Preparation and Characterization some New of Naproxen Drug Derivatives

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Abstract:
In this research four steps of the new derivatives of Naproxen drug have been made which are known as a high medicinal effectiveness; the first step involved converting Naproxen into the corresponding ester (A) by reaction Naproxen with methanol absolute in presence H₂SO₄. While the second step involved treatment methyl Naproxen ester (A) with hydrazine hydrate 80% in presence of ethanol. The third reaction requires synthesis of Schiff bases (C₁-C₁₀) by condensation of Naproxen hydrazide (B) with many substituted aromatic aldehydes. Finally, the fourth step synthesized new tetrazole derivatives (D₁-D₁₀) by the reaction of the prepared Schiff bases (in the third step) with Sodium azide in THF as a solvent. The prepared compounds were characterized by physical properties, (FT-IR),UV, and somewhat of them by ¹H-NMR, ¹³C-NMR spectroscopy.

Key words: Naproxen drug, Schiff base, Tetrazol compounds.

Introduction:
The Chemistry of heterocyclic compounds has been a fascinating scope of schooling of long time. The synthesis of piece Trrazole derivatives and inquiry of their biological and chemical conduct has gained more momentousness in modern decades for all biologic and pharmaceutical reasons [1]. Tetrazole is a hetero cyclic compound which containing carbon atom and four nitrogen atoms in a five member ring[2]. Tetrazole compounds are used broadly in biochemistry, medicine pharmacology, explosives, and other scopes. Its derivatives have signification implementation in major scopes, like agriculture, imaging technology, and medicine and they are very stimulating hetero cycles from an academic view point [2-3]. Tetrazole and its derivatives have attracted much attention because of their individual form and implementation as anti-allergic, anti-hyper tense nti-consultant agents anti, and biotic. Synthesis of tetrazole derivatives is obviously an important task in recent medicinal chemistry. [4] The development of the tetrazole chemistry has been imported, in the main as upshot result of the center roles played by tetrazoles in coordination chemistry as nitrogen containing heterocyclic legends[5-6] Naproxen is one of the most uniform used as a
propanoic acid derivative for the treatment of pain, joint swelling and symptoms of arthritis [7] is believed to work by blocking the action of cyclooxygenase (Cox) in evolved in the production of prostaglandins or prostaglandins straight after they have already been formed there by relieving pain and inflammation [8]. It is among the most commonly prescribed non-steroidal anti-inflammatory drugs (NSAIDs) for the management of inflammation and pain [9]. They display biological activities that contain antibacterial, antifungal [9-10] anticancer [11], and herbicidal activities [12].

**Materials and Methods:** [13]
Chemicals employed were of analytical grade and used without further purification. Melting points were specified in Gallen Kamp melting point appliance and ethanol were not corrected. UV-visible spectra were recorded on T60u shi madzu spectrophotometer used as a solvent. FT-IR 8400 Fourier transform infrared spectrophotometer as KBr disc. $^1$H-NMR and $^{13}$C-NMR spectra were written down on Bruker spectra spin Ultra shield magnets 300 MHz device using tetra methyl silane (TMS) as an inner standard and DMSOd$_6$ as a result in – Al bait University in the country of Jordan.

**Procedure for the composition of methyl Naproxen [14]**
Naproxen drug (1 gm, 0.004 mole) was taken in round bottom flask (250 ml) fitting tightly with a reflux condenser and calcium Chloride guard tube add 25 ml methyl alcohol 99% add one or two drops of intense sulfuric acid and the mixture was refluxed for pouring in to 250ml of water incoming in a separating funnel add 20ml from dichloromethane to the separating funnel and the blend were jolted strenuously. The mixture was stopped and methyl Naproxen in dichloromethane detached and retained at the down of the separating funnel. The tower layer was cautiously split and the higher aqueous solution stratum was refused methyl Naproxen was returned to the funnel and shaken with a powerful bicarbonate solution up to all the free aid was outside methyl Naproxen was washed one time with solution water and dried by gushing to a mini dry conical flask be comprised two gm of anhydrous magnesium sulphate. This solution was shaken for 5 min and permit it to stand for 60 minutes. The methyl Naproxen solution was filtrated through a filter paper futed filter paper into a filtration flask. The flask was shaped with 360˚C concenter and receiver flask. Dichloride methane was distilled of at 40˚C and precipitate methyl Naproxen was acquired from flask. Ethanol was used solvent for purification of the ester is listed in Table (1).

**Procedure of the preparation of naproxen hydroxide (B). [14]**
A mixture of compound (A)(0.5g,0.004mole), Hydrazine hydrate 80% (0.7ml and 0.004mole, ethanol (10ml) were put in round bottom flask and refluxed for 6 hrs. The mixture was contracted, cooled ,and the white crystal filtered derided and recrystallized from ethanol. The physical properties of compound (B) is listed in Table (1).

**Preparation of Schiff bases (C1 -C10) [6]**
A chain of Schiff bases (C1-C10) were ready from the reaction of (0.01 mole) with different aromatic aldehydes (0.01 mole) in 25 ml ethanol absolute and one or two drops of glacial acetic acid. This blend was refluxed for 6 hrs. The precipitate was recrystallized from ethanol. The physical properties of compound (B) is listed in Table (1).

**Preparation of Tetrazole derivatives (D1 -D10) [15].**
Compounds of (C1 -C10) (0.16gm, 0.01 mole) was dissolved in(20ml) tetra
hydro furan and mixed with (0.01ml) sodium azide. Those mixtures were heated in water bath at 75°C for 6 hrs. The precipitate was filtered and recrystallized from ethanol. The limit of reaction was checkup by TLC in methanol [16]. Melting points and yield % data are listed in Table(3).

Results and Discussion:
Schiff bases can be prepared from condensing hydrazine with varies aromatic aldehydes; they have been prepared in the ratio 1:1 of to aromatic carbonyl compounds. The present investigation describes synthesis that is isolated and characterized by physical properties, spectroscopic data (Tables 1,2) .The FT-IR spectral data of Schiff bases compounds show the bands of the stretching vibrations due to the fact that (C-H) aromatic , (C-H) aliphatic , (C=N) imine group in the regions ( 3005-3180) cm⁻¹, (2852-2999) cm⁻¹ and (1654-1739)cm⁻¹ straight [14]. Schiff bases FT-IR spectrum of compound (C₆) show absence at (4) cm⁻¹ for (NH₂) group in the starting material and appearance of the imine group (C=N)at (1654) cm⁻¹ which is a good indication of successful condensation . Compound (C₆) shows absorption band at (2974) cm⁻¹ due to (C-H) aliphatic , (3001-3180) cm⁻¹ for (C-H) aromatic , (1654) cm⁻¹ (C=N) and (1471) cm⁻¹ (C-N) listed in Table (4), Figure(7). The UV. Spectrum of ( C₃) Figure (1) shows the absorption λ max of (235) nm due to the (π-π*) transition, whereas compound (C₅) Figure (2) shows the absorption λ max at (232) nm and (299)nm due to the (π-π*) and (n-π) transition¹H –NMR spectrum of compound (A) shows the signals (1.67) ppm is attributed to (CH₃) proton, multiple signals at (6.85-7.81) due to aromatic protons and singlet signal at (3.59) ppm due to (CO-CH) proton as shown in Figure (9) . ¹³C-NMR spectrum of the same compound shows the signal at (147) for (C=O) amide and absorption at (119-136) for aromatic carbons as shown in Figure (10). The other route, reaction of Schiff bases with sodium azide [17] in dioxan with water bath produces tetrazol compound dispossess wide spectrum of biological activities, the overall steps of synthesized compounds are shown in Scheme(1)
The mechanism of reacting systematically investigation as [3-2] cycloaddition which is called as 1,3 – dipolar cycloaddition reaction. It involves the addition of unsaturated systems, dipolarphiles, to 1,3 – dipoles a molecule possessing resonance contributors in which appositive and negative charge are placed in 1,3-position relative to each other .The accession results in five member rings, azides are a prominent class of 1,3-dipoles and azide1,3-dipolar cycloaddition [18].

Scheme (2) Structure of tetrazol

The formula structure for tetrazol compound (D1-D10) is confirmed by spectroscopic data and physical properties in Table (3) and (2) . FT-IR spectra of the products show the absorption of the starching vibrations due to (C-H) aliphatic , (C-H) aromatic and (N=N) tetrazol group in the region (2937-2833)cm⁻¹, (3122-3008) cm⁻¹ and (1653-1593)cm⁻¹ respectively. Moreover, the FT-IR spectra of these compounds are devoid of starches band at (2160 -2120) cm⁻¹attributed to starching frequency of azide group[19]. The above data agrees with the proposed structures assigned to these compounds. Compound [D6] shows absorption band at (2848-2999) cm⁻¹ for (C-H) aliphatic (3043-3182) cm⁻¹ for (C-H) aromatic, (1654) cm⁻¹ for (N=N)cm⁻¹, and (2144) cm-1 for (=N-N=C-) ,tetrazol ring listed in Table (3) Figure (8). The UV. Spectrum of compound (D5 and D8) Figure (3 and 4) show the absorption λ max at (233,299) nm due to the (π-π*). 1H-NMR Spectrum of compound (D6 ) show the signals (1. 46 ppm) due to (CH₃ ) proton, multiple signals at (7.14-7.89) due to aromatic protons and singlet signal at(3.86) due to (N-H) proton as shown in Figure (15), 13C-NMR spectrum of the same compound shows the signal at (160-176) for (C=N) and absorption at(105-135) for (aromatic carbons as shown in Figure(16).

| Comp. No. | Compound structure | Color     | Melting Point/ °C | Percentage % | Solvent used In recrystallization |
|-----------|--------------------|-----------|-------------------|--------------|----------------------------------|
| A.        | ![Structure](image) | Off White | 82-84             | 83           | Methanol                         |
|           | C₁₄H₁₆O₃           |           |                   |              |                                  |
| B.        | ![Structure](image) | Brown     | 119-121           | 44           | Ethanol                          |
|           | C₁₄H₁₆N₃O₂         |           |                   |              |                                  |
Table (2) The Physical properties for Schiff base C (1-10)

| Comp. No. | Compound structure | Color            | Melting Point/°C | Percentage% |
|-----------|--------------------|------------------|------------------|-------------|
| C1        | ![Structure](image) | Light Yellow     | 88-90            | 51          |
| C2        | ![Structure](image) | Yellowish brown  | 94-96            | 67          |
| C3        | ![Structure](image) | Light brown      | 96-98            | 72          |
| C4        | ![Structure](image) | Brown            | 89-91            | 63          |
| C5        | ![Structure](image) | Dark yellow      | 165-167          | 52          |
| C6        | ![Structure](image) | Yellow           | 160-163          | 56          |
| C7        | ![Structure](image) | Light yellow     | 80-82            | 66          |
| C8        | ![Structure](image) | Light yellow     | 90-92            | 77          |
| C9        | ![Structure](image) | Brown            | 84-86            | 56          |
| C10       | ![Structure](image) | Brown            | 86-88            | 51          |
Table (4) The FT-IR spectral data for all compounds

| Comp. No | V(C=O) | V(C-H) aromatic | V(C-H) aliphatic | V(N-H) | V(C-N) | V(=N-N=C–) | (C=O) | Others                  |
|----------|--------|-----------------|------------------|--------|--------|-------------|-------|-------------------------|
| A        | -      | 3080            | 2939             | -      | -      | -           | -     | V(C-O)1193              |
| B        | -      | 3040            | 2979             | 3244   | -      | -           | 1700  | -                       |
| C        | -      | 3059            | 2978-2935        | 3294   | 1385   | -           | 1635  | -                       |
| C1       | 1678   | 3055            | 2954-2854        | 3213   | 1346   | -           | 1635  | V(O-H)3394              |
| C2       | 1716   | 3070            | 2974-2830        | 3366   | 1336-1394 | -           | 1639  | -                       |
| C3       | 1660   | 3050            | 2976-2941        | 3350   | 1330   | -           | 1637  | V(C-OH)3566             |
| C4       | 1639   | 3005            | 2848-2976        | 3246   | 1336   | -           | 1620  | V(C-OH)3587             |
| C5       | 1700   | 3080            | 2925-2860        | 3300   | 1350   | -           | 1605  | V(C-NO2) 1365-1506      |
| C6       | 1654   | 3001            | 2974-2840        | 3292   | 1371   | -           | 1635  | -                       |
| C7       | 1680   | 3053            | 2935-2870        | 3238   | 1348   | -           | 1683  | -                       |
| C8       | 1675   | 3050            | 2999-2810        | 3223   | 1300   | -           | 1625  | V(C-Cl)825-1174         |
| C9       |        |                 |                  |        |        |             |       |                         |
| C10      | 1662   | 3014            | 2852-2962        | 3250   | 1350   | -           | 1629  | -                       |
| D1       |        |                 |                  |        |        |             |       |                         |
| D2       | -      | 3088            | 2929-2980        | 3290   | 1392   | 2127        | 1630  | V(C-Br)640              |
| D3       | -      | 3080            | 2930-2810        | 3190   | 1356   | 2125        | 1670  | V(C-OH) 3500            |
| D4       | -      | 3070            | 2850-2933        | 3298   | 1350   | 2129        | 1630  | V(C-OH)3388             |
| D5       | -      | 3113            | 2914-2981        | 3390   | 1360   | 2137        | 1620  | V(C-NO2) 1367-1550      |
| D6       | -      | 3043-3082       | 2848-2999        | 3296   | 1385   | 2144        | 1670  | -                       |
| D7       | -      | 3070            | 2976-2850        | 3290   | 1385   | 2142        | 1668  | -                       |
| D8       | -      | 3070            | 2933-2855        | 3390   | 1350   | 2123        | 1639  | V(C-Cl) 1159-856        |
| D9       | -      | 3061            | 2825-2976        | 3296   | 1344   | 2108        | 1660  | -                       |
| D10      | -      | 3100            | 2940-2820        | 3390   | 1392   | 2127        | 1631  | -                       |

Fig. (1) UV spectrum for compound C3

Fig. (2) UV spectrum for compound C5
Fig. (3) UV spectrum for compound D5

Fig. (4) UV spectrum for compound D8

Fig. (5) FT-IR spectrum for compound (Ester) (A)

Fig. (6) FT-IR spectrum for compound (Hydrazid) (B)
Fig. (7) FT-IR spectrum for compound (Schiff base) (C6)

Fig. (8) FT-IR spectrum for compound (Titrazole) (D6)

Fig. (9) $^1$H-NMR spectrum for compound (Ester) (A)

Fig. (10) $^{13}$C-NMR spectrum for compound (Ester) (A)
Fig. (11) $^1$H-NMR spectrum for compound (Hydrazed) (B)

Fig.(12) $^{13}$C-NMR spectrum for compound (Hydrazed)(B)

Fig. (13) $^1$H-NMR spectrum for compound (Schiff base) (C$_6$)

Fig. (14) $^{13}$C-NMR spectrum for compound (Schiff base) (C$_6$)
Fig. (15) $^1$H-NMR spectrum for compound (Titrazol) (D8)

Fig. (16) $^{13}$C-NMR spectrum for compound (Titrazol) (D8)

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**Translator's Note:**

**Title:** تحضير وتشخيص بعض المشتقات الجديدة لدواء النبر وكسين

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**Summary:**

حضرت مشتقات دواء النبروكسين ذو التأثيرات الدوائية بأربع خطوات تضمنت الخطوة الأولى تحويله إلى استر (A) عن طريق تفاعل النبروكسين مع الميثانول المطلق بوجود الوسط الحامضي. ثم الخطوة الثانية التي تضمنت تفاعل الاستر المحضر في الخطوة الأولى مع الهيدرازين المائي لإنتاج المركب (B) بوجود مذيب الايثانول المطلق، في حين الخطوة الثالثة من البحث تضمنت تفاعل المركب (B) مع بعض الألكدتها الإثينولات المختلفة التعويض أولاً في الخطوة الرابعة يتم مفاعله قواعد شيف (C1-C10) (في الخطوة الثالثة) مع أزيد الصوديوم في مذيب THF كمذيب لإنتاج المركبات (D1-D10) UV,FTIR، المركبات فيزيائيًا وطيفيًا وذلك عن طريق قياس الخصائص الفيزيائية وباستخدام التقنيات الطيفية 1H NMR - 13C NMR - 1H- NMR - 13C NMR

**Keywords:** دواء نبروكسنين، قواعد شيف، مركبات تترازول.