Synthesis, Characterization and study biologicalactivity of several 1-cyclopentene-1,2-dicarboxylimidyl Containing oxadiazole and Benzothiazole

*Shetha. N. Alzubaidy** *Mustafa A. Yasin***
*Omar A. lateef**** *Hind F. Thamer**

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Abstract:

In this work involved prepared of several new 1-cyclopentene-1,2-dicarboxylimide linked to oxadiazole and benzothiazole moiety were synthesized by two steps:
The first step 2-amino-substituted-1,3,4-oxadiazoles and substituted-2-aminobenzothiazole were reaction with 1-cyclopentene-1,2-dicarboxyl anhydride producing N-(5- substituted-1,3,4-oxadiazole-2-yl)-1-cyclopentene-1,2-dicarboxyl amic acids and N-(Substitutedbenzothiazole-2-yl)-1-cyclopentene-1,2-dicarboxyl amic acids which in turn were dehydrated in the second step via fusion method to afford he desirable N-(5-substituted-1,3,4-oxadiazole-2-yl)-1-cyclopentene-1,2-dicarboxylimides and N-(Substituted benzothiazole-2-yl)1-cyclopentene-1,2-dicarboxylimides respectively. Structures of the prepared compounds were characterized by depending on FTIR, U.V spectral data which were in agreement with the proposed ones. Finally antibacterial activity of some of the prepared new cyclic imides were studied by two types of bacteria and the results showed that the most of the tested imides posses good biological activity against these bacteria.

Key word: 1-cyclopentene-1,2-dicarboxylimidyl, oxadiazol, benzothiazol.

Introduction:

Various substituted benzothiazoles are known to cover a large domain of pharmacological activities serving as antitumor[1,2], antimicrobial[3,4], antihelmintic[1], anti-inflammatory[5,6] and anticonsulsive agents[1,4] also 1,3,4-Oxadiazoles have attracted an interesting medicinal chemistry as ester and amide for a number of biological targets[6]. More over these compounds have also demonstrateda broad spectrum of biological properties in both pharmaceutical and agrochemical fields such as antibacterial, anti – inflammatory, antimitotic, antiarrhythic and anticancer activities [7-12].

On the other hand synthetic cyclic imides such as succinimides, glutarimides, phthalimides and related compounds contain an imide ring and a general structure (-CO-N(R)-CO-) that confers hydrophobicity and neutral characteristic and can therefore cross biological membranes in vivo . A diversity of biological activities and pharmaceutical uses have been attributed to them such as antibacterial, antifungal, antinociceptive, anticonvulsant and antitumor [13-16].

On the other hand, imides are chemical compounds that have a biological activity, there are a lot of studies in which this fact first discovered by Brana and coworkers[17,18] are DNA – targeted chemotherapeutic agents acting primary by attacking DNA at

*Department of chemistry, college of science for women, Baghdad University, Iraq.
**Chemistry division, Department of applied science, University of technology.
***Department of chemistry, college of science, Baghdad University, Iraq.

some level (synthesis, replication or processing).

The therapeutic importance of these rings prompted us to synthesize new compounds by incorporating imide and benzothiazole, oxathiazole moieties in a single molecular framework.

The obtained new compounds were expected to possess biological activity since they were derived from biologically active components.

Materials and Methods:

Chemicals used in this work are supplied from Sigma Aldrich, B.D.H and Fluka companies and are used without further purification.

Melting points were determined on Gallenkamp capillary melting point apparatus and were uncorrected. FTIR spectra were recorded on SHIMADZU FTIR-8400

U.V spectra were recorded on SHIMADZU U.V-visible recording spectrophotometer U.V 1650. Melting point on STAURT-SMP10 Incubator Heraeus D-63450 (Germany) model was used for incubation samples in biological study.

1. Synthesis of N-(Substituted benzothiazole-2-yl)-1-cyclopentene-1,2-dicarboxyl amic acids and N-(5-substituted-1,3,4-oxadiazole-2-yl)-1-cyclopentene-1,2-dicarboxyl amic acids [1-8].

1-cyclopentene-1,2-dicarboxyl anhydride (0.01 mol) was dissolved in (20mL) of dry acetone in a suitable round bottomed flask fitted with dropping funnel which was supplied with (0.01 mol) of substituted-2-aminobenzothiazole and substituted-2-amino-1,3,4- oxadiazole dissolved in (30mL) of dry acetone[19].

The solution in dropping funnel was added drop wise to the mixture with stirring and cooling, then stirring was continued for additional two hours. The amic acid was filtered off, then purified by recrystallization from a suitable solvent.

Physical properties of 1-cyclopentene-1,2-dicarboxyl amic acids [1-8] are listed in Table (1).

2. Synthesis of N-(Substituted benzothiazole-2-yl)-1-cyclopentene-1,2-dicarboxylimides and N-(5-substituted -1,3,4-oxadiazole-2-yl)- 1-cyclopentene-1,2-dicarboxylimides Dehydration by using fusion method [9-16].

The titled compound were prepared by applying fusion method according to literature[19] via fusion of the prepared amic acids in oil bath for one hour with keeping oil temperature above melting point of the used amic acid by ten degrees.

The obtained solid was purified by recrystallization from a suitable solvent.

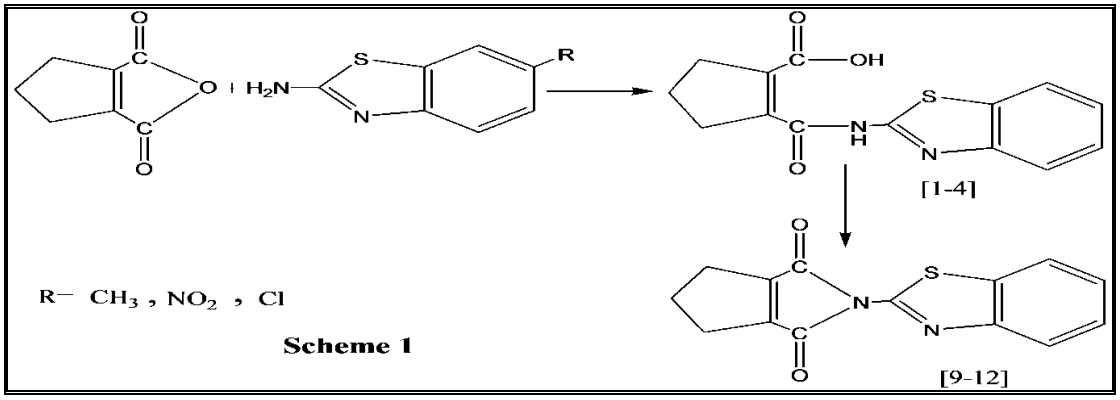
Physical properties of 1-cyclopentene-1,2-dicarboxylimides [9-16] are listed in Table (2).

3. Biological study

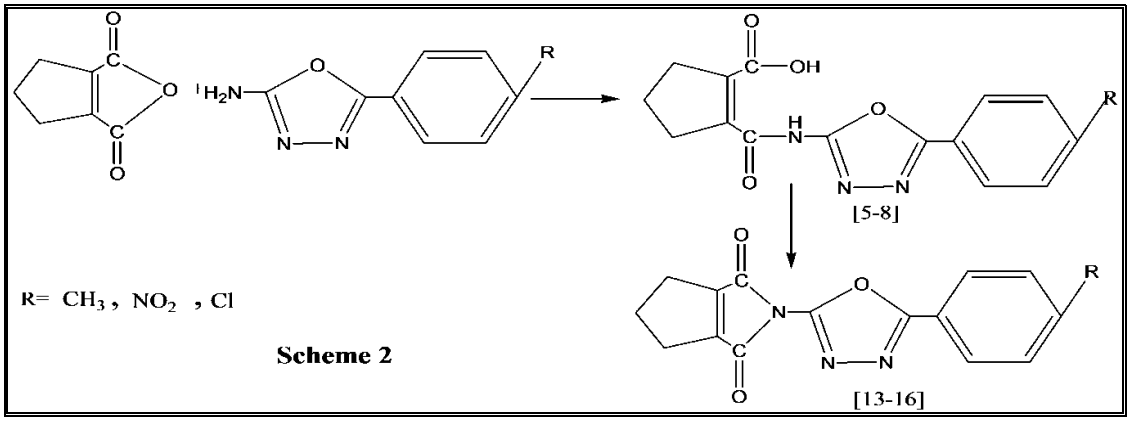
The cup plate method using nutrient agar medium was employed in studying the antibacterial activity of some of the prepared compounds[20,21] against two types of bacteria, staphylococcus aureous (Gram positive) and Escherichia Coli (Gram negative) respectively and DMF was used as sample solution .Using 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 (0.1mL) was added in the cups and the Petri dishes were subsequently incubated at (37 0C) for 48 hrs.

Zones of inhibition produced by each compound was measured in mm and the results are listed in Table (5).



Scheme 1



Scheme 2

Results and Discussion:

some compounds that using in this work are biologically active components having wide spectrum of medicinal and pharmacological applications, the present work is directed toward synthesis of new compounds containing these two active moieties with expected biological activity. The present work involved synthesis of new cyclic imides connected to different heterocycle. Strategy for performing this target involved many steps in the first one a series of substituted 2-amino-1,3,4-oxadiazole and substituted-2-aminobenzothiazole were introduced in reaction with1-cyclopentene-1,2-dicarboxyl anhydride in suitable solvent in the second step to obtain a series of N-(5-substituted-1,3,4-oxadiazole-2yl)-1-cyclopentene-1,2-dicarboxylamic acids and N-(Substituted benzothiazole-2-yl)-1-cyclopentene-1,2-dicarboxylamic acids respectively. The prepared amic acids were white to yellow and brown solids having sharp melting points and were afforded in good yields. Physical properties of the prepared amic acids are listed in Tables (1).

The second step of the present work involved dehydration of the prepared amic acids by fusion method. The prepared imides were colored solids with Sharp melting points and afforded in high percent yields. Physical properties of the prepared imides are listed in Tables (2).

FTIR, U.V spectral data were used for confirming structures of the prepared compounds and the obtained spectral data were in full agreement with the proposed structures. FTIR spectra of the prepared N-(Substituted benzothiazole-2-yl)-1-cyclopentene-1,2 dicarboxylamic acids[1-4] and Synthesis of N-(5-substituted-1,3,4-oxadiazole-2-yl)-1-cyclopentene-1,2-dicarboxylamic acids [5-8] showed many characteristic absorption bands including bands at (3195-3377) cm^{-1}

due to υ(O-H) carboxylic and (3296-3525) cm^{-1} to υ(N-H) amide, bands at (1685-1720) cm^{-1} and (1620-1653) cm^{-1} were assigned for υ(C=O) carboxylic and υ(C=O) amide, bands at(1585-1610) cm^{-1} belong to υ(C=N) benzothiazole (1550-1620) cm^{-1} to υ(C=N) oxadiazole and υ(C=C) aromatic bands at (1500-1550) cm^{-1} and (675-705) cm^{-1}, (1120-1150) cm^{-1} due to υ(C-S) benzothiazole and υ(C-O-C) in oxadiazole ring respectively[22,23] FTIR spectral data of the prepared imides are listed in Tables (3) .FTIR spectra of prepared imides [9-16] showed clear absorption bands at (1710-1766) cm-1 and (1340-1385) cm^{-1} due to υ(C=O) imide and υ(C-N) in imides. Other bands appeared at (1630-1685) cm^{-1}, (1645-1685) $cm^{-1}$to υ(C=N) in thiazole moiety and diazole moiety respectively, (620-710) cm^{-1} υ(C-S) in thiazole ring and (1140-1177) in υ(C-O-C) in oxadiazole ring[22]. U.V spectra of imides [9-16] showed clear absorptions at wavelengths (245-275) nm and (266-364) nm. These absorptions were due to (*) and (n→*) transitions in the conjugated system of benzothiazole, oxadiazole moiety and attached imide moiety, FTIR and U.V spectral data of the prepared imides are listed in Tables (4).

Biological activity

The prepared compounds were screened for their antibacterial activity against two microorganism including Staphylococcus aureus and E. coli. The tested compounds showed different biological activities against the studied types of bacteria as shown in Table (5). It was noticeable that biological activity of these compounds depend on nature of substituents in their molecules thus compounds [9,11,15,16] showed high activity against E.coli, compounds [12] showed moderate activity against this bacteria while compounds [13,14] showed slight activity and compounds [10] showed inactivity against this bacteria. On the other hand compounds [10,12,15,16] showed moderate activity against S.aureus while compounds [13] showed slight activity and compounds [9,11,14] showed inactivity against this bacteria.

Table (1): Physical properties of Amic acids

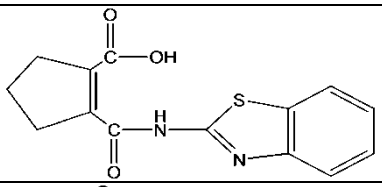
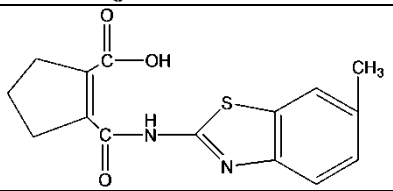
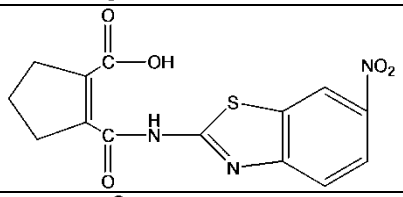
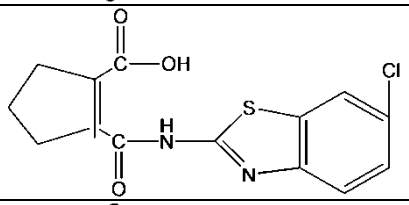
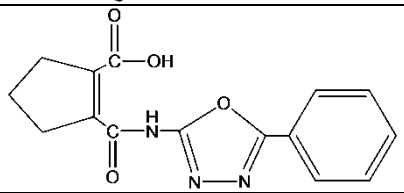
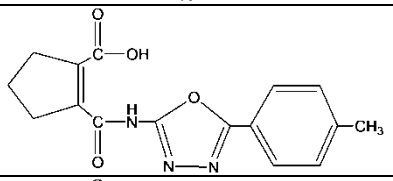
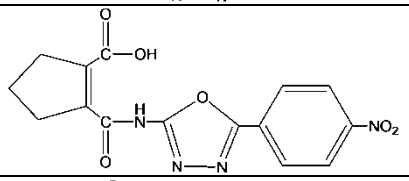
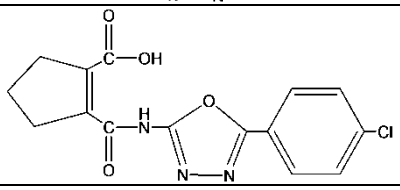
Comp. No.	Compound structure	Yield %	Color	Melting points ^0C	Solvent of Recrystallization
1		80	Yellow	160-162	Ethanol
2		88	Light brown	180-182	Ethanol
3		85	Brown	188-190	Methanol
4		84	White	177-179	Ethanol
5		87	Yellow	166-168	Ethanol
6		90	White	173-175	Methanol
7		79	Deep yellow	195-197	Ethanol
8		85	Off white	183-185	Ethanol

Table (2): Physical properties of imides

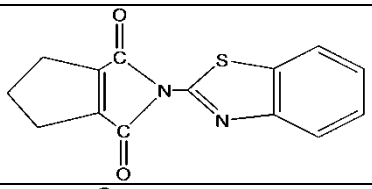
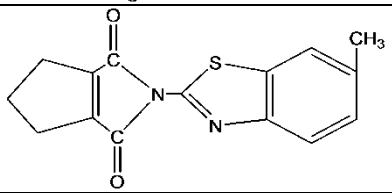
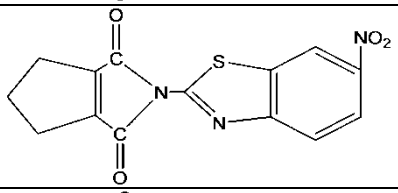
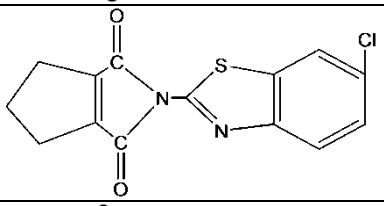
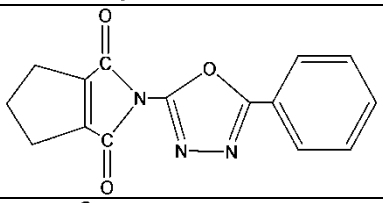
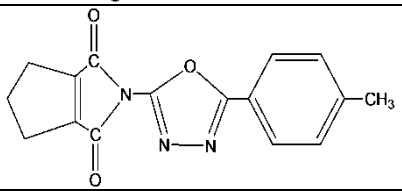
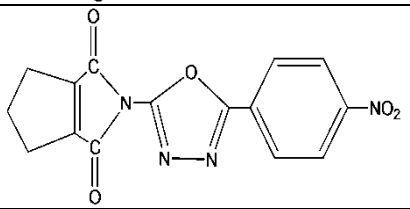
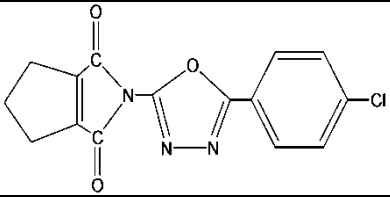
Comp. No.	Compound structure	Yield %	Color	Melting points ^{0}C	Solvent of Recrystallization
9		77	Pale Yellow	233-235	Cyclohexane
10		75	Brown	262-264	Cyclohexane
11		75	White	270-272	Ethanol/chloroform (1:1)
12		80	Yellow	255-257	Ethanol
13		80	Brown	143-145	Dioxane
14		79	Brown	127-129	Dioxane
15		65	Deep yellow	162-164	Dioxane
16		77	Brown	150-152	Cyclohexane

Table (3) FTIR spectral data of the prepared amic acids

Comp. No.	υ(O-H) Carboxyl	υ(N-H) Amide	υ(C=O) Carboxyl	υ(C=O) Amide	υ(C=C) Aromatic	υ(C=N)	Others
1	3218	3479	1704	1636	1508	1590	**υ (C-S)** 675
2	3257	3296	1697	1650	1521	1610	**υ(C-S)** 677
3	3220	3356	1701	1637	1550	1610	**υ(C-S)** 705 **υ(C-NO_2)** 1310
4	3257	3325	1710	1632	1540	1585	**υ (C-S)** 685 **υ(C-Cl)** 1110
5	3335	3525	1690	1653	1500	1550	**υ(C-O-C)** 1120
6	3377	3390	1720	1635	1509	1550	**υ(C-O-C)** 1120
7	3195	3356	1685	1628	1508	1605	**υ(C-O-C)** 1143 **υ(C-NO_2)** 1340
8	3335	3479	1697	1620	1540	1620	**υ(C-O-C)** 1150 **υ(C-Cl)** 1059

Table (4) FTIR and U.V spectral data of the prepared imides

Comp. No.	FTIR spectral data cm-1						U.V λmax nm
	υ(C=O) Imide	υ(C-N) Imide	υ(C=C) Aromatic	υ(C-H) Aromatic	υ(C=N)	Others	
9	1710	1340	1580	3055	1680	**υ (C-S)** 620	264,291
10	1714	1348	1589	3057	1685	**υ(C-S)** 700	248,278
11	1720	1355	1570	3030	1630	**υ(C-S)** 710 **υ(C-NO_2)** 1303	246,266
12	1726	1360	1583	3070	1677	**υ (C-S)** 630 **υ(C-Cl)** 1100	260,295
13	1750	1360	1595	3020	1650	**υ(C-O-C)** 1170	275,364
14	1766	1385	1580	3050	1645	**υ(C-O-C)** 1144	245,320
15	1760	1355	1590	3077	1680	**υ(C-O-C)** 1177 **υ(C-NO_2)**1390	250,291
16	1750	1350	1588	3044	1685	**υ(C-O-C)** 1140 **υ(C-Cl)** 1060	245,360

Table (5): Antibacterial activity for some of the prepared compounds

Comp. No.	Gram positive bacteria	Gram negative bacteria
	Stapylococcus aureus	**Escherichia coli**
9	-	+++
10	++	-
11	-	+++
12	++	++
13	+	+
14	-	+
15	++	+++
16	++	+++

Key to symbols = Inactive = (-) (inhibition zone < 6mm)
Slightly active = (+) (inhibition zone 6-9 mm)
Moderately active = (++) (inhibition zone 9-12 mm)
Highly active = (+++) (inhibition zone > 12mm)

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تخليق وتشخيص مركبات ١-سايكلوبنتين-٢،١-ثنائي كاربوكسيل ايميديل حاوية على مجاميع الاوكسادايزول والبنزوثايازول ودراسة فعاليتها البايولوجية

شذى فاضل نارين الزبيدي* ***مصطفى عدنان ياسين****
عمر عبد اللطيف** ***هند فاضل الجبوري****

*قسم الكيمياء/ كلية العلوم للبنات/ جامعة بغداد/ العراق.
**الجامعة التكنولوجية/قسم العلوم التطبيقية/فرع الكيمياء التطبيقية.
*** قسم الكيمياء/ كلية العلوم / جامعة بغداد/ العراق.

الخلاصة:
تضمن البحث تحضير عدد من الايمايدات الحلقية الجديدة وهي 1-سايكلوبنتين -2,1-كاربوكسيل ايماید الحاوية في تركيبها على مكونة البنزوثايازول والاوكسادايزول واجريت عملية التخليق بعدد من الخطوات:
الخطوة الاولى اجريت باخذ كميات مو لية متساوية من الحامض اللامائي المستخدم في البحث وتفاعله مع مركبات 2-امينو- معوض-4,3,1-أوكساثايازول ومركبات معوض-2-أمينو-بنزوثايازول حيث كان الناتج مركبات حوامض الاميك المعوضة وباستخدام تقنية الصهر لهذه المركبات الناتجة تم سحب جزيئة الماء من تلك المركبات وكان الناتج هي مركبات الايمايدات المعوضة واجريت هذه العملية في الخطوه الثانية من البحث.
تم تشخيص المركبات الناتجة وذلك من خلال مطيافية الاشعة تحت الحمراء ومطيافية الاشعة الفوق البنفسجية وحيث كانت نتائج المركبات المحضرة مطابقة للتراكيب المقترحة .
اضافة الى ذلك تم في هذا البحث دراسة الفعالية البايولوجية لتلك المركبات المحضرة ضد نوعين من البكتريا حيث اضهرة تلك الايمايدات المحضرة فعالية بايولوجية جيدة ضد انوع هذه البكتريا