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In Vitro Evaluation of Novel Designed, and Synthesized Naproxen Derivatives Bearing 1,2,4 Triazole Moiety

Sajjad. A. Hafedh[1], Noor H. Naser[2,*] and Sahar A. Hussein[2]
[1]Department of pharmaceutical chemistry, Faculty of Pharmacy, University of Kufa, Najaf, Iraq.
[2]College of pharmacy, Al-Zahraa University for Women, Karbala, Iraq.

Corresponding author: Noor H. Naser (e-mail: noor.hatef@alzahraa.edu.iq).

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Abstract: The Objective of this study is created a novel derivative of the naproxen with the heterocyclic (1,2 and 4 the triazole) ring that reacted with benzoyl chloride derivatives, as well as preliminary antibacterial activity testing of the formed products. The derivatives are synthesized by esterifying naproxen hydrazine hydrate, then reacting with hydrated hydrazine and carbon disulfide, and finally reaction the benzoyl chloride derivatives (in the final step) with the triazole the derivatives of the naproxen including of amino group via a nucleophilic substitution reaction. In addition to naproxen, the antibacterial properties of the novel compounds (Va-Vd) were evaluated in agar at known doses (IN vivo). The antibacterial action of the compounds Va and Vd against staph was demonstrated in the topmost inhibited zone. In the case of E. coli, compound Vb has the smallest inhibitory zone. The findings of this study have implications to produce naproxen 1,2 and 4 the triazole-three-thiol derivatives, which reacted including the variety of benzoyl chloride derivatives. The potential of naproxen will be affected by the attraction of benzoyl chloride derivatives with para-groups on the benzen ring.

Key Words: analogue of naproxen, synthesizing of new derivatives for naproxen, five membered ring (triazole) heterocyclic ring, benzoyl chloride derivatives

I. INTRODUCTION

Nonsteroidal anti-inflammatory drugs medications (NSAIDs) are non-opiate chemicals that are often used to treat pain, fever, and inflammation around the world [1]. stopping the cyclooxygenase (COX) passageway, which mean converting of the arachidonic acidic to prostaglandins via an enzyme (COX) is prevented, is their mode of action [2]. They work by inhibiting cyclo-oxygenase-one (cyclooxygenase. COX-1) and cyclo-oxygenase-two (cyclooxygenase. COX-2) enzymes in a competitive manner [3], [4]. Various studies have shown strength antibacterial and anti-fungal actions in NSAIDs [5], [6]. In addition to their analgesic and antipyretic qualities, NSAIDs were utilized to treat inflammatory disorders such as rheumatoid arthritis and osteoarthritis [7], [8]. Figure 1 shows the Naproxen, or 2-(6-methoxynaphthalen-2-yl) propionic acid, is a propionic acid derivative that is commonly used to treat a variety of injuries and symptoms. Naproxen is a type of medications (NSAID) that is commonly used. Because of its good cardiovascular sight, naproxen has been used safely for long time despite its gastrointestinal side effects. Naproxen also has another pharmacological potential, particularly anti-cancer, and antibacterial activity, have recently piqued the curiosity of scientists, in addition to its anti-inflammatory benefits. The COX-2 enzyme is inhibited by naproxen, which demonstrates its activity [9]. Naproxen firstly got the approval for prescription utilizing in 1976, and it stilled to 1994, after that got the approval as an over the counter (OTC) medicine. Drugs that treat acute gout and ankylosing spondylitis, as well as rheumatoid arthritis, osteoarthritis and tendonitis have all been approved by the FDA [10], [11].

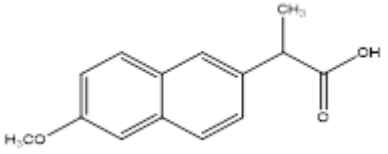

FIGURE 1: Naproxen, or 2-(6-methoxynaphthalen-2-yl) propionic acid

To generate pharmaceutically important compounds, a wide range of heterocyclic systems have been investigated. Many drugs contain nitrogen-containing heterocycles. The medicinal characteristics of triazole derivatives are particularly intriguing. Triazoles are five-membered rings with

the chemical formula C2H3N3 that involve 2 carbon and 3 nitrogen atoms. According to the position of the nitrogen atoms, triazoles can be classified into two isomeric forms: 1,2 and 3 the triazole as well as 1,2 and 4 the triazole [12]. The biological actions of 1,2 and 4 the triazoles and their fused heterocyclic derivatives are diverse. The 1,2 and 4 the triazole core has been used in the enormous range of medically relevant medicines, including antibacterial, antifungal, antiviral, and anticancer drugs [13]–[18]. In vitro growth inhibitory activity of newly formed 1,2,4-triazole compounds was evaluated against conventional Gram ve+ and Gram ve- microbial strains. It is also a well idea to experiment with recently acquired compounds together with antiseptic action against drug-resistant microorganisms (e.g., MRSA, VRE). In addition, some chemicals were studied for their anti-tuberculosis properties. Methods for detecting the activity of triazole as antimicrobial agents were used for preliminary screening [19]–[23].

II. MATERIALS AND METHODS

From (sigma- aldrich Germ any, reidal dehean Germany, Hangzhou Hyper Chemicals and mer ck, Germany) provided all reagents and anhydrous solvents. Thomas hover device was used to determine melting points using the capillary tube method (England). To confirm the steps of the reaction and the purification process of the formed compounds, to determining the retention factor (Rf) values, ascending thin layer chromatography was utilized, with chloroform and acetate of the ethyl (7:3) serving like the mobile phasis [24]. The College of Pharmacy at the University of Kufa utilized a spectrophotometer manufactured by Shimadzu Japan to scan FT-IR and estimate spectra by making use of KBr discs. The Bruker 500 MHz at the University of Tehran was utilized to record H1NMR with DMSO serving as the solvent.

A. GENERAL PROCEDURE

The entire list of chemicals as well as their intermediates are shown in the figure 2. In the presence of thionyl chloride and while the methanol is cold, the esterification of naproxen carboxyl (-COOH) takes place (SOCl2). A methyl ester of naproxen, which was then reacted with hydrazine, produced hydrazide, which was then responded by carbon disulfide at a presence of hydroxide of the potassium to product potassium di thiocarbazone derivative, which was then cyclized at the presence of hydrous hydrazine to product the heterocyclic ring (1,2,4-triazole-3-thiol) derivative of a naproxen. This process has been repeated multiple times a primary amine group of the synthesized ring was the target of the reactions that were carried out to bring about the outcomes that are outlined in Table 1.

III. SYNTHESIS OF (S) METHYL-2-(6-METHOXY NAPHTHALENE-2-YL) PROPANOATE (I)

The liquid (containing naproxen) (0.9 gram, 4.2 milli mole) in 99% methanol (50 ml) cooled to -10 °C before gradually adding thionyl chloride (0.31 ml, 4.3 mmol). The mix stayed

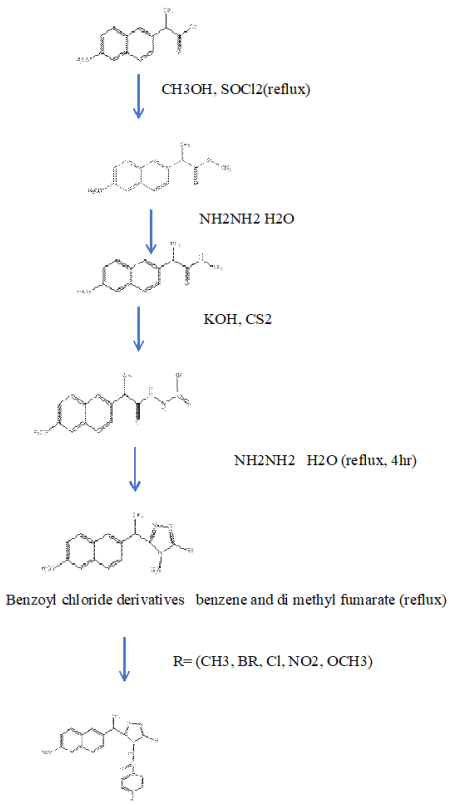

FIGURE 2: The target of the combinations and synthesis of the intermediates

at 40 °C for 3 hours, then refluxing for 4hrs before being left at for one night. A methanol vapored to drought before being redissolved at ethanol then evaporation is done again. This procedure repeated more than one time until the SOCl2 removed. The ether-methanol residue was recrystallized [25]. Table 2 showed Rf values and percent yield are included in the physical data.

A. (6-METHOXY NAPHTHALEN-2-YL) PROPANE HYDRAZIDE SYNTHESIS (S) (II)

After heating a mix methyl group ester (naproxen ester) (I) (2.5 g, 10.8 mmol) as well as hydrazine hydrate (1.6 ml, 32.5 mmol) by refluxing for 15 minutes, a clear solution obtained by dropping (10 ml) of 99% ethanol from the head of the condensing apparatus. The mixture was reflux for 5 hours before the condenser properly closed. The alcohol evaporated, and the residue cooled [26]. The hydrazide crystal separated by filtration, recrystallized from ethanol, and washed several times with ether (diethyl ether and petroleum ether) to obtain compound powder (II). Table 2 displays the physical data, Rf values, and % yield.

B. A SYNTHETIC (S) APPROACH TO THE PREPARATION OF POTASSIUM -2-(2-(6-METHOXY NAPHTHALEN-2-YL) PROPANOYL) HYDRAZINE CARBODITHIOATE (III)

A cold liquid of potassium(K) hydroxide (0.6 g, twelve mmol) dissolved in 100 percent ethanol mixed with 2 g of propane hydrazide (II) (250 ml). The mixture was then stirred in continuous way at 25 °C for 36 hours while carbon disulfide (0.9 ml, fifteen mmol) added drop by drop. After that, the precipitated K-di-thiocarbazone derivative filtered, then washing together with anhydrous diethyl ether, plus dried. A salt (of K) formed and utilized without further purification in the following step [27]. Table showed the physical properties, R-f values, and % yield.

C. AMINO ACID SYNTHESIS (S) -5-(1-(6-METHOXYNAPHTHALEN-2-YL) ETHYL) -4H-1,2,4-TRIAZOLE THIOL-3-THIONE (IV)

For 6 hours, the comment of the combination (III) (1g, 2.75 mmol), hydrated hydrazine (80%, 0.275 ml, 5.5 mmol), and D, W (10 ml) refluxed. When the condenser's opening opened, hydrogen sulfide gas released, the response mix color switched to greenish brown, as well as the homogenous liquid generated. The addition of freezing water liquid in the formation of a deep brown solid (50ml). To get a deep brown powder, filtration of the solution, rinsing with freezing water (250 ml), and re-crystallized from ethanol and diethyl ether. [25]. Table 2 displays the physical data, Rf values, and % yield.

D. SYNTHESIS OF FINAL PRODUCTS (VA- VE)

Compound (IV) (0.1gm, 0.33 mmol) dissolved in amount of benzen and di methyl fumarate (3:1) and then 0.05 ml of tri ethyl amine was added to the solution (first), the whole mixture was stirred ice bath for 1/2 hour and then (0.05 gm Va,0.073 gm of Vb,0.06 gm of Vc, 0.0612gm of Vd ,and 0.06 gm of Ve) were dissolved in benzene as other solution(second) and added to first one and then refluxed for 12hr,6hr,8hr,50hr and 15hr for Va ,Vb ,Vc ,Vd ,and Ve respectively . It has been filtered, cleaned under freezing water many times, dry, and washed with petroleum ether [28]. Table 2 showed the % yield, physical data, and Rf values.

E. THE TARGET MOLECULES' CHARACTERIZATION AND PHYSICAL PROPERTIES, AS WELL AS THEIR INTERMEDIATES

1) Naproxen (C14H14O3) M.WT =230.26,off white crystals ,Melting point In Co =170 and RF. Values =0.67.
2) Compound I (C15H16O3) M.WT=244.10 , Off white crystals, % yield = 97 , Melting point =93-91 and RF valu is 0.89.
3) Compound II (C14H16N2O2) M.Wt is 289.31, %yield 62.979, pale-Brown crystals, melting point = 127-129 and Rf value is 0.7.
4) Compound III (C15H16KN2O2S2) M.WT =403.54, Brown, % yield =78.86231, melting point = 190-192 and RF value is 0.65.
5) Compound IV (C15H16N4OS) Mwt =345.4, brown, %yield = 48, melting point is 120-122 and RF value is 0.867.
6) Compound Va (C23H22N4O2S) M.wt =528.4,off white crystals, % yield =83.7, Melting point = 138-140 and Rf vlaue =0.571.
7) Compound Vb (C22H19BrN4O2S). M.WT =528.4,Brown-crystal %yield 43.63%, melting point =170-172and Rf value =0.4285.
8) Compound Vc (C22H19ClN4O2S). M.wt = 483.95, Pale-Brown-crystal, %yield =41% , melting point=198-200 and Rf value =0.5.
9) Compound Vd(C22H21N5O2S) . M.wt = 494.5, Brown-crystal, %yield =88.1, melting point=190-192and Rf value =0.4857.
10) Compound Ve(C23H22N4O3S). M.wt=479.3, Grey-crystal, %yield =93.7%, melting point = 148-150 and Rf value=0.488.

IV. SPECTROSCOPIC ANALYSIS

Compound (I) (C15H16O3); IR (cm-1): 3061 (C-H) of AR, 1,736 (C=O) of ester, 2937(symmetric CH,CH3) ,2974 (asymmetric CH,CH3) 1446-1604 (C=C aromatic) and 1267 (C-O) . 1H-NMR (D MSO-d6) δ(ppm):7.79-7.1 (m,6H,ArH), 3.85 (s,3H,CH3), 3.92 (m,1H,CH), 3.6 (s,3H,CH3), 1.47 (d,3H,CH3) .13C -NMR(DMS O-d6) δ(ppm): 106.14-157.67 (m. 10c.aromatiC),174.8 (s.1C.C), 55.62(s.1C,CH3),44.77(S.1C.CH),18.91(S.1C.CH3) And 52.25(s.1C,CH3).

Compound (II) (C14H16N2O2); IR (cm-1): 3,284 of (N H2), 3010(CH of aroma tic) , 2.963 (C-H) of alkane, 1,637(C=O) and 1211(C-O).

Compound (III) (C15H16KN2O2S2); IR (cm-1): 3194 (N-H) of secondary (NH-), 2972 and 2937 (C-H) of alkane, 1.367 (C=S) str etching, 1211(C-O), and 1,657 (C=O).

Compound (IV) (C15H16N4OS); IR (cm-1): 3,280and 3206 (N-H) of NH2, 1,605 (C=N) stretching of triazole, 1215 (C-O) and 1.367 (C=S) stretching. 1H-NMR (DMS O-d6) δ (ppm): 3.36 (s,1H, SH), 7.78-7.14 (m,6H, Ar-H), 9.24(s,2H,NH2), 3.65 (m,1H, CH), 4.22 (s,3H,CH3), 1.42 (d,3H,CH3).

13CNMR (DM SO-d6)δ(ppm) :106.09 157.42 (m,11c, arylC), 173.34(S,1C,CSH), 55.59(S,1C,CH3), 43.67 (S, 1C, CH), 173.34 (S. S-C) and 18.80 (S,1C,CH3) and 173.34(s.S-C).

Compound (Va) (C23H22N4O2S); IR (cm-1): 3201 (N-H) stre ching ,2976 and 2941 (C-H) stretching of aromatic CH3, 2605 (S-H) st retching, 1215(C-O) , 1600 (C=O), 1475 (C=N) stretching of heterocyclic ring, 1394 stretch of (C=S). 1H-NMR (DMS O-d6) δ (ppm): 3.05 (s,1H,SH), 3.87 (s,3H,OCH3), 7.78-7.16 (m,11H,Ar-H), 3.91 (q,1H,CH), 2.35 (s,1H, AR-CH3), 1.49 (d,3H,CH3), 10.44 (s,1H,NH). 13C -NMR (D MS O-d6) δ (ppm) : 106.12-157.49 (S,17C,Ary-C) ,173.33 (S,1C,C), 55.61(S, 1C,CH3), 45.72(S, 1C, CH3), 43.47 (S, 1C, CH), 21.47 (S, 1C, CH3), 165.78 (s. Carbonyl carbon) and 173.33 (s. S-C).

Benzoyl chloride	Aromatic benzoyl chloride names	P. number	R- group	Quantity
1	4-methyl benzoyl chloride	Va	CH3	0.05gm (0.0435 ml)
2	4-bromo benzoyl chloride	Vb	Br	0.073gm
3	4-chloro benzoyl chloride	Vc	Cl	0.06gm(0.0438ml)
4	4-nitro benzoyl chloride	Vd	NO2	0.0612gm
5	4-methoxy benzoyl chloride	Ve	OCH3	0.06gm

TABLE 1: Numbers of benzoyl chlorides and their names

Compound (Vb) (C22H19BrN4O2S). ; IR (cm-1): 3184 (N-H) streching of 2970 and 2886 (C-H) stretch of alkane, 1215(C-O) 2,746 (S-H) stretc hing, 1662 (C=O) stre tching of carbonyl of Amide 1,513 (C=N) stretching of heterocycle, 1,392 stretch of (C=S) stretch, 663 stretch of (C- Br) . 1H-NMR (DM SO-d6) δ (ppm): 3.04 (s,1H,SH), 10.50 (s,1H, NH), 7.77-7.16 (m,10H,Ary-H), 3.93 (q,3H, CH3), 3.78 (s,3H,CH3), 1.50 (d,3H,CH3). 13C-NMR(DMS O-d6)δ(ppm). 106.12-157.50 (m,17c,aryC), 173.29(S,1C,C), 55.61 (S,1C,CH3), 43.45(S,1C,CH) and 18.81(S,1C,CH3) 165.02(s. Carbonyl carbon) and 173.29 (s. S-C).

Compound (Vc) (C22H19ClN4O2S); IR (cm-1): 3184 (N-H) Stre ching ,3022 and 3053 (C-H) stretching of alkane, 2603(S-H) stretching, 1473,1595 (C=C) streching 1,633(C=O) streching , 1215(C-O) , 1560 (C=N) stretching of heterocyclic ring, 848 (C-Cl) stretching ; 1,323 1,392 (C=S) stretching. 1H-NMR (D MSO-d6) δ (ppm): 3.07 (s,1H,SH), 10.49 (s,1H, NH), 7.88-7.16 (m,10H,Ar-H), 3.87 (q,3H, CH3), 3.88 (s,3H,CH3), 1.49 (d,3H,CH3). 13C-NMR(DMSO-d6)δ(ppm). 106.11-137.64(m,17c,aryC) , 173.29(S,1C,C), 55.61(S,1C,CH3), 43.49(S,1C,CH), 18.81 (S,1C,CH3) 157.42 (s. Carbonyl carbon) and 173.34 (s. S-C).

Compound (Vd) Vd(C22H21N5O2S); IR (cm-1): 3226 (N-H) stretching , 2,978 and 2,942 (C-H) stretching of alkane, 2603 (S-H) stretching, , 1213(C-O) ,sharp 1,602 (C=C), 1,571 (C=N) stret ching of heterocycle, 1,305,1394 (C=S) stretching 1471 (NO2) stretching . 1H-NMR (DM SO-d6) δ (ppm): 3.06(s,1H,SH), 10.77 (s,1H, NH), 8.33-7.16 (m,10H,Ary-H), 3.87 (s,3H,CH3), 3.93 (q,1H, CH), 3.83 (s,3H,CH3), 1.50 (d,3H,CH3). 13C-NMR(DMSO-d6)δ(ppm). 106.11-162.40 (m,17c,AryC), 173.38(S,1C,C), 55.61(S,1C,CH3), 43.46(S,1C,CH), 18.81(S,1C,CH3) and 55.84(S,1C,CH3) 165.41(s. Carbonyl carbon) and 173.38 (s. S-C).

Compound Ve (C23H22N4O3S).; IR (cm-1): 3228(N- H) stretching ,2978 and 2941(c-H) alkane stretching , 2603 (S-H) stretching, 1,602 (C=O) stretching, 1504 (C=N) stretching of heterocycle, 1394 (C=S) stretching 1213(C-O) strech-ing of methoxy and (symmetric 1366 and asymmetric 1417 (NO2) streching) . 1H-NMR (DMS O-d6) δ (ppm): 3.02 (s,1H,SH), 10.51 (s,1H, NH), 7.86-7.02 (m,10H,Ar-H), 3.1(s,3H ,CH 3), 3.92 (q,1H, CH), 3.87 (s,3H, CH3), 1.49 (d,3H,CH3). 13C-NMR(DMSO-d6)δ(ppm). 106.12-157.52 (m,17c,aryC), 173.23(S,1C,C), 55.61(S,1C,CH3), 43.48(S,1C,CH) and 18.81(S,1C,CH3) 164.35(s. Carbonyl carbon) and 173.23(s. S-C).

Compound	Molecular weight (g/mol) (g/mol)	Dose (µg/ml)
Naproxen	230.26	23.026
Va	463	46.3
Vb	528.4	52.4
Vc	483.95	48.39
Vd	494.5	49.5
Ve	479.3	47.93

TABLE 2: Doses of combinations (naproxen, Va, Vb, Vc, Vd and Ve) used in biological study

A. ANTIBACTERIAL STUDY

Using the agar-well diffusion method, the in vitro antibacterial activity of investigated compounds was assessed towards together gram ve+ and gram ve- bacteria Staph. aureus as well as E. coli, individually.

V. METHOD

Utilizing the agar very publishing method and Mueller-Hinton agar as a medium, the in vitro antibacterial effect of the obtained chemicals was investigated towards several pathogenic relevant Gram-positive bacterium like Staphylococcus aureus as well as Gram-negative bacteria like Escherichia coli. All bacteria were gathered from Middle Euphrates Hospital's microbiology laboratory. Each bacterium's spore solution was distributed equally [29] all over the surface of the cold solid media in the petri-dish. The compounds that were assessed were dissolved in DSMO. An exact number of the solutions (0.1ml) was injected into spots on top of the surface of an injected solid mass media. The Petri-dishes have been incubated overnight in 37ºc. The antiseptic action of synthesized combinations was measured via an inhibition zone produced by the compounds against by the two types of bacteria examined. The zone of growth inhibition of each chemical was determined through using mean value collected from two individual samples. The calculated amounts in (mcg/ml) for tested compounds are in Table 3.

VI. THE OUTCOMES AND DISCUSSIONS

The final synthesis combinations (Va,Vb,VC,Vd and Ve) will be covered completely in this chapter as well as their characterization and identification. The evaluation of the target final compounds was performed by studying the antibacterial activity. The overall synthetic ways are designed to be as follows:

The synthetic steps for the final combinations and their mediate were mentioned at the system (1). The first step is naproxen esterification by utilizing methanol where the thionyl chloride also presented in the response to produce

(1-Ve)$(110^{-}4mol/L)$	Bacterial growth inhibition zone (average in millimeters)	
	Staph. Aureus (G+ve)	Escherichia coli (G-ve)
Naproxen	27	19
Va	29	17
Vb	20	13
Vc	26	15
Vd	29	20
Ve	24	16

TABLE 3: Results of bacterial growth inhibition zones

acyl chloride intermediate that will go on other response together with an alcohol to provide methyl group ester of the naproxen. A broadband group of the carboxyl set disappeared (3250-3000 cm1), and C=O stretching shifted as of 1722 cm-1 to 1735 cm-1refere that a carboxyl collection in naproxen is converted of the methyl group ester (carbonyl group) derivative, this confirmed via a presence to singlet sign in 3.60 δ (ppm) of the methyl group ester collection and disappearance of singlet signal of carboxyl of naproxen at 12.38 δ (ppm) of in 1H-NMR spectrum and presence of singlet signal at 52.25 δ (ppm) of the ester of methyl on 13C-NMR. The formed ester was treated again with hydrated hydrazine to yield propane hydrazide in which the carbonyl of amide band stretched at 1637 cm-1, and a main amine group presented overlapped in 3284 cm-1, these groups were confirmed via 1H-NMR range in which indication of a sign of a primary (NH2) presented in 9.24 δ (ppm) and a methyl ester was disappeared on 13C-NMR. The response is catalyzed via basis. A salt of the potassium of propionyl HC2 was produced via reacting a latter chemical with a similar molar of disulfide of the carbon in essential state medium of hydroxide of the potassium. A nucleophilic addition reaction occurs when the amine from compound (II) reacts with the carbon disulfide's carbon through a nucleophilic in nature, this reaction is confirmed where the primary amine on IR reading was disappeared and presence of carbonyl of amide at 1,657 cm-1 and methyl ester on 13C-NMR was disappeared. after that cyclization of The potassium salt intermediate by utilizing hydrated hydrazine to produce the triazole ring intermediate (IV) and confirmed by appearance again of band of primary amine on heterocyclic ring 3411 cm-1 as well as NH in 3290 cm-1 and a presence of the group of HNMR for SH group in range of 3.36 δ (ppm) and the same group on C13 .NMR are 173 δ (ppm).The unrestricted amine in the formed five membered ring reacted with five benzoyl chloride derivatives , to produce many final derivatives of naproxen and all of the last products are supported via FT-IR , HNMR as well as 13C-NMR reading values were C-Br IR ,C-Cl and Nitro FT-IR are 663 cm-1 ,848 cm-1 and symmetric 1366 cm-1 and asymmetric 1417 cm-1 nitro respectively also confirmed by presence of new carbonyl band of 13C-NMR at range 150-166 δ (ppm) , this reaction involves nucleophilic substitution. The physical properties of the formed agents(1-Ve) as melting points and R-f data are arranged in Table 2.

A. ANTIBACTERIAL STUDY

The target compounds' antibacterial activity in vitro was assessed utilizing the agar-good publishing the method. An antibacterial action of a compounds Va and Vd against staph was demonstrated in the topmost inhibitory zone. Compound Vb has the lower inhibitory activity versus E. coli, as shown at the table 3.

VII. CONCLUSION

In vivo anti-bacterial testing revealed if the 1 ,2 and 4 the triazole containing thiol group (5 membered -ring) reacted with the naproxen molecule preserved and augmented antibacterial activity, depending upon the nature of benzoyl chloride derivatives that form a nucleophilic-substitution reaction along with the unrestricted amine in the five membered ring. The addition of benezoyl chloride derivatives with para- groups on the benzene ring will augment naproxen's antimicrobial property.

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None.

CONFLICTS OF INTEREST

No conflicts of interest have been declared by the authors.

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