to compound [1] (0.01 mol, 3.29 g dissolved in (15 mL) methanol then the mixture was heated under reflux for 12 hrs. [16]. After the completion of reflux, the liquid was cooled and then poured into ice water while being stirred. The resulting solid was then filtered, dried, and recrystallized using dioxane.

3-6] 2-3 Synthesis of N-[4-(sulfamethoxazole-4-y1) thiazole-2-yl] amic acids [

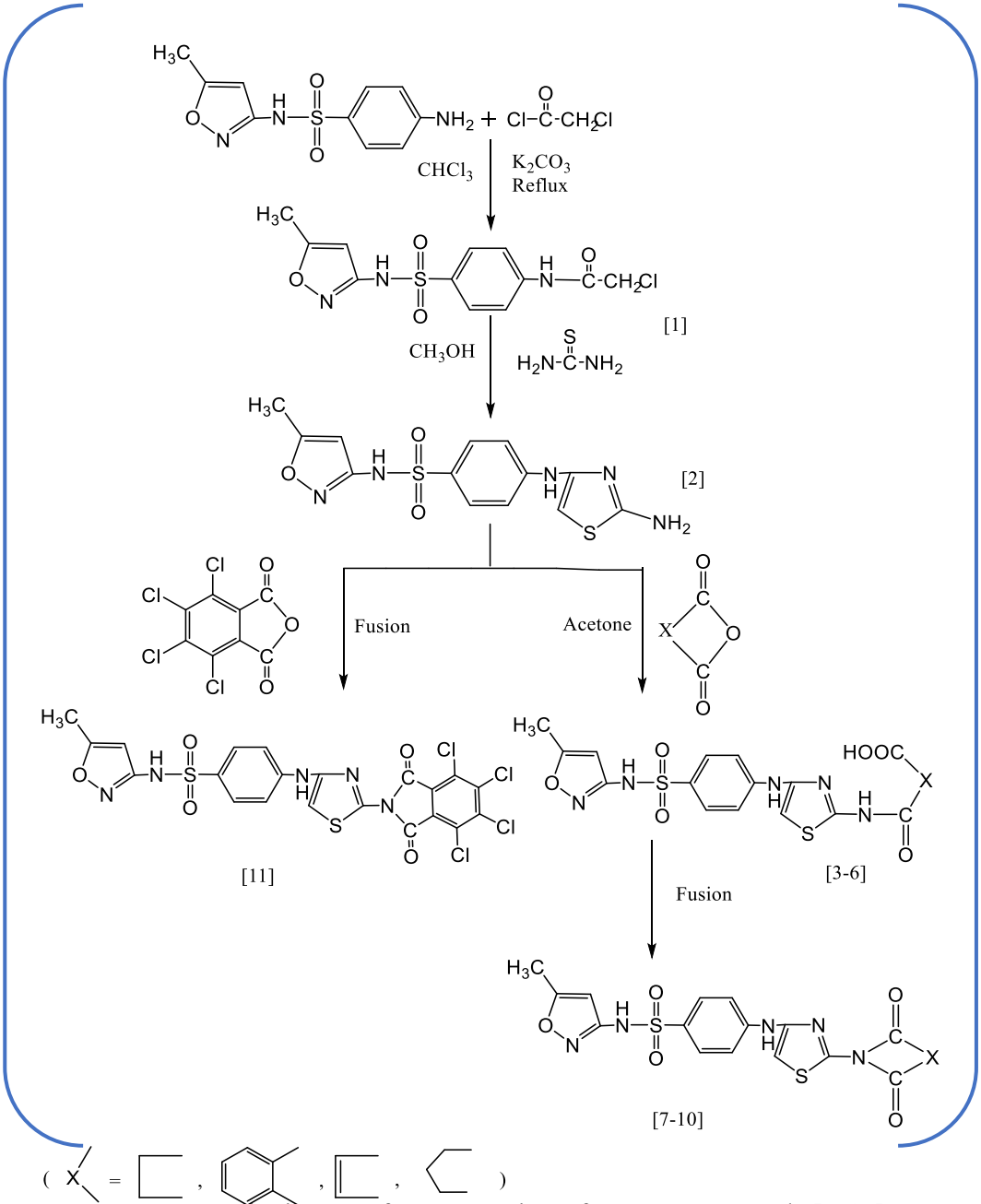
A solution of the cyclic anhydride (0.005 mol), namely succinic, phthalic, maleic, or glutaric anhydride, was prepared by dissolving the respective anhydride in 20 mL of acetone. Concurrently, compound [2] (0.005 mol, 1.75 g) was dissolved in 15 mL of acetone in a separate vessel. Under constant stirring and maintaining a cooled environment, the anhydride solution was added dropwise to the solution containing compound [2]. This gradual addition ensured a controlled reaction condition and facilitated the desired interaction between the reactants [17]. After all the additions were made, the mixture was stirred for two hours. The precipitate that was formed was filtered, washed with diethyl ether, dried, and then re-crystallized using the right solvent.

2-4 Synthesis of N-[4-(sulfamethoxazole-4-yl) thiazole-2-yl] imides [7-10]

The compounds with the mentioned titles [7-10] were synthesized by the process of dehydrating amic acids. [3-6] by fusion process through heating (0.01 mol, 1g) of amic acid [3-6] in oil bath until complete melting then temperature was raised for few degrees and heating was continued for two hours [12]. The final product was purified by recrystallization employing an appropriate solvent.

2-5 Synthesis of N-[4-(sulfamethoxazole- 4 -y1) thiazole -2-y1] tetra chloro phthalimide [11]

A blend of compound [2] (0.005 mol, 1.75g) and tetrachlorophthalic anhydride (0.005 mol, 1.43 g) was combined and pulverized, then subjected to heat in an oil bath until total fusion occurred. The temperature was sustained slightly above the melting point for a duration of 2 hours. The resulting substance was retrieved and refined using recrystallization from dioxane.



Scheme 1: synthetic steps for preparation of target compounds [1-11]

Results and Discussion

The core of this work based on designing and synthesis of new molecules via combination of three well known biologically active components namely sulfonamide, thiazole and imide cycle together in the same molecule. This combination of the three active components together in the same fram work can lead to new compounds with interesting biological activities. The desired chemicals were synthesized by a series of processes outlined in scheme (1). The synthetic manner started out with the derivatization of a biologically active sulfonamide, in which sulfamethoxazole became strategically decided on because the starting material. This became accompanied via a nucleophilic substitution reaction concerning sulfamethoxazole and the reactive acyl halide, chloroacetyl chloride. This key reaction step facilitated the introduction of a chloroacetamido moiety onto the sulfamethoxazole scaffold, hence yielding compound [1], N-chloroacetamido sulfamethoxazole. The a hit synthesis of this intermediate

compound has laid the muse for further synthetic adjustments and large research into potential biological activities, establishing the way for exploration of capability healing and linkages between its shape and characteristic. Subsequently, this compound was reacted with thiourea through nucleophilic substitution followed by ring-closure, leading to the production of compound [2], [4-(sulfamethoxazole-4-y1)-2-amino thiazole]. The molecule mentioned in this study, referred to as molecule 2, is a crucial precursor for the synthesis of the desired imides. The target imides [7-10] were synthesized by reacting compound [2] with various cyclic anhydrides, such as succinic, phthalic, maleic, and glutaric anhydrides. This reaction produced the corresponding amic acids [3-6], which were then dehydrated through fusion to yield the target imides. Additionally, the target imide [11] was synthesized by fusing a mixture of compound [2] with tetrachloro phthalic anhydride. The physical characteristics of compounds [1-2], amic acids [3-6]; and cyclic imides [7-11] are presented in Tables (1), (2), and (3) accordingly.

Table 1: The physical properties of synthesized compounds [1-2]

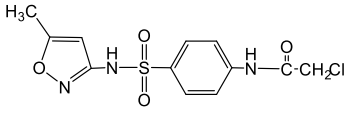
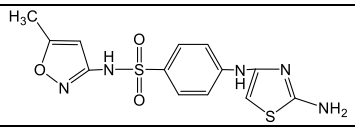
Comp. No	Compound Structure	Colour	Yield %	Melting point C^0	Recrystallization solvent
1		Light yellow	95	181-183	Dioxane
2		Light green	92	169-172	Dioxane

Table 2: The physical properties of Amic acids [3-6]

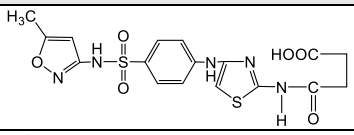
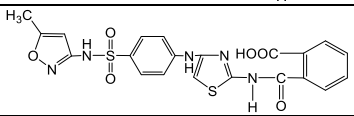
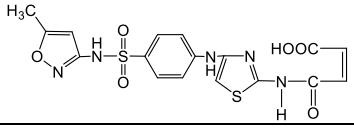
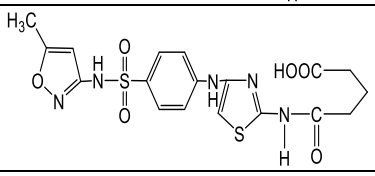
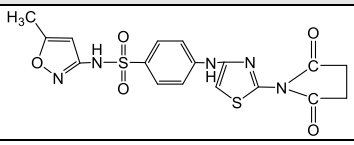
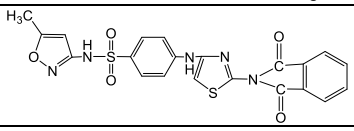
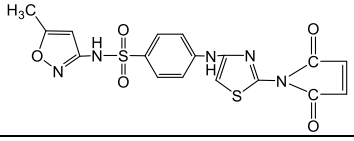
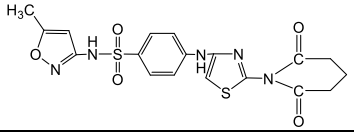
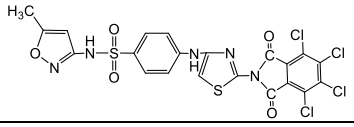
Comp. No	Compound Structure	Colour	Yield %	Melting point C^0	Recrystallization solvent
3		Light brown	83	112-113	Ethanol
4		Light brown	93	166-167	Acetone
5		Reddish brown	88	124-126	Ethanol
6		Brown	86	108-110	Ethanol

Table 3: The physical properties of Cyclic imides [7-11]

Comp. No	Compound Structure	Colour	Yield %	Melting point C^0	Recrystallization solvent
7		Reddish brown	79	124-125	Ethanol
8		Black	90	175-176	Acetone
9		Black	81	133-135	Acetone
10		Dark brown	82	119-120	Ethanol
11		Dark yellow	90	220-222	Dioxane

FTIR spectrum of the substance [1] showed absoption bands at (3103-3390) cm^{-1} due to υ(N-H) and (1697) cm^{-1}, (1612) cm^{-1} , (1595,1546) cm^{-1}, (1336) cm^{-1} , (1163) cm^{-1} and (794)cm^{-1} they are caused by υ (C=O) amide, υ (C=N), υ (C=C), asym υ (SO_2), sym υ (SO_2) and υ (C-C1) respectively [18]. FTIR spectrum of compound [2] showed appearance of clear absorption bands at (3379-3467) cm^{-1} due to υ(NH_2) and disappearance of absorption bands due to υ(C=O) amide and υ(C-Cl), and these points are good proofs for the formation of compound [2]. Other absorption bands appeared at (1620) cm^{-1}, (1595, 1575) cm^{-1} (1367) cm^{-1} and (1157) cm^{-1}, which are due to υ(C=N) υ(C=C), asym υ(SO_2) and sym υ(SO_2) respectively [18]. FTIR spectra of amic acids [3-6] exhibited broad bands of absorption at (3110-3485) cm^{-1} due to υ(O-H) carboxyl and υ(N-H) amide. Additional absorption bands emerged at (1701-1708) cm^{-1}, (1633-1683) cm^{-1} , (1610-1616) cm^{-1} , (1541-1593) cm^{-1} , (1315-1365)cm^{-1} and (1163-1166) cm^{-1} which are due to υ (C=O) carboxyl ,υ(C=O) amide, υ(C=N), υ(C=C), asym.υ(SO_2) and sym.υ(SO_2) respectively. FTIR spectra of cyclic imides [7-11] exhibited appearance of two absorption bands at (1772-1780) cm^{-1} and (1704-1716) cm^{-1} which are due to asym.υ(C=O) imide and sym. υ(C=O) imide, beside appearance of other absorption band at (1367-1392) cm^{-1} due to υ(C-N) imide. These two points are good proofs for formation of imides [7-11]. other absorption bands appeared at (3118-3380) cm, (1610-1639) cm^{-1} (1539 -1598)cm^{-1} (1319-1369) cm^{-1} and (1163-1174) cm^{-1} which are due to υ(N-H), υ(C=N), υ(C=C), asym. υ(SO_2) and sym.υ(SO_2) respectively. The FTIR spectral data for compounds [1,2], amic acids [3-6], and imides [7-11] may be found in Tables (4), (5), and (6) as necessary.

Table 4: The FTIR spectral data (cm^{-1}) of compounds [1] and [2]

Comp. No.	υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Amide	υ (C=N)	υ (C=C)	υ (SO_2)	υ (C-Cl)
1	3390 3236 3103	3055	2993 2729 2850	1679	1612	1595 1546	1336 1163	794
2	υ ($N-H_2$) υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=N)	υ (C=C)		υ (SO_2)	
	3467 3379 3298 3143	3068 3004	2956 2923 2852	1620	1595 1575		1367 1157	

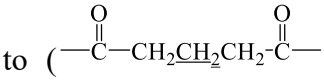
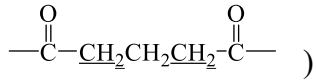
Table 5: The FTIR spectral data (cm^{-1}) of Amic acids [3-6]

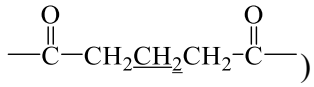
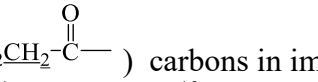
Comp.No.	υ (O-H) υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Carboxyl	υ (C=O) Amide	υ (C=N)	υ (C=C)	υ (SO_2)
3	3485 3377 3315 3110	3020	2929 2862	1701	1681	1616	1593	1326 1164
4	3446 3373 3280 3195	3062 3002	2933 2806	1704	1645	1612	1593 1541	1344 1164
5	3438 3419 3380 3285	3060	2983 2893	1708	1633	1610	1593 1541	1365 1166
6	3460 3384 3315 3267	3070	2979 2937 2852	1704	1683	1616	1575 1548	1315 1163

Table 6: The FTIR spectral data (cm^{-1}) of cyclic imides [7-11]

Comp.No.	υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Imide	υ (C=N)	υ (C=C)	υ (C-N) Imide	υ (SO_2)
7	3380 3137	3060	2987 2931 2881	1704	1616	1593	1375	1319 1163
8	3282 3118	3001	2958 2925 2864	1772 1716	1610	1593	1369	1369 (over lap) 1164
9	3334 3199	3082	2991 2937 2860	1716	1612	1593 1539	1367	1367 (over lap) 1164
10	3276 3157	3074	2958 2923 2852	1778 1716	1612	1589 1575	1392	1319 1166
11	3310 3141	3074	2923 2852	1780 1716	1639 1614	1598 1548	1392	1369 1174

The 1H-NMR spectrum of compound [1] showed characteristic proton signals. A singlet appeared at δ 2.34 ppm, corresponding to the methyl protons. A multiple was observed at δ 4.06 ppm, which can be assigned to the methylene protons. A doublet of doublets was present from δ 6.12-6.14 ppm, attributed to the vinylic proton. Additional signals were detected from δ 6.60-7.95 ppm, attributed to the aromatic ring protons. A broad singlet at δ 10.45 ppm represented the amide NH proton. Finally, a singlet at δ 11.91 ppm corresponded to the

sulfonamide NH proton. These NMR data are consistent with the proposed structure of compound [1]. ^{13}C-NMR spectrum of compound [1] showed signals at δ=(12.63), (51.12) , (96.96-144.08) , (159.53) , (166.33) and (171.45) ppm which are belong to (CH_3), (CH_2), (vinyl and aromatic carbons) , (C-O carbon in isoxazole ring) , (C=N) and (C=O) amide carbons respectively. The 1 H-NMR spectra of the novel imides [7, 10, 11] exhibited signals at δ=(2.29-2.38) ppm, (5.97-6.59) ppm, (6.46-8.11) ppm, (8.31-9.95) ppm, and (10.77-11.68) ppm, which are CH_3 protons, vinylic protons, aromatic protons, (NH) protons, and ($NHSO_2$) protons respectively [18]. ^{1}H-NMR spectrum of compound [7] showed signals at (δ= 2.73, 2.87) ppm belong to (-CH_2-CH_2-) protons in imide ring while ^{1}H-NMR spectrum of compound [10] showed signals at (δ = 2.22) ppm belong to ()protons and other signals at (δ= 2.47-2.52) ppm belong to () protons in imide ring . On the other hand ^{13}C-NMR spectra of the new imides [7, 10,11] showed signals at δ=(12.50-12.61) ppm , (95.82-144.20) ppm, (153.76-162.87) ppm, (157-84-171.47) ppm and (171.04-174.24) ppm which are belong to (CH_3) carbon, aromatic carbons, vinylic carbons, (C=N) carbons and (C=O) imide carbons respectively.[18]

^{13} C-NMR spectrum of Compound [7] showed signals at(δ= 29.05-31.63) ppm which belong to (-CH_2-CH_2-) carbons in imide ring while ^{13}C-NMR spectrum of compound [10] showed signals at δ= (31.24) ppm and (36.28) ppm which are belong to () and () carbons in imide ring. [18]

All details of ^{1}H-NMR and ^{13}C-NMR spectral data are listed in Tables (7) and (8)

Table 7: The ^{1}H-NMR spectral data (δ, ppm) of compounds [1, 7, 10 ,11]

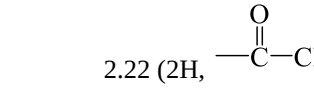
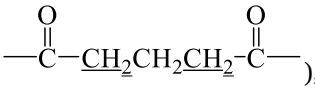
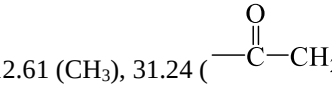
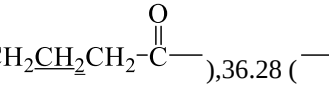
Comp.No.	^{1}H-NMR spectral data (δ , ppm)
1	2.34 (s,3H,CH_3), 4.06 (s,2H, CH_2), 6.12-6.14 (1H, vinylic), 6.60-7.95 (4H, Ar-H), 10.45 (1H, NH), 11.91 (1H, NH)
7	2.29 (s,3H,CH_3), 2.73-2.87 (4H, CH_2–CH_2), 5.97-6.1(2H, vinylic),6.46-7.99 (4H, Ar-H), 8.31 (1H, NH), 11.05 (1H, NH)
10	2.22 (2H, ), 2.31 (3H, CH_3), 2.47-2.52 (4H, ), 6.15-6.64(2H, vinylic),6.47-7.87(4H, Ar-H), 9.95 (1H, NH), 10.77 (1H, NH)
11	2.38(3H,CH_3), 6.22,6.59 (2H, vinylic), 7.67-8.11 (4H, Ar-H), 11.68 (2H, NH, NH)

Table 8: ^{13}C-NMR spectral data (δ , ppm) of compounds [1, 7, 10 ,11]

Comp.No.	^{13}C-NMR spectral data (δ , ppm)
1	12.63 (CH_3), 51.12 (CH_2), 96.96-144.08 (vinyl and Ar-C), 159.53 (C-O) isoxazole ring), 166.33 (C=N), 171.45 (C=O) amide
7	12.50 (CH_3), 29.05-31.63 (-CH_2 –CH_2-), 95.82-143.98 (Ar-C), 153.76-158.43 (vinylic carbon), 170.37-171.47 (C=N) isoxazole and thiazole , 174.13-174.24(C=O) imide
10	12.61 (CH_3), 31.24 (),36.28 (), 96.70-144.20 (Ar-C), 159.56-162.87 (vinylic carbon), 165.91-168.54 (C=N) isoxazole and thiazole , 171.48(C=O) imide
11	12.57 (CH_3), 95.92-139.47 (Ar-C), 157.84-162.56 (C=N) isoxazole and thiazole , 171.04(C=O) imide

Biological Activity Study

The produced imides' antibacterial activity was investigated against two different species of bacteria: ***E. Coli*** (gram negative bacterium) and ***Staphylococcus aureus*** (gram positive bacteria). Additionally, the produced imides' antifungal efficacy against Candida albicans fungi was assessed; where the antimicrobial activity of the synthesized compounds was examined using the cup plate method against two types of bacteria as well as, a one type of fungus. The outcomes were then compared to one type of antibiotic (Fluconazole). Nutrient agar medium was also used to sample the solution in addition to DMSO. The agar medium in Petri dish, which had previously been treated with microorganisms, was scooped out into cups Following the addition of the examined compound solutions to the cups, the Petri dishes were incubated at 37°C for 48 hr., the outcomes are reported in Table 9.

Table 9: Inhibition zones of antibacterial and antifungal activities in (mm)

Comp. No	*staphylococcus aureus*	*E-Coli*	Candida Albicans
7	19	20	17
8	14	12	23
9	19	16	20
10	15	14	27
11	14	12	24
Fluconazole	9	9	9
DMSO	0	0	0

The results indicated that compound [7] compound [9] showed high antibacterial activity against the two types of bacteria and they showed also high antifungal activity. On the other hand, the prepared imides [8], [10] and [11] showed good to moderate antibacterial activity against the two types of bacteria but they showed high antifungal activity.

Conclusion

The multistep synthetic methodology successfully provided the target cyclic imide compounds linking thiazole and sulfamethoxazole drug subunits. Evaluation of antibacterial and antifungal activities revealed that all the newly synthesized imides demonstrated good antibacterial properties, especially compounds [7] and [9]. Notably, in antifungal testing, all of the new imides exhibited very promising activity results. Overall, this work validates the potential of the multistep imidisation strategy to furnish bioactive derivatives through fusion of thiazole and sulfamethoxazole pharmacophores.

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