Synthesis, Characterization and Evaluation of Biological Activity of Novel Cyclic Imides Containing Heterocycles Based on 2,5-disubstituted-1,3,4-thiadiazoles

A. M. Al-Azzawi[*] and A. S. Hamd[**]
[*]College of Science\ University of Baghdad
[**]College of Veterinary Medicine\ Al-Anbar University

Abstract

Starting from 2-amino-5-mercapto-1,3,4-thiadiazole a variety of new cyclic imides linked to 1,3,4-thiadiazole moiety were synthesized via following different methods. The first method involved synthesis of a series of amic acids containing 1,3,4-thiadiazole ring via reaction of different cyclic anhydrides with 2-amino-5-mercapto-1,3,4-thiadiazole, then the resulted amic acids were dehydrated by using acetic anhydride and anhydrous sodium acetate as dehydrating agent to produce the corresponding cyclic imides. The strategy used in performing the second method involved reaction of 2-amino-5-mercapto-1,3,4-thiadiazole with (bis naphthalic anhydride, 2,3-pyridinic anhydride and 1,8-naphthalic anhydride) in the presence of glacial acetic acid. The present work involved also synthesis of six new cyclic imides linked to 1,3,4-thiadizole ring and containing six-membered (phthalazine, 4-methyl pyridazine, pyridazine and tetrahydropyridazine)-3,6-dione moiety. Synthesis of four of these imides based on introducing 2-amino-5-hydrazino-1,3,4-thiadiazole on reaction with different cyclic anhydrides producing the corresponding bis amic acids which were subsequently introduced in dehydration reaction producing the desirable new compounds while the other two imides were prepared via direct reaction of 2-(N-maleimidyl)-5-hydrazino-1,3,4-thiadiazole with cyclic anhydride in glacial acetic acid under reflux conditions. The synthesized compounds were screened for their antimicrobial activity and were found to exhibit good to moderate antimicrobial activity against the tested organisms.

تحضير وتشخيص وتقدير الفعالية البايولوجية لعدد من الايمايدات الحلقية الجديدة الحاوية على حلقات غير متجانسة والمعتمدة على المركب 5,2 – ثنائي معوض 4,3,1– ثايادايازول

أحلام معروف العزاوي[*] واحمد سليمان حمد[**]
[*]كلية العلوم/ جامعة بغداد
[**]كلية الطب البيطري/ جامعة الأنبار

الخلاصة

تم في هذا البحث تحضير عدد من الايمايدات الحلقية الجديدة ابتداء من المركب 2– امينو–5– ميركبتو– 4,3,1–ثايا دايازول بإتباع طرق تحضير مختلفة. تضمنت الطريقة الأولى تحضير سلسلة من حوامض الاميك الحاوية على حلقة 4,3,1 – ثايا دايازول وذلك من خلال تفاعل انهيدريدات حلقية مختلفة مع المركب 2– امينو–5– ميركبتو– 4,3,1 – ثايا دايازول، بعدها تم سحب الماء من حوامض الاميك المحضرة باستخدام انهيدريد الخليك وخلات الصوديوم اللامائية كعامل ساحب للماء للحصول على الايمايدات المقابلة. أما الطريقة الثانية فقد تضمنت تفاعل المركب 2– امينو–5– ميركبتو– 4,3,1 – ثايا دايازول مع كل من انهيدريد ثنائي نفثاليك، انهيدريد البيريدينيك وانهيدريد 8,1– نفثاليك بوجود حامض الخليك الثلجي. إضافة إلى ذلك فقد تضمن البحث الحالي

تحضير ستة ايمايدات حلقية جديدة مرتبطة بحلقة 4,3,1- ثايا دايازول وحلقة سداسية متمثلة بالمكونة (فثالازين، 4- مثيل بيريدازين، بيريدازين، رباعي هيدرو بيريدازين)-6,3- ثنائي دايون. يعتمد تحضير أربعة من هذه الايمايدات على إدخال المركب 2-امينو -5- هيدرازينو-4,3,1- ثايا دايازول في تفاعل مع انهيدريدات حلقية مختلفة للحصول على حوامض ثنائي الاميك التي يسحب منها الماء لاحقا لتحويلها إلى الايمايدات المطلوبة، إما الايمايدين الاثنين الباقيين فقد تم تحضيرهم من خلال التفاعل المباشر بين المركب 2- (N- مالي اميديل)-5- هيدرازينو-4,3,1-ثايا دايازول مع الانهيدريد الحلقي في حامض الخليك الثلجي. تمت دراسة الفعالية البايولوجية لبعض المركبات المحضرة ضد أربعة أنواع من البكتريا ونوع من الفطريات وقد أظهرت النتائج بان اغلب المركبات المختبرة ذات فعالية جيدة ضد المايكروبات قيد الدراسة.

Introduction

Five membered heterocyclic compounds show various types of biological activities, among them 2,5-disubstituted-1,3,4-thiadiazoles are associated with diverse biological activities probably by the virtue of -N=C-S- grouping, some of them possess antibacterial(1), antifungal(2) and antitubercular(3) while others showed anti-inflammatory(4) and anticonvulsant(5) activities. On the other hand cyclic imides are an important class of substrates for biological and chemical applications thus a diversity of biological activities and pharmaceutical uses have been attributed to them such as antibacterial(6) antifungal and some of them are extensively used as analgesic(7) and antinociceptive agents(8). An imide nucleus can be also found in a structure of anticancer(9), anxiolytic(10) and anti-inflammatory(11) substances. All these biological data prompted us to synthesize a series of new molecules containing the two active moleties (cyclic imide and 1,3,4-thiadiazole) with expected biological activity.

Materials and Methods

FTIR spectra were recorded on SHIMADZU FTIR-8400 Fouries Transform Infrared spectrophotometer using KBr discs. Melting points were determined on Thomas Hoover apparatus and were uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded on Bruker 300MHz instrument using DMSO-d^{6} as a solvent and TMS as internal reference.

- **Synthesis of 2-amino-5-mercapto-1,3,4-thiadiazole [1]:** The titled compound was prepared from thiosemicarbazide according to literature(12) as yellow crystals, m.p. (227-228)°C.
- **Synthesis of N-(5-mercapto-1,3,4-thiadiazole-2-yl) amic acids [2-6]:** The titled amic acids were prepared according to literatures with some modifications (13,14).

A solution of (0.01 mol) of 2-amino-5-mercapto-1,3,4-thiadiazole dissolved in (25 mL) of acetone was added dropwise to a solution of (0.01 mol) of cyclic anhydride (maleic, citraconic, phthalic, succinic and pyridinic anhydrides) dissolved in (25 mL) of acetone with stirring and cooling. Stirring was continued for 4hrs at R.T. and the resulted precipitate was filtered then purified by recrystallization from a suitable solvent.

- **Synthesis of Bis-N-(5-mercapto-1,3,4-thiadiazole-2-yl) amic acid [7-8]:** Bis amic acids [7] and [8] were prepared by following the same procedure used in the synthesis of amic acids [2-6] except using of (0.01 mol) of cyclic anhydride (pyromellitic and bis naphthalic anhydrides) with (0.02 mol) of 2-amino-5-mercapto-1,3,4-thiadiazole.

The resulted bis amic acids were purified by recrytallization from a suitable solvent. Physical properties of compounds [2-8] are listed in Table (1).

- **Synthesis of N-(5-mercapto-1,3,4-thiadiazole-2-yl) cyclic imides [9-1]:** The titled imides were synthesized via dehydration of the corresponding amic acids(15,16).

A mixture of (0.01 mol) of amic acid, (25 mL) acetic anhydride and 5% of amic acid weight of anhydrous sodium acetate was refluxed for 3hrs with stirring. The resulted mixture was poured into crushed ice with vigorous stirring and the obtained precipitate was filtered, dried then purified by recrystallization from a suitable solvent. Physical properties of the new imides [9-15] are listed in Table (2).

- **Synthesis of N- (5- mercapto- 1,3,4- thiadiazole -2-yl) -1,8- naphthalimide [16]:** A mixture of (0.01 mol 1.33g) of 2-amino-5-mercapto-1,3,4-thiadiazol, (0.01 mol 1.98g) of 1,8-naphthalic anhydride and (30 mL) of glacial acetic acid was refluxed for 6hrs with stirring.

The resulted mixture was cooled to R.T. before pouring into crushed ice with vigorous stirring. The obtained precipitate was filtered, washed thoroughly with water and dried then purified by recrystallization from a suitable solvent. The two imides N-(5-mercapto-1,3,4-thiadiazole-2-yl) pyridinimide and N-(5-mercapto-1,3,4-thiadiazole-2-yl)bis naphthalimide were synthesized also by following this method.

- **Synthesis of 2-amino-5-hydrazino-1,3,4-thiadiazole [17]:** Compound [17] was synthesized as reported in literature(17). The obtained compound having melting point (242-244)°C, yield 75%, IR: 3400-3250 cm^{-1} ($NHNH_2$), 3200, 3168 cm^{-1} (NH_2), 1600 cm^{-1} ν(C=N) and 688 cm^{-1} ν(C-S).
- **Synthesis of 5-(N-hydrazinomaleamic acid)-1,3,4-thiadiazole-2-yl-maleamic acid [18]:** Compound [18] was prepared via the reaction of (0.01 mol) of compound [17] and (0.02 mol 0.98g) of maleic anhydride following the same procedure used in the synthesis of amic acids [2-6]. The resulted solid was purified by recrystallization from ethanol.
- **Synthesis of Compounds [19-21]:** Compound [19] 5-(N-hydrazinocitraconamic acid)-1,3,4-thiadiazole-2-yl-citraconamic acid, compound [20] 5- (N-hydrazinosuccinamic acid)-1,3,4-thiadiazole-2-yl-succinamic acid and compound [21] 5-(N-hydrazinophthalamic acid)-1,3,4-thiadiazole-2-yl-phthalamic acid were synthesized via the reaction of (0.01 mol) of compound [17] and (0.02 mol) of cyclic anhydrides (citraconic, succinic and phthalic anhydrides) following the same procedure used in the synthesis of compounds [2-6]. Physical properties of compounds [18-21] are listed in Table (5).
- **Synthesis of N-[5-(1,2-dihydropyridazine-3,6-dione-1-yl)-1,3,4-thiadiazole-2-yl]maleimide [22]:** Compound [22] was synthesized via dehydration of compound [18] using acetic anhydride and anhydrous sodium acetate as dehydrating agent following the same procedure used in the synthesis of compounds [9-15]. The obtained imide was purified by recrystallization from ethanol.
- **Synthesis of Compounds [23-25]:** Compound [23] N-[5-(1,2-dihydro-4-methylpyridazine-3,6-dione-1-yl)-1,3,4-thiadiazole-2-yl]citraconimide, compound [24] N-[5-(1,2,4,5-tetrahydropyridiazine-3,6-dione-1-yl)-1,3,4-thiadiazole-2-yl]succinimide and compound [25] N-[5-(1,2-dihydrophthalazine-3,6-dione-1-yl)-1,3,4-thiadiazole-2-yl]phthalimide were synthesized via dehydration of compounds [19, 20, 21] using acetic anhydride and anhydrous sodium acetate as dehydrating agent following the same procedure used in the synthesis of compounds [9-15]. Physical properties of compounds [22-25] are listed in Table (6).
- **Synthesis of 2-(N-maleimidyl)-5-hydrazino-1,3,4-thiadiazole [26]:** Compound [26] was synthesized via treatment of compound [9] N-(5-mercapto-1,3,4-thiadiazole-2-yl)maleimide with hydrazine hydrate depending on literature procedure (17). The solid that separated in cooling was filtered off and dried. M.p.

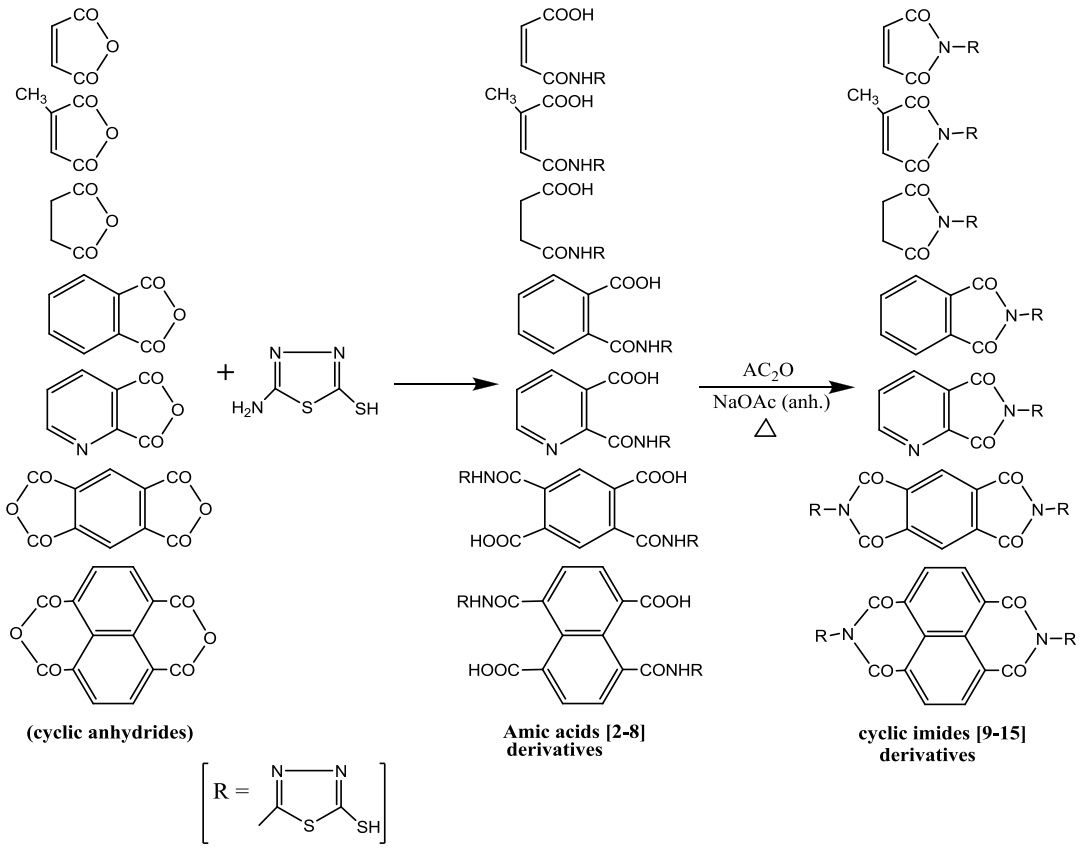
(122-124)°C, yield 78%, IR: 3398, 3278 cm^{-1} ($NHNH_2$), 3174 cm^{-1} (NH_2), 1720 cm^{-1} ν(C=O) imide, 1600 cm^{-1} ν(C=N), 1365 cm^{-1} ν(C-N)imide, 1535 cm^{-1} ν(C=C) and 667 cm^{-1} ν(C-S).

- **Synthesis of N-[5-(1,2-dihydro-4-methylpyridazine-3,6-dione-1-yl)-1,3,4-thiadiazole-2-yl]maleimide [27]:** Compound [27] was synthesized via reaction of compound [26] with citraconic anhydride in glacial acetic acid following the same procedure used in the synthesis of compound [16]. The resulted solid was purified by recrystallization from ethanol.
- **Synthesis of N-[5-(1,2-dihydrophthalazine-3,6-dione-1-yl)-1,3,4-thiadiazole-2-yl]maleimide [28]:** Compound [28] was synthesized via reaction of compound [26] with phthalic anhydride in glacial acetic acid following the same procedure used in the synthesis of compound [16]. Physical properties of compounds [27-28] are listed in Table (8).
- **Biological Evaluating:** The cup plate method using nutrient agar medium was employed in studying the antimicrobial activity of the prepared imides against four types of bacteria including *Staphylococcus aureous*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aureginosa* respectively and *Candida albicans* fungi.

DMF was used as sample solution and sample size for all the compounds was fixed at (0.1 mL). Using a sterilized cork borer cups were scooped out of agar medium contained in a petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the petri dishes were subsequently incubated at 37°C for 48 hrs. Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (9).

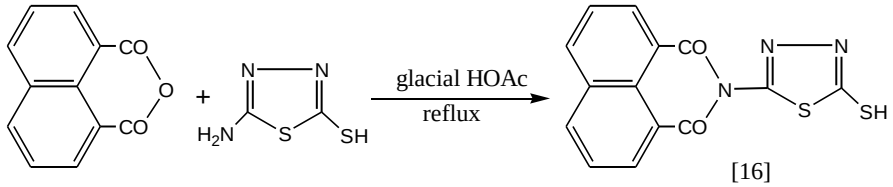
Results and Discussion

Since both cyclic imides and 1,3,4-thiadiazoles are known biologically active components having wide spectrum of biological and pharmacological applications, the aim of the present work is directed toward synthesis of new compounds containing these two active moieties with expected biological activity. Many strategies were used to perform this target, the first one involved synthesis of seven new cyclic imides linked to 5-mercapto-1,3,4-thiadiazole moiety via reaction of 2-amino-5-mercapto-1,3,4-thiadiazole with different cyclic anhydrides including (maleic, citraconic, succinic, phthalic, pyridinic, pyromellitic and bis napthalic anhydrides) producing N-(5-mercapto-1,3,4-thiadiazole-2-yl)amic acids which subsequently dehydrated via treatment with acetic anhydride and anhydrous sodium acetate to produce the desirable corresponding imides as shown in scheme (1).



Scheme (1)

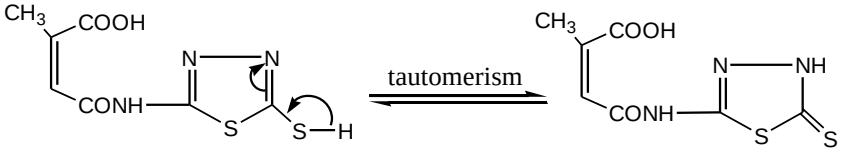
The second strategy used in the present work involved treatment of cyclic anhydride with 2-amino-5-mercapto-1,3,4-thiadiazole in glacial acetic acid under reflux condition for many hours. This method was applied successfully in the preparation of N-(5-mercapto-1,3,4-thiadiazole-2-yl)-1,8-naphthalimide [16].



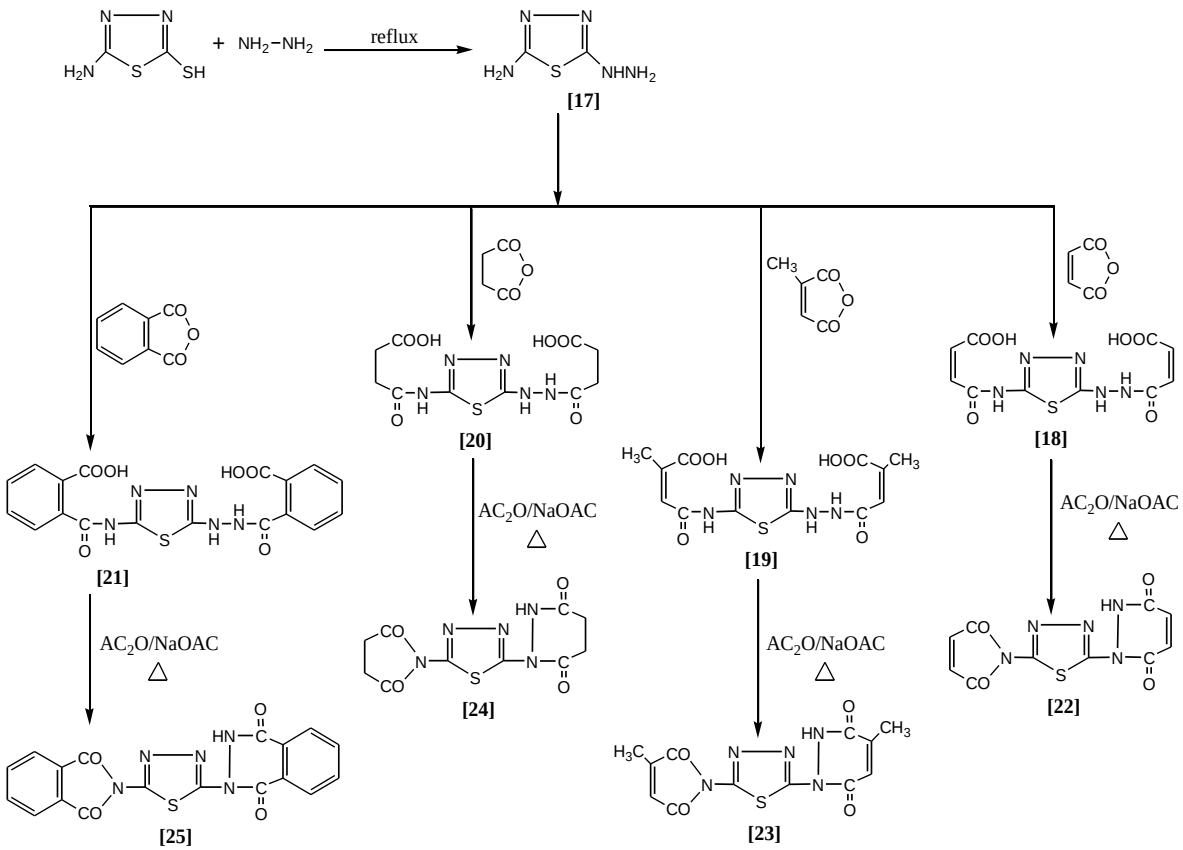
[16]

It is necessary to mention here that imides [13] and [15] were also prepared successfully by application of this method and physical properties, spectral data of these two imides prepared by the two methods are identical. Physical properties of the prepared amic acids [2-8] and imides [9-15] are listed in Tables (1) and (2). Structures of the prepared compounds [2-16] were confirmed by FTIR and HNMR, ^{13}CNMR for some of them. FTIR spectra of the prepared amic acids [2-8] showed many characteristic absorption bands including bands at (3170-3549) cm^{-1} belong to ν(N-H) amide and ν(O-H) carboxylic, other bands appeared at (1666-1735) cm^{-1}, (1650-1689) cm^{-1}, (1562-1624) cm^{-1}, (1480-1573) cm^{-1} and (605-686) cm^{-1} due to ν(C=O) carboxylic, ν(C=O) amide, ν(C=N), ν(C=C) and ν(C-S) respectively(15). On the other hand FTIR spectra of the prepared imides [9-16] showed disappearance of absorption bands belong to ν(O-H) carboxylic and ν(N-H) amide indicating success of dehydration

reaction. Also, FTIR spectra showed many clear absorption bands including bands at (1697-1739) cm^{-1}, (1604-1687) cm^{-1}, (1546-1585) cm^{-1}, (1342-1373) cm^{-1} due to ν(C=O) imide, ν(C=N), ν(C=C), ν(C-N) imide and ν(C-S) respectively. All details of FTIR spectral data of compounds [2-8] and [9-16] are listed in Tables (3) and (4). Structures of some amic acids and imides are confirmed also by depending on HNMR and ^{13}CNMR spectral data thus, HNMR spectrum of compound [3] N-(5-mercapto-1,3,4-thiadiazole-2-yl) citraconamic acid showed signals at (δ=1.6, 2.5, 6.6, 12.6 and 14) ppm belong to NH, CH_3 protons, vinylic proton, SH, NH and OH protons(18). ^{13}CNMR spectrum of compound [3] showed signals at δ= (11.4-27.1) and (51.11 and 55.31) ppm which belong to methyl group and two vinylic carbons. Other signals appeared at (δ= 127.1-184.1) ppm due to (C=N), (C=O carboxylic), (C=O) amide and (C=S) which present because of tautomerism as shown in equation below.

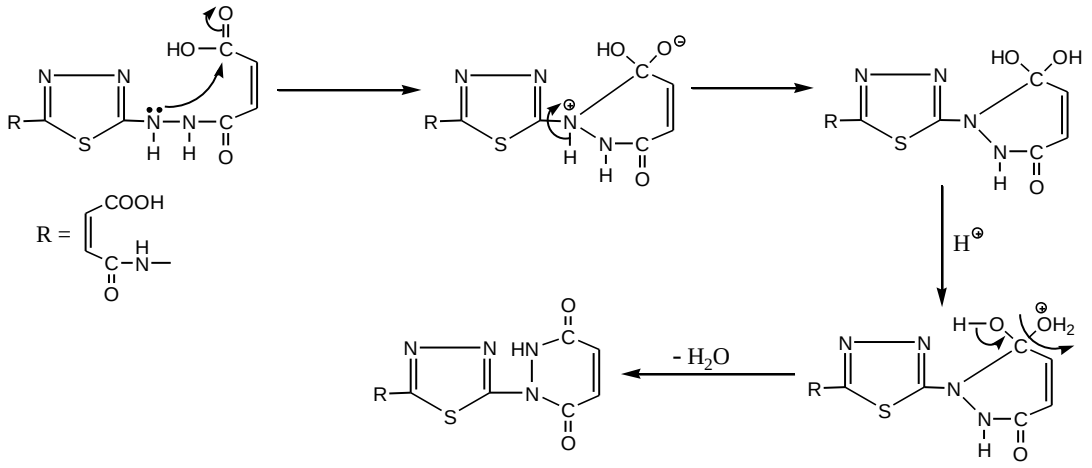


HNMR spectrum of compound [4] N-(5-mercapto-1,3,4-thiadiazole-2-yl) succinamic acid showed signals at (δ = 2 and 2.4) ppm belong to aliphatic protons (-CH_2-CH_2), signals at (δ = 12.25, 13.1 and 13.9) ppm due to SH, NH and OH protons. ^{13}CNMR spectrum of compound [4] showed many signals including signals at δ= 22.69, 22.73, 152.6, 161.9, 169.8, 181.3 and 183.9) ppm belong to aliphatic carbons, (C=S), (C=N), (C=O) amide and (C=O) carboxylic carbons(18). HNMR spectrum of compound [11] N-(5-mercapto-1,3,4-thiadiazole-2-yl) succinimde showed signals at (δ=1.9, 2.1, 2.5, 11.9) ppm due to amine proton, aliphaltic protons (-CH_2CH_2-) and NH tautomer. ^{13}CNMR spectrum of the same compound [11] showed signals at δ= (21.5-26.1) and 169.79 ppm belong to aliphatic carbons, (C=N) and (C=O). Finally HNMR spectrum of compound [16] N-(5-mercapto-1,3,4-thiadiazole-2-yl)-1,8-naphthalimide showed signals at (δ= 2.5, (7.8-8.4) and 11.8) ppm belong to amine proton, aromatic protons and NH proton. ^{13}CNMR spectrum of the same compound showed signals at δ= (123-136) ppm and at (δ= 164.5) ppm belong to aromatic ring carbons, (C=N) and (C=O). The second part of this work involved synthesis of four new cyclic imides containing 1,3,4-thiadiazole ring and six-membered (phthalazine, pyridazine, 4-methylpyridazine and tetrahydropyridazine)-3,6-dione moiety. The strategy followed in performing this part based on synthesis of 2-amino-5-hydrazino-1,3,4-thiadiazole which represents a diamino compound introduced successfully in reaction with different cyclic anhydrides including (maleic, citraconic, succinic and phthalic) anhydrides producing bis acids [18-21] which inturn were dehydrated to the corresponding imides [22-25] via treatment with acetic anhydride and anhydrous sodium acetate as described in Scheme (2).



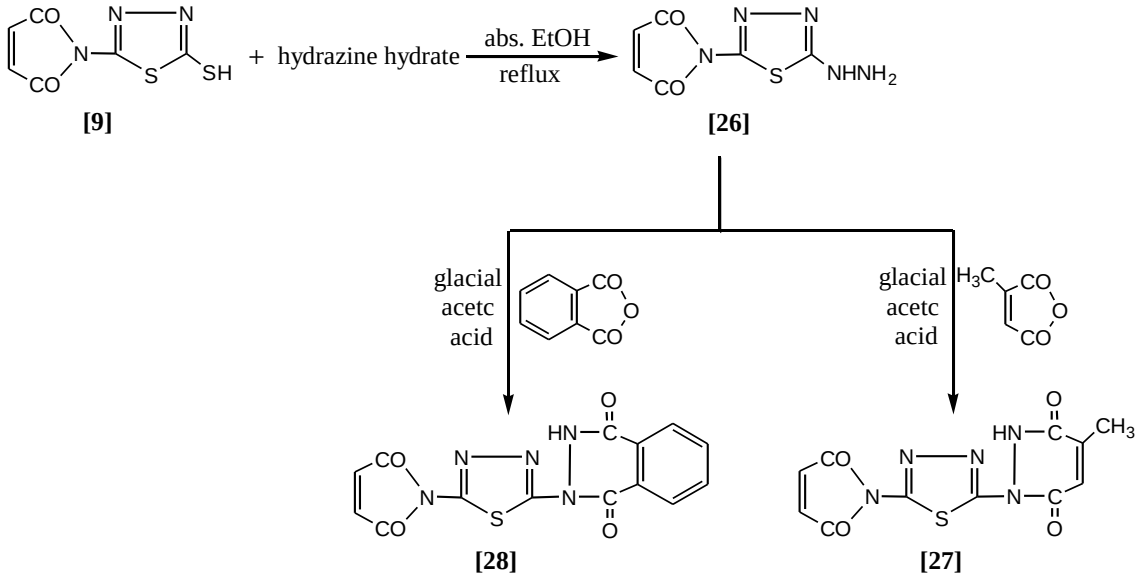
Scheme (2)

Formation of the six-membered hetero ring was performed via nucleophilic attack of amino group (the strongest nucleophile in the molecule) on electron-deficient carbon in carboxyl group causing ring-closure followed by elimination of water molecule producing the six-membered diazine ring as shown in Scheme (3).



Scheme (3)

At the same time in the other side of the molecule which containing the amic acid moiety a nucleophilic attack of amido group on carboxylic carbon happened under the influence of (AC_2O/NaOAC) following mechanism steps as reported in literature(13) producing finally the new cyclic imides [22-25]. FTIR spectra of compounds [18-21] showed clear absorption bands at (3267-3456) cm^{-1} due to ν(O-H) carboxylic and ν(N-H) amide, other absorption bands appeared at (1654-1693) cm^{-1} due to ν(C=O) carboxylic and ν(C=O) amide, bands at (1585-1604) cm^{-1}, (1530-1539) cm^{-1} and (640-702) cm^{-1} were due to ν(C=N) and ν(C-S) respectively. FTIR spectra of compounds [22-25] showed disappearance of ν(O-H) carboxylic absorption band and appearance of many absorption bands at (3059-3324) cm^{-1}, (1696-1780) cm^{-1}, (1635-1735) cm^{-1}, (1593-1604) cm^{-1}, (1320-1431) cm^{-1} and (609-689) cm^{-1} due to ν(N-H), ν(C=O) imide, ν(C=O) amide, ν(C-N) imide and ν(C-S) respectively. HNMR spectrum of compound [23] showed two signals at (δ= 1.92 and 2.02) ppm belong to two methyl groups, signal at (δ= 5.8) ppm belong to NH proton and signal at (δ= 6.8) ppm belong to vinylic protons. ^{13}CNMR spectrum of compound [23] showed signals at (δ= 11.57-21.5) ppm belong two methyl groups, signals at (δ= 123-130) ppm belong to vinylic carbons and signals at (δ= 145.5-171.5) ppm belong to (C=N) and carbonyl groups. HNMR spectrum of compound [25] showed clear signals at (δ = 7.9-8.3) ppm belong to aromatic protons and (NH) proton. ^{13}CNMR spectrum of compound [25] showed signals at (δ= 124.7-146.4), (164.3) and (186.4) ppm which belong to aromatic ring carbons, C=N and carbonyl groups respectively. The third part in this work involved synthesis of two compounds containing maleimide ring and six-membered (phthalazine and 4-methylpyridazine)-3,6-dione moiety. The strategy used for synthesis of these two imides based on the synthesis of compound [26] 2-(N-maleimidyl)-5-hydrazino-1,3,4-thiadiazole which inturn was introduced subsequently in reaction with cyclic anhydride (citraconic and phthalic anhydrides) in glacial acetic acid producing the new imides as shown in scheme (4).



[9] **[26]** **[28]** **[27]**

Scheme (4)

FTIR spectra of compounds [27, 28] showed many clear absorption bands at (3394-3433) cm^{-1}; (1735-1743) cm^{-1} (1620) cm^{-1}, (1512-1519) cm^{-1}, (1311-1350) cm^{-1} and at (660-709) cm^{-1} which belong to ν(N-H) amide, ν(C=O) imide and amide, ν(C=N), ν(C=C), ν(C-N) imide and ν(C-S) respectively. Physical properties and FTIR spectral data of compounds [27, 28] are listed in Table (8).

Table (1) Physical properties of amic acids [2-8]

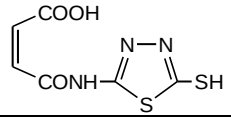
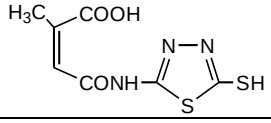
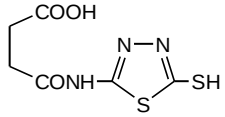
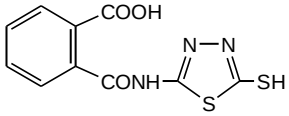
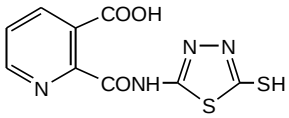
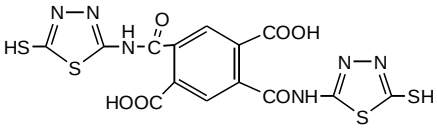
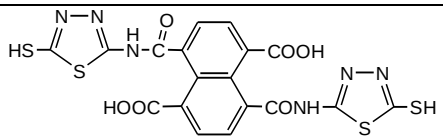
Comp. No.	Compound structure	color	Melting points °C	Yield %	Recrystallization solvent
2		Faint yellow	255-257	75	Methanol
3		Greenish yellow	226-227	85	Methanol
4		Yellow	230-232	65	Methanol
5		Deep yellow	258-260	90	Ethanol
6		Pale yellow	183-185	70	Ethanol
7		Orange	> 300	90	Ethanol
8		Green	> 300	86	Ethanol

Table (2) Physical properties of cyclic imides [9-16]

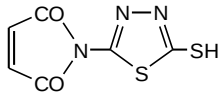
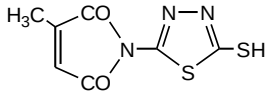
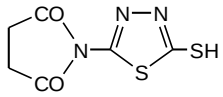
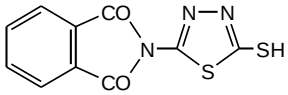
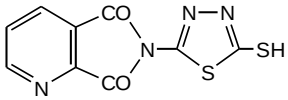
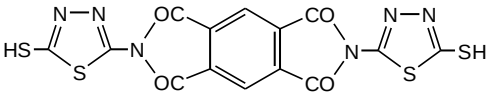
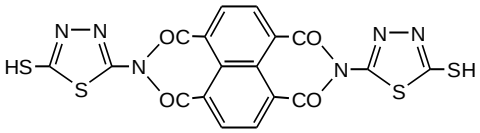
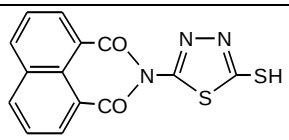
Comp. No.	Compound structure	color	Melting points °C	Yield %	Recrystallization solvent
9		Light brown	262-264	78	Methanol
10		Deep yellow	> 300	82	Methanol
11		Yellow	203-205	70	Methanol
12		Pale yellow	208-209	85	Ethanol
13		Pale yellow	264-266	80	Acetone
14		Redish brown	> 300	88	Ethanol
15		Deep green	> 300	75	Acetone
16		Faint yellow	250-252	77	Ethanol

Table (3) FTIR spectra data of amic acids [2-8]

Comp. No.	FTIR spectral data cm^{-1}						
	ν(O-H) carboxylic ν(N-H) amide	**ν(C=O) carboxylic**	**ν(C=O) amide**	**ν(C=N)**	**ν(C=C)**	**ν(C-S)**	**ν(C=S)**
2	3340 3255	1704	1681	1604	1550	648	1320
3	3448 3170	1704	1650	1566	1480	655	1311
4	3549 3452	1666	1666	1573	1489	605	1307
5	3456 3197	1735	1666	1573	1546 aromatic	644	1365
6	3441 3205	1681	1662	1562	1500 aromatic	686	1307
7	3483	1735	1689	1624	1573 aromatic	621	1307
8	3456 3290	1728	1678	1616	1581 aromatic	678	-

Table (4) FTIR spectra data of cyclic imides [9-16]

Comp. No.	FTIR spectral data cm^{-1}					
	ν(C-H)	ν(C=O) imide	ν(C=N)	ν(C-N) imide	ν(C=C)	ν(C-S)
9	3151	1724 1701	1616	1357	1550	617
10	3224	1728	1612	1357	1550	632
11	3155	1697	1620	1361	1562	624
12	3236 aromatic	1735	1608	1350	1566 aromatic	678
13	3232 aromatic	1739	1604	1346	1546 aromatic	675
14	3232 aromatic	1735	1620	1350	1554 aromatic	624
15	3197 aromatic	1724	1678	1342	1581 aromatic	640
16	3170 aromatic	1770 1701	1678	1373	1585 aromatic	694

Table (5) Physical properties of compounds [18-21]

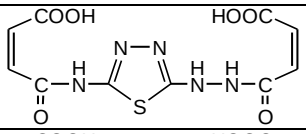
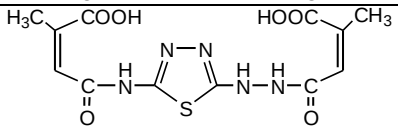
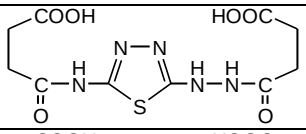
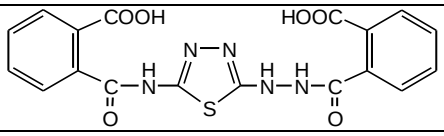
Comp. No.	Compound structure	color	Melting points °C	Yield %	Recrystallization solvent
18		Off white	180-182	78	Ethanol
19		Greenish yellow	194-195	81	Ethanol
20		White	183-185	69	Ethanol
21		Off white	213-215	85	Ethanol

Table (6) Physical properties of compounds [22-25]

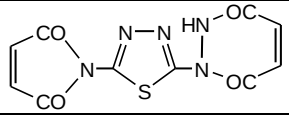
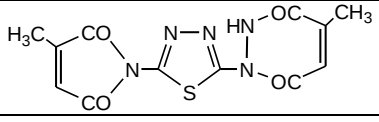
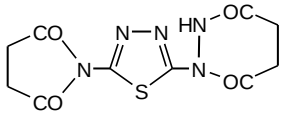
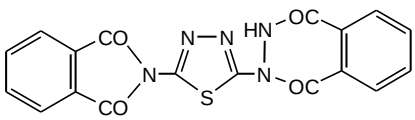
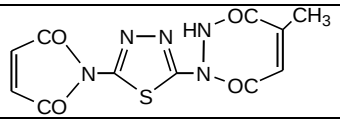
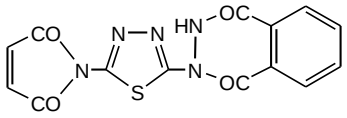
Comp. No.	Compound structure	color	Melting points °C	Yield %	Recrystallization solvent
22		Orange	Oily	82	Ethanol
23		Faint yellow	134-136	74	Ethanol
24		Faint yellow	165-166	70	Ethanol
25		Yellow	270-272	76	Ethanol

Table (7) FTIR spectra data of compounds [18-25]

Comp. No.	FTIR spectral data cm^{-1}					
	ν(O-H) carboxylic ν(N-H) amide	ν(C=O)	ν(C=N)	ν(C=C)	ν(C-S)	ν(C-H)
18	3456 3270	1654	1600	1530 Vinylic	702	3178
19	3400 3269	1652	1604	1550 vinylic	671	3087
20	3394 3267	1693	1604	-	640	3089
21	3400	1685	1585	1539 aromatic	675	3074

Comp. No.	ν(N-H) amide	ν(C=O) imide	ν(C=O) amide	ν(C=N)	ν(C=C)	ν(C-N) imide	ν(C-S)
22	3059	1770 (sholder) 1708	1635	1593	1566 vinylic	1431	609
23	3324	1762	1762	1652	1483 vinylic	1372	689
24	3091	1696	1696	1600	-	1320	638
25	3201	1780	1735	1604	1542 aromatic	1360	640

Table (8) Physical properties and FTIR spectral data of compounds [27, 28]

Comp. No.	Compound structure	color	Melting points °C	Yield %	Recrystallization solvent
27		Brown	> 300	72	Ethanol
28		Brown	> 300	74	Ethanol

Comp. No.	FTIR spectral data cm^{-1}					
	ν(N-H) amide	ν(C=O)	ν(C=N)	ν(C=C)	ν(C-N) imide	ν(C-S)
27	3433	1780 (sholder) 1735	1620	1519	1311	660
28	3394	1780 (sholder) 1743	1620	1512	1350	709

Table (9) Antibacterial and antifungal activity for some of the prepared compounds

Comp. No.	Gram-positive bacteria		Gram-negative		Fungi
	Staphylococcus aureus	*Streptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*
3	-	+	++	++	++
5	++	++	++	+++	++
9	+++	++	+	++	+
10	++	+	+++	++	++
12	++	+	+	+	-
16	++	++	-	+++	+++++
22	++	++	+++	-	-
23	++	++	++	++	++

Key to symbols: inhibition zone <6 = (-) inactive, (6-9) mm =(+) slightly active, (9-12) mm=(++) moderately active, (13-16)mm = (+++) highly active, >17 mm = (++++) very high activity.

References

1. Thomasco, M. L.; Godwood, C. R.; Weaver, A. E.; Ochoada, M. J. & W.C. Ford, W. C. (2003). The synthesis and antibacterial activity of 1,3,4-Thiadiazole phenyl oxazolidinone analogues Bioorg. Med. Chem. Lett., 13: 4193-4196.
2. Bano. Q. & Nizamudin, N. T. (1992). Sythesis and fungicidal activities of 3-aryl-loxmethyl-6-substituted-1,2,4-triazole[3,4-b]-1,3,4-thiadiazole. Indian J. Chem.,31B: 714-718.
3. Joshi, S. H. & Thaker, M. K. (2005). Synthesis and pharmacological evaluation of 2-(3',5'-dichlorobenzo[b]thiophen-2'-yl)-5-arylamino-1,3,4-thiadiazoles.
4. Plaska, E.; Shahin, G.; Kelicen, P.; Duslu, T. N. & Altino, G. (2002). Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides,1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones II Farmaco. 57: 101-107.
5. Siddiqui, N.; Rana, A.; Khan, S. A.; Bhat, M. A. & Haque, S. E. (2007). Synthesis of benzothiazole semicarbazones as novel anticonvulsants-The role of hydrophobic domainBioorg. Med. Chem. Lett., 17: 4178-4182.
6. Struga, M.; Kossakowski, J.; Stefanska, J.; Zimmiak, A. & Koziol, A. (2008). Synthesis and antibacterial activity of bis-[2-hydroxy-3-(1,7,8,9,10-pentamethyl-3,5-dioxo-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yloxy)-propyl]-dimethyl ammoniumchloride. Eur. J. Med. Chem., 43:1309-1314.
7. Borchhardt, D. M. & Andricopulo, A. D. (2009). CoMFA and CoMSIA 3D QSAR models for a series of cyclic Imides with analgesic activityMed.Chem.,5: 66-73.
8. Zhang, L.; Hao, G. F.; Tan, Y.; Xi, Z.; Huang, M. Z. & Yang, G. F. (2009). Bioactive conformation analysis of cyclic imides as protoporphyrinogen oxidase inhibitor by combining DFT calculations,QSAR and molecular dynamic simulations, Bioorg. Med. Chem., 17: 4935-4942.
9. Yunesa, J. A.; Cardoso, A. A.; Yunes, R. A.; Correa, R. & Filho, V. C. (2008). Antiproliferaive effects of a series of cyclic imides on primary endothelial cells and leukemia cell line. Z. Naturforsch, 63: 675.
10. Bojarski, A. J.; Kuran, B.; Kossakowski, J.; Koziol, A. & Chodkowska, A. (2009). Synthesis and serotonin receptor activity of the arylpiperazine alkyl/propoxy derivatives of new azatricycloundecanes Eur. J. Med. Chem., 44; 152-164.
11. Sondhi, S. M.; Rani, R.; Roy, P.; Agrawal, S. K. & Saxena, A. K. (2009). Microwave-assisted synthesis of N-substituted cyclic imides and their evaluation for anticancer and anti-inflammatory activities Bioorg. Med. Chem. Lett., 19: 1534-1538.
12. Katritzky, A. R.; Wang, Z. & Offerman, R. J. (1990). *S,S'*- and *S,N*disubstitut- ed derivatives of 1,3,4-thiadiazoledithiones J. Heterocyclic Chem., 27:139-142.
13. Al-Azzawi, A. M. & Al-Obydi, K. K. (2003). Polymerization of N-substituted phthalimidyl acrylates, National J. Chem., 12: 576.
14. Al-Azzawi, A. M. & Ali, M. S. (2008). Synehesis and curing of novel phenol-phormaldehyde resins containing pendant citraconimides, J. of Al-Nahrain University, 11(3): 15.
15. Al-Azzawi, A. M. & Mehdi, S. A. (2010). Synthesis, characterization and biological activity study of N-substituted sulfonamide maleimides substituted with heterocycles., Baghdad Sci. J., 7(1): 641.
16. Pyriadi, T. M.; Al-Azzawi, A. M. & Al-Obaidi, K. K. (2009). Synthesis, characterization and polymerization of N-substituted maleimidyl acrylates, J. Al-Nahrain University Sci., 12(2): 1.
17. Salih, N. A. (2005). Synthesis of new heterocyclic compounds and studying their antimicrobial activity, Ph.D. thesis, Chem. Dept., College of Sci., Al-Nahrain University.
18. Silverstein, R. M. & Bassler, G. C. (1981). "Spectrometric identification of organic compounds", 4th Ed., John and Sons.
19. Chava, A. A. & Pai, N. R. (2007). Synthesis and biological activity of N-substituted -3-chioro-2-azetdines. Molecules, 12: 2467-2477.
20. Al-Azzawi, A. M. & Hassan, A. S. (2010). Synthesis and evaluation of biological activity of new cyclic imides derived from 4-amino phenazone, J. of Kerbala University, 8(1): 387.