

Synthesis, Characterization and Antibacterial Activities of Some Heterocyclic Compounds from valproic Acid Drug

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Abstract

With a view to reducing the acidic effect of valproic acid, its carboxylic group has been recoated to produce 5-membered and 6-membered heterocyclic rings. Heterocyclic derivative as -Thiadiazole, Imidazole, -Oxazine, Quinazoline, Pyrazole and Oxadiazole. Derivatives of valproic acid were prepared by cyclization under different reaction states to produce a good yield. The microbial inhibitory effect of these compounds was assessed in vitro against Gram-positive and Gram-negative bacteria as well as tested against two strains of bacteria (*Escherichia coli* and *Staphylococcus aureus* compared with starting material. Compounds (4, 5, 8) showed the highest antibacterial as well as antifungal activities. All compounds have been characterized by IR, ¹H NMR and C.H.N analysis.

Keywords: Valproic acid, Thiadiazole, Imidazole,-oxazine, Quinazoline, Pyrazole, Oxadiazole, biologically active compounds.

Introduction

Valproic acid is an industrial derivative of propyl butanoic acid [1] Valproic acid is a saturated fatty acid, medicinal compound and possesses anti-convulsive properties used for the treatment of epilepsy and acts as a mood stabilizer, its mechanical and pharmacological work is not well known [2,3]. It either works by increasing levels of gamma-aminobutyric acid in the brain or by changing the voltage by its interaction with sodium.

The physiologic effect of valproic acid is by means of Decreased Central Nervous System Disorganized Electrical Activity with antiepileptic properties and potential antineoplastic and antiangiogenesis activities. And in epilepsy, valproic acid appears to act by increasing the concentration of gamma-aminobutyric acid in the brain. This agent's antitumor and Antiguogenesis activities may be related to the inhibition of histone diacetate and nitric oxide synthesis, which results in the inhibition of nitric oxide synthesis [4, 5, 6]. One or more atoms (oxygen, nitrogen, or

sulfur) are replaced by one or more carbon atoms within the ring structure of the chemical compounds, resulting in the synthesis of heterocyclics compounds [7, 8]. The heteroatom must be should more than one bond in the composition of heterocyclic rings, so halogens do not create heterocyclics compounds but may be as substituted group on the compounds heterocyclic. Heterocyclic compounds are one or more rings. A recent literature survey revealed that the different heterocyclic moiety has been widely used by the medicinal chemist in the past to explore its biological activities [9, 10].

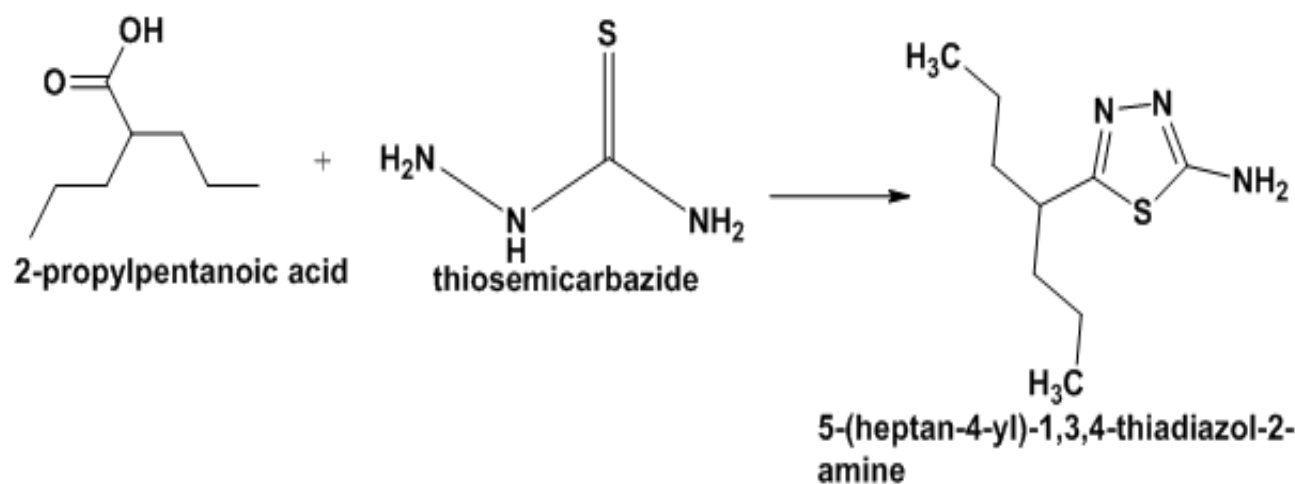
Heterocyclic compounds (Imidazole, Thiadiazole, quinazoline,) have an essential role in pharmacy, particularly when studying the chemical composition of the drug, deepening pharmacological processes, and bioconcentration. There are abundant in vitamins, dyes and many other natural products. Most heterocyclic organic compounds are derived from animal sources or plant sources. In many industries, such as the nylon industry used in the garment

industry, and in the manufacture of vitamin C. The active group is represented in many enzymes, helper enzymes, polymers, and the manufacture of nucleic acids. In the present study, we have aimed to check a best anti mycobacterial at lower concentrations, by preparing valproic derivatives.

Experimental

Instrumentation

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification; melting points were recorded on electro thermal melting point apparatus and are uncorrected. Thin layer chromatography (TLC) controls were



Compound (x) was obtained according to the procedure described by Al-Omar et al. [11] and Mazzone et al. [12] with a modification. A mixture of equimolar quantities of valproic acid (0.1 mmol), thiosemicarbazide (0.1 mmol), and phosphorus oxychloride (30 ml) was refluxed gently for half an hour, after cooling water was added (90 ml) and the mixture was refluxed for 4 h and filtered, the precipitate was filtered and recrystallized from ethanol.

Yield: 80%, M.p. 205°C - 208°C, IR (KBr, cm^{-1}): 3593, 3120, 1630. ^1H NMR (δ , ppm, DMSO- d_6): 0.89 (dd, 6H, $(\text{CH}_3)_2$), 2.61-3.61 (six, 4H, CH_2CH_2), 4.31 (pp, 4H, CHCH_2), 6.85 (pp 2H, NH_2).

Synthesis of 6-(4-Substituted phenyl)-2-(heptan-4-yl)-5,6-dihydroimidazo [2,1-b] [1,3,4] thiadiazole(xa-d) [13]

Compound (X) (0.01m mol) and an sub-bromoacetophenon (0.01m mol) was reflexed in dry ethanol (300 ml) for 10 h, excess of

carried out on silica gel plates (F254 Merck). The IR spectra were recorded on Shimadzu Shimadzu (Japan) 470, 8400 FT-IR infrared spectrophotometer using KBr pellets. HNMR, ^{13}C NMR, and 2D-COSY dimensions were measured using a Bruker 400 MHz instrument at the University of Science and Technology-Jordan and ^1H NMR spectra were recorded on ^1H NMR Bruken ultra shield 300 MHz. Using TMS as a reference and using CDCl_3 or $\text{DMSO}-d_6$ as a solvent.

Synthesis

Synthesis of 5-(heptan-4-yl)-1,3,4-thiadiazol-2-amine (x)

solvent was removed under reduced pressure the solid hydrobromide salts suspended in water, and neutralized by aqueous sodium carbonate solution to get free base, it was filtered, washed with water, dried and recrystallized from suitable solvent. 2-(4-n-heptyl)-6-phenylimidazo [2,1b] [1,3,4] thiadiazoles (Xa) yield: 70%, M.p. 215-217 °C, IR (KBr, cm^{-1}): 3095, 3033, 2943, 1576, 1490, 1339, 1130, 843. ^1H NMR (δ , ppm, DMSO- d_6): 0.88 (tt, 6H, $(\text{CH}_3)_2$), 2.61 (qq, 4H, CH_3CH_2), 3.61 (pp, 4H, CH_2CH_2), 4.31 (p, H, CHCH_2), 7.28-7.40 (m, 5H, ArH), 4.75 (s, 1H, H-5 imidazole).

(Xb) Yield: 73%, M.p. 196-198 °C, IR (KBr, cm^{-1}): 3085, 3043, 2973, 1596, 1481, 1343, 1150, 843. ^1H NMR (400 MHz, δ , ppm, DMSO- d_6): 0.83 (tt, 6H, $(\text{CH}_3)_2$), 2.61 (qq, 4H, CH_3CH_2), 3.61 (six, 4H, CH_2CH_2), 4.31 (p, H, CHCH_2), 7.08-7.18 (m, 4H, ArH), 8.74 (s, 1H, H-5 imidazole).

(Xc) Yield: 70%, M.p. 216-218 °C, IR (KBr, cm^{-1}): 3085, 3043, 2973, 1596, 1481, 1343, 1150, 843. ^1H NMR (400 MHz, δ , ppm,

DMSO-d₆: 0.83 (tt, 6H, (CH₃)₂), 2.61 (qq, 4H, CH₃CH₂), 3.61 (pp, 4H, CH₂CH₂), 4.31 (si, H, CHCH₂), 7.08-7.18 (m, 4H, ArH), 8.74 (s, 1H, H-5 imidazole).

Synthesis of 2-(heptan-4-yl)-4H-3, 1-benzoxazin-4-one (2) [14]

A mixture of valproic acid (0.03 mol) and phosphorus pentachloride (0.07 mol) in anhydrous carbon tetrachloride (20 ml) were refluxed for 2h at 100 °C. The solvent was distilled off for further reaction without any purification. To the acid chloride solution was added dry pyridine (30 ml), was refluxed for 3h the reaction mixture was cooled and poured into cold diluted HCl, the solid that separated filtered off and recrystallized from benzene to give (2), yield: 77%, M.p. 202°C - 204°C, IR (KBr, cm⁻¹): 3044, 2920, 2850, 1703, 1620,1543 . ¹H NMR (400 MHz), δ, ppm, DMSO-d: 0.83 (tt, 6H, (CH₃)₂), 2.61 (qq, 4H, CH₃CH₂), 3.61 (pp, 4H, CH₂CH₂), 4.31 (si, H, CHCH₂), 7.15 - 7.66 (m, 4H, ArH) for anthranilate ring

Synthesis of 2-(heptan-4-yl) quinazolin-4(3H)-one (3)

A mixture of (2) (6 mmol) and ammonium acetate (6 mmol) was fused in an oil bath for 2 h, then poured into water, the separation solid after concentration and cooling was filtered off and recrystallized from ethanol to give (3), yield 66%, M.p. 217°C - 219°C, IR (KBr, cm⁻¹): 3325, 2910, 2850, 1679,1589. ¹H NMR (400 MHz), δ, ppm, DMSO-d: 0.95 (tt, 6H, (CH₃)₂), 1.72 (qq, 4H, CH₃CH₂), 3.04 (pp, 4H, CH₂CH₂), 3.31 (si, H, CHCH₂), 5.04 (s, H, NH), 8.02- 7.86 (m, 4H, ArH) for quinazoline ring

Synthesis of 2-(heptan-4-yl) quinazoline-4(3H)-thione (4)

A mixture of (3) (5 mmol) and phosphorus pentasulfide (5 mmol) in dry xylene (50 ml) was heated under reflux for 1h, then concentration the solution, the product was obtained by filtration and recrystallized from xylene to give (4), yield 68%, M.p. 222°C - 224°C, IR (KBr, cm⁻¹): 3360, 3075,2920, 2850, 1634,1587, 1325. ¹HNMR (δ, ppm, DMSO-d₆): ¹H NMR (δ, ppm, DMSO-d₆): 0.87 dd, 6H, (CH₃)₂), 2.01 (qq, 4H, 2CH₂), 2.61(pp, 4H., 2CH₂), 3.31 (t, 4H, CHCH₂), 7.12-8.82 (m, 4H, ArH). 6.5 - 7.2 (m, 4H, ArH), 9.1 (s, 1H, NH, exchangeable).

Synthesis of 5-(heptan-4-yl) [1, 2, 4]triazolo [1,5-c]quinazoline-2(3H)-thione (5)

A mixture of (4) (5 mmol) and thiosemicarbazide (5 mmol) and phosphorus oxychloride (5 mmol) was warmed at 60°C for 1 h and the temperature was raised to 90°C for additional 2 h, the contents were poured onto crashed ice, cooled to 10°C, pH adjusted to 8 - 10 M NaOH and the resulting solid was crystallized from DMF to give (5), yield 63%, M.p. 231°C - 233°C, IR (KBr, cm⁻¹): 3406,30790, 2943,1620,1532, 1210, 1075, 980. ¹H NMR (δ, ppm, DMSO-d₆): 0.98 (tt, 6H, (CH₃)₂), 1.53 (qq, 4H, CH₂), 2.07 - 1.78 (pp, 4H, CH₂), 2.39 (six, H, CH), 7.16 - 7.37 (m, 4H, ArH), 6.2 (s, 1H, NH).

Results and Discussion

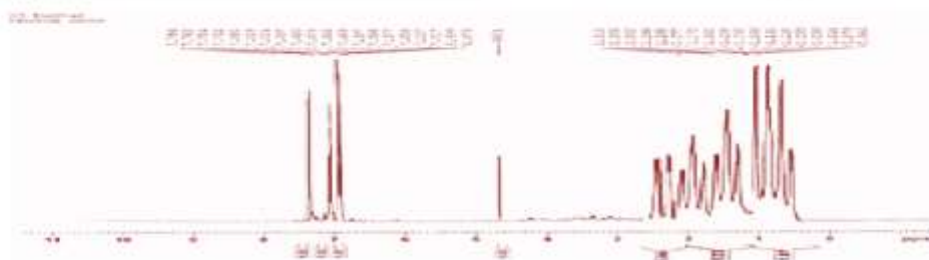
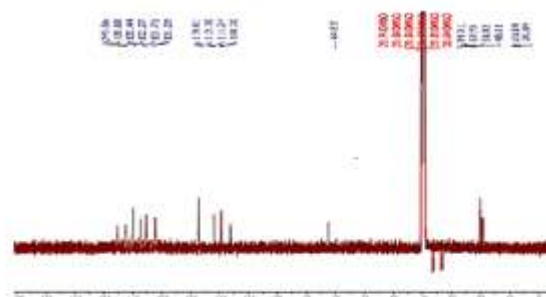
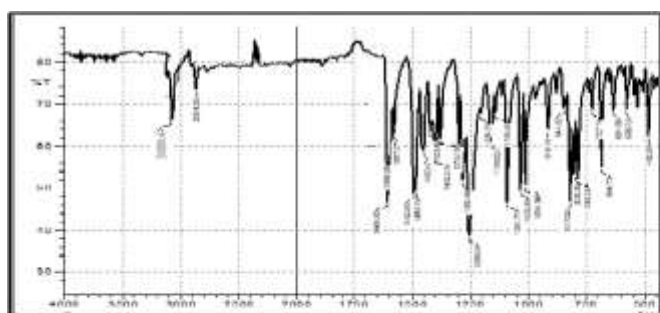
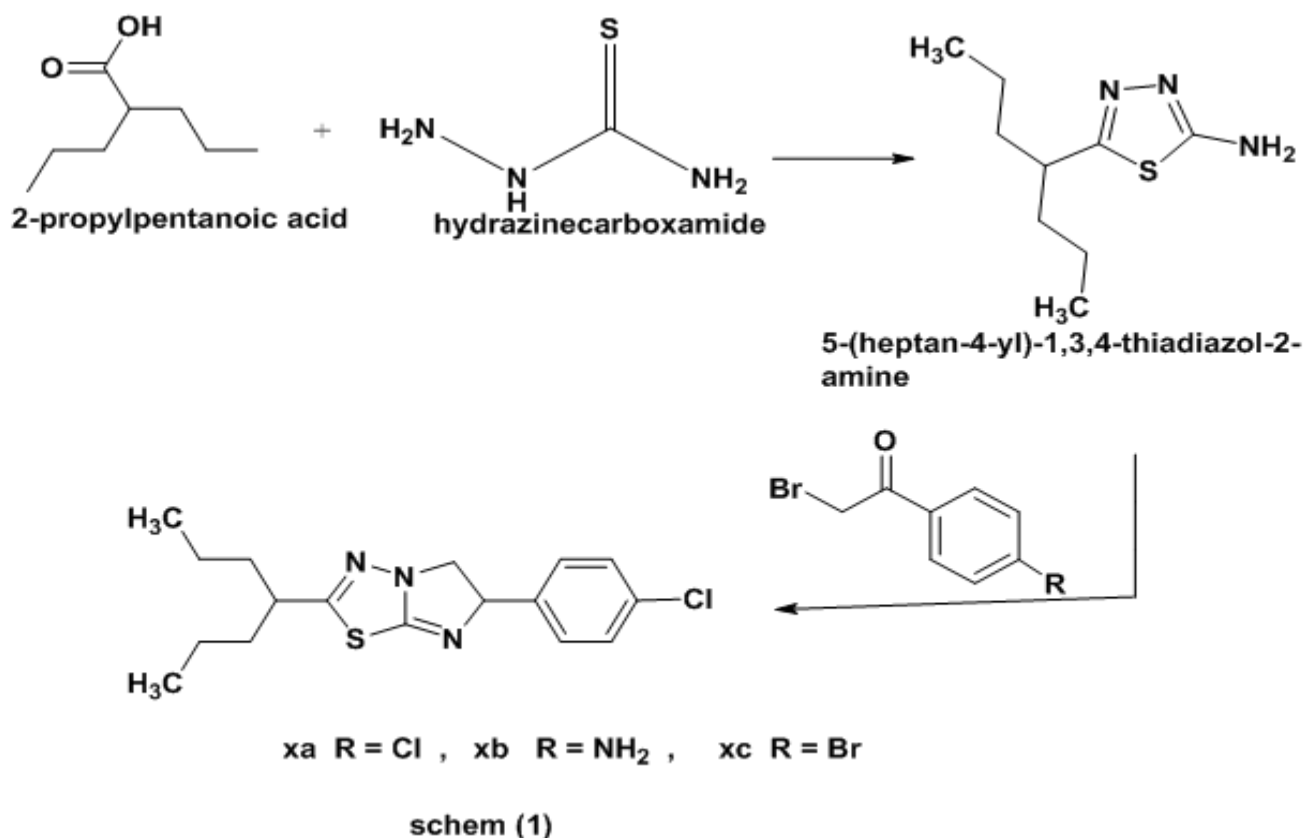
In the practical part of a synthesis of valproic acid derivatives, is divided into two parts of organic synthesis schemes, and the two parts will be discussed separately. The first part includes the preparation of these derivatives according to the scheme of synthesis (1) scheme 1. Synthesis valproic acid derivatives (X, Xa, Xb, Xc). The derivative (X) was obtained by direct reaction of valproic acid and thiosemicarbazide in the presence of phosphorus oxychloride to produce the intermediate compound thiadiazole imino, which has a cyclic reaction with ketone derivatives in dry ethanol, thus obtaining the derivatives of Xa-d and a good product ratio.

The derivatives of valproic were identified by physical methods (TLC, M.p, and color). And the spectral methods included first the infrared spectra, which showed a strong association of the amino group (NH₂) of the derivative (x), while the rest of the derivatives (Xa, Xb, Xc) did not this signal appears in its range.

The spectrum of all derivatives doesn't show a frequency of carbonyl and hydroxyl groups. And the HNMR spectrum of the derivative (X) showed a single signal for the NH group, while the derivatives (Xa, Xb, and, Xc) did not show this signal and instead showed signs of the aromatic protons. The HNMR spectrum for all the derivatives prepared in the scheme showed multiple signals of protons aliphatics for (2CH₃,4CH₂, CH).

Finally showed ^{13}C NMR spectrum, identical signals for the number of all carbon atoms. The 2D-COSY dimensions spectrum of the Xa derivative, shown in Fig. 1, was measured

the appearance of four signals for the 4CH_2 groups. This discussion of all spectral data was identical to all the chemical structures proposed in the synthesis Scheme (1).

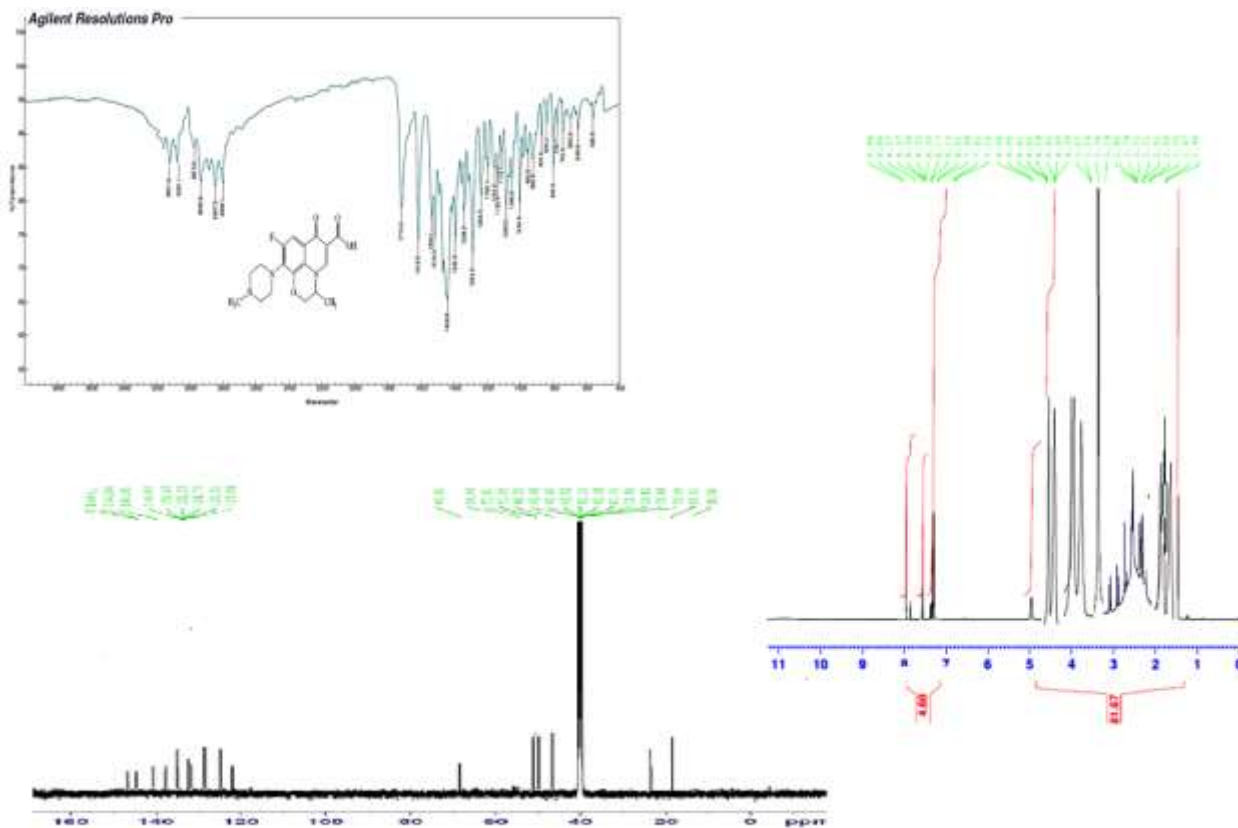
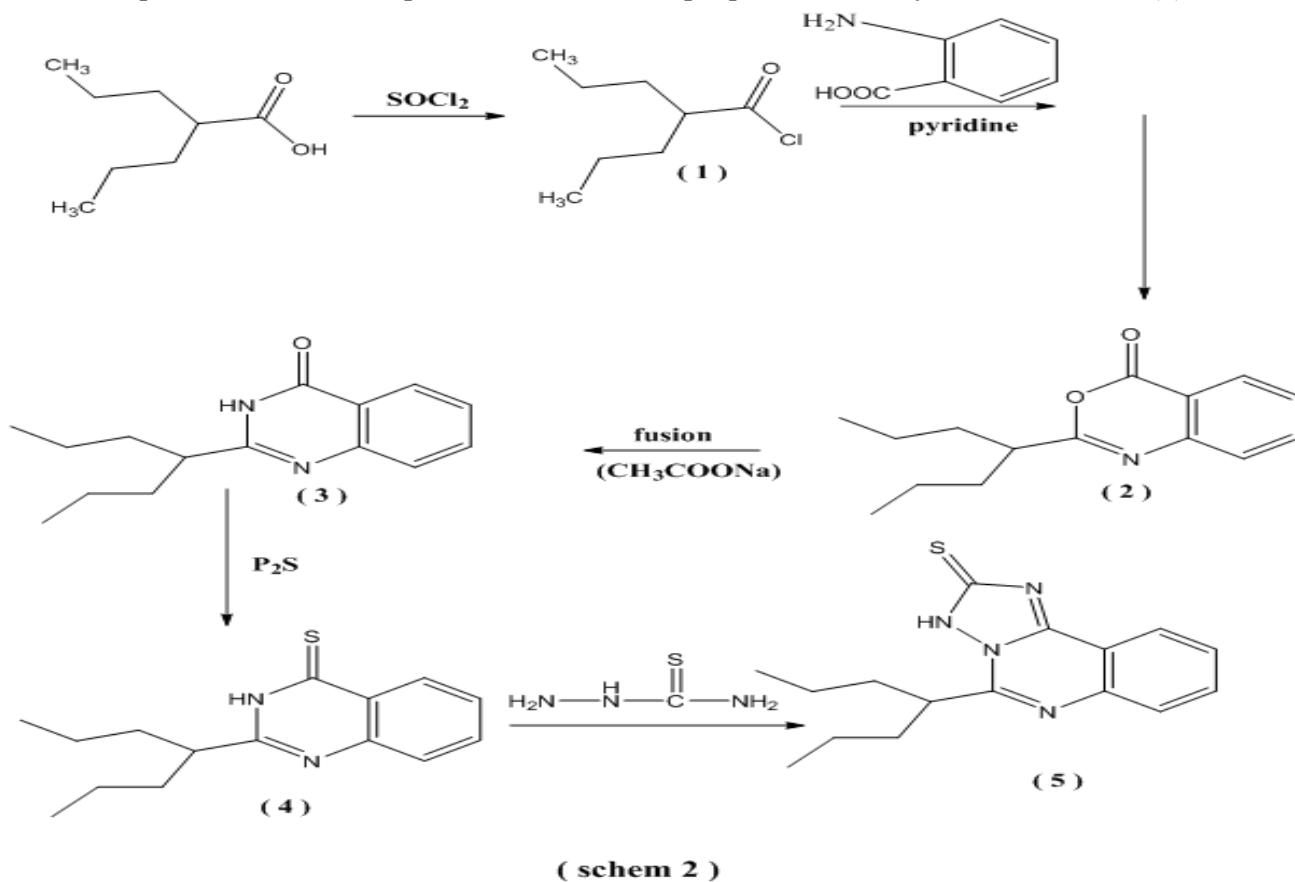


The second part for organic reactions involves the synthesis of derivatives (2, 3, 4, 5) according to the synthesis scheme 2. Follow the sequential steps to obtain these derivatives. The reaction of valproic chloride (y) with appropriate promo acetoacetate in ethanol with the presence of glacial acetic acid. The structures of compounds (2-5) were established by. Physical methods (TLC, M.p,

and color).And the spectral methods included of IR, ^1H NMR, ^{13}C NMR spectrum and 2D - COSY dimensions. First the infrared spectra, which showed a strong C=O stretching vibration. On at (1675-1715 cm^{-1}) and at (1551-1606 cm^{-1}) for C=N and stretching vibration at(3400-3350) for (NH) for compounds (3,4,5).Furthermore, The structure was further supported by its ^1H

NMR spectra, the ¹H NMR spectra showed singlet at δ 8.5-9.7ppm for NH(2,3,4) ring. And appeared signal multiplet was obtained in the aromatic region at δ7-8 ppm for the sub. ArH protons. ¹³CNMR spectrum and 2D

-COSY dimensions spectrum, identical signals for the number of all carbon atoms, in Fig. 2, Discussion of the all spectral data was identical to all the chemical structures proposed in the synthesis Scheme (2).



Figur 2 compound 2

Biological Activity [12, 14]

Since the prepared valproic acid derivatives in this work were built from two biologically active components (5 and 6-membered heterocyclic rings) they were expected to possess biological activity, thus studies on the antibacterial activity of synthesized ibuprofen derivatives have been carried out against two pathogenic organisms including *Staphylococcus aureus* (Gram-positive) and *Escherichia Coli* (Gram-negative) using cup-plate method. The results of the antibacterial studies are shown in the Table (2). It was noticeable that the nature of substituted on

heterocyclic molecules affected their biological activities against the studied bacteria [15]. Thus, among the tested compounds (, **Xbox,3**) which were substituted with (Cl or NH, O) groups showed high biological activity against *Escherichia Coli* and slight to moderate activity against *Staphylococcus aureus*. Compound (**Xa, 2,4,5**) which was substituted with (OCH₃) group showed high biological activity against *Staphylococcus aureus* while it showed slight activity against this bacteria. All compounds other showed high activity against Gram-positive bacteria and Gram-negative bacteria represented by large inhibition zones.

Table 2: antibacterial activity of compounds (x,xi,xb,xc) and (2,3,4,5)

Compounds No.	Gram positive bacteria	Gram negative bacteria
	<i>Staphylococcus aureus</i>	<i>Escherichia Coli</i>
X	++	++
Xa	+++++	+
Xb	++	+++++
Xc	++	+++++
2	++++	++
3	+	+++++
4	+++++	+++
5	+++	+++

Conclusion

Synthesis (imidazole, quinazoline, pyrazole) derived from valproic acid. And the systems

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