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ORIGINAL ARTICLE

Synthesis, Characterization and Study the Biological Activity of Some New Heterocyclic Compounds Derived from Terephthalic Acid

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KEYWORDS

Acid hydrazide;
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Thiourea derivatives

ABSTRACT: The organic compound imidazole has the chemical formula $C_3N_2H_4$. Numerous significant biological compounds contain imidazole. The amino acid histidine is the most prevalent. The substituted imidazole derivatives have great potential for treating a variety of systemic fungi infections. Thiourea is an organosulfur compound with the formula $SC(NH_2)_2$. It is a reagent in organic synthesis. In this paper, some new imidazole and thiourea derivatives are synthesized, characterized, and studied for their biological activity. These new compounds were synthesized from the starting material terephthalic acid, which was transformed to corresponding ester [I] by the refluxing of diacid with methanol in the presence of H_2SO_4 as a catalyst, compound [I] condensation with hydrazine hydrate 80% to yielded acid hydrazide [II], which was refluxed with 2 moles of various aromatic aldehydes in the presence of few drops of glacial acetic acid as a catalyst to yielded Schiff bases[III_{a-d}]. Refluxing of chosen derivative [III_{a-d}] with acetyl chloride in dry benzene gave new acetyl compounds [IV_{a-d}] which were reacted with thiourea and anhydrous sodium carbonate with acetone as a solvent to give new thiourea derivatives[V_{a-d}]. Compounds [V_{a-d}] were used to synthesize new imidazole derivatives [VI_{a-d}] by the reaction of appropriate compound [V_{a-d}] with 2 moles of benzoin in dry DMF under cyclization reaction. FTIR, ^{1}HNMR, and mass spectroscopy are used to characterize the synthesized compounds.

INTRODUCTION

Imidazole is a heterocyclic aromatic compound with five -member ring, consisting of two nitrogen atoms and three carbon atoms. The imidazole ring has two types of lone-pair first is delocalized and the other non-delocalized. Imidazole is by nature an amphoteric compound, acting once as an acid and once as a base [1, 2]. It has the molecular formula $C_3H_4N_2$ [3, 4]. Imidazole ring is found in many natural products such as histidine, nucleic acid, purine and histamine [2, 5, and 6]. Alkaloids, in particular, which are prevalent in nature, include the imidazole ring [7]. The first name of imidazole was (glyoxaline) due to the method of its synthesis from glyoxal and ammonia [8]. There are several methods for the synthesis of imidazole and its derivatives, some of them by the reaction of 1, 2- diphenylethane-1, 2-dione with benzaldehyde and ammonia (Re- Diszewski synthesis) [9, 10], other method by refluxing of *N*-ethyl-N-methylethanediamide with phosphorus pentachloride and phosphorus oxychloride (Wallach synthesis) [11–13]. New derivatives of 5-aryl-1*H*-imidazoles were synthesized by cycloaddition of p- tolyacetonitrile with aldehydes and imines [14]. N- fused imidazo-6,11-dihydro-β-carboline derivatives were synthesized from the reaction of p-toluenesulfonyl methyl isocyanides

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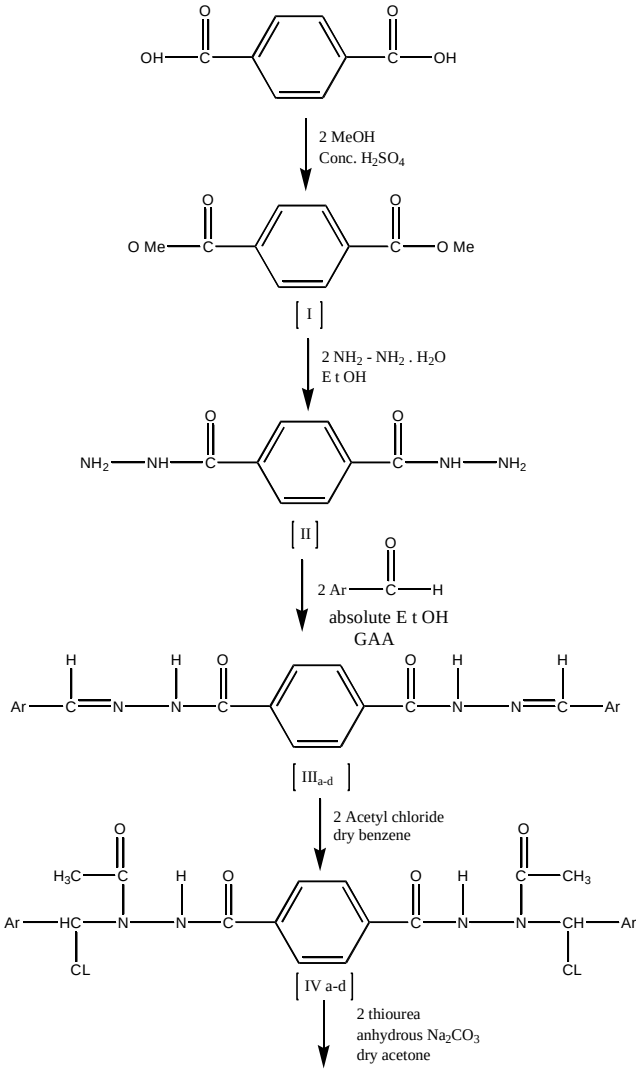
with dihydro- β- carboline imines [15, 16]. Imidazole has wide applications in the treatment of many diseases due to its high biological efficacy, as it is used in the preparation of many pharmaceutical compounds, such as anticancer [17,18], antibacterial [19, 20], anti-inflammatory [21, 22], antiparasitic [23, 24] and enzyme inhibition [25, 26].

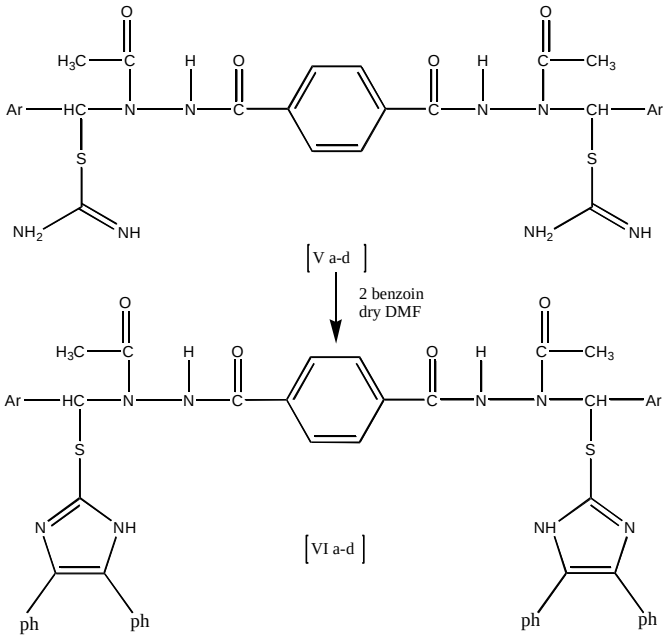
In this research, new imidazole derivatives were synthesized starting from terephthalic acid. The synthesized compounds were diagnosed and their effect on lipase, amylase, glutamate pyruvate transaminase (GPT) and glutamate oxaloacetate transanunase (GOT) enzymes has been studied.

MATERIAL AND METHODS

All chemicals and solvents that were used in this research were supplied by Aldrich, Fluka, BDH and Merck companies. The melting points were measured via Gallenkamp melting device. Shimadzu FTIR 8400 spectrometer was used as KBr disk to record the Fourier transform infrared spectroscopy (FTIR) data. The ^{1}HNMR spectra were measured by a Bruker 400 MHz in DMSO-d_6 solution with Tetramethylsilane (TMS) as an internal reference. Mass spectra were measured on a quadrupole (QP) type mass spectrometer, Agilent Technology (HP). For biological study, use the Reflotron plus device. The steps for the synthesis of new compounds are illustrated in Figure 1.

The nomenclature, percentage yield and physical properties for all new derivatives are listed in Table 1.





Ar: p - $C_6H_5NO_2$, p - $C_6H_5NMc_2$, p- C_6H_5OH, p - $C_6H_5OCH_3$

Figure 1. The procedures for synthesizing new compounds.

Table 1. Physical properties of compounds $[\mathbf{III_{a-d} - VI_{a-d}}]$.

Comp. Names	Nomenclature	Molecular Formula	M.W. (g mol^{-1})	Yield (%)	M.P. (°C)	Solvent recrystallization	Color
III_a	$N'^1, N'^4 - \text{bis}((E) - 4 -$ nitrobenzylidene)- terephthalohydrazide	$C_{22}H_{16}N_6O_6$	460	85	271-273	Ethanol	Yellow
III_b	$N'^1, N'^4 - bis((E) - 4 -$ N, N- dimethyl benzylidene) terephthalo-hydrazide	$C_{26}H_{28}N_6O_2$	456	72	230-233	Ethanol	Deep Yellow
III_c	$N'^1, N'^4 - bis((E) - 4 -$ hydroxybenzylidene)- terephthalohydrazide	$C_{22}H_{18}N_4O_4$	402	80	> 300	Ethanol	Orange
III_d	$N'^1, N'^4 - bis((E) - 4 -$ methoxybenzylidene)- terephthalohydrazide	$C_{24}H_{22}N_4O_4$	430	70	200-203	Ethanol	Pail yellow
IVa	N'^1, N'^4 – diacetyl - N'^1- (chloro (4-((methyl-λ^2- azaneyl) - λ^5 – methyl) phenyl) methyl) - N'^4- (chloro (4-(nitro) phenyl) methyl) terephthalohydrazide	$C_{26}H_{22}N_6O_8Cl_2$	616	76	298-300	acetone	Deep yellow
IV_b	N'^1, N'^4 – diacetyl - N'^1- (chloro (4-(methyl-λ^2- azaneyl) - λ^5 – methyl) phenyl) methyl) - N'^4- (chloro (4-dimethylamino) phenyl) methyl) terephthalohydrazide	$C_{30}H_{34}N_6O_4Cl_2$	632	81	250-252	methanol	Red
IV_c	N^1, N^4 – diacetyl - N^1- (chloro (4-(methyl-λ^2- azaneyl) - λ^5 – methyl) phenyl) methyl) - N'^4- (chloro (4-hydroxy) phenyl) methyl) terephthalohydrazide	$C_{26}H_{24}N_4O_6Cl_2$	558	75	182-185	Ethanol	Deep yellow
IV_d	N'^1, N'^4 – diacetyl - N'^1- (chloro (4-(methyl-λ^2 -azaneyl) - λ^5- methyl) phenyl) methyl) - N'^4- (chloro (4-methoxy) phenyl) methyl) terephthalohydrazide	$C_{28}H_{28}N_4O_6Cl_2$	586	68	138-140	Ethanol	Orange
V_a	(terephthaloyl bis (1-acetylhydrazine -2,1-diyl)) bis ((4-nitrophenyl) methylene) dicarbami-midothioate	$C_{28}H_{28}N_{10}O_8S_2$	696	72	284-286	Methanol	Orange

V_b	(terephthaloyl bis (1-acetylhydrazine -2,1-diyl)) bis ((4-dimethylamino-phenyl) methylene) dicarbamimidothioate	$C_{32}H_{40}N_{10}O_4S$	692	76	280-283 Decompose	Methanol	Deep yellow
V_c	(terephthaloyl bis (1-acetylhydrazine -2,1-diyl)) bis ((4-hydoxyphenyl) methylene) dicarbami-midothioate	$C_{28}H_{30}N_8O_6S_2$	638	70	238-241	Acetone	Brown
V_d	(terephthaloyl bis (1-acetylhydrazine -2,1-diyl)) bis ((4-methoxyphenyl) methylene) dicarbamimidothioate	$C_{30}H_{34}N_8O_6S_2$	666	81	147-149	Ethanol	Yellow
VI_a	N'^1, N'^4 – diacetyl - N'^1-N'^4-bis (((4,5-diphenyl-4,5-dihydro-1 *H*-imidazol-2-yl) thio) (P- nitrophenyl) methyl) terephthalohydrazide	$C_{56}H_{44}N_{10}O_8S$	1048	86	270-273	Ethanol	Orange
VI_b	N^1, N^4 – diacetyl - N'^1-N'^4-bis (((4,5-diphenyl-4,5-dihydro-1 *H*-imidazol-2-yl) thio) (p- nitrophenyl) methyl) terephthalohydrazide	$C_{60}H_{56}N_{10}O_4S$	1044	80	248-250	Ethanol	Yellow
VI_c	N'^1, N'^4 – diacetyl - N'^1-N'^4-bis (((4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl) thio) (p- hydroxyphenyl) methyl) terephthalohydrazide	$C_{56}H_{46}N_8O_6S_2$	990	72	> 300	Methanol	Pale yellow

***Preparation of 1,4- phenylene-dimethylcarboxylate* [*I*]**

Terephthalic acid (4.08 gm, 0.024 mol), was dissolved in absolute sulfuric acid (1 ml) and methanol (20 ml). The mixture was refluxed for 6 hrs. Then it was cooled, washed with water and sodium bicarbonate solution, to produce white precipitate, yield 88%, m.p. = 142 – 144^{o}C [27].

***Preparation of 1, 4-phenylenc- di- acid hydrazide* [*II*]**

Six mL of 80% hydrazine hydrate in 10 mL of absolute ethanol and a mixture of compound [I] (2.32 gm, 0.012 mol) were refluxed for 6 hrs. Following the evaporation of the solvent, ethanol was used to recrystallize the precipitate that had formed. The color of the acid hydrazide was white yield 75% m. p. > 300^{o}C [28].

***Preparation of Schiff-bases derivatives* [III_{a-d}]**

A mixture of di-acid hydrazide [II] (0.01 mol, 2 gm), appropriate aldehyde (0.02 mol), 3 drops of glacial acetic acid and absolute ethanol (15 mL) were refluxed for six hrs. Then evaporated the solvent under reduced pressure. The solid residue recrystallized from ethanol [29]. All the physical data of the prepared Schiff-bases are listed in Table 1.

***Synthesis of N-acyl derivatives* [IV_{a-d}]**

To a cold solution of one of the selected Schiff bases [III_{a-d}] (0.01 mol) in 15 ml dry benzene, acetyl chloride (0.02 mol) was added dropwise. After letting the mixture cool, it was refluxed for six hours. Acetone was recrystallized from the precipitate formed following the evaporation of the solvent [30].

***Synthesis of N- acetyl thiourea derivatives* [V_{a-d}]**

A mixture of chosen compound [IV_{a-d}] (0.01 mol), 30 ml dry acetone, anhydrous sodium carbonate (2.12 gm, 0.02 mol), and thiourea (1.52 gm, 0.02 mol) were refluxed for 6 hrs. After letting the mixture cool, the ice water was added (250 ml). The precipitate formed was filtered off and recrystallized from appropriate solvent to get colored compounds[V_{a-d}] [31].

***Synthesis of diphenylimidazoles derivatives* [VI_{a-d}]**

Benzoin (0.42 gm, 0.02 mol) was added to a stirred solution of appropriate compound [VI_{a-d}] (0.01 mol) in dry DMF. The mixture was let to refluxed for 7 hrs. After leaving the reaction mixture to cool, a few drops of water were added with stirring until the precipitate appeared [31]. Table 1 contains a list of all the new compounds' physical characteristics.

Vital efficacy

The vital efficacy of the prepared compounds ($V_{a,d}$ and VI_{a-d}) was studied by measuring their effect on the activity of liver enzymes (GOT and GpT) in addition to the enzymes lipase and amylase using Reflotron Plus

device (Bio Stat Ltd. Stockport, UK).

RESULTS

The esterification of terephthalic acid in absolute methanol and few drops of H_2SO_4 gave ester derivative [I], which was identified by melting point and FTIR. The absence of absorption stretching bands of carbonyl and hydroxyl group for the carboxylic moiety with the presence of new stretching bands due to (C=O) and (C-O) groups at (1716) cm^{-1} and (1195) cm^{-1} respectively for ester derivative [I] were revealed by the FTIR spectrum of compound [I].

The acid hydrazide [II] was produced when 1 mole of compound [I] was combined with 80% hydrazine hydrate in ethanol, which was diagnosed by the FTIR technique and melting point. The FTIR of [II] revealed stretching vibration of symmetry and asymmetry of NH_2 and NH groups at (3290-3195) cm^{-1} also new absorption band at (1660) cm^{-1} for amide carbonyl group with the vanishment of absorption stretching band due to ester carbonyl group.

Compounds $[III_{a-d}]$ were prepared by the condensation of derivative [II] with the selected aromatic aldehyde with few drops of glacial acetic acid. The FTIR for the derivatives $[III_{a-d}]$ indicated the vanishment of bands at (3290-3195) cm^{-1} of the $\mathcal{V}(NH-NH_2)$ groups occurrence of new bands at rang between (1653-1641) cm^{-1}, (1618-1608) cm^{-1} and at (1595-1564) cm^{-1} refers to $\mathcal{V}$ (C=O) amide, $\mathcal{V}$ (C= N) imine and $\mathcal{V}$ (C=C) of aromatic ring respectively other bands are listed in Table 2.

Table 2. The FTIR data of compounds [$III_{a-d} - VI_{a-d}$].

Comp. No.	$\mathcal{V}$ NHCO	$\mathcal{V}_{C-H}$ Arom.	$\mathcal{V}_{(C-H)}$ Aliph.	$\mathcal{V}$ (C =O)	$\mathcal{V}$ C = N	$\mathcal{V}$ C = C	$\mathcal{V}$ Others
III_a	3198	3041	2952	1653	1610	1564	NO_2 (1519, 1348)
III_b	3134	3053	2941	1610	1606	1593	
III_c	3120	3045	2960	1643	1612	1567	OH (3477)
III_d	3153	3012	2946	1641	1618	1595	
IV_a	3101	3040	2939	1678 1631		1573	NO_2 (1519, 1348) C – Cl (840)
IV_b	3110	3032	2908	1678 1651		1597	C – Cl (817)
IV_c	3178	3066	2939	1681 1627		1597	OH (3425) C – Cl (825)
IV_d	3175	3030	2927 2966	1678 1630		1508	C – Cl (845)
V_a		3057	2945	1653 1606		1564	NH_2, NH, NHCO (3427 – 3198) NO_2 (1514, 1342) C – S (688)
V_b		3062	2912	1678 1658		1550	NH_2, NH, NHCO (3479 – 3175) C – S (644)
V_c		3050	2919	1658 1608		1585	OH, NH_2, NH, NHCO (3479 – 3190) C – S (624)
V_d		3012	2966 2924	1620 1600		1508	NH_2, NH, NHCO (3495 – 3160) C – S (621)
VI_a	3140	3062	2927	1687 1658	1627	1597	NH (3417) NO_2 (1519, 1346) C – S (682)
VI_b	3194	3063	2912	1678 1658	1604	1550	NH (3417) C – S (644)
VI_c		3065	2954	1675 1662	1625	1597	OH, NH, NHCO (3443 - 3120) C – S (686)
VI_d	3120	3022	2966	1675 1620	1600	1518	NH (3414) C – S (621)

Imidazole derivatives were synthesized by serial steps as shown in Figure 1. The first step included the synthesis

of the N-acyl derivatives [IV_{a-d}] by the reaction of acetyl chloride with Schiff-bases. The new derivatives were diagnosed by FTIR and some of them by ^{1}HNMR and mass spectroscopy. The mechanism of this reaction included the attack of the nitrogen atom of azomethine group on the carbonyl group of acid chloride to form the iminium cation with the loss of the chloride anion which is bonded with the Carbon atom of the azomethine group to produce N-acetyl derivatives [IV_{a-d}] [31]. The FTIR absorption spectrum for derivative [IV_a] in Figure 2 showed vanishment band due to (C = N) stretching with occurrence of a new carbonyl group (CH_3CO) allocated to a new absorption band at 1678 cm^{-1}, and new peak at 840 cm^{-1} due to (C-Cl) substituted.

Other absorption bands for this compound and the derivatives [III_{b-d}] were listed in Table 2. The ^{1}HNMR data for compound [IV_a] in Figure 3 showed signals at δ 3ppm ($6H, s, CH_3$), δ 7.3 ppm ($2H, s, CHCl$), δ (7.87-8.63) ppm (12H, arom. H) and at δ 8.88 (2H, s, NHCO) [32], while comp. [IV_b] showed signals at δ 3 ppm (12H, s, NMe_2), δ 3.25 ppm ($6H, s, CH_3CO$) , δ 6.8 ppm ($2H, s, CHCl$), δ (7.46-8.8) ppm (12H, arom. H) And at $9.1(2H, s, NHCO)$.

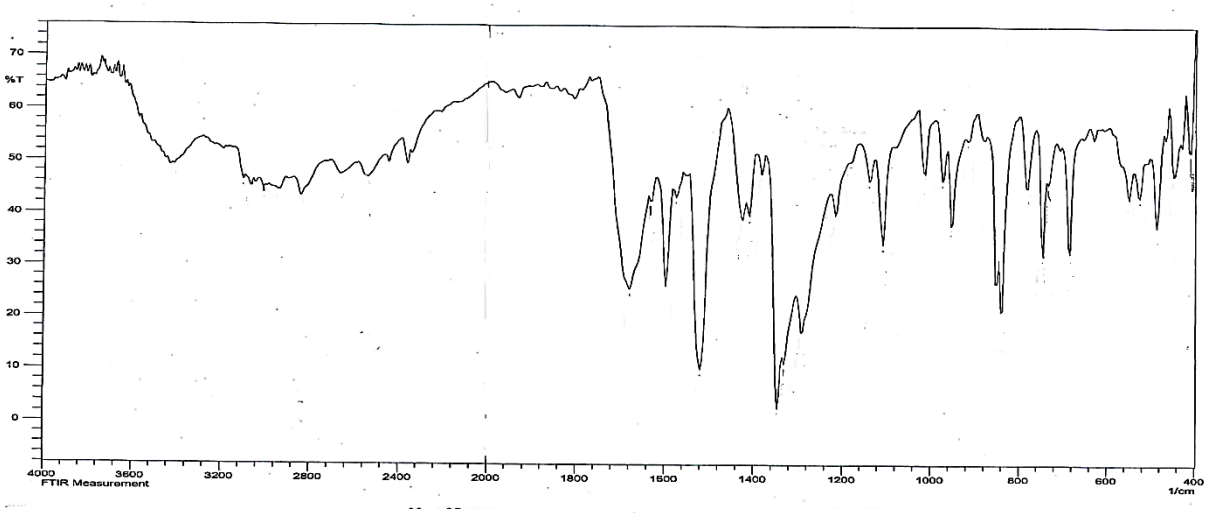


Figure 2. FTIR of comp. IV_a.

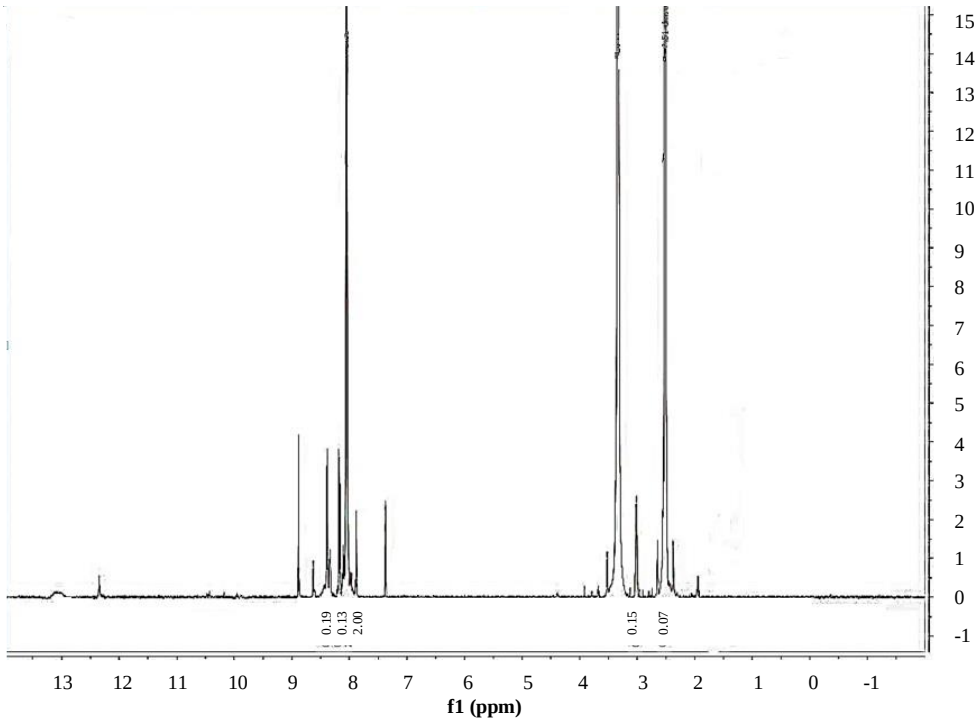


Figure 3. ^{1}HNMR spectrum of comp. IV_a.

The mass spectrum for comp. [IV_c] in Figure 4 gave the set molecular weight at m/z = 558. The N – acetyl thiourea derivatives [V_{a-d}] were synthesized by converted thiourea into its salt by using anhydrous sodium carbonate, which attacks the (C-Cl) group in an S_N2 like mechanism [31].

Compounds [V_{a-d}] were characterized by FTIR and ^{1}HNMR for derivatives [V_c and V_d] FTIR for comp. [V_a] in Figure 5 showed vanishing absorption band at 840 cm^{-1} due to (C-Cl) group with occurrence of new band at 688 cm^{-1} and absorption bands at (3572-3198) cm^{-1} due to (C-S) and (NH_2, NH, NHCO) groups respectively, other absorption bands for comp. [V_b] and the derivatives [$V_{a,c,d}$] were listed in Table 1.

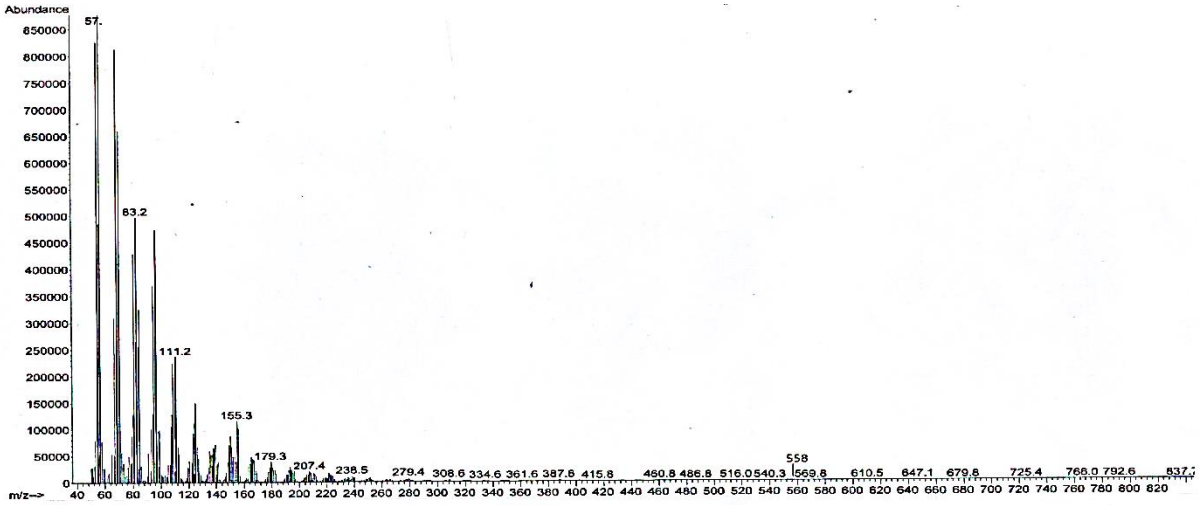


Figure 4. Mass spectrum of comp. IV_C.

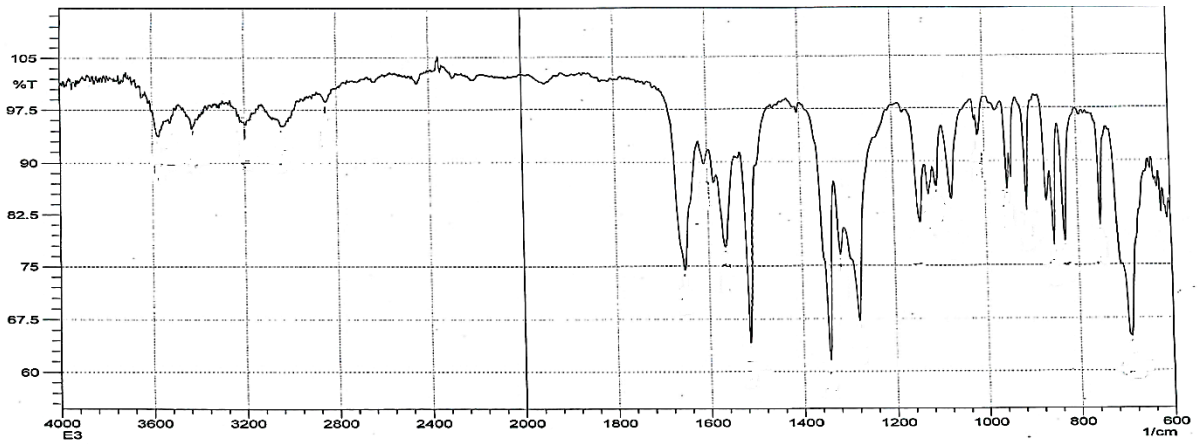


Figure 5. FTIR of comp. V_a.

^{1}HNMR for comp. [V_c] in Figure 6 showed signals at δ 3.2 ppm $(6H, s, COCH_3)$, δ 5.43 $(2H, s, OH)$, δ 6.82 ppm $(4H, s, NH_2)$ δ 7.16 ppm $(2H, s, CH)$, δ $(7.51 - 8.53)$ ppm (12H, aromatic protons and 2H of NHCO), δ 9.5 ppm $(2H, s, NH)$.

Compound [V_d] gave the following signals: δ 3.22ppm (6H, s, $COCH_3$),δ 3.8 $(6H, s, OCH_3)$, δ 6.77 $(4H, s, NH_2)$, δ 7.18 ppm $(2H, s, CH)$, δ (7.45-8.9) ppm (12 aromatic protons and 2H of NHCO group) and at δ 9.6 $(2H, s, NH)$. The last step involves the synthesis of the imidazole ring by adding benzoin to the thiourea derivatives and using DMF as a solvent to obtain the new imidazole derivatives [VI_{a-d}]. These products are characterized by mass spectroscopy, ^{1}HNMR and FTIR. The FTIR absorption spectrum of comp. [VI_d] in Figure 7 shows the following peaks: 3223 cm^{-1} (NH), 3120 cm^{-1} (NHCO), 3045 cm^{-1} (CH aromatic). The rest of FTIR spectral data for this compound and other derivative were summarized in Table 2.

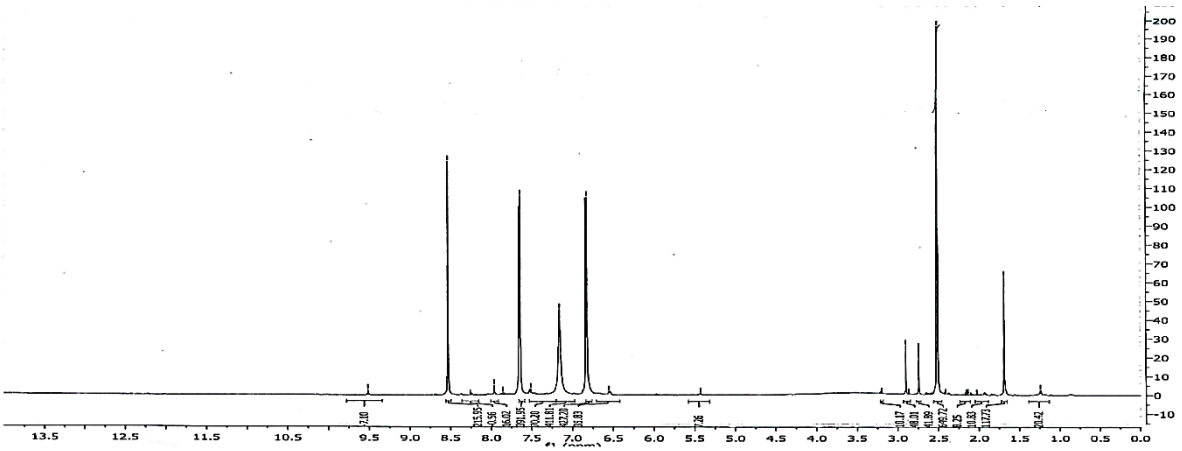


Figure 6. [1]HNMR spectrum of comp. V_c.

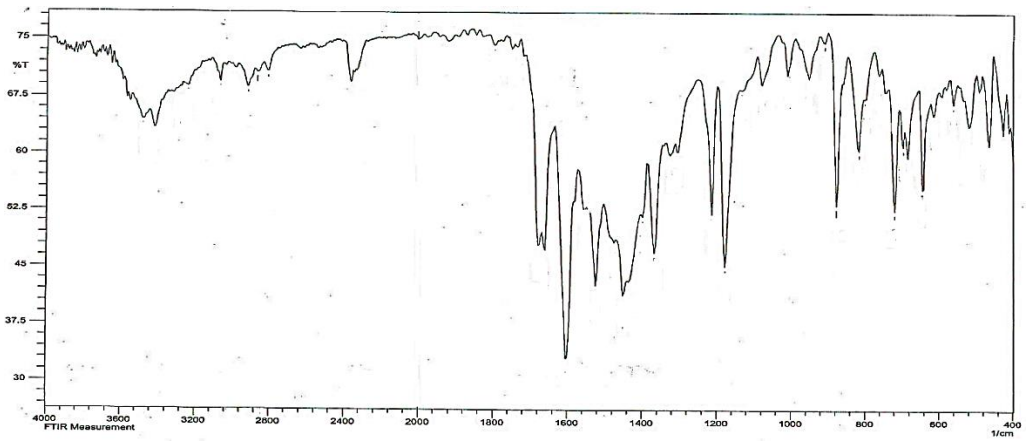


Figure 7. FTIR spectrum of comp. VI_d.

The [1]HNMR of comp. $[VI_b]$ in Figure 8 showed signal at δ 3 ppm $(12H, s, NMe_2)$, δ 3.33 ppm $(6H, s, COMe)$ interference with H_2O signal at δ 3.27 ppm , δ 6.78 ppm $(2H, \delta, CH)$ δ (7.47-8.51) ppm (32H aromatic protons and 2H for NHCO) and at δ 8.56 ppm $(2H, \delta, NH)$.

The biological action of the prepared compounds was studied by measuring their effect on enzyme activity (Table 3 and Figure 9). Compound $[VI_d]$ did not show any effect on the activity of lipase enzyme, but it had a catalytic ability for the activity of the amylase enzyme, its activity increased significantly and had the same effect on the GOT enzyme and had no effect on the activity of the GPT enzyme. The rest of the derivatives [V_a, V_b and VI_{a-c}] had the same effect, as we note that all of them had an inhibitory effect on the lipase enzyme and no action was shown towards the amylase enzyme and the GPT enzyme, except the comp. VI_d which contributed to the increase in the activity of the GOT enzyme.

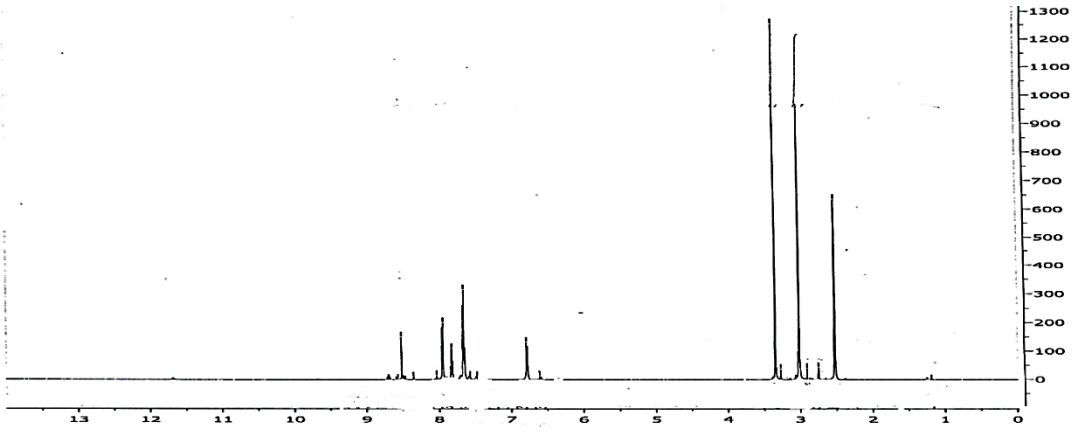


Figure 8. ^{1}HNMR spectrum of comp. VI_b.

Table 3. Comparison of the results of the biological study of the selected prepared compounds.

Comp. No.	Amylase (U/L)	Lipase (U/L)	GOT (U/L)	GPT (U/L)
V_a	73	8	5.7	12.2
V_b	85	8	5	11.2
VI_a	86	12	5	12
VI_b	75	8.1	8	8
VI_c	80.3	29	50	15.3
VI_d	127.1	57	56.7	21.5
Normal level of the enzymes	<100	<60	5-35	7-56

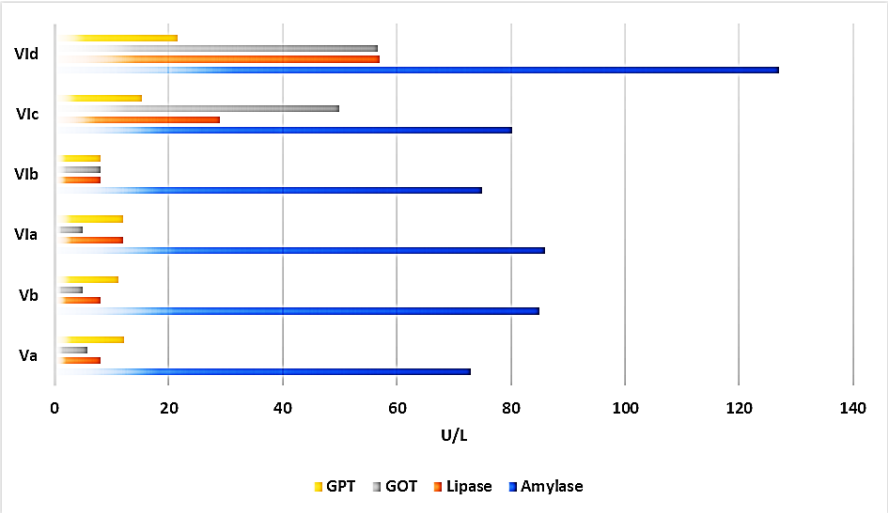


Figure 9. Comparison of the synthesized compounds on enzyme activity.

CONCLUSIONS

The term heterocyclic compound refers to a cyclic compound that contains carbon and other elements in the ring, the component being sulfur, nitrogen, and oxygen. These compounds are one of the main and important branches of organic chemistry, including imidazole compounds, which have many applications in many fields, especially the biological field. Therefore, in this study, new derivatives were synthesized by sequential steps. The effect of these derivatives on some enzymes represented by lipase, amylase, GOT and GPT was studied. The results showed a remarkable effect of these compounds on the selected enzymes.

Conflict of interests

Regarding the publication of this article, the authors declare that there are no conflicts of interest.

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