



Synthesis and Characterization of Azetidine-2-One and Pyridazine Derivatives from Substituted Benzimidazole

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ABSTRACT

In this work, the azetidine substitutes and pyridazine compounds derived from benzimidazole substitute were prepared by two routes, where the first route included the preparation of the benzimidazole substitute (SA₁) with a high yield, then it was reacted with ethyl chloroacetate in the presence of a base to obtain the corresponding ester (SA₂) and then the ester was converted to hydrazide (SA₃) by reacting the ester (SA₂) with aqueous hydrazine, and the hydrazide (SA₃) was reacted with different aldehydes to obtain azetidine derivatives (SA₉₋₁₃), while the second route included the reaction of hydrazide with maleic anhydride, succinic anhydride and phthalic anhydride to obtain pyridazine compounds (SA_{14,15,16}). The prepared compounds were characterized physically and spectroscopically by both ¹H-NMR and FT-IR.

Keywords: Benzimidazole substitute, azetidine, pyridazine, hydrazone.

INTRODUCTION

Azetidine compounds and their derivatives have received the attention of many researchers because they are important in organic synthesis and pharmaceutical industries. Azetidine compounds consist of a four-ring ring containing one nitrogen atom and a carbonyl group at position (2). The importance of these compounds is not limited to their use as raw materials, intermediates, and catalysts in organic synthesis, but their importance lies in the fact that they are included in the structural framework of amino acid units, alkaloids, and many natural, industrial and medical active biological compounds (Fu and Xu, 2018). On the other hand, pyridazine derivatives have a variety of pharmaceutical properties such as anticancer, analgesic, antidepressant, antihypertensive, anti-anemic, antibacterial, anticoagulant, and antifungal. (Asif, 2017). As for benzimidazole derivatives, they are more effective and useful compounds from a medical point of view and broad-spectrum biochemicals. (Pathare and Bansode, 2021). Benzimidazole derivatives are considered more effective and medically beneficial compounds, in addition to being broad-spectrum biomolecules. Benzimidazole derivatives have shown practical applications in various fields, with many derivatives exhibiting various pharmacological activities, such as antimicrobial against different types of microbes. (Küçükbay *et al.*, 2003), as well as antiviral (Liu *et al.*, 2018), and a potent antidote for various types of cancer (Gellis *et al.*, 2008), analgesic (Gaba *et al.*, 2014), antihypertensive (Al-Wasidi *et al.*, 2021), and so on. Given the applications of these drugs in treating microbial infections and other biological activities, they have been shown to stimulate the development of more effective and important drugs. Their antibacterial activity against various bacteria strains has been studied. (Pathare and Bansode, 2021). Found that benzimidazole derivatives resemble natural products, and this similarity allows them to interact easily with biopolymers, resulting in low toxicity in chemotherapeutic approaches (Laczowski, 2013).

MATERIALS AND METHODS

All chemicals used were produced by Fluka, BDH, and Aldrich Companies. Melting points were recorded in open capillaries using electro thermal digital Stuart SMP 30 melting point apparatus and were uncorrected. The infrared spectrum of the prepared compounds was measured in the central laboratory/ College of Science/ University of Mosul using FT-IR Spectrophotometer, Bruker. ¹H-NMR spectra were measured on a Bruker Ascend 400 MHz spectrometer at the University of Basra/ College of Education for Pure Sciences, in deuterated dimethyl sulfoxide (DMSO-d₆) as a solvent and tetramethyl silane (T.M.S) as an internal standard. Thin layer chromatography (TLC) was used to monitor the reaction's progress and product purity. On pre-coated silica gel (60 F254) aluminum plates, visualization was achieved in a UV chamber using a solvent mixture of ethyl acetate and n-hexane (3:7).

Synthesis 6-methyl-2-(3-nitrophenyl)-1H-1,3-benzimidazole (SA₁)

Dissolve (0.0327 mol, 4 g) of 4-methyl-ortho-phenylenediamine in (30 ml) of absolute ethanol and add (0.0372 mol, 4.952 g) of 3-nitrobenzaldehyde and (0.0327 mol, 1.75 g) of ammonium chloride as a catalyst. Then the reaction mixture refluxed with stirring for (12) hours, this reaction was monitored by T.L.C., and the contents were poured in ice-cold water. Filtered, dried, and recrystallized by absolute ethanol, to give a dark brown precipitate M.P.135-137 °C, yielding 94% (Rithe *et al.*, 2015).

Synthesis ethyl [6-methyl-2-(3-nitrophenyl)-1H-1,3-benzimidazol-1-yl] acetate (SA₂)

A mixture of (SA₁) (0.0118 mol, 3 g) with (0.0118 mol, 1.64 g) of anhydrous potassium carbonate is heated in (40 ml) of dry acetone with continuous stirring for (15) minutes, then (0.028 mol, 3.43 g) is added of ethyl chloroacetate gradually, the mixture is refluxed for (9) hours, The reaction was monitored by (T.L.C), the contents were poured into ice water. Filtered (20 ml x 3) is washed with distilled water and dried then washed several times using petroleum ether, afforded solid as brown M.P. 98-100 °C, yielding 83% (Ilgin *et al.*, 2017).

Synthesis 2-[6-methyl-2-(3-nitrophenyl)-1H-1,3-benzimidazol-1-yl] acetohydrazide (SA₃)

A mixture of (0.0029 mol, 1 g) of ester (SA₂) with (0.0118 mol, 0.59 g) of hydrazine hydrate (80%) was refluxed in (20 ml) of absolute ethanol for (6) hours, The completion of the reaction was monitored using thin layer chromatography (TLC), then the mixture was poured on to crushed ice, it was filtered, dried, and recrystallized. From ethanol, give a white precipitate M.P. 122-124 °C, yield 94% (Yahya, 2024; AL-Khazraji *et al.*, 2024).

General procedure for synthesis of hydrazone derivatives (SA₄₋₈)

With stirring (0.003 mol, 1 g) of hydrazide (SA₃) in (20 ml) of absolute ethanol, was added to the substituted benzaldehyde mixture (0.003mol), and add to it few drops of glacial acetic acid the mixture was refluxed for (6-11) hours. Monitored by TLC, then the reaction mixture is poured into a beaker containing ice water. The resulting precipitate is separated by filtration and washed (10 ml x 3) of distilled water and dried, then washed several times using ether. It is recrystallized using a mixture of benzene/1,4-dioxane. The Physical properties of compounds are shown in the (Table 1) (Merhi and Abood, 2024; Shah *et al.*, 2022).

Table 1: Physical constants of hydrazine derivatives (SA₄₋₈)

Comp. No.	R	m.p. (°C)	Yield %	Colour
SA ₄	3-CH ₃	129-131	86	Light brown
SA ₅	4-N(CH ₃) ₂	202-204	72	Yellowish brown
SA ₆	4-OH	291-293	53	brown
SA ₇	3-OCH ₃ -4-OH	211-213	71	brown
SA ₈	3-NO ₂	114-116	72	light brown

Synthesis substituted of azetidine-2-one (SA₉₋₁₃)

A cold solution of one of the hydrazone substitutes (SA₄₋₈) (0.5 g) and triethylamine (0.01 mol) dissolved in (20 ml) of dry 1,4-dioxane is stirred, then (0.01 mol) of chloroacetyl chloride is added with cooling and stirring gradually and in drops for (15) minutes. Cooling and stirring continue for (20) minutes, after which the reaction mixture is refluxed for (8) hours monitored by TLC, Then the reaction mixture is poured into a glass flask containing ice water. The precipitate formed is separated by filtration and (10 ml x 3) is washed with distilled water and dried, then washed several times with benzene. (Nagavolu *et al.*, 2017). The physical properties of the compounds are displayed in the (Table 2).

Table 2: Physical constants of azetidine derivatives (SA₉₋₁₃)

Comp. No.	R	m.p. (°C)	Yield%	Colour
SA ₉	3-CH ₃	252-254	51	Dark Brown
SA ₁₀	4-N(CH ₃) ₂	257-260	52	Brown
SA ₁₁	4-OH	260-262	51	Light Brown
SA ₁₂	3-OCH ₃ -4-OH	144-147	51	Light Brown
SA ₁₃	3-NO ₂	187-189	52	Dark Brown

Synthesis 1-[[6-methyl-2-(3-nitrophenyl)-1H-1,3-benzimidazol-1-yl] acetyl]-1,2-substituted diazine-3,6-dione (SA₁₄₋₁₆)

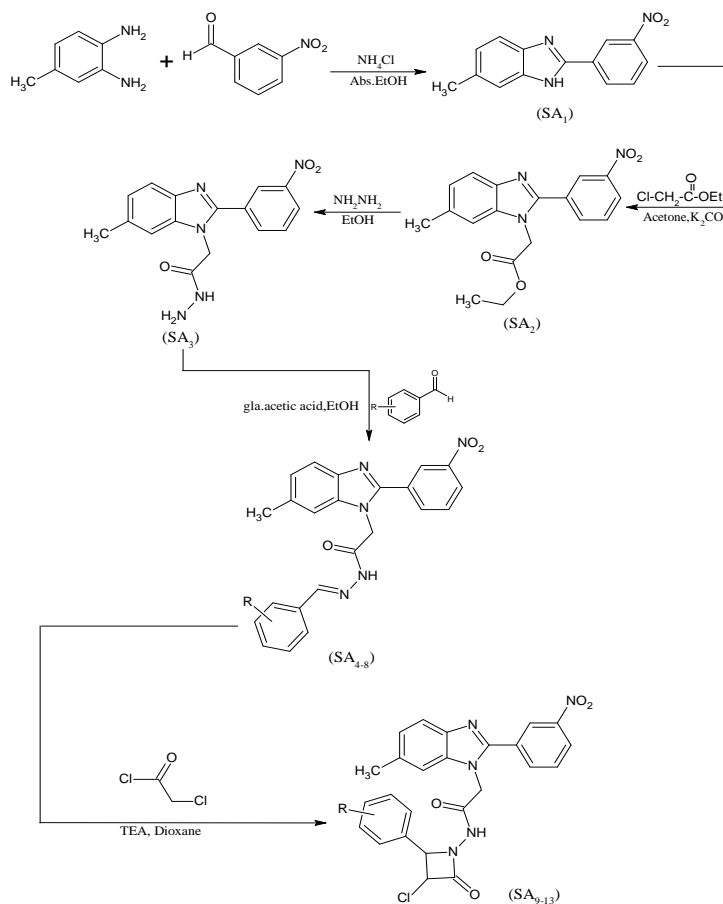
A mixture of (0.00184 mol, 0.6 g) of hydrazide (SA₃) with (0.00184 mol) of maleic anhydride, succinic anhydride, or phthalic anhydride is refluxed in (20 ml) of absolute ethanol, for (5) hours, monitored by TLC. Then poured into ice water, the resulting precipitate is separated by filtration and washed several times with distilled water, dried, and recrystallized using absolute ethanol. (Eicher *et al.*, 2003; Coates, 1996). The physical properties of pyridazine compounds are shown in the (Table 3).

Table 3: Physical constants of compounds (SA₁₄₋₁₆)

Comp. No.	m.p.(°C)	Yield%	Colour
SA ₁₄	181-182	70	Brown
SA ₁₅	192-194	69	Dark Brown
SA ₁₆	148-151	73	Light Brown

RESULTS AND DISCUSSION

In this study, the benzimidazole substitute was used as a nucleus to prepare a number of heterocyclic compounds as in scheme (1). The prepared starting material (SA₁) was identified spectroscopically by the appearance of a band for NO₂ at (1345-1519 cm⁻¹). It was then reacted with ethyl chloroacetate in the presence of K₂CO₃ as a base to obtain the corresponding ester (SA₂). The results showed a distinct band at (1739 cm⁻¹), indicating the presence of a carbonyl group attached to the ester. This peak is consistent with the data published in the literature, confirming that the structure includes the carbonyl group. Then the ester was converted to hydrazide (SA₃) through the reaction of the ester (SA₂) with hydrazine hydrated and was spectroscopically characterized by the appearance of a stretching band at (1665 cm⁻¹) due to amide carbonyl group (C=O). It was noted that the absorption of the carbonyl group of the hydrazide was shifted to a lower frequency compared to the absorption of the carbonyl group in the ester. This is attributed to the presence of resonance phenomenon in the hydrazide, which leads to a reduction in the double bond character (C=O), and then the force constant of this bond decreases and its frequency decreases. (Silverstein *et al.*, 1974). Hydrazones (SA₄₋₈) were prepared from the condensation of hydrazide (SA₃) with different aldehydes and in the presence of glacial acetic acid as a catalyst. Hydrazones give when reacted with chloroacetyl chloride in dioxane containing triethyl amine the azetidine-2-one (SA₉₋₁₃). The prepared compounds were characterized spectroscopically by: (¹H-NMR and FT-IR), as shown in the following (Table 4-6) and Fig. (1).



R= 3-CH₃ (SA_{4,9}), 4-N(CH₃)₂ (SA_{5,10}), 4-OH (SA_{6,11}), 3-OCH₃-4-OH (SA_{7,12}), 3-NO₂ (SA_{8,13}).

Scheme 1: The route of synthesis of benzimidazole substitute, hydrazone derivatives, azetidine-2-one derivatives.

Table 4: The prepared compounds ' FT-IR absorption spectra data (in cm⁻¹) are shown.

Comp. No.	vN-H	vC-H arom.	vC-H alph.	vC=O	vC=N	Others
SA ₁	3153	3097	2981, 2923, 2858	–	1651	as.1519(NO ₂) sy.1345(NO ₂)
SA ₂	–	3088	2978, 2919, 2863	1739	1621	as.1202(C-O-C) sy.1165(C-O-C)
SA ₃	3087	3034	2920, 2861	1665	1621	as.3304(NH ₂) sy.3195(NH ₂)
SA ₄	3198	3040	2920, 2862	1665	1602	–
SA ₅	3187	3035	2918, 2893	1650	1618	–
SA ₆	3196	3044	2919-2873	1661	1606	3442(OH)
SA ₇	3198	3096	2999-2932	1651	1597	3555(OH) as.1269(C-O-C) sy.1131(C-O-C)
SA ₈	3192	3097	2923-2859	1698	1615	as.1519(NO ₂) sy.1345(NO ₂)

Table 5: FT-I R absorption spectra data (cm⁻¹) of the prepared compounds.

Comp. No.	R	vC=O Lactam	vC=O amide	Ar C-C	C-Cl	Other
SA ₉	3-CH ₃	1685	1621	1455	784	–
SA ₁₀	4-N(CH ₃) ₂	1679	1642	1456	758	–
SA ₁₁	4-OH	1681	1604	1455	729	3442(OH)
SA ₁₂	3-OCH ₃ -4-OH	1681	1621	1488	745	3533(OH) as.1269(C-O-C) sy.1121(C-O-C)
SA ₁₃	3-NO ₂	1717	1697	1489	705	as.1527(NO ₂) sy.1347(NO ₂)

Table 6: ¹H-NMR spectra data (ppm) of the prepared compounds.

Comp. No.	¹ H-NMR δ (p pm) DMSO-d ₆
SA ₁	13.22 (s, 1H) NH, (9.04-7.10) Ar-H, 2.43(s, 3H) CH ₃ Ph.
SA ₂	(8.53-7.12) Ar-H, 5.34 (s, 2H) CH ₂ CO, 4.25–4.14 (q, 2H) CH ₂ -O, 2.50 (s, 3H) CH ₃ , 1.23 (t, 3H) CH ₃ ester.
SA ₃	9.04 (s, 2H) NH, (8.79-7.22) Ar-H, 4.94 (s, 1H) CH ₂ CO, 4.51 (s, 1H) NH ₂ , 2.48 (s, 3H) CH ₃ .
SA ₄	11.88 (s, 1H) NH, (8.53-7.24) Ar-H, 8.02 (s, 1H) CH=N, 5.58 (s, 2H) CH ₂ CO, 2.45 (s, 3H) CH ₃ , 2.32 (s, 3H) CH ₃ .
SA ₅	11.64 (s, 1H) NH, (8.60-6.76) Ar-H, 8.15 (s, 1H) CH=N, 5.56 (s, 2H) CH ₂ CO, 3.00 (s, 6H) 2CH ₃ , 2.53 (s, 3H) CH ₃ .
SA ₆	11.69 (s, 1H) NH, (9.95-6.81) Ar-H, 7.96 (s, 1H) CH=N, 5.53 (s, 2H) CH ₂ CO, 2.49 (s, 3H) CH ₃ .
SA ₇	11.71 (s, 1H) NH, 9.53 (s, 1H) OH, (8.55-6.81) Ar-H, 7.94 (s, 1H) CH=N, 5.55 (s, 2H) CH ₂ CO, 3.78 (s, 3H) OCH ₃ , 2.47(s,3H) CH ₃ .
SA ₁₀	12.15 (s, 1H) NH, (8.56-6.71) Ar-H, 5.54 (s, 1H) CH-Cl, 5.51 (s, 2H) CH ₂ CO, 5.07 (s, 1H) CH-Ph, 2.96 (d, 6H) 2CH ₃ , 2.51 (s, 3H) CH ₃ .
SA ₁₁	11.74 (s, 1H) NH, (8.67-6.81) Ar-H, 5.57 (d, 2H) CH-Cl, 5.08 (d, 3H) CH, 4.29 (s, 2H) CH ₂ CO, 2.47 (S, 3H) CH ₃ .
SA ₁₂	12.03 (s, 1H) NH, 9.67 (s, 1H) OH, (8.58-6.82) Ar-H, 5.52 (d, 1H) CH-Cl, 5.16 (d, 1H) CH, 4.74 (s, 2H) CH ₂ , 3.79 (s, 3H) OCH ₃ , 2.49 (s, 3H) CH ₃ .
SA ₁₃	12.26 (s, 1H) NH, (8.84 - 7.14) Ar-H, 5.78 (d, 1H) CH-Cl, 5.30 (d, 1H) CH, 4.28 (s, 2H) CH ₂ CO, 2.51 (s, 3H) CH ₃ .

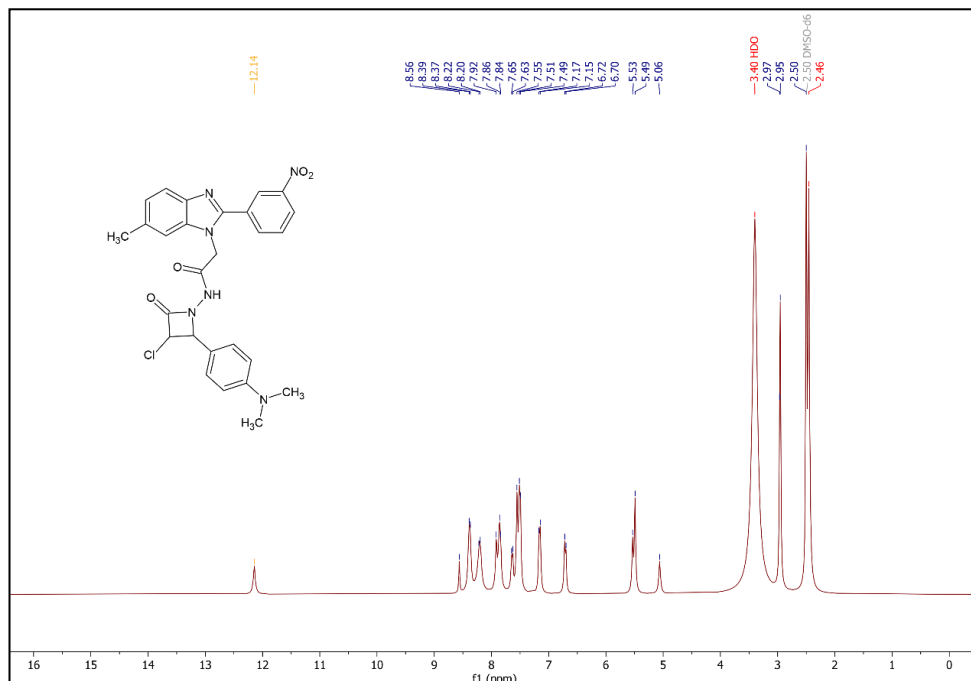
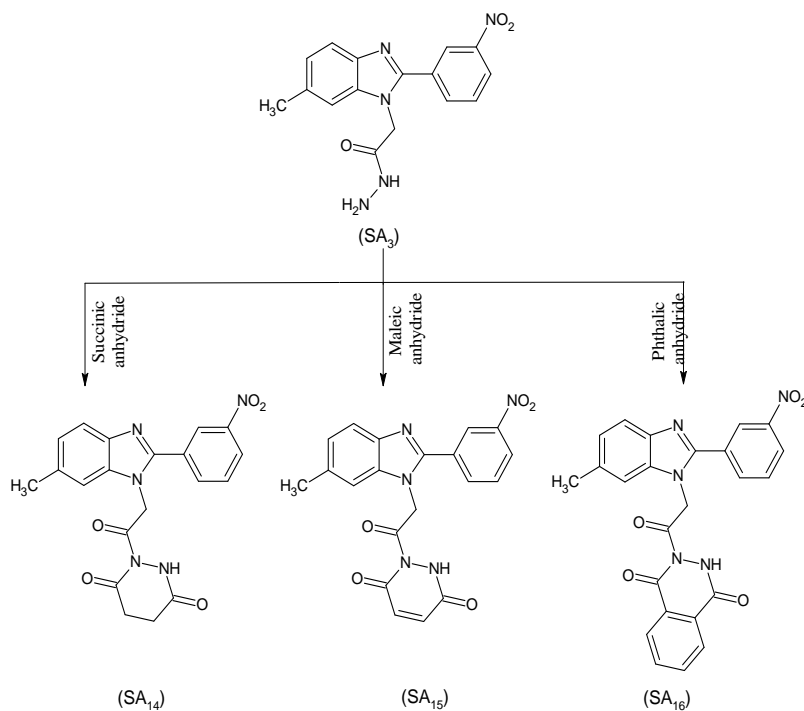


Fig. 1: ^1H NMR. Spectrum of Compound (SA_{10}).

Pyridazine compounds ($\text{SA}_{14,15,16}$) were also prepared from the reaction of phthalic, maleic and succinic anhydride in ethanol as in scheme (2), where they gave distinctive carbonyl stretch bands at ($1797\text{-}1679\text{ cm}^{-1}$). The compounds were confirmed spectroscopically by ^1H - NMR- FT-IR, as shown in the following (Table 7- 8) and Fig. (2, 3).



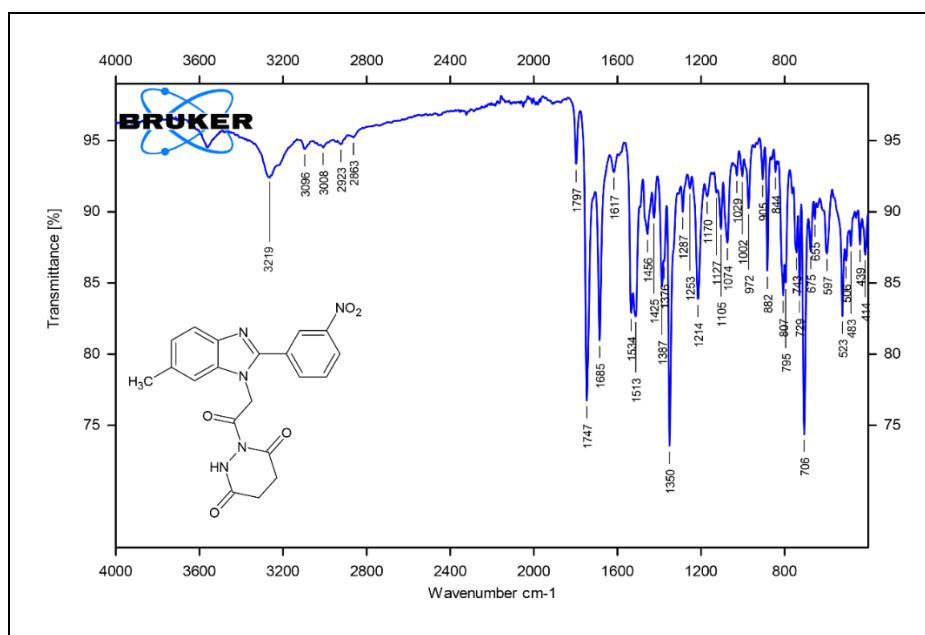
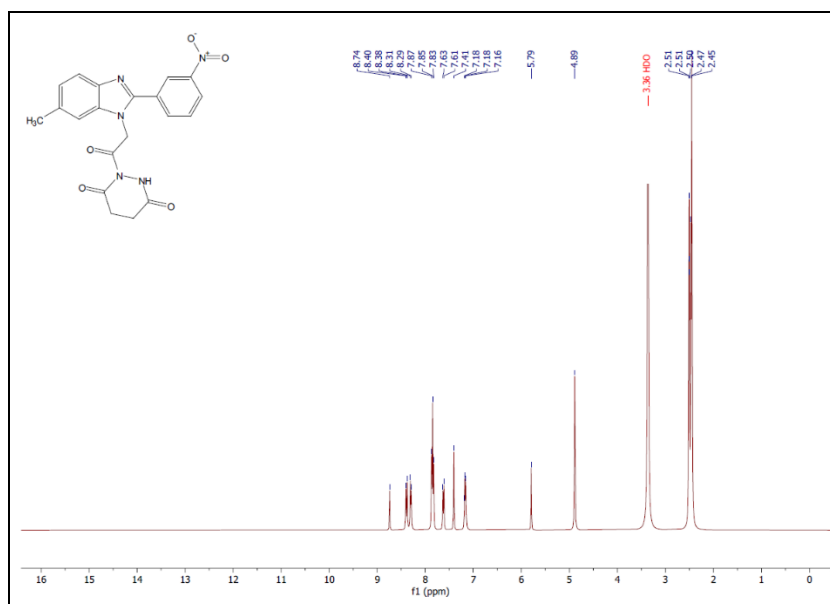
Scheme 2: The route of synthesis of pyridazine derivatives from hydrazide.

Table 7: FT-IR absorption spectra data (cm⁻¹) of the prepared compounds.

Comp. No.	ν N-H	ν C=O	ν C=O
SA ₁₄	3219	1797,1747	1685
SA ₁₅	3218	1732,1717	1681
SA ₁₆	3173	1796,1738	1679

Table 8: ¹H-NMR spectra data (ppm) of the prepared compounds.

Comp. No.	¹ H-NMR δ (p pm) DMSO-d ₆
SA ₁₄	(8.74-7.17) Ar-H, 5.79 (s, 1H) NH, 4.88 (s, 2H) CH ₂ CO, 2.51 (m, 4H) 2CH ₂ , 2.47 (s, 3H) CH ₃ .
SA ₁₅	(8.66-7.08) Ar-H, 5.79 (s, 1H) NH, 5.08 (s, 2H) CH ₂ CO, 2.46 (s, 3H) CH ₃ .
SA ₁₆	(8.62-7.16) Ar-H, 6.31(s, 1H) NH, 5.29 (s, 2H) CH ₂ CO, 2.45 (s, 3H), CH ₃ .

**Fig. 2: FT-IR. Spectrum of Compound (SA₁₄).****Fig. 3: ¹H-NMR. Spectrum of Compound (SA₁₄).**

CONCLUSIONS

The study demonstrated the effectiveness of the methods used in the preparation of azetidine and pyridazine derivatives from substituted benzimidazoles. The uses of substituted benzimidazoles as starting materials were beneficial due to their versatility in reactivity and high yield. The chemical structures of the prepared compounds were successfully confirmed by spectroscopic analysis and physical properties. Based on this, we recommend conducting comprehensive biological activity studies of azetidine and pyridazine compounds.

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تحضير وتشخيص مركبات الازيتدين-2-أون والبايرادازين المشتقة من معوض البنزيميدازول

سالم جاسم محمد صالح

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قسم الكيمياء / كلية العلوم / جامعة الموصل

الملخص

في هذا البحث تم تحضير معوضات الازيتدين ومركبات الباييرادازين المشتقة من معوض البنزيميدازول بمسارين حيث تضمن المسار الأول: تحضير معوض البنزيميدازول (SA₁) ذو الحصيعة العالية، ثم يتم مفاعلة معوض البنزيميدازول (SA₁) مع كلورو خلات الاثيل في وجود القاعدة للحصول على الإستر المقابل (SA₂) ومن ثم تم تحويل الإستر إلى هيدرازيد (SA₃) عن طريق تفاعل الإستر (SA₂) مع هيدرازين المائي، ويتفاعل الهيدرازيد (SA₃) مع الديهالادات المختلفة للحصول على مشتقات الازيتدين

(SA₉₋₁₃)، بينما تضمن المسار الثاني: تفاعل الهيدرازيد مع أنهيدريد الماليك، أنهيدريد السكسينيك وأنهيدريد الفثاليك للحصول على مركبات الباييرادازين (SA_{14,15,16}) وتم تشخيص المركبات المحضرة فيزيائياً وطيفياً بواسطة كل من (¹H-NMR and FT-IR).

الكلمات الدالة: معوض بنزيميدازول، الازيتدين، الباييرادازين، الهيدرازون.