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SYNTHESIS AND PRELIMINARY PHARMACOLOGICAL EVALUATION OF SOME NEW TRIAZOLE DERIVATIVES BEARING NABUMETONE MOIETY TARGETING CYCLOOXYGENASE ENZYME

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Abstract

Objective To synthesize and initial pharmacological evaluation of new derivatives of nabumetone by incorporating of triazole heterocyclic ring systems into the nabumetone moiety to optimize the activity against COX enzymes. Examination of their in vivo results by using egg white to induce acute inflammation.

Methods A group of triazole carrying nabumetone moiety have been designed, prepared, and assessed as a potential COX-inhibitors. These new derivatives were evaluated for their in vivo anti-inflammatory activity.

Results most of the tested compounds have good results in acute anti-inflammatory in vivo tests better than nabumetone.

Conclusion The synthesis of the designed derivatives (3a-e) has been successfully occurred , the anti-inflammatory evaluation of the final products shows that the addition of triazole pharmacophore into nabumetone enhanced its anti-inflammatory activity, the Preliminary study of anti-inflammatory action indicates that compound (3a-e especially 3c and 3d) have significantly more anti-inflammatory outcome than nabumetone(except 3b).

Keywords Nabumetone, triazole, chalcone, anti-inflammatory activity

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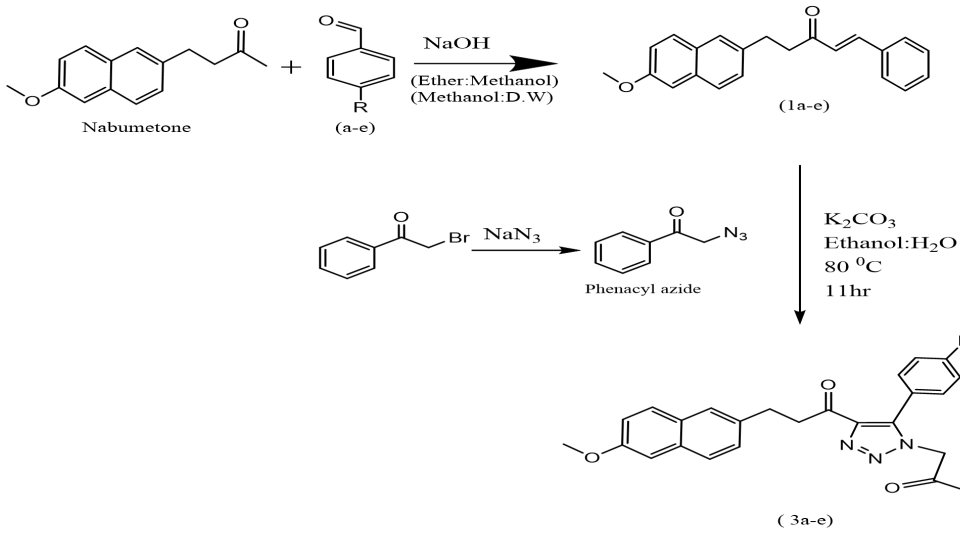
GRAPHICAL ABSTRACT



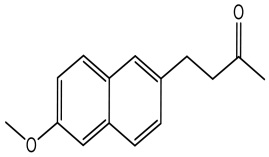
R= (a= H), (b=OCH3), (c= Cl), (d=NO2), (e= N(CH3)2)

INTRODUCTION:

Inflammation is the response of the body to harmful stimuli, so the body can initiate repair action.[1] It can be triggered by many stimuli like infection, injury, thermal and mechanical damage .[2] Inflammation started by cells found in tissue that discover the stimuli and then transmitted alarm signals as chemical messengers that distribute the local response and attract other cells to the area. The main symptoms of inflammation are pain, heat, redness and swelling .[3] Inflammation classified to acute and chronic.[4] The chemical messengers that involve in inflammation are locally acting bioactive lipids called prostaglandins.[5,6]Prostaglandins synthesized from membrane phospholipids mainly arachidonic acid (A.A) .[7] Synthesis of prostanoids (prostaglandin and thromboxane A2 (TXA2)) happened by dioxygenation of A.A to the hydroperoxide prostaglandin G2 (PGG2) and then reduction to prostaglandin H2 (PGH2) by enzyme cyclooxygenase

(COX).[8] The subsequent synthesis of other prostaglandins from PGH2 (PGE2, PGI2, PGD2, TXA2) is stimulated by prostaglandin synthases.[9] There are 3 types of COX enzymes COX-1, COX-2 [10] and COX-3.[11] COX-1 constitutively present in many cells and do housekeeping role while COX-2 is inducible mainly in inflammation where its expression rise by 20-fold .[12,13] The main structural differences between COX-1 and COX-2 are the replacement of IL-523 in COX-1 by Y -523 in COX-2 , H-513 in COX-1 by R-513 in COX-2 and IL-434 in COX-1 by Y -434 in COX-2, these changes make COX-2 active site more flexible .[14] NSAIDs are drugs that are used for their anti-inflammatory, analgesic and antipyretic effects .[15] These drugs acting by inhibiting the action of COX enzymes so they will inhibit the production of prostaglandins in the body .[16] These drugs have many actions like; Anti-inflammatory effect, Antipyretic effect and Analgesic effect.[17] These drugs used to reduce pain like in renal colic [18], osteoarthritis [19] and endometriosis.[20] The side effects of these drugs includes; increase risk of hypertension and bleeding.[21] may cause nephrotoxicity.[22] The most common side effect is GI upset and ulceration.[23] NSAID can be classified into COX-1 selective , non-selective , COX-2 selective .[24] Nabumetone (1) [4-(6-methoxy-2-naphyl)-butan-2-one] is NSAID. It is used in the treatment of pain and inflammation in patient with osteoarthritis, rheumatoid arthritis and severe injuries of soft tissues. Nabumetone is a prodrug after oral intake it metabolized in the liver (oxidative cleavage of its side chain) to active metabolite (2) named 6-methoxy-2-naphthyl-acetic acid this act by inhibiting of COX-1 and COX-2 so inhibit prostaglandin synthesis.[25] Chalcone is a significant group of both natural and artificial poly phenols. They are present naturally in fruits and cereals like; apples, pears, strawberries and wheat. They are secondary metabolites and precursor in the biosynthesis of flavonoids. They also have many biological activities like; antioxidant, chemo protective actions, antimutagenic, antimitotic, ant metastatic and anti-inflammatory. [26]

1,2,3-Triazoles are groups of nitrogen-containing heterocyclic products that have 3 nitrogen and 2 carbon in 5-membered ring. they are not widely found in nature. 1, 2, 3 triazoles have many applications in medicinal chemistry due to their unique properties like; hydrogen bond formation, dipole-dipole and π stacking interaction, stable to reduction and oxidation and stable to hydrolysis under acidic and basic conditions. the compounds that contain 1, 2, 3 triazole have many activities like antimicrobial, anti-tuberculosis, anti-inflammatory, Antiviral, anticancer, anti-diabetes and many others. [27]



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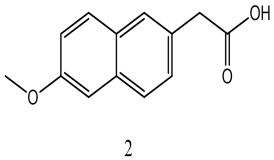

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MATERIALS AND METHODS

MATERIALS

All reagents and anhydrous solvents were of analytical type and generally used as received from the commercial suppliers (Merck, Germany, Reidel-DeHaen, Germany, Sigma-Aldrich, Germany, Himedia,India, Rubilabor chemical , Spain and BDH, England). Nabumetone was provided by the Shanghai Renyoung Company, China. Melting points were measured by capillary method on Bam stead / Electro-thermal 9100 an Electric melting point apparatus (England). Ultrasonic generation by using ultrasonic bath SB25-12 DTDN, China. The characterization of compounds was done using a FTIR spectrum were recorded on a FTIR-spectrophotometer FTIR-6100 Type A as KBr disks. 1H-NMR and 13C-NMR determined by Shimadzu Bruker 300 MHz, 75.65 (Japan) and MHz Y arian, Agilant 500 MHz, 125.64 MHz (USA).

GENERAL PROCEDURE FOR THE SYNTHESIS OF CHALCONE DERIVATIVES,

5-(6-methoxynaphthalen-2-yl)-1-(4-aryl)-pent-1-en-3-one (1a-e):

Solution of (0.088 g, 2.2 mmol) of NaOH dissolved in absolute methanol : D.W. (5:2.5) was added on solution of (0.500 g, 2.2 mmol) of nabumetone (1) dissolved in solvent system diethyl ether: methanol (5:10) and stirred until the compound will thoroughly dissolved, then benzaldehyde derivatives (a-e) (2.2 mmol) was added to this mixture. The mixture was irradiated by an ultrasonic generator in a water bath at (30-35 °C) for (25 min.) turbidity appeared in the mixture; the mixture stirred for about 24 hrs. at room temperature.

The mixture filtered and washed with water until the filtrate became neutral to the litmus paper. The filtered precipitate washed with ether and left to dry. [28]

GENERAL PROCEDURE FOR THE SYNTHESIS OF PHENACYL AZIDE:

To a suspension of 2-bromo-1-phenyl ethenone (1.7 gm, 8.5 mmol) in DMF (15ml) was added sodium azide (0.6 gm, 9.4 mmol) and this mixture was stirring at 20 °C for about 2 h during this time the mixture became homogenized and red colored. The mixture was diluted with ethyl acetate and washed with water. The water phase extracted the times with ethyl acetate. the combined ethyl acetate layers were washed with brine and dried over anhydrous sodium sulfate, and evaporated to dryness. [29]

GENERAL PROCEDURE FOR THE SYNTHESIS OF TRIAZOLE DERIVATIVES,

1-(5-(4-Aryl)-1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)-3-(6-methoxynaphthalen-2-yl) propan-1-one (3a-e):

Under air atmosphere, a 20 ml, oven dried sealable reaction vessel contains magnetic bar chalcone (1a-e, 0.03 mmol), K2CO3 (8.3 mg, 0.06 mmol), solvent (absolute ethanol: water = 6:1) and phenacyl azide (9.66 mg, 0.06 mmol). The vessel sealed with Teflon-coated screw cap, and the reaction vessel placed in an oil bath at 80 °C and kept on stirring for 11 hrs. After completion of the reaction, the reaction vessel left overnight and then the mixture poured on watch glass to allow the solvent evaporate, then the remaining precipitate dissolved in equal portions of ethyl acetate and water and extracted with ethyl acetate (15 ml *3). The combined organic layers washed with brine and then dried over anhydrous sodium sulfate. The desired product achieved after evaporation of ethyl acetate. [30]

5-(6-Methoxynaphthalen-2-yl)-1-phenylpent-1-en-3-one (1a): white powder (78% yield); m.p 118–120°C; IR (KBr) υ (cm−1): 1267(C–O–CH3), 1548 (aromatic),1604 (C=C), 1658 (C=O); 1H-NMR (DMSO-d6, 300 MHz): δ 3.01-3.06 (t, 2H, CH2–CH2), δ 3.12-3.17 (t, 2H, CH2–CH2), δ 3.87 (s, 3H, O–CH3), δ 6.92-6.97 (d, 1H, CH=CH), δ 7.40-7.42 (d, 1H, CH=CH), δ 7.13–7.78 (m, 11H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 29.96 (1C,CH2-aryl), δ 41.88 (1C, CH2–C=O), δ 55.57 (1C, CH3-O), δ 126.90 (1C, =C-C=O), δ 142.64 (1C, =C-aryl), δ 157.23 (1C, C–O–CH3), δ 199.65 (1C, C=O).

5-(6-methoxynaphthalen-2-yl) -1-(4-methoxyphenyl)-pent-1- en-3-one (1b): milky colored powder (80% yield); m.p 126–128 °C; IR (KBr) υ (cm−1): 1249 (C–O–CH3), 1508 (aromatic),1600(C=C), 1641 (C=O); 1H -NMR (DMSO-d6,

500 MHz): δ 2.97-3.02 (t, 2H, CH2–CH2), δ 2.07-3.13 (t, 2H, CH2–CH2), δ 3.85,3.79 (s, 3H, O–CH3), δ 6.95-6.99 (d, 1H, CH=CH), δ 7.56-7.59 (d, 1H, CH=CH), δ 7.07–7.74 (m, 10H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 30.08 (1C, CH2-aryl), δ 41.72 (1C, CH2–C=O), δ 55.57 (1C, CH3- δ 55.79 (1C, CH3-O), δ 126.46 (1C, =C-C=O), δ 142.64 (1C , =C-aryl), δ 157.71 (O), 1c , C–O–CH3), δ 161.61 (1c , C–O–CH3), δ 199.41 (1C, C=O).

5-(6-methoxynaphtha- len-2-yl) -1-(4-chlorophenyl)-pent-1-en-3-one (1c): light yellow crystals (87% yield); m.p 128-130°C; IR (KBr) υ (cm−1): 559.02 (C-Cl) ,1265.35 (C–O–CH3), 1535.39 (aromatic), 1604.83 (C=C),1683.91 (C=O); 1H-NMR (DMSO-d6, 300 MHz): δ 3.00-3.05 (t, 2H, CH2–CH2), δ 3.11-3.16 (t, 2H,CH2–CH2), δ 3.87(s, 3H, O–CH3), δ 6.93-6.99 (d, 1H, CH=CH), δ 7.49-7.52 (d, 1H, CH=CH), δ 7.13–7.77 (m, 10H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 29.92 (1C, CH2-aryl), δ 41.97 (1C , CH2–C=O), δ 55.57 (1C, CH3-O), δ 127.14 (1C, =C-C=O), δ 135.35 (1c , C-Cl),δ 141.17 (1C, =C-aryl), δ 157.24 (1C, C–O–CH3) , δ 199.54 (1C, C=O).

5-(6-methoxynaphtha- len-2-yl) -1-(4-nitrohenyl)-pent-1-en-3-one (1d): brown powder (60% yield); m.p decomposed at 165-167°C; IR (KBr) υ (cm−1): 1228 (C-NO2),1265(C–O–CH3),1346, 1487 (N02) 1518.03 (aromatic), 1602 (C=C), 1631 (C=O); 1H -NMR (DMSO-d6, 500 MHz): δ 2.83 (t, 2H, CH2–CH2), δ 2.89 (t, 2H,CH2–CH2), δ 3.83(s, 3H, O–CH3), δ 6.69 (d, 1H, CH=CH), δ 7.42 (d, 1H, CH=CH), δ 7.13–7.77 (m, 10H, aromatic H).

5-(6-methoxynaphtha- len-2-yl) -1-(4-(Dimethylamino)phenyl)-pent-1-en-3-one (1e): Yellow powder (70% yield); m.p 137–139°C; IR (KBr) υ(cm−1): 1155 (N–CH3), 1265 (C–O–CH3), 1535 (aromatic), 1599 (C=C), 1629 (C=O); 1H-NMR (DMSO-d6, 500 MHz): δ 2.95 (s, 6H,N(CH3)2), 2.99-3.01 (t, 2H, CH2–CH2), δ 3.04 (t, 2H, CH2–CH2) , δ 3.84 (s, 3H, O–CH3),δ 6.68-6.69 (d, 1H, CH=CH), δ 7.50-7.51 (d, 1H, CH=CH), δ 7.11–7.73 (m, 10H, aromatic H).

2-azido-1-phenylethan-1-one (phenacyl azide): Yellow oil (48% yield);IR (KBr) υ(cm−1): 1219 (C-N), 1597(aromatic), 1695 (C=O), 2098 (N3) ; 1H-NMR (DMSO-d6, 500 MHz): δ 4.89 (s, 2H,N3-CH2-C=O), 7.43—8.03 (m, 5H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 55.57 (1C,N3-CH3-C=O), δ 194.92 (1C, C=O).

3-(6-methoxynaphthalen-2-yl)-1-(1-(2-oxo-2-phenylethyl)-5-phenyl-1H-1,2,3-triazol-4-yl)propan-1-one (3a): light brown powder (81 % yield); m.p 84-86 °C; IR (KBr) υ (cm−1): 1168 (C–N of triazole), 1230 (N=N), 1265 (C–O–CH3), 1529 (aromatic), 1610 (C=C of triazole), 1662 (combined for both C=O); 1H -NMR (DMSO-d6, 500 MHz): δ 3.00-3.03 (t, 2H, CH2CH2), δ 3.10-3.13 (t, 2H, CH2-CH2), δ 3.84 (s, 3H, O–CH3), δ 5.94 (s, 2H, triazole-CH2-C=O), δ 7.11–8.08 (m, 16H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 29.96 (1C, CH2-aryl), δ 41.89 (1C , CH2–C=O), δ 55.56 (2C , CH3-O and triazole-CH2-C=O), δ 133.52 (1C, C=C of triazole next to C=O), δ 142.23 (1C, C=C of triazole next to phenyl ring), δ 157.62 (1C,C–O–CH3), δ 191 (1C, C=O next to phenyl ring), δ 199.63 (1C, C=O next to triazole ring).

3-(6-methoxynaphthalen-2-yl)-1-(5-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)propan-1-one (3b): brown powder (71 % yield); m.p 78-80 °C; IR (KBr) υ (cm−1): 1174 (C–N of triazole), 1240 (N=N), 1276 (combined for both C–O–CH3), 1556 (aromatic), 1606 (C=C of triazole), 1664 (combined for both C=O); 1H -NMR (DMSO-d6, 500 MHz): δ 3.01 (t, 2H, CH2CH2), δ 3.08 (t, 2H, CH2-CH2), δ 3.74 (s, 3H, O–CH3 of phenyl ring), δ 3.85 (s, 3H, O–CH3 of naphthyl ring), δ 5.94 (s, 2H, triazole-CH2-C=O), δ 7.12–8.07 (m, 15H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 30.29 (1C, CH2-aryl), δ 41.12 (1C , CH2–C=O), δ 55.03 (1C, CH3-O of naphthyl ring), δ 55.84 (2C , CH3-O of phenyl ring and triazole-CH2-C=O), δ 133.07 (1C, C=C of triazole next to C=O), δ 141.38 (1C, C=C of triazole next to phenyl ring), δ 157.09 (1C,C–O–CH3 of naphthyl ring), δ 158.24 (1C,C–O–CH3 of phenyl ring), δ 193.07 (1C, C=O next to phenyl ring), δ 199.64 (1C, C=O next to triazole ring).

1-(5-(4-chlorophenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)-3-(6-methoxynaphthalen-2-yl)propan-1-one (3c): brown powder (95 % yield); m.p 94-96 °C; IR (KBr) υ (cm−1): 532 (C-Cl), 1170 (C–N of triazole), 1236 (N=N), 1278 (C–O–CH3), 1552 (aromatic), 1608 (C=C of triazole), 1670 (combined for both C=O); 1H -NMR (DMSO-d6, 500 MHz): δ 3.01 (t, 2H, CH2CH2), δ 3.11 (t, 2H, CH2-CH2), δ 3.84 (s, 3H, O–CH3), δ 5.94 (s, 2H, triazole-CH2-C=O), δ 7.12–8.15 (m, 15H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 29.91 (1C, CH2-aryl), δ 41.95 (1C , CH2–C=O), δ 55.53 (1C , CH3-O), δ 55.61 (1C, triazole-CH2-C=O), δ 133.33 (1C, C=C of triazole next to C=O), δ 134.45 (C-Cl), δ 141.12 (1C, C=C of triazole next to phenyl ring), δ 157.23 (1C,C–O–CH3), δ 191.93 (1C, C=O next to phenyl ring), δ 199.62 (1C, C=O next to triazole ring).

3-(6-methoxynaphthalen-2-yl)-1-(5-(4-nitrophenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)propan-1-one (3d): dark brown powder (49 % yield); m.p 62-64 °C; IR (KBr) υ (cm−1): 1170 (combined for C–N of triazole and C-NO2), 1230 (N=N), 1267 (C–O–CH3), 1556 (aromatic), 1604 (C=C of triazole), 1666 (combined for both C=O); 1H -NMR (DMSO-d6, 500 MHz): δ 2.96 (t, 2H, CH2CH2), δ 3.01 (t, 2H, CH2-CH2), δ 3.83 (s, 3H, O–CH3), δ 5.94 (s, 2H, triazole-CH2-C=O), δ 7.15–8.08 (m, 15H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 30.69 (1C, CH2-aryl), δ 41.05 (1C , CH2–C=O), δ 55.06 (1C , CH3-O), δ 55.90 (1C, triazole-CH2-C=O), δ 133.61 (1C, C=C of triazole next to C=O), δ 142.30 (1C, C=C of triazole next to phenyl ring), δ 147.69 (C-NO2), δ 157.75 (1C,C–O–CH3), δ 191.31 (1C, C=O next to phenyl ring), δ 200.07 (1C, C=O next to triazole ring).

1-(5-(4-(dimethylamino)phenyl)-1-(2-oxo-2-phenylethyl)-1H-1,2,3-triazol-4-yl)-3-(6-methoxynaphthalen-2-yl)propan-1-one (3e): brown powder (80 % yield); m.p 104-106 °C; IR (KBr) υ (cm−1): 1170 (combined for C–N of triazole and N(CH3)2), 1246 (N=N), 1288 (C–O–CH3), 1548 (aromatic), 1606 (C=C of triazole), 1670 (combined for both C=O); 1H -NMR (DMSO-d6, 500 MHz): δ 3.00 (t, 2H, CH2CH2), δ 3.02 (t, 2H, CH2-CH2), δ 3.84 (s, 3H, O–CH3), δ 5.94 (s, 2H, triazole-CH2-C=O), δ 7.11–8.08 (m, 15H, aromatic H); 13C-NMR (DMSO-d6 125.64 MHz): δ 30.29 (1C, CH2-aryl), δ 41.58 (1C , CH2–C=O), δ 41.61 (1C , N(CH3)2), δ 55.53 (1C , CH3-O), δ 55.60 (1C, triazole-CH2-C=O), δ 131.11 (1C, C=C of triazole next to C=O), δ 141.24 (1C, C=C of triazole next to phenyl ring), δ 152.20 (C-N(CH3)2), δ 157.20 (1C,C–O–CH3), δ 192.92 (1C, C=O next to phenyl ring), δ 199 (1C, C=O next to triazole ring).

ANTI-INFLAMMATORY EVALUATION STUDY:

In vivo, the acute anti-inflammatory activity for the chemically synthesized derivatives (3a-e) had been evaluated in egg-white stimulated paw edema. The assessment of their ant-inflammatory effect was based on measuring the decreases of paw thickness.[31] Albino rats of female sex

weighing (170 ± 10 g) were provided by National Center for Drug Control and Research and were kept in the animal house of the College of Pharmacy, Mustansiriyah University under constant circumstances. A commercial chaw was used for feeding animals and they had free entrance to water.

They were separated into different 7 groups (each one contains of 6 rats) as follow: group 1 (control [ethylene glycol])/ group 2 (nabumetone) / group 3-7 (synthesized compounds 3a-e). By utilizing the egg-white prompted edema model was examined the anti-inflammatory action of the tested compounds. Through using Vernia could be calculating the paw thickness at seven times intervals: (0, 30, 60, 120, 180, 240 and 300-min.) next to administration of the agent. For delivering of an acute inflammation through utilizing the undiluted egg-white by subcutaneous injection (s.i) of (0.05 ml) into the left hind paw at the plantar side of the rats after the drug or vehicle administration intra peritoneal by (30 min.).The data, which was expressing by the (mean ± SEM) and products were analyzing to significantly statistic for correlation among mean values by utilizing student t-test two (Sample Assuming Equal Y variances). By utilizing ANOVA: two elements without repetition, the correlation among various collections could be making. Probability (P) value of below (0.05) was considering significantly.[32] Also by calculating the percentage of paw thickness change then drawing the percentage of change with time and calculating the area under the curve for each of the tested compounds to compare between them.[33]

RESULTS AND DISCUSSION

The intraplanar injection of egg-white into rat hind paw causes a progressive edema. To determine the validity of the method (paw-edema) used for the assessment of newly prepared anti- inflammatory compounds, nabumetone was used as a reference compound of known anti-inflammatory activity profile, the results are shown in Table 1. The percentage of change in paw thickness for each of the tested compounds described in Table 2. The relationship between the percentages of change in paw thickness with time showed in Figure 1. The calculated area under the curve for Figure 1 described in Table 3.

Numbers are stated in mm paw width as mean ± SEM. n = number of rats. Time (0) is the time of i.p. injection of tested compounds. Time (30) is the time of egg-white injection.

Percentage of paw thickness change = [paw thickness at time (t) – paw thickness at time (0) / paw thickness at time (0)] * 100. Time (0) is the time of i.p. injection of Nabumetone, examined agents and control agent. Time (30) is the time of egg white injection. (Control is propylene glycol).

Table 1: The anti-inflammatory action of synthesized compounds (3a-e), nabumetone and control on egg-white induced paw edema in rats:

Time (min)							compounds	Paw thickness (mm)/n=6
300	240	180	120	60	30	0		
5.72±0.05	6.06±0.05	6.24±0.04	6.64±0.04	6.43±0.07	5.64±0.04	2.31±0.06	control	
2.32±0.06	2.32±0.06	2.66±0.06	3.68±0.06	4.63±0.07	4.38±0.05	2.32±0.06	nabumetone	
2.27±0.06	2.27±0.06	2.57±0.06	3.59±0.05	4.22±0.06	4.31±0.05	2.27±0.07	3a	
2.31±0.06	2.31±0.06	2.66±0.05	3.63±0.07	4.53±0.06	4.57±0.06	2.31±0.06	3b	
2.28±0.06	2.28±0.06	2.53±0.06	3.19±0.06	3.88±0.05	4.35±0.06	2.28±0.06	3c	
2.26±0.06	2.26±0.06	2.44±0.05	3.12±0.07	3.82±0.06	4.18±0.05	2.26±0.06	3d	
2.29±0.06	2.29±0.06	2.59±0.06	3.62±0.07	4.31±0.05	4.53±0.06	2.29±0.06	3e	

Table 1: The percentage of paw thickness change for the synthesized compounds (3a-e), nabumetone and control on egg-white induced paw edema in rats:

Time (min)							compounds	Percentage of paw thickness change
300	240	180	120	60	30	0		
147%	162%	170%	187%	178%	144%	0	control	
0	0	14.5%	58.5%	99.5%	89%	0	nabumetone	
0	0	13%	58%	86%	90%	0	3a	
0	0	15%	57%	96%	98%	0	3b	
0	0	11%	40%	70%	91%	0	3c	
0	0	8%	38%	69%	85%	0	3d	
0	0	13%	58%	88%	98%	0	3e	

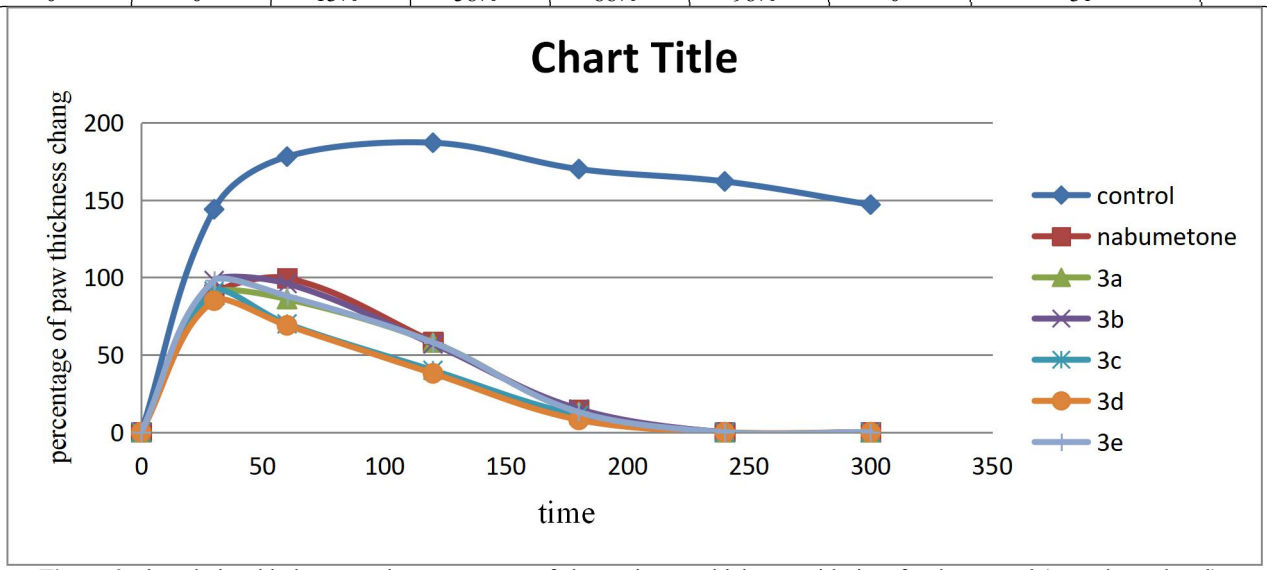

Figure 2: the relationship between the percentages of change in paw thickness with time for the control (propylene glycol), nabumetone, compounds (3a-e).

Table 3: The calculated area under the curve for Figure 1:

Area under the curve	compound
69930	control
11527.5	nabumetone
10830	3a
11580	3b
8940	3c
8415	3d
11160	3e

According to the above results, all the tested derivatives (3a-e) have more rapid onset of action than nabumetone and all of them (except 3b) have better anti-inflammatory outcome than nabumetone especially (3c and 3d).

CONCLUSION

1. The designed compounds have been successfully synthesized.
2. The synthesized compounds have been characterized and identified by determination of physical properties (melting point and description), FT-IR spectroscopy, 1H-NMR spectra and 13C-NMR.
3. The anti-inflammatory evaluation of the final products shows that the addition of triazole pharmacophore into nabumetone enhanced its anti-inflammatory action.
4. The preliminary study of anti-inflammatory activity indicates that all of the synthesized compounds have more rapid onset of action and better anti-inflammatory outcome (except 3b) than nabumetone especially (3c and 3d).

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