Rafidain Journal of Science

https://rsci.mosuljournals.com

Vol. 32, No. 1, pp.110-120, 2023

Synthesis, Characterization of Substituted 1,3-Oxazepine, Thiazolidine-4-one and Azetidine-2-one Using Benzimidazole as a Synthon

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p-ISSN: 1608-9391

e -ISSN: 2664-2786

Article information

Received: 3/7/2022

Accepted: 21/9/2022

DOI: 10.33899/rjs.2023.177292

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ABSTRACT

Starting from benzimidazole moiety, several heterocyclic compounds (1,3-Oxazepine, thiazolidin-4-one, azetidin-2-one) were synthesized, thus the Ethyl Benzimidazole acetate (1) was synthesized from the reaction of benzimidazole with ethylchloroacetate on treatment with hydrazine hydrate is giving the corresponding hydrazide (2). The reaction of this hydrazide with, 4-substituted acetophenone afforded hydrazones which on reaction with some reagents to produce synthesized compounds, (4a-c), (5a-c), (6a-c), (7a-c), (8a-c) and (9a-c). All the synthesized products were confirmed by physical and spectral methods.

Keywords: Heterocyclic, 1,3-Oxazepine, Thiazolidine-4-one, Azetidine-2-one.

INTRODUCTION

Due to its wide range of biological activities, including antibacterial, antitubercular, anticancer, anticonvulsant, and antifungal properties, the derivatives of the thiazolidin-4-one nucleus have taken a special place in the field of medicinal chemistry (Christophe *et al*., 2022; Pandurangan *et al*., 2022). Azitidine-2-one are heterocyclic compounds frequently found in compounds of biological interest, and have been shown to exhibit a wide range of biological activities (Maria *et al*., 2020). The pharmacophore of lactam antibiotics, the most commonly used family of antibiotics, is well established as the azetidine-2-one skeleton (Trivedi *et al*., 2008). Properly substituted azitidine synthesis techniques have been developed with control of functional group and stereochemistry through the structural diversity of physiologically active β-lactam antibiotics (Hanoon *et al.,* 2021). The 1,3-oxazepine is heterocyclic ring and contains two heterocyclic atoms (oxygen and nitrogen) (Tong, 2013), which have been found to exhibit biological activities (Maysaa and Moayed, 2022). The identification of 1,3-oxazepine's CNS action (Deng *et al*., 2016).

EXPERIMENTAL

Instrumentation

The uncorrected melting points were all calculated using Thiel's tube At Kirkuk University/ College of Science/ Department of Chemistry. Using a Bruker Model Tensor 27 Co., Germany spectrophotometer, infrared spectrums were captured At the University of Baghdad/ Central Service Research Center/ Ibn Al-Haytham. Chemical shifts were expressed in parts per million (ppm) downfield from TMS using the proton resonance magnetic spectra (^{1}H-NMR and ^{13}C-NMR) recorded on a 400MHz spectrophotometer using TMS as an internal standard At the University of Isfahan/ Central Laboratories/ Islamic Republic of Iran. The elemental analysis was carried out by using EA Euro vector 3000 element analyzer At Al-Bayt University/Water Research Center/The Hashemite Kingdom of Jordan. Thin layer chromatography (TLC) was used to monitor the reaction's progress and product purity. Iodine fumes were present where the spots were.

Synthesis of Ethyl benzimidazole acetate (1)

The solution of Benzimidazole (0.06 mole) in acetone (40 ml) was mixed with 0.07 moles of ethyl chloroacetate and 0.12 mole of potassium carbonate, and the mixture was refluxed for six hours this reaction was monitored by TLC, the reaction mixture was filtered, and excess acetone was then distilled out of the clean filtrate before water was added. The separated solid product was filtered, collected, and dried. Ethyl acetate crystallization was used to provide further purification Afforded solid as white color M.P. 88-90 °C, yield 86%, as well as identification of the ester (1) by using chemical detectors, the detection test known as (Ferric hydroxamate) give positive result, which denotes the existence of ester (John *et al*., 1986;Gowda *et al*., 2010).

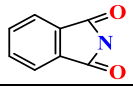
Synthesis of Benzimidazole acetic acid hydrazide (2)

The solution of ethyl benzimidazole acetate (1) (0.04 mole) in ethanol (25 ml) was mixed with hydrazine hydrate (99%) (0.04 mole) and refluxed for (4hr), completion of the reaction was monitored by TLC, the excess of solvent was removed by distillation and the contents were added to an excess of water. The crude product was purified by recrystallization from ethanol to give grey precipitate M.P. 180-181 °C, Yield 90%, (Gowda *et al*., 2010).

Synthesis of 4-substituted acetophenone (3a-c)

A mixture of 4-amino acetophenone (0.01 mole) in (50 ml) ethanol, and succinic anhydride or maleic anhydride or phthalic anhydride (0.01 mole). Reflux heating was used to warm the reaction mixture for (3 hr). TLC was performed after the reaction, and then the reaction mixture was allowed to cool, the precipitate was filtered and recrystallized from ethanol. The properties of compounds show in the (Table 1) (El-Hashash, 2010; Ahmed and Adnan, 2021).

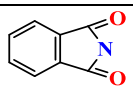
Table 1: Physical data for compounds (3a-c)

No.	Ar	% Yield	Colour	M.W.	M.P. C°	C%	H%	N%
						Cal./found		
3a		85	White	265.27	126	-	-	-
3b		89	White yellow y	215.21	141	-	-	-
3c		82	Yellow	217.22	165-166	66.35/66.70	5.10/5.16	6.45/6.48

Synthesis of 2-(benzimidazole)-N'-(1-(4-substitutedphenyl) ethylidene) acetohydrazide (4a-c)

A mixture of hydrazide (2) (0.01 mole) in (50 ml) ethanol, and 4-substituted acetophenone (0.01 mole) in (25 ml) ethanol was added. The reaction mixture was heated under reflux for (2 hrs.). the reaction was followed TLC, the reaction mixture was allowed to cool. The precipitate was filtered and recrystallized from ethanol, to give the hydrazones. Some physical for compounds (4a-c) indicated in (Table 2), (Attallah and Rafid, 2019).

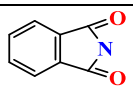
Table 2: Physical data for compounds (4a-c)

No.	Ar	% Yield	Colour	M.W.	M.P. C°	C%	H%	N%
						Cal./found		
4a		75	Gray	437.46	197-198	-	-	-
4b		70	White	387.40	212-214	65.11/65.22	4.42/4.48	18.08/18.16
4c		86	Orange	389.42	230-232	-	-	-

Synthesis of 2-(benzimidazole)-N-(3-chloro-2-(4- substitutedphenyl)-2-methyl-4-oxoazetidin-1-yl) acetamide (5a-c)

Mix cold solution of compounds (4a-c) (0.005 mole) Triethyl amine (TEA) (0.01 mole) was dissolved in 40 ml of 1,4-dioxane before being mixed with chloro acetyl chloride (0.01 mole) and shaken and cooled for 20 minutes. The reaction was then heated and mixed for 8 hours before TLC was used to separate the product. The product was concentrated, cooled, and added crushing ice before being separated by ethyl acetate then recrystallized from ether/n-hexane The properties of compounds (5a-c) as shown in the (Table 3) (kelarav *et al*., 2003).

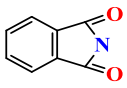
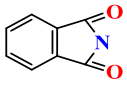
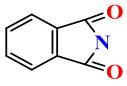
Table 3: Physical data for compounds (5a-c)

No.	Ar	% Yield	Colour	M.W.	M.P. C°	C%	H%	N%
						Cal./found		
5a		90	Leady	513.94	210-211	63.10/64.12	3.92/3.98	13.63/13.68
5b		92	Light grey	463.88	278-280	-	-	-
5c		88	White	465.89	184-186	-	-	-

Synthesis of 1,3-Oxazepine compounds (6a-c), (7a-c) and (8a-c)

Refluxed the mixture of (0.002 mole) Schiff base (4a-c) in (50 ml) of dry benzene, then added (0.002 mole) succinic anhydride, maleic anhydride, or phthalic anhydride for (4 hours) in a water bath. After the heating process was complete, the solution was concentrated under rarefied pressure, the remaining anhydride washed with cold methanol, and it was then dried and recrystallized from dioxane. The properties of compounds (6a-c), (7a-c) and (8a-c) shown in (Table 4) (Kelarav *et al*., 2003).

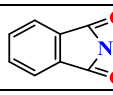
Table 4: Physical data for compounds (6a-c), (7a-c) and (8a-c)

No.	Ar	% Yield	Colour	M.W.	M.P. C°	C%	H%	N%
						Cal./found		
6a		85	Yellow	537.53	155-156	64.80/64.86	4.31/4.35	13.03/13.06
6b		76	White	487.47	230	-	-	-
6c		82	White	489.49	114-116	-	-	-
7a		65	Leady	535.52	140-142	-	-	-
7b		78	Orange	485.46	195-196	-	-	-
7c		75	Light grey	487.47	202-203	61.60/61.68	4.34/4.42	14.37/14.40
8a		70	White	585.58	265-267	-	-	-
8b		69	Yellow	535.52	249	65.04/65.10	3.95/3.98	13.08/13.11
8c		78	Leady	537.53	238-239	-	-	-

Synthesis of 2-(benzimidazole)-N-(2-(4-substitutedphenyl)-2-methyl-4-oxothiazolidin-3-yl) acetamide (9a-c)

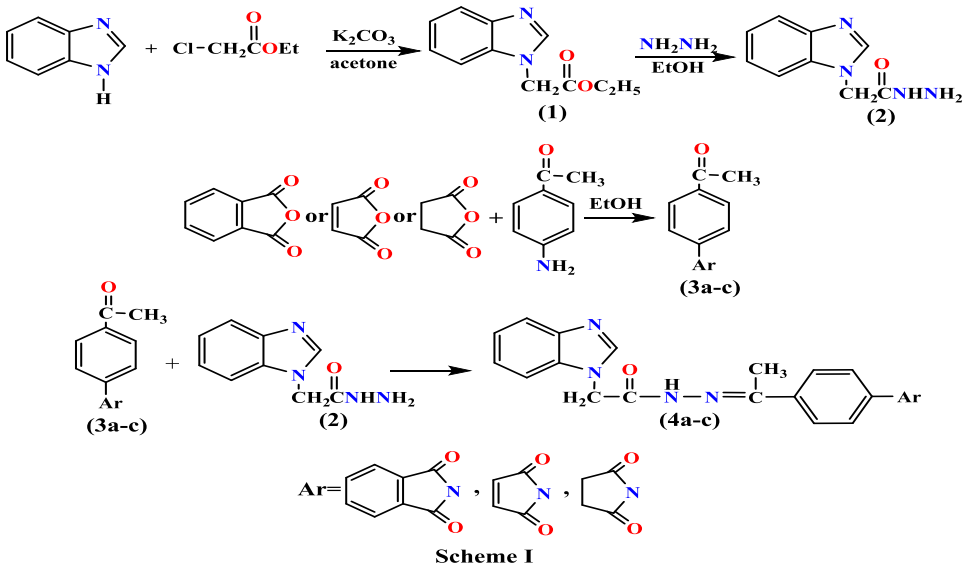
Refluxed the mixture of (0.002 mole) Schiff base (4a-c) in (50 ml) of dry benzene and (0.004 mole) thioglycolic acid and (0.2 g) anhydrous zinc chloride. The reaction was followed TLC After the reaction was finished, the solvent was evaporated under rarefied pressure, and the product was washed with (3 percent) sodium bicarbonate (3*20 ml) and (2*20 ml) of water the recrystallized from ethanol. The properties of compounds (9a-c) show in the table 5 (kelarav *et al*., 2003).

Table 5: Physical data for compounds (9a-c)

No.	Ar	% Yield	Colour	M.W.	M.P. C°	C%	H%	N%
						Cal./found		
9a		95	Pink	511.56	282-284	63.39/63.41	4.14/4.22	13.69/13.76
9b		92	Light red	461.50	267-268	-	-	-
9c		94	Yellow	463.51	250	-	-	-

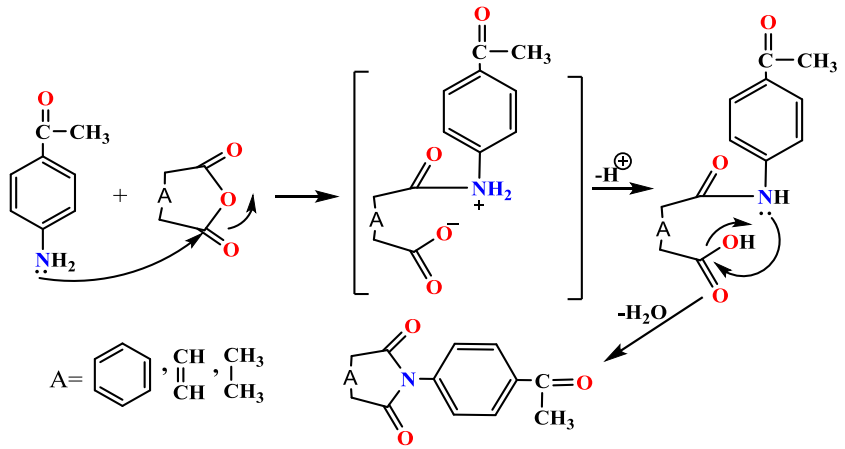
RESULTS AND DISCUSSION

The compounds (3a-c) were preparation from the reaction 4-amino acetophenone with maleic anhydride or succinic anhydride or phthalic anhydride in ethanol absolute, As shown in scheme I, and also shown in mechanism.



Scheme I

All new synthesized compounds have been characterized by their FT-IR spectra; results showed in (Table 6). The structure of compounds (3a-c) were identified by IR as follows: (1672-1680 cm^{-1} For (C=O) group, (1210-1224 cm^{-1}) due to (C-N) group and at (1706-1712 cm^{-1}) for the (C=O) ring.



Suggested reaction mechanism of compounds (3a-c)

Table 6: The spectra data for the compounds (3a-c)

Comp. No.	IR υ(cm^{-1}), KBr		
	C=O	(C=O) ring	C-N
3a	1672	1706	1210
3b	1680	1712	1224
3c	1676	1708	1211

The hydrazones (4a-c) were preparation from the reaction compounds (3a-c) with hydrazide (2) in ethanol absolute (Scheme I). The structures of the obtained products were elucidated based on spectral and analytical data. results showed in (Table 7), as follows: (1610-1616 cm^{-1}) (C=N), (1650-1675 cm^{-1}) (C=O) amide, (1700-1707 cm^{-1}) (C=O) ring, (3220-3366 cm^{-1}) (NH), Fig. (1).

Table 7: The spectra data for the compounds (4a-c)

Comp. No.	IR υ(cm^{-1}), KBr			
	C=N	(C=O) amide	(C=O) ring	NH
4a	1614	1675	1700	3304
4b	1616	1653	1707	3220
4c	1610	1650	1706	3366

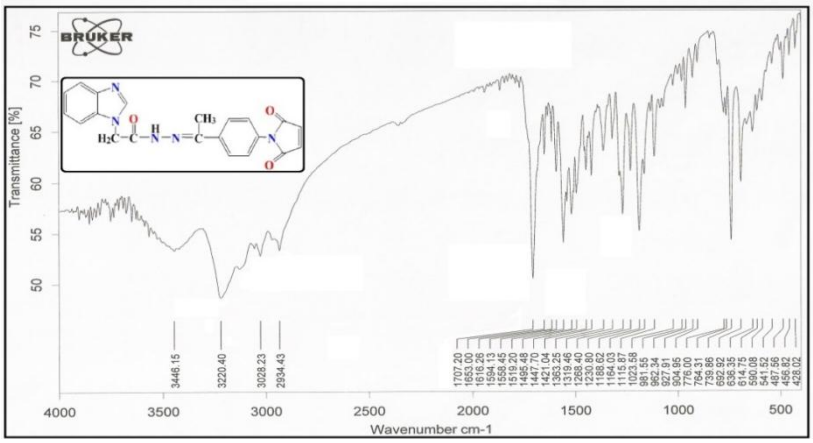
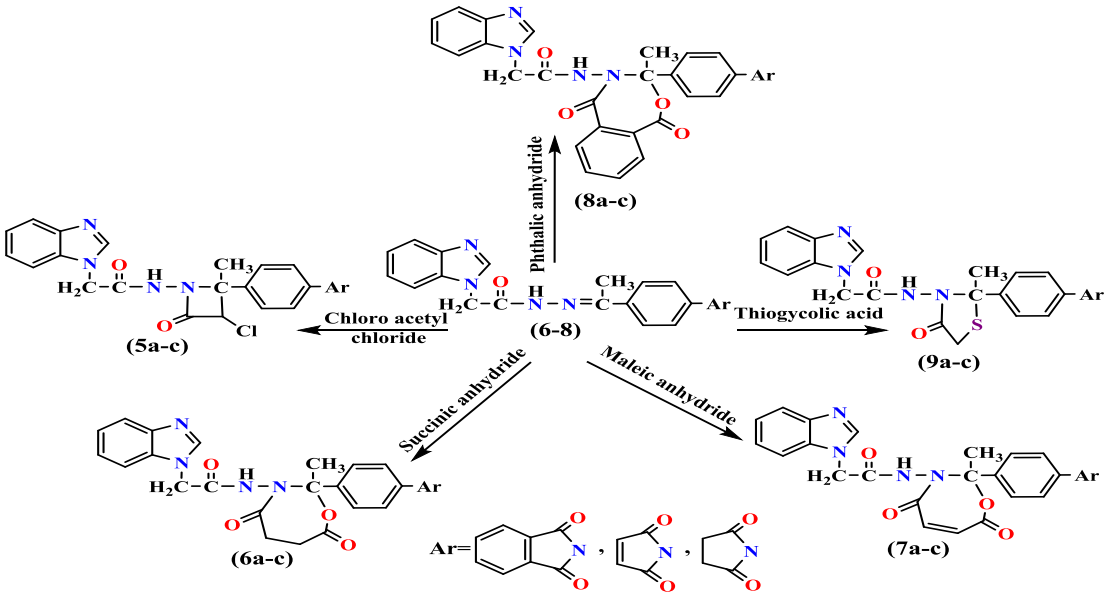


Fig. 1: IR spectrum of compound (4b)

The azetidin-2-one (5a-c), 1,3-Oxazepine (6a-c), (7a-c), (8a-c) and oxathiazolidin-4-one derivatives (9a-c) were synthesized (5a-c) as shown in Scheme II.



Scheme II

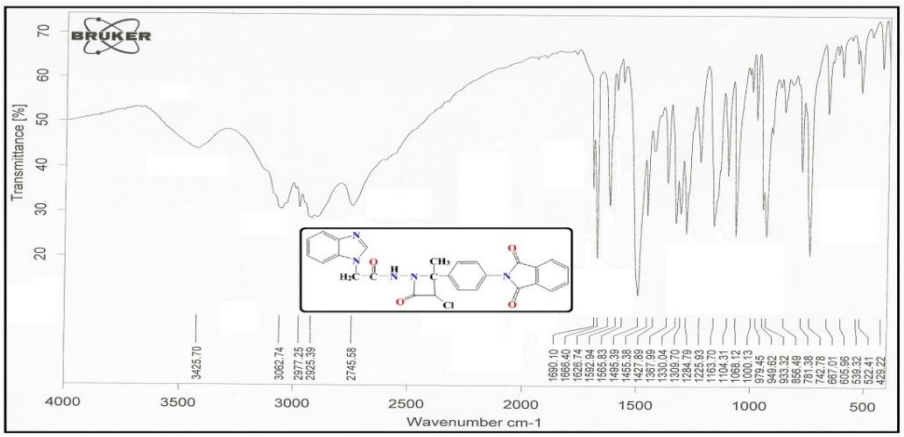


Fig. 2: IR spectrum of compound (5a)

In the IR spectra of compounds (5a-c), appearances of absorption peak for (C=O cyclic) was found in range of (1690-1699 cm^{-1}) which was suggesting the cyclization, and appearance of the vibration between (704-752 cm^{-1}) was due to the (C-Cl) B-lactam, (3246-3425 cm^{-1}) (NH), (1644-1666 cm^{-1}) (C=O) amide. The ^{13}C-NMR spectrum for compound (5c) showed results that confirm our expectation as mention in (Table 8), Fig. (2 and 3).

Table 8: The spectra data for the compounds (5a-c)

Comp.No.	IR υ(cm^{-1}), KBr				^{13}CNMR, DMSO-d6, δ (ppm)
	C=O Cyclic	C-Cl	NH	C=O amide	
5a	1690	742	3425	1666	-
5b	1694	704	3246	1644	-
5c	1699	752	3301	1648	[26.34(CH_3)],[32.75(CH_2 pyrrolidine-2,5-dione)], [40.53(N-CH_2)],[68.07(N-C azetidin-2-one)], [93.48(C-Cl azetidin-2-one)], [112.72-123.00(Phenyl benzimidazole)], [176.18(C=O pyrrolidine-2,5-dione)],[155.82(NH-C=O)], [153.66(C=O azetidin-2-one)], [131.12(C=N Benzimidazole)], [131.12-135.81(C-Phenyl)]

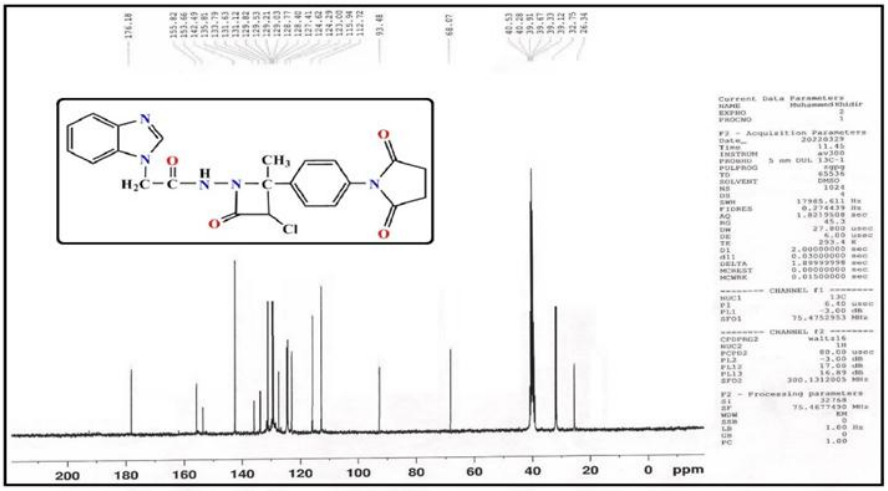


Fig. 3: ^{13}CNMR spectrum of compound (5c)

FT-IR Spectra of oxazepine for compounds (6a-c),(7a-c) and (8a-c) showed clear absorption bands at (3446-3204 cm^{-1}) to N-H, (3065-3011 cm^{-1}) for C-H aromatic, (1602-1630 cm^{-1}) for (C=N) While this bands is disappear and two bands are appear at (1650-1736 cm^{-1}) due to (lacton-lactam) group of oxazepine compounds are appear on band at (1699-1655 cm^{-1}) due to lactam group and absorption peak of (1677-1641) for (C=O) amide. The ^{1}HNMR spectrum for compound (8a) showed results that confirm our expectation as mention in (Table 9), Fig. (4 and 5).

Table 9: The spectra data for compounds (6a-c), (7a-c) and (8a-c)

Comp. No.	IR υ(cm^{-1}), KBr						Comp. No.	^{1}HNMR, DMSO-d6, δ (ppm)
	NH	C-N	(CO) Lactam	C=O Lactam	C=O amide	C-H aromatic		
6a	3234	1612	1722	1655	1644	3011	8a	[3.45(CH_3)],[4.74(N-CH_2)], [6.07-7.27(4H-Phenyl)], [7.28-7.32(C-Phenyl Benzimidazole)], [7.35-7.40(C-Phenyl oxazepine)], [7.43-7.92(isoindoline-1,3-dione)], [8.11(CN Benzimidazole)],[11.75(NH)]
6b	3306	1610	1650	1665	1645	3025		
6c	3446	1602	1734	1699	1677	3064		
7a	3202	1630	1692	1672	1651	3044		
7b	3377	1624	1736	1680	1648	3048		
7c	3399	1620	1701	1656	1652	3065		
8a	3288	1614	1716	1678	1652	3050		
8b	3298	1622	1698	1681	1647	3045		
8c	3369	1618	1710	1669	1643	3034		

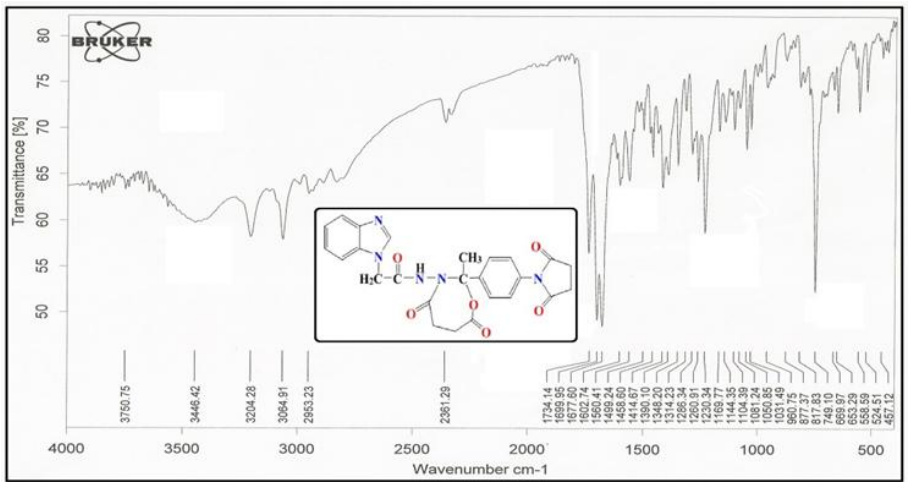


Fig. 4: IR spectrum of compound (6c)

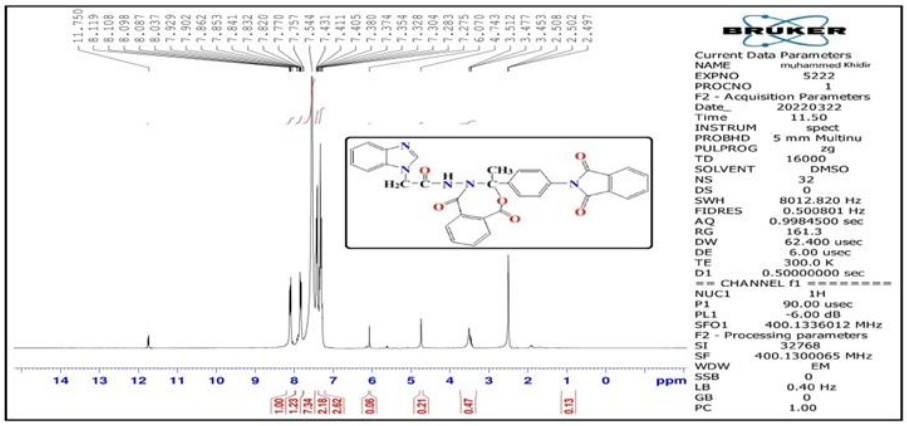


Fig. 5: ^{1}HNMR spectrum of compound (8a)

The structure of synthesized thiazolidin-4-one derivatives (9a-c) was elucidated with the help of FT-IR, the sharp band appeared at (3366-3412 cm^{-1}) (NH), (1696-1700 cm^{-1}) (C=O), (1674-1680 cm^{-1}) (C=O) amide, (777-790 cm^{-1}) (C-S-C), (1114-1165 cm^{-1}) (C-O-C), Fig. (6) and (Table 10).

Table 10: The Spectra data for compounds (9a- c)

Comp. No.	IR υ(cm^{-1}), KBr				^{1}HNMR, DMSO-d6, δ (ppm)
	C=O	C-S-C	NH	CO amide	
9a	1696	777	3366	1676	-
9b	1699	790	3412	1674	-
9c	1700	782	3396	1680	[2.95(CH2 pyrrolidine-2,5-dione)], [3.43(CH2 thiazolidin-4-one)], [5.62(N-CH2)],[7.37-7.45(Phenyl)], [7.53-7.79(Benzimidazole)], [8.97(CN Benzimidazole)],[12.09(NH)]

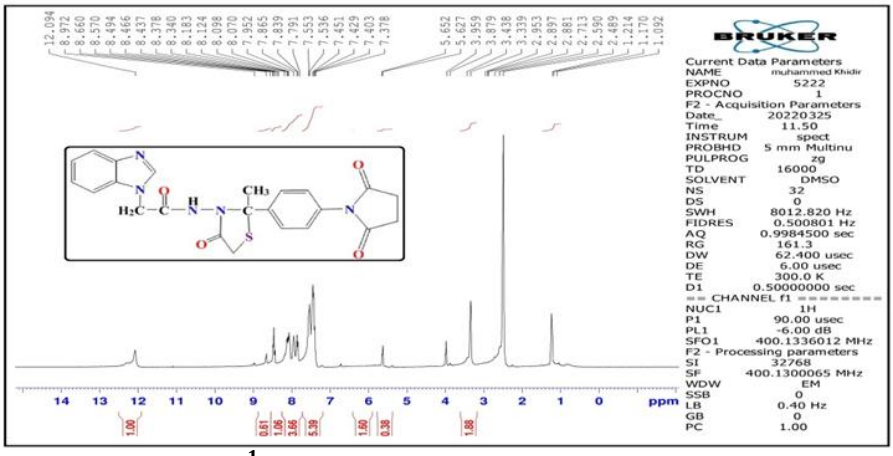


Fig. 6: ^{1}HNMR spectrum of compound (9c)

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تحضير وتشخيص معوضات 3،1–أوكسازبين، ثايازولدين–4–أون، وأزتدين–2–أون باستخدام البنزيميدازول

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الملخص

ابتداء من مركب البنزيميدازول تم تحضير العديد من المركبات الحلقية غير المتجانسة مثل 3،1–أوكسازبين و ثايازولدين–4–أون وأزتدين–2–أون، حيث تم تحضير بنزيميدازول خلات الاثيل (1) من تفاعل البنزيميدازول مع كلورو خلات الأثيل، الذي عند تفاعله مع الهيدرازين المائي يعطي الهيدرازيد المقابل (2)، أعطى تفاعل الهيدرازيد مع 4–معوضات الاسيتوفينون مركبات الهيدرازونات (3a-c) والتي بدورها تتفاعل مع بعض الكواشف الكيميائية لإنتاج مركبات مركبة (4a-c) و (5a-c) و (6a-c) و (7a-c) و (8a-c) و (9a-c)، تم التأكد والتشخيص لجميع المركبات المحضرة بالطرائق الفيزيائية والكيميائية.

الكلمات الدالة: غير متجانسة، 3،1–أكسازبين، ثايازولدين–4–أون، أزتدين–2–أون.