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Synthesis of new cyclic imides bearing drug or heterocycles, depending on Mannich and Gabriel Reactions, with study of their antimicrobial activity

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Abstract

This study describes the synthesis of two novel cyclic imide derivatives incorporating drug components or heterocyclic moieties. The first series (compounds 6-13) features a cyclic imide connected to a hetero ring through methylene group, synthesized via the Mannich reaction using N-unsubstituted cyclic imide with heterocyclic amine and formaldehyde. The second series (compounds 15-18) involve cyclic imide fused with the drug molecule (sulfamethoxazole) through acetamido group, achieved via the Gabriel reaction by reacting the potassium salt of N-unsubstituted imide with chloro acetamido sulfamethoxazole. The antimicrobial activity of the newly synthesized imides was evaluated, yielding promising results. The synthesized compounds have been characterized by FTIR, ^{1}HNMR and ^{13}CNMR.

Key words: cyclic imide, Mannich reaction, Gabriel reaction, sulfamethoxazole ,heterocyclic amine.

تحضير ايمايدات حلقية جديدة حاملة لدواء أو حلقات غير متجانسة اعتماداً على تفاعلات مانخ وجابريل مع دراسة فعاليتها المضادة للمايكروبات

زينب ماجد صادق* ، أحلام معروف العزاوي
قسم الكيمياء , كلية العلوم , جامعة بغداد , بغداد . العراق

الخلاصة

يتناول هذا البحث تحضير مشتقين جديدين من الإيمايدات الحلقية، تم دمج كل منهما إما مع وحدات دوائية فعالة أو مع حلقات غير متجانسة .تمثلت السلسلة الأولى من المركبات (6–13) إيمايدات حلقية مرتبطة بحلقة غير متجانسة عبر مجموعة ميثيلين، وقد تم تحضيرها اعتمادًا على تفاعل مانيخ، من خلال تفاعل إيميد حلقي غير مستبدل عند ذرة النيتروجين مع أمين الغير متجانس والفورمالديهايد.

أما السلسلة الثانية (15–18)، فقد تضمنت مركبات ناتجة عن دمج الإيمايد الحلقي مع جزيء السلفاميثاوكسازول عبر مجموعة الأسيتاميدو، وتم تحضيرها باستخدام تفاعل غابرييل، وذلك من خلال تفاعل ملح البوتاسيوم للإيمايد غير المستبدل مع مركب كلورو–أسيتاميدو–سلفاميثاوكسازول.

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تم تقييم الفعالية الحيوية للمركبات المحضّرة ضد عدد من الكائنات الحية الدقيقة، وأظهرت النتائج نشاطاً مضادًا للميكروبات. وقد تم توصيف البنية الكيميائية للمركبات المُحضّرة باستخدام تقنيات التحليل الطيفي، بما في ذلك FTIR , ^{1}HNMR و ^{13}CNMR

1-Introduction:

Most approaches for synthesizing cyclic imides rely on dehydration of amic acids, which are organic compounds containing both carboxyl and amide functional groups within their molecules. Cyclic imides are valuable organic compounds that have received much attention due to their antifungal [1], antibacterial [2,3], antitumore [4], analgesic [5]and anticancer activities [6]. In addition, cyclic imides are a key structural component in the development of new pharmaceuticals, drugs, polymers, corrosion inhibitors and pigments [7-9].

On the other side sulfur, nitrogen and oxygen containing heterocyclic systems mainly five and six-membered constitute a valuable class of organic compounds with a wide spectrum of various biological activities [10-15] thus heterocyclic scaffolds incorporated successfully into a wide range of bioactive compounds, drugs, pharmaceuticals and therapeutic agents like metronidazole used as antimoebic thiabendazole used as anthelmintic and fluconazole used as antifungal drug [16]. The study aimed to design and synthesis new compounds containing the two bioactive moieties cyclic imide and heterocycle (or drug) together, followed by evaluation of their antimicrobial activity. Synthesis of these compounds using two well-established chemical reactions: the Mannich and Gabriel reactions. The newly synthesized compounds were screened for their antimicrobial, antifungal and antioxidant activities, yielding promising results.

2-Experimental

Gallen Kamp capillary melting point apparatus was used to determine the melting points for the newly prepared compounds, while Shimadzu FTIR-8400 Fourier Transform spectrophotometer was used for recording their FTIR spectra. Ultrashield 400MHz Bruker apparatus was used for recording both ^{1}H-NMR and ^{13}C-NMR spectra in the presence of the solvent DMSO-d_6 and the internal standard tetramethyl silane.

2-1 Preparation of N-unsubstituted cyclic imides (phthalimide, tetrachlorophithalimide, succinimide, dimethyl maleimide, Glutarimide) (1-5)

The unsubstituted cyclic imides were synthesized by thoroughly mixing cyclic anhydride(1-5), including phthalic, tetrachloro phthalic, succinic, dimethyl maleic or glutaric anhydrides (0.02 mol) with urea (0.03 mol,1.8g). The resulting mixture was then heated in a domestic microwave oven for 10 minutes [17] [18]. The resulting product was collected and then purified by recrystallization from a suitable solvent.

2-2 Synthesis of N-(4-methylene amino pyridine) phthalimide (6), N-(2-methylene amino thiazole) phthalimide (7), N-(4-methylene amino antipyrine) phthalimide (8)

A solution of compound (1) phthalimide (0.01 mol, 1.47g) in 10 mL of absolute ethanol was combined with 1 mL of 37% formaldehyde. This mixture was then added to a solution of 0.01 mol of 0.01mol of heterocyclic amine (4-amino pyridine, 2-amino thiazole, 4-amino antipyrine) dissolved in 10 mL of absolute ethanol, with continuous stirring [19]. After completion of the addition, the mixture was heated under reflux for 12 hrs. The obtained solid after cooling was filtered, dried then recrystallized from a suitable solvent.

2-3 Synthesis of N-(2-methylene amino thiazole) tetrachlorophthalimide (9) and N-(4-methylene amino antipyrine) tetra chloro phthalimide(10)

Compound (9) was synthesized by reacting tetrachlorophthalimide (0.01 mol, 1.25g) (2) and formaldehyde with 2-amino thiazole(0.01mol , 1g). Similarly, compound (10) was synthesized via reaction of tetra chloro phthalimide (2) and formaldehyde with 4-amino antipyrine, following the same steps [19] that are used in synthesis of compounds (6-8). The products were purified through recrystallization using an appropriate solvent.

2-4 Synthesis of N-(4-methylene amino antipyrine) succinimide (11)

Compound [11] was synthesized via reaction of succinimide (3) (0.01mol, 0.99 g) with 4-amino antipyrine (0.01mol, 2.03 g) and formaldehyde in absolute ethanol, following the same steps which were used in compounds (6-8). The collected product was purified by recrystallization from acetone. [20]

2-5 Synthesis of N-(4-methylene amino antipyrine) di methyl maleimide (12)

Compound (12) was synthesized by reacting dimethyl maleimide (4) (0.01 mol, 1.25g) with 4-amino antipyrine (0.01mol, 2.03g) with formaldehyde in absolute ethanol, following the same steps [19, 20] which were used in compounds (6-8). The product was purified by recrystallization from acetone.

2-6 Synthesis of N-(4-methylene amino pyridine) glutarimide(13)

Compound (13) was synthesized via reaction of glutarimide (5) (0.01mol, 1.13g) with 4-amino pyridine(0.01mol , 0. 94 g) and formaldehyde in absolute ethanol, following the same steps which were used in compounds (6-8). The product was purified by recrystallization from acetone.

2-7 Preparation of chloro acetamido derivative of sulfamethoxazole (14)

In a suitable flask,(0.005mol ,1.26g) of sulfamethoxazole was dissolved in 25 mL of chloroform, followed by the addition of (0.005 mol ,0.69g) of potassium carbonate with stirring [21]. To this mixture,(0.005 mol ,0.56g) of chloroacetyl chloride was added dropwise while cooling and stirring continuously. After the addition was complete, the mixture was refluxed for twelve hours before being poured into 25 mL of ice water with vigorous stirring. The formed precipitate was filtered, then washed with $NaHCO_3$ solution then with water. The dried product was purified by recrystallization from dioxane [22].

2-8 Synthesis of N-(aceramido sulfamethoxazole-4-41) phthalimide (15)

A mixture of phthalimide (1) (0.003 mol, 0.44g), (0.003 mol, 0.98g) of compound (14) and (0.003 mol, 0.82g) of potassium carbonate in ethanol absolute (25mL) was refluxed for fourteen hours [17, 23]. After cooling, the resulting mixture was poured onto ice water with vigorous stirring, and the formed solid was filtered, washed with water, dried and finally recrystallized from ethanol.

2-9 Synthesis of N-(acetamido sulfamethoxazole-4-yl) tetra chloro Phthalimide (16)

Compound (16) was synthesized via reaction of (0.003 mol, 0.85g) of tetra chloro phthalimide (2) with (0.003 mol, 0.989) of compound (14) and (0.003 mol, 0.82 g) of potassium carbonate in ethanol absolute following the same steps[17] which were used in synthesis of compound (15) compound (16) was purified by recrystallization from acetone.[23]

2-10 Synthesis of N-(acetamido sulfamethoxazole-4-yl) Succinimide (17)

Compound (17) was synthesized via reaction of (0.003 mol, 0.29g) of succinimide (3) with (0.003mol, 0.98g) of compound (14) and (0.003 mol, 0.82g) of potassium carbonate in absolute ethanol, following the same steps that are used in the synthesis of compound (15). Compound (17) was purified by recrystallization from acetone [23].

2-11 Synthesis of N-(aceramido sulfamethoxalole-4-41) dimethyl maleimide (18)

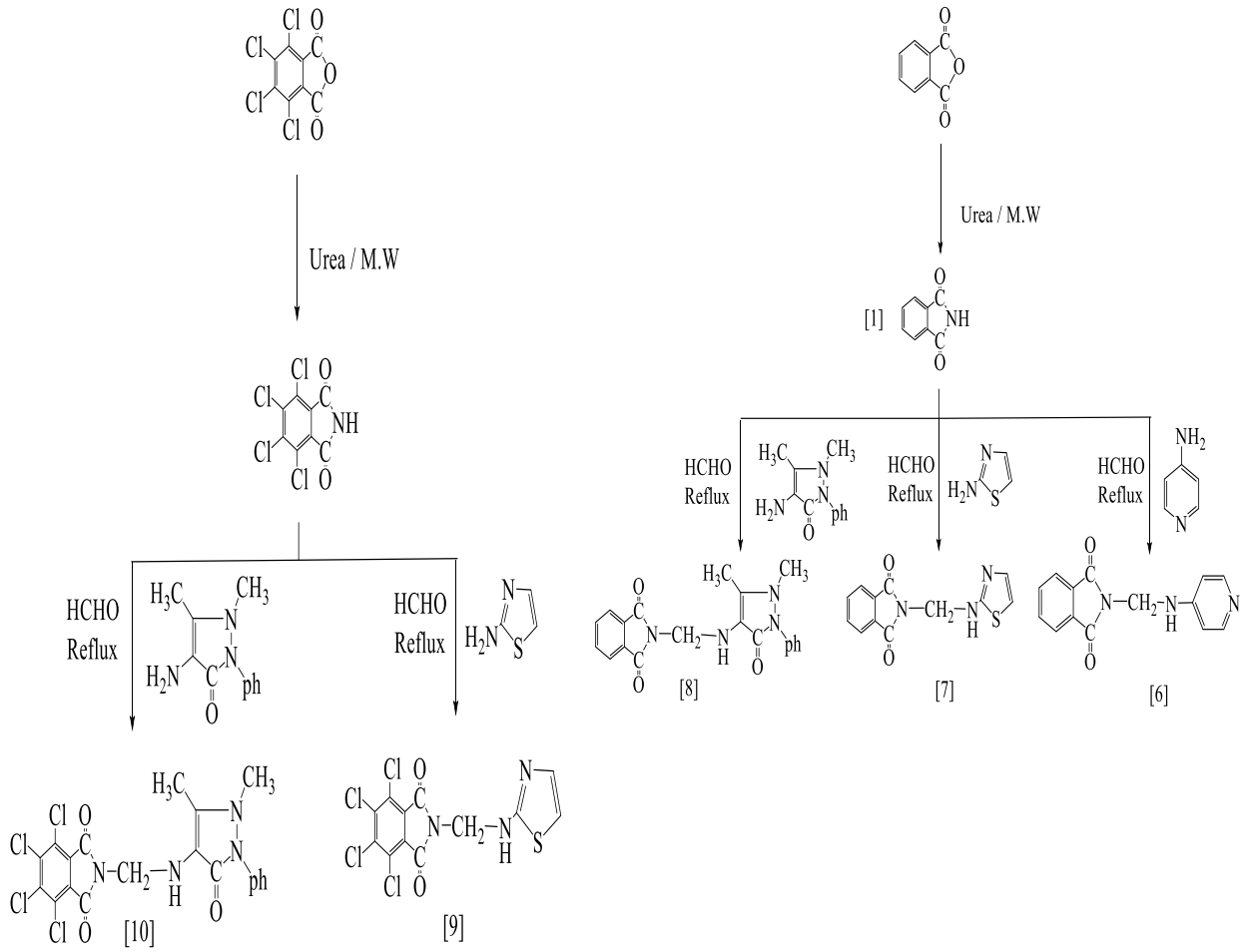
Compound (18) was synthesized via reaction of dimethyl maleimide (4) (0.003 mol, 0.37g) with (0.003 mol, 0.98g) of compound (14), and (0.003 mol, 0.829 g) of potassium carbonate in absolute ethanol, following the procedure used for compound (15). Purification was achieved via recrystallization from acetone [23].

3.Results and Discussion

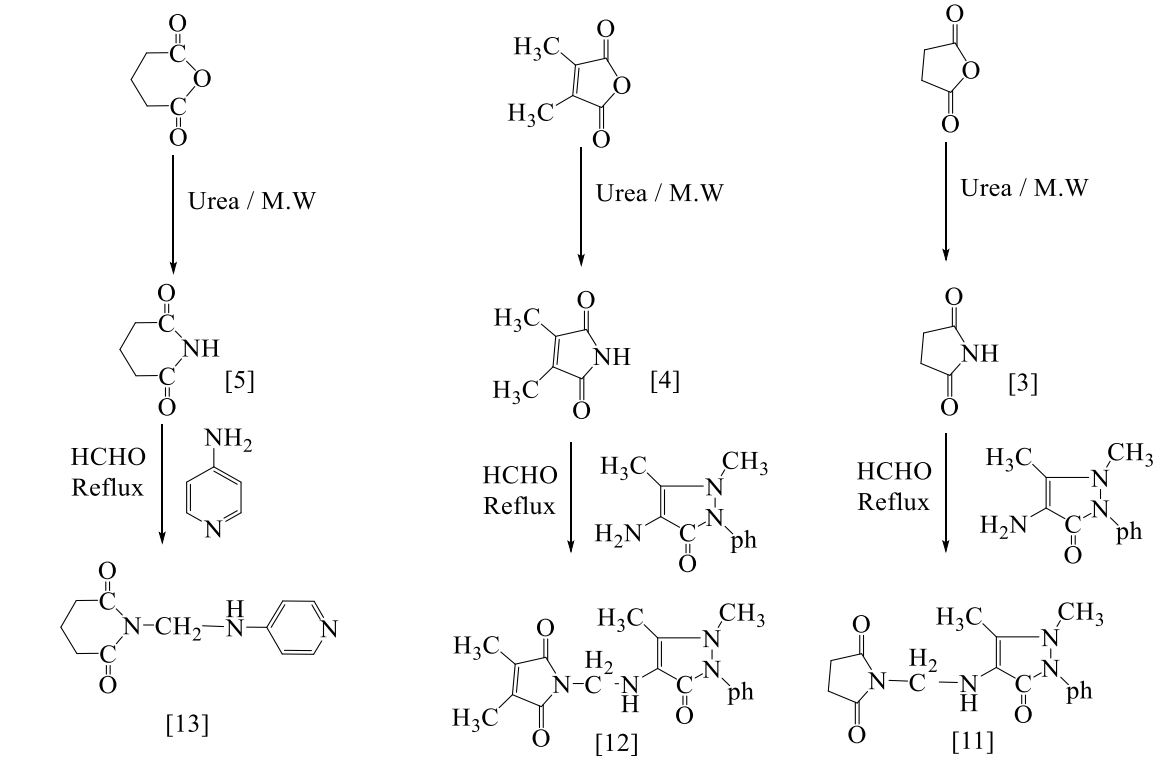
Both cyclic imides and heterocyclic compounds are well-recognized bioactive moieties in organic chemistry, each with a broad range of applications in drugs and pharmaceuticals. The main focus of this work is the design of new molecules containing these two active components through the synthesis of new cyclic imides containing heterocycles or a drug moiety (which already contains a heterocycle). The new compounds are expected to exhibit high biological activity since they are built from bioactive components.

Two new series of cyclic imides were synthesized here. The first series (compounds (6-13) comprises cyclic imides connected via a methylene group to various heterocycles, including pyridine, thiazole, and antipyrine. Synthesis of imides (6-13) was conducted by depending on the Mannich reaction through performing two steps, in the first one, a series of N-unsubstituted cyclic imides (1-5) were synthesized via a reaction between cyclic anhydride and urea under microwave irradiation for a suitable period. In the second step compounds (1-5) were introduced in reaction with heterocyclic amines, including (4-aminopyridine, 2-amine thiazole, 4-amino antipyrine) and formaldehyde, producing the target imides (6-13) as described in scheme(1) and scheme (2)

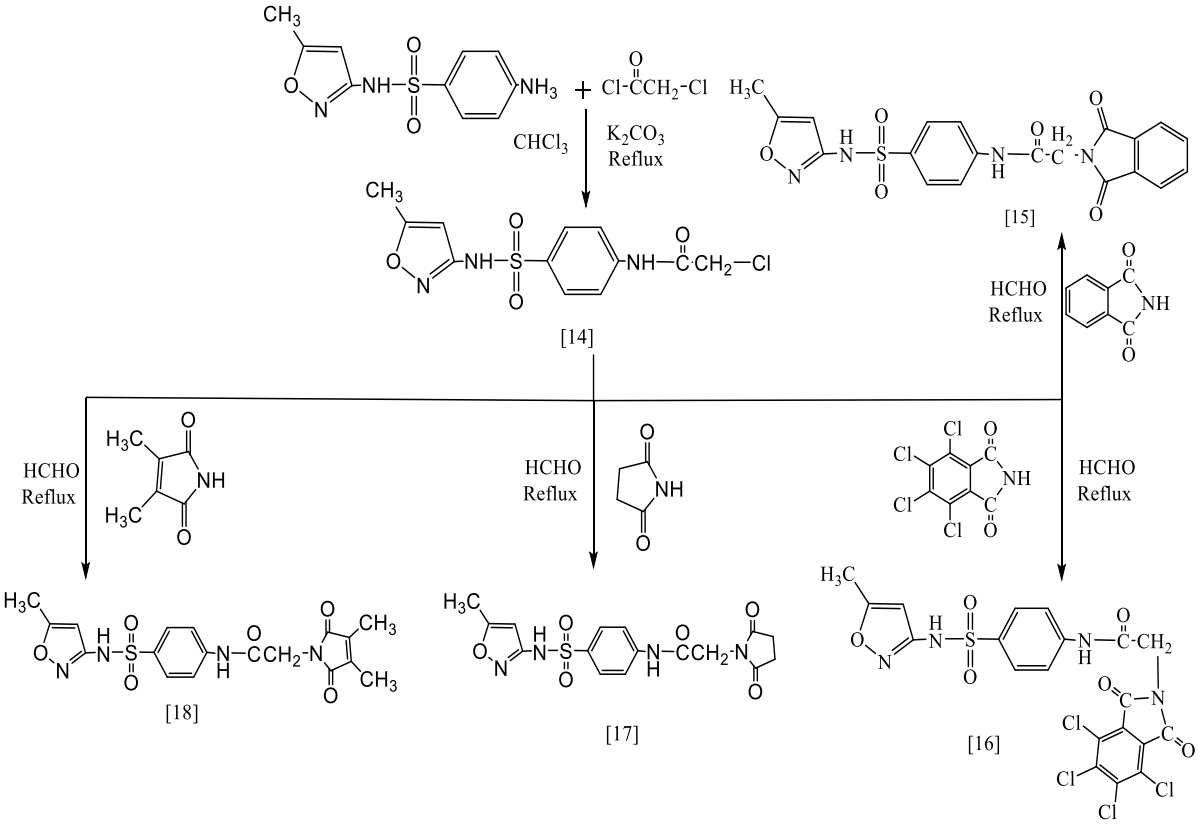
On the other hand, the second series of the new imides (15-18) contains an imide cycle linked to the drug component (Sulfamethoxazole) through acetamido group. Synthesis of imides (15-18) based on Gabriel reaction was performed by two steps, the first one involved conversion of sulfamethoxazole drug to the corresponding chloroacetamido derivative (14) through reaction of sulfamethoxazole with chloro acetyl chloride, while the second step involved introducing of compound (14) in reaction with the prepared N-unsubstituted cyclic imides (1-5) in presence of K_2CO_3 in absolute ethanol under reflux as described in scheme (3). During this reaction, the first cyclic imide potassium salt was formed, and this strong nucleophile subsequently attacked compound (14) chloro acetamido sulfamethoxazole, producing the target imides (15-18) .



Scheme (1)



Scheme (2)



Scheme (3)

Physical properties of compounds [1-5], compounds [6-13] and compounds [14-18] are shown in Tables (1), (2) and (3), respectively.

Table 1: The physical properties of Cyclic imides [1-5]

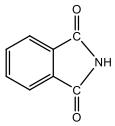
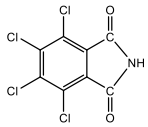
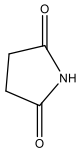
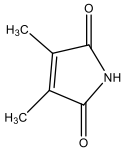
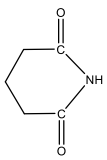
Comp. No	Compound Structure	Colour	Yield %	Melting point C^0	Recrystallization solvent
1		yellow	93	238-240	water
2		yellow	90	>300	water
3		brown	80	123-125	water
4		off white	92	116-118	water
5		off white	90	156-158	water

Table 2: The physical properties of Compounds [6-13]

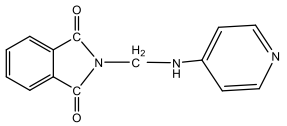
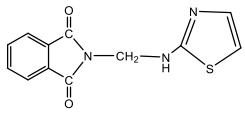
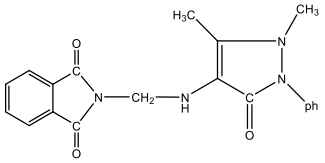
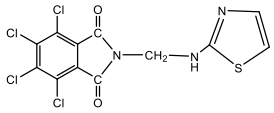
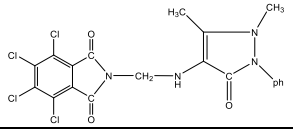
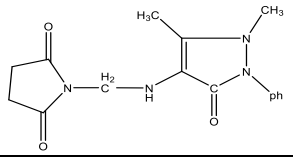
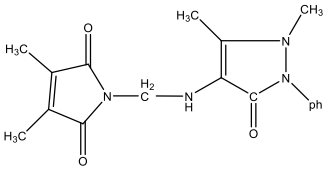
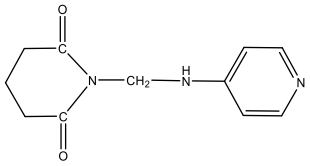
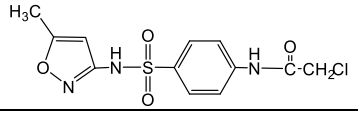
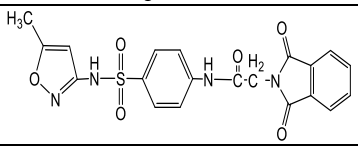
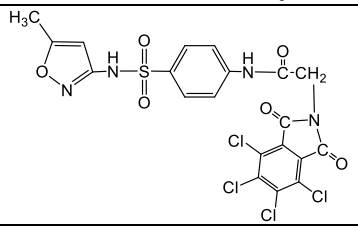
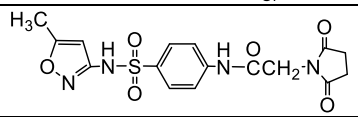
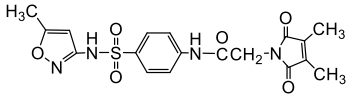
Comp.No	Compound Structure	Colour	Yield %	Melting point C^0	Recrystallization solvent
6		off white	80	107-109	Ethanol
7		off white	75	124-126	Ethanol
8		off white	83	150-152	Ethanol
9		brown	88	188-190	Ethanol
10		brown	90	204-206	Ethanol
11		off white	69	119-121	acetone
12		yellow	91	136-138	acetone
13		brown	67	94-96	acetone

Table 3: The physical properties of Compounds[14-18]

Comp. No	Compound Structure	Colour	Yield %	Melting point C^0	Recrystallization solvent
14		Light yellow	95	181-183	dioxane
15		Light red	85	>300	ethanol
16		Dark brown	92	>300	acetone
17		brown	74	247-249	acetone
18		Dark brown	80	253-255	acetone

FTIR spectra of N-unsubstituted cyclic imides (1-5) showed clear absorption bands at (3475-3172) cm^{-1} due to υ(N-H) and two absorption bands at (1774-1710) cm^{-1}and (1749-1660) cm^{-1}, which are due to asym.υ(C=O) imide and sym.υ (C=O)imide respectively [21]. Other bands appeared at (1602-1566) cm^{-1} due to υ(C=C) respectively [24].

FTIR spectra of the synthesized cyclic imides (6-13) showed clear absorption bands at (3465-3157) cm^{-1}, (1784-1765) cm^{-1} and (1741-1680)cm^{-1}, which are attributed to υ(N-H) [21] ,asym, υ(C=O) imide and sym.υ(C=O) imide respectively.

The spectra also showed absorption bands at (1610-1460)cm^{-1} and (1388-1340) cm^{-1} due to υ(C=C) and υ(C-N) imide, respectively.

In the FTIR spectra, compounds (6, 7, 9, and 13) showed bands at 1650-1639 cm^{-1} assigned to υ(C=N), while compounds (8), (10), (11), and (12) exhibited bands at 1639-1629 cm^{-1} attributed to amide υ(C=O). Furthermore, bands corresponding to υ(C-Cl) (1089-1070 cm^{-1}) were observed for compounds (9) and (10).

Table 4: The FTIR spectral data (cm^{-1}) of compounds [1-5]

Comp.No.	υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Imide	υ (C=C)	others
1	3444 3201	3062	-	1774 1749	1602 1573	-
2	3475 3220	-	-	1772 1708	1566	(C-Cl) 1085
3	3380 3172	-	2933 2812	1772 1699	-	-
4	3431 3259	-	2997 2927	1768 1704	1596	-
5	3448 3384 3193	-	2975 2945 2883	1710 1660	-	-

Table 5: The FTIR spectral data (cm^{-1}) of compounds [6-13]

Comp. No.	υ (N-H)	υ (C-H) Arom.	υ (C-H) Aliph.	υ (C=O Imide	υ (C=O) Amide	υ (C=C)	υ (C-N) Imide	Others
6	3427 3284	3066	2975 2877	1772 1716	———	1604 1556	1375	**υ (C=N)** 1645
7	3407 3288	3010	2974 2939 2873	1772 1718	———	1558	1361	**υ (C=N)** 1639
8	3433 3286	3030	2972 2939 2860	1770 1708	1639	1558	1340	———
9	3465 3433	3085	2977 2937 2875	1774 1714	———	1573	1373	**υ (C=N)** 1650 **υ (C-Cl)** 1070
10	3434 3286	3080	2970 2939 2829	1778 1716	1639	1560	1369	**υ (C-Cl)** 1089
11	3438 3263	3064	2968 2923 2879	1741	1633	1610 1492	1344	———
12	3427	3085	2960 2921 2852	1784 1714	1629	1460	1373	———
13	3259 3157	3068	2974 2933 2896	1765 1680	———	1602 1550	1388	**υ (C=N)** 1647

^{1}H-NMR spectra of the newly synthesized imides (8), (9) and (13) showed signals at (δ=4.06-4.54) ppm belonging to (CH_2) protons which linked between heterocyclic to the amine and imide rings. Also, signals appeared at (δ=6.19-7.81) ppm belong to (NH) proton. Spectra of compounds (8) and (13) showed signals at (δ=6.60-7.8) ppm belonging to aromatic protons, while ^{1}H-NMR spectrum of compound (9)showed signals between (δ=7.72-7.89) ppm belonging to protons in thiazole rings

^{1}H-NMR spectrum of compound (8) showed signals also at (δ=2.24) and (δ=2.98) ppm be belong to (CH_3) and (N-CH_3) protons[26] while ^{1}H-NMR spectrum of compound (13)showed signals at (δ =2.34) and (2.45) ppm belong to (-$CH_2CH_2CH_2$-) protons in glutarimide ring.

On the other hand, ^{13}C-NMR spectra of imides (8), (9) and (13) showed signals at (δ=44.35-65.4ppm belong to (NCH_2-N) carbon, signals at (δ= 108.40-149.80)ppm belonging to aromatic carbons and thiazole ring carbons and signals at (δ=165.85-171.87) ppm belonging to (C=O) imide.

^{13}C-NMR spectra of compounds (9) and (13) showed signals at (δ=162.81-168.64) ppm belonging to (C=N), while the spectrum of compound (13) showed signals at (δ= 15.42 and 19.0) ppm belonging to ($CH_2CH_2CH_2$) carbons in the glutarimide ring.

^{13}C-NMR spectrum of compound [8] also showed signals at (δ= 15.54) and (36.08) ppm belonging to (CH_3) and (N-CH_3) carbons, and another Signal at (δ=153.90) ppm belongs (N-C=C-N) carbons in hetero ring [26].

On the other side FTIR spectrum of compound (14) showed absorption bands at (3103, 3236)cm^{-1}, (1679)cm^{-1} , (1612) cm^{-1} (1595) ,(1336) cm^{-1} and (1163) cm^{-1} which are attributed to υ(N-H), υ (C=O) amide, υ(C=N), υ(C=C), asym. υ (SO_2) and sym.(SO_2) respectively [25].

FTIR spectra of the new imides (15-18) showed absorption bands at (3191-3444)cm^{-1}, (1745-1776)cm^{-1} and (1670-1731) cm^{-1} due to (N-H), asym υ (C=O)imide and sym. υ(C=O) imide

respectively. Other absorption bands appeared at (1631-1660)cm^{-1} , (1612-1631) (1560-1595), (1350-1379)cm^{-1}, (1311-1379)cm^{-1} and (1130-1164) cm^{-1} which are attributed to υ(C=O) amide, υ(C=N), υ(C=C), υ(C-N) imide, asym. (SO_2) and sym. υ(SO_2) respectively [25, 27-28].

^{1}H-NMR spectra of imides (17) and (18) showed signals at (δ=2.22-2.29) ppm belonging to protons of CH_3 linked to isoxazole ring, signals at (δ= 4.66-4.74) ppm belong to (-CH_2-) protons and signals at (δ=5.97-6-14) ppm belong to protons in the hetero ring. Other signals appeared at (δ=6.44-8.31) ppm (10.5-10.73) ppm and (10-78-11-05) ppm, which belong to aromatic protons, (NH) proton and ($NHSO_2$) proton, respectively [26, 28-29].

^{1}H-NMR spectrum of compound (17) showed signals at(δ=2.73-2.87) ppm belong to (-CH_2CH_2-) protons in succinimide ring, while ^{1}H-NMR spectrum of compound [18] showed signal at (δ=2.47)ppm belong to protons of two CH_3 linked to imide ring.

^{13}C-NMR spectrum of compound (17) showed signals at (δ=12.61), (31.24) and (51.11) ppm, which belong to (CH_3), (-CH_2CH_2-) and (-CH_2-N-) carbons.[29]

Further signals appeared at (δ=96.93-159.56) ppm (162.87) (165.91), (168.54) and (171.48) ppm, which belong to aromatic carbons, (C-O) Carbon in isoxazole ring, (C=N), (C=O) amide and (C=O) imide respectively [27].

FTIR spectral data of compounds (14-18) are listed in Table 6, while ^{1}H-NMR and ^{13}C-NMR spectral data of compounds (8, 9, 13, 17, 18) are listed in Tables 7 and 8.

Table 6: FTIR spectral data (cm^{-1}) of compounds[14-18]

Comp. No.	υ (N-H)	υ (C-H) Arom.	υ (C-H) Aliph.	υ (C=O) Imide	υ (C=O) Amide	υ (C=N)	υ (C=C)	υ (C-N) Imide	Asym. υ (SO_2)	Sym. υ (SO_2)
14	3236 3103	3055	2993 2927 2887	——	1679	1612	1595	——	1336	1163
15	3352 3191	3062	2991 2933 2880	1753 1704	1660	1612	1593	1357	1311	1164
16	3444 3245	3085	2931 2850	1776 1731	1649	1616	1595	1367	1336	1157
17	3398 3228	3050	2974 2925 2860	1745 1670	1631	1631 overlap	1571	1350	1350 overlap	1132
18	3413 3396	3060	2927 2860	1670	1643	1618	1560	1379	1379 overlap	1130

Table 7: ^{1}H-NMR spectral data of compounds [8, 9, 13 ,17, 18]

Comp.No.	^{1}H-NMR spectral data (δ , ppm)
8	2.24 (s,3H,CH_3),2.98 (s,3H, N-CH_3), 4.54 (s,2H, N-CH_2N),7.32-7.53 (m,9H, Ar-H), 7.81 (s,1H, NH)
9	4.54 (s,2H, N-CH_2N),6.98 (s,1H, NH), 7.72-7.89(d,2H in thiazole ring)
13	2.34 (m,2H, CO-$CH_2$$CH_2$$CH_2$CO-), 2.45 (t,4H, CO-$CH_2$$CH_2$$CH_2$CO-), 4.06(s,2H, N-$CH_2$-N), 6.19 (s,1H,NH), 6.60-7-80 (m,4H, Ar-H)
17	2.29 (s,2H, CH_3), 2.73-2.87(d,4H, -CH2-CH2-), 4.74(s,2H, CO-CH_2-N) , 5.97(s,1H in) hetero ring ,6.44-8.31 (dd,4H-Ar-H) 10.73 (s,1H , NH) , 11.05 (s,1H, $NHSO_2$)
18	2.22s, (3H. CH_3), 2.47(s,6H, 2CH_3 imide ring) 4.66(s,2H,-CO-CH_2-N), 6.14 (s,1H in hetero ring), 6.46-8.19 (m,4H-Ar-H), 10.5 (s, 1H , NH) , 10.78(s,1H, $NHSO_2$)

Table 8: ^{13}C-NMR spectral data (δ , ppm) of compounds [8, 9, 13 ,17]

Comp.No.	^{13}C-NMR spectral data (δ , ppm)
8	15.54 (CH_3) 36.08 (N-CH_3) 65.45 (N-CH_2-N) , 117.6-136.87(Ar-C) , 153.90 (N-C=C-N) , 164.66 (C=O) imide
9	44.35 (N-CH_2-N), 129.1-136.28(Ar-C) carbon in thiazole ring) , 162.81 (C=N) , 165.85 (C-O) imide
13	15.42(CO-$CH_2$$\underline{CH_2}$ CH_2CO) 19.0 (CO-$\underline{CH_2}$$CH_2$ $\underline{CH_2}$CO), 56.58 (N-CH_2N) , 108.40 -149.80 (Ar-C) 167.93-168.64 (C=O) , 169.61-171.78 (C=O) imide
17	12.61 (CH3) , 31.24 (-CH2-CH2-) . 51.11 (CO CH2NO) , 96.93-159.56 (Ar-C) , 162.78 (C-O) isoxazole ring) , 165.91(C=N), 168.54 (C=O) amide, 171.48 (C=O) imide.

Biological Activity Study

The study assessed the antibacterial activity of the synthesized compounds against four bacterial strains: *E.Coli, Bacillus subtilis, proteus and staphylococcus the aureous*. Additionally, antifungal activity was evaluated against *Candida albicans* fungi. The cup plate method was employed, using DMSO as the solvent for the samples, while Amoxicillin and Fluconazole were used as reference drugs. Inhibition zones caused by the tested compounds are measured in (mm), and the results are listed in Table (9).

According to Table 9, compounds (6-8, 10) displayed exceptionally potent antibacterial activity against E. coli, with compounds (11, 12, 15, 17, 18) also demonstrating significant, though somewhat reduced, efficacy against this pathogen. Compounds (6, 10 and 18) showed very high activity against *Bacillus subtilis* bacteria, while compounds (7 and 11) showed high activity against these bacteria.

Compounds (6,7,8, 10, 11 and 18) showed very high activity against both *proteus* and *staphylococcus* bacteria, while compounds (9, 12, 15, 16 and 17) showed high antibacterial activity against proteus bacteria and compound (12) showed high activity against *staphylococcus* bacteria. The remaining compounds showed moderate antibacterial activity [30].

Overall, all the tested compounds showed very promising antifungal activity against *Candida albicans* fungi.

Thus, compounds (6, 7, 8, 10, 11, 15, 16 and 18) showed excellent results through very high antifungal activity against [30] *Candida albicans* fungi, while compounds (9, 12 and 17) showed high activity against these fungi.

Table 9: Inhibition zones of antibacterial and antifungal activity (mm) of the prepared compounds

Comp.No.	*E.Coli*	*Bacillus subtilis*	*proteus*	*staphylococcus*	*Candida albicans* fungi
6	26	20	20	19	30
7	20	15	16	22	32
8	22	8	15	24	23
9	8	8	11	8	13
10	20	25	20	25	24
11	15	12	14	22	32
12	13	9	10	15	16
15	13	8	13	9	35
16	8	8	9	8	20
17	13	8	8	8	17
18	16	20	17	22	21
Amoxicillin	15	17	2	15	0
Fluconazole	0	0	0	0	18
DMSO	0	0	0	0	0

Conclusion

The synthesis of novel cyclic imides linked to various heterocycles or pharmaceuticals was successfully achieved using both Mannich and Gabriel reactions. Biological evaluations revealed that the newly synthesized compounds exhibit strong antibacterial and antifungal efficacy. These promising results confirm that combining cyclic imide structures with drug or heterocyclic moieties within the same molecule produces compounds with significant biological efficacy, as anticipated.

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