Synthesis and preliminary pharmacological evaluation of some new pyrimidine derivatives bearing nabumetone moiety targeting cyclooxygenase enzyme.

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Abstract

Objective To synthesize and initial pharmacological assessment of new analogues of nabumetone by incorporating of pyrimidine heterocyclic ring system in the nabumetone moiety to increase the activity toward COX enzymes. Examination of their in vivo results by using egg white to induce acute inflammation.
Methods A series of pyrimidines bearing nabumetone moiety have been designed, synthesized and evaluated as a potential COX inhibitors. These new compounds were evaluated for their in vivo anti-inflammatory activity.
Results All tested compounds have good results in acute anti-inflammatory in vivo tests better than nabumetone.
Conclusion The synthesis of the designed compounds has been successfully achieved, the anti-inflammatory assessment of the final products indicates that their incorporation of pyrimidine pharmacophore into nabumetone improved its anti- inflammatory action, the Preliminary study of anti-inflammatory activity showed that compound (2a-2e especially 2c and 2d) have significantly more anti-inflammatory outcome than nabumetone.

Keywords nabumetone, pyrimidine, chalcone, anti-inflammatory activity

1. Introduction

Inflammatory Response is the reaction of the body to deleterious stimuli. The aim of it is to make rapid defense action that eliminates pathogens, restrict more tissue damage and initiates repair mechanism.[1] Inflammation stimulated by pathogens, damage cell, toxic compounds, irradiation, infection, thermal or chemical injuries .[2] Inflammation started by cells present in tissue that discover pathogens or trauma and then transmitted alarm signals as chemical messengers that spread the local response and draft other cells to the area. Inflammation characterized by 4 main symptoms known by their Latin term dolor (pain), calor (heat), rubor (redness) and tumor (swelling) .[3] Inflammation classified to acute and chronic.[4] Prostaglandins are group of highly bioactive lipid[5] and they are part of eicosanoids family[6] that play an important role in inflammation. Prostaglandins synthesis started by enzymes called phospholipase A2, these enzymes liberate C-20 polyunsaturated fatty acids (of which is arachidonic acid (A.A) from the SN2 position of membrane phospholipids.[7] Synthesis of prostanoids (prostaglandin and thromboxane A2 (TXA2)) occur 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 catalyze by prostaglandin synthases.[9] There are 3 isoform of COX enzymes COX-1, COX-2 [10] and COX-3.[11] COX-1 perform housekeeping role while COX-2 expression stimulated by many triggers like lipopolysaccharides, pro inflammatory cytokines and others The increase COX-2 expression lead to increase in the synthesis of PGs in the inflamed and neoplastic tissues.[12] COX-1 is constitutive while COX-2 is inducible .[13] The structure of both enzymes are similar except for some differences mainly the substitution of IL-523 in COX-1 by ϒ -523 in COX-2 , H-513 in COX-1 by R-513 in COX-2 and IL-434 in COX-1 by ϒ -434 in COX-2, these substitutions cause higher flexibility in COX-2 active site.[14] NSAIDs are used vastly throughout the world due to their properties (anti-inflammatory, analgesic and antipyretic).[15] NSAID act primarily by blocking Cox enzymes and so block the synthesis of prostaglandins.[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; NSAID increase risk of hypertension and bleeding.[21] NSAID 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 and part of class of naphthylalkanone. It is having good effect 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 administration convert by metabolism in the liver (oxidative cleavage of its side chain) to active metabolite (2) named 6-methoxy-2-naphthyl-acetic

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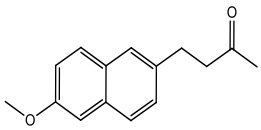
acid this act by inhibiting of COX-1 and COX-2 so inhibit prostaglandin synthesis.[25] Chalcone is a significant group of both natural and artificial poly phenols. They are naturally found in fruits and cereals like; apples, pears, strawberries and wheat. They are secondary metabolites and precursor in the biosynthesis of flavonoids. They also have many biological actions like; antioxidant, chemo protective actions, antimutagenic, antimitotic, ant metastatic and anti-inflammatory. [26]

Pyrimidine is six membered heterocyclic organic compounds contain two nitrogen atoms at position 1 and 3 of the ring. It is present in the structure of DNA, RNA and vitamins like; thiamine, riboflavin and folic acid. Pyrimidine and its derivatives found to have many biological activities like anticancer, antiviral, anti-microbial, anti-inflammatory, analgesic, antioxidant antimalarial and many others. [27]



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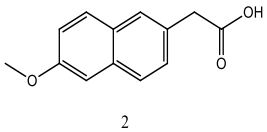

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2. Materials and Methods

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 supplied by the Shanghai Renyoung Company, China. Melting points were determined 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 identification of compounds was done using a FTIR spectrum were recorded on a FTIR-spectrophotometer FTIR-6100 Type A as KBr disks. ^{1}H-NMR and ^{13}C-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 completely 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 pyrimidine derivatives,

4-(2-(6-methoxynaphthalen-2-yl) ethyl)-6-(4-aryl)-5,6-dihydropyrimidin-2(1H)-one (2a-e):

Chalcone (1a-e) (1 mmole) was dissolved in absolute ethanol (20ml) stirred at (75 °C) until complete dissolution, a solution of urea (0.06 gm, 1 mmole) in 5ml absolute ethanol and 2.5 ml of 30% KOH was added. The mixture was refluxed for 10hrs. at (80°C) with continuous stirring. The mixture was left over night at room temperature; the mixture was added onto crushed ice with stirring. The separated solid was filtered, then washed with water until the filtrate became neutral to litmus paper and dried, finally recrystallized from ethanol 95%. [29,30]

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–CH_3), 1548 (aromatic),1604 (C=C), 1658 (C=O); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 3.01-3.06 (t, 2H, CH_2–CH_2), δ 3.12-3.17 (t, 2H, CH_2–CH_2), δ 3.87 (s, 3H, O–CH_3), 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); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 29.96 (1C,CH_2-aryl), δ 41.88 (1C, CH_2–C=O), δ 55.57 (1C, CH_3-O), δ 126.90 (1C, =C-C=O), δ 142.64 (1C, =C-aryl), δ 157.23 (1C, C–O–CH_3), 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–CH_3), 1508 (aromatic),1600(C=C), 1641 (C=O); ^{1}H -NMR (DMSO-d6, 500 MHz): δ 2.97-3.02 (t, 2H, CH_2–CH_2), δ 2.07-3.13 (t, 2H, CH_2–CH_2), δ 3.85,3.79 (s, 3H, O–CH_3), 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); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 30.08 (1C, CH_2-aryl), δ 41.72 (1C, CH2–C=O), δ 55.57 (1C, CH_3- δ 55.79 (1C, CH_3-O), δ 126.46 (1C, =C-C=O), δ 142.64 (1C , =C-aryl), δ 157.71 (O), 1c , C–O–CH_3), δ 161.61 (1c , C–O–CH_3), 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–CH_3), 1535.39 (aromatic), 1604.83 (C=C),1683.91 (C=O); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 3.00-3.05 (t, 2H, CH_2–CH_2), δ 3.11-3.16 (t, 2H,CH_2–CH_2), δ 3.87(s, 3H, O–CH_3), 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); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 29.92 (1C, CH_2-aryl), δ 41.97 (1C , CH2–C=O), δ 55.57 (1C, CH_3-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–CH_3) , 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-NO_2),1265(C–O–CH_3),1346, 1487 (NO_2) 1518.03 (aromatic), 1602 (C=C), 1631 (C=O); ^{1}H -NMR (DMSO-d6, 500 MHz): δ 2.83 (t, 2H, CH_2–CH_2), δ 2.89 (t, 2H,CH_2–CH_2), δ 3.83(s, 3H, O–CH_3), 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–CH_3), 1265 (C–O–CH_3), 1535 (aromatic), 1599 (C=C), 1629 (C=O); ^{1}H-NMR (DMSO-d6, 500 MHz): δ 2.95 (s, 6H,N(CH_3)$_2$), 2.99-3.01 (t, 2H, CH_2–CH_2), δ 3.04 (t, 2H, CH_2–CH_2) , δ 3.84 (s, 3H, O–CH_3),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).

4-(2-(6-methoxynaphthalen-2-yl)ethyl)-6-phenyl-5,6-dihydropyrimidin-2(1H)-one (2a): light brown powder (48 % yield); m.p 80-82 °C; IR (KBr) υ (cm^{-1}): 1166 (C–N of pyrimidine), 1265 (C–O–CH_3), 1492 (aromatic), 1606 (C=N of pyrimidine), 1710 (C=O of pyrimidine) , 3385.18 (N-H of pyrimidine); ^{1}H -NMR (DMSO-d6, 500 MHz): δ 2.20-2.28 (dd, 1H, CH_2 of pyrimidine), δ 2.83 (t, 2H, CH_2CH_2), δ 2.89 (t, 2H, CH_2- CH_2), δ 3.00-3.04 (dd, 1H, CH_2 of pyrimidine), δ 3.84 (s, 3H, O–CH_3), δ 6.49 (dd, 1H, CH of pyrimidine), δ 6.66–7.84 (m, 11H, aromatic H). δ 7.95 (N-H of pyrimidine); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 29.52 (1C, CH_2-aryl), δ 30.23 (1C , CH2–pyrimidine), δ 32 (1C, CH_2 of pyrimidine), δ 44.56 (1C, C-N of pyrimidine), δ 55.55 (1C , CH_3-O), δ 141.17 (1C, aromatic C-pyrimidine), δ 152.81 (1C, C=N of pyrimidine), δ 155.61 (1C, C=O of pyrimidine), δ 157.16 (1C,C–O–CH_3).

4-(2-(6-methoxynaphthalen-2-yl)ethyl)-6-(4-methoxyphenyl)-5,6-dihydropyrimidin-2(1H)-one (2b) : brown powder (60 % yield); m.p 69-72 °C; IR (KBr) υ (cm^{-1}): 1174 (C–N of pyrimidine), 1257 (C–O–CH_3), 1510 (aromatic), 1604 (C=N of pyrimidine), 1710 (C=O of pyrimidine), 3340 (N-H of pyrimidine); ^{1}H -NMR (DMSO-d6, 500 MHz): δ 2.32 (dd, 1H, CH_2 of pyrimidine), δ 2.83 (t, 2H, CH_2CH_2), δ 2.89 (t, 2H, CH_2- CH_2), δ 3.08-3.14 (dd, 1H, CH_2 of pyrimidine), δ 3.79 (s, 3H, O–CH_3), δ 3.84 (s, 3H, O–CH_3), δ 6.57 (dd, 1H, CH of pyrimidine), δ 6.67–7.82 (m, 10H, aromatic H). δ 7.94 (N-H of pyrimidine); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 29.51 (1C, CH_2-aryl), δ 30 (1C, CH2–pyrimidine), δ 34 (1C, CH_2 of pyrimidine), δ 44.55 (1C, C-N of pyrimidine), δ 55.56 (1C, CH_3-O), δ 55.78 (1C, CH_3-O), δ 136 (1C, aromatic C-pyrimidine), δ 150.22 (1c , C=N of pyrimidine),δ 152.17 (1C , C=O of pyrimidine), δ 157.12 (1C, C–O–CH_3), δ 158.69 (1C, C–O–CH_3).

4-(2-(6-methoxynaphthalen-2-yl)ethyl)-6-(4-chlorophenyl)-5,6-dihydropyrimidin-2(1H)-one (2c) : brown powder (67 % yield); m.p 61-63 °C; IR (KBr) υ (cm^{-1}): 528.51 (C-Cl), 1165.04 (C–N of pyrimidine), 1265 (C–O–CH_3), 1491 (aromatic), 1604 (C=N of pyrimidine), 1708 (C=O of pyrimidine), 3356 N-H of pyrimidine); ^{1}H-NMR (DMSO-d6, 500 MHz): δ 2.14-2.18 (dd, 1H, CH_2 of pyrimidine), δ 2.81-2.84 (t, 2H, CH_2CH_2), δ 2.88-2.91 (t, 2H, CH_2- CH_2), δ 2.99-3.05 (dd, 1H, CH_2 of pyrimidine), δ 3.84 (s, 3H, O–CH_3), δ 6.54 (dd, 1H, CH of pyrimidine), δ 6.87–7.74 (m, 10H, aromatic H). δ 7.93 (N-H of pyrimidine); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 29.52 (1C,CH_2-aryl), δ 30.22 (1C , CH2–pyrimidine), δ 32 (1C, CH_2 of pyrimidine), δ 44.56 (1C, C-N of pyrimidine), δ 55.55 (1C , CH_3-O), δ 133.06 (1C , C-Cl), δ 136.71 (1C, aromatic C-pyrimidine), δ 151 (1C, C=N of pyrimidine), δ 155.16 (1C, C=O of pyrimidine), δ 157.23 (1C, C–O–CH_3).

4-(2-(6-methoxynaphthalen-2-yl)ethyl)-6-(4-nitrophenyl)-5,6-dihydropyrimidin-2(1H)-one (2d) : Dark brown powder (40 % yield); m.p 95-97 °C; IR (KBr) υ (cm^{-1}): 528.51 (C-Cl), 1165.04 (C–N of pyrimidine), 1228.70 (C-NO_2), 1267.77 (C–O–CH_3), 1346.36,1485.24 (NO_2), 1518.03 (aromatic), 1602.90 (C=N of pyrimidine), 1710.92 (C=O of pyrimidine) , 3367.63 (N-H of pyrimidine); ^{1}H -NMR (DMSO-d6, 500 MHz): δ 2.20 (dd, 1H, CH_2 of pyrimidine), δ 2.81 (t, 2H, CH_2CH_2), δ 2.85 (t, 2H, CH_2- CH_2), δ 2.99 (dd, 1H, CH_2 of pyrimidine), δ 3.83 (s, 3H, O–CH_3), δ 6.58 (dd, 1H, CH of pyrimidine), δ 6.93–8.92 (m, 10H, aromatic H), δ 8.47 (N-H of pyrimidine).

4-(2-(6-methoxynaphthalen-2-yl)ethyl)-6-(4-(Dimethylamino)phenyl)-5,6-dihydropyrimidin-2(1H)-one (2e) : brown material (59 % yield); m.p sticky material ; IR (KBr) υ (cm−1): 1165 (C–N of pyrimidine and N(CH_3)$_2$), 1226 (C-N(CH_3)$_2$), 1263 (C–O–CH_3), 1519 (aromatic), 1602 (C=N of pyrimidine), 1710 (C=O of pyrimidine) , 3367 (N-H of pyrimidine); 1H-NMR (DMSO-d6, 500 MHz): δ 2.26-2.29 (dd, 1H, CH_2 of pyrimidine), δ 2.87 (t, 2H, CH_2CH_2), δ 2.90 (t, 2H, CH_2- CH_2), δ 2.93 (s,6H,N(CH_3)$_2$), δ 3.00-3.03 (dd, 1H, CH_2 of pyrimidine), δ 3.84 (s, 3H, O–CH_3), δ 6.57 (dd, 1H, CH of pyrimidine), δ 6.58–7.82 (m, 10H, aromatic H). δ 7.86 (N-H of pyrimidine); ^{13}C-NMR (DMSO-d6 125.64 MHz): δ 29.51 (1C,CH_2-aryl), δ 30.29 (1C , CH_2–pyrimidine), δ 33.62 (1C, CH_2 of pyrimidine), δ41.55(N-(CH_3)$_2$, δ 44.56 (1C, C-N of pyrimidine), δ 55.55 (1C, CH_3-O), δ 137.04 (1C, aromatic C-pyrimidine) δ 143.62 (1C, C-N(CH_3)$_2$), δ 152.23 (1C, C=N of pyrimidine), δ 156.70 (1C, C=O of pyrimidine), δ 157.23 (1C, C–O–CH_3).

Anti-Inflammatory Evaluation Study:

In vivo, the acute anti-inflammatory effects for the chemically synthesized compounds (2a-e) had been evaluated in egg-white stimulated paw edema. The evaluation for their ant-inflammatory activity 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 2a-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 ʏ 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]

3. Results and Discussion

The intraplanar injection of egg-white into rat hind paw induces a progressive edema. To assess the validity of the method (paw-edema) used for the evaluation of newly synthesized 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 2. The calculated area under the curve for Figure 2 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 (2a-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	
2.28±0.06	2.28±0.06	2.53±0.06	3.60±0.07	4.20±0.06	4.31±0.06	2.28±0.06	2a	
2.28±0.06	2.28±0.06	2.56±0.04	3.36±0.07	4.42±0.07	4.54±0.05	2.28±0.06	2b	
2.29±0.06	2.29±0.06	2.52±0.04	3.13±0.06	3.51±0.07	4.37±0.05	2.29±0.06	2c	
2.31±0.06	2.31±0.06	2.52±0.05	3.47±0.05	4.33±0.07	4.29±0.07	2.31±0.06	2d	
2.23±0.06	2.23±0.06	2.59±0.06	3.28±0.06	4.34±0.06	4.45±0.07	2.23±0.06	2e	

Table 2: The percentage of change in rats paw thickness for the control, nabumetone and compounds (2a-e) in 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	12%	59%	84%	89%	0	2a	
0	0	12%	47%	94%	99%	0	2b	
0	0	10%	36.5%	53%	91%	0	2c	
0	0	9%	50%	87.5%	86%	0	2d	
0	0	16%	47%	94.5%	99.5%	0	2e	

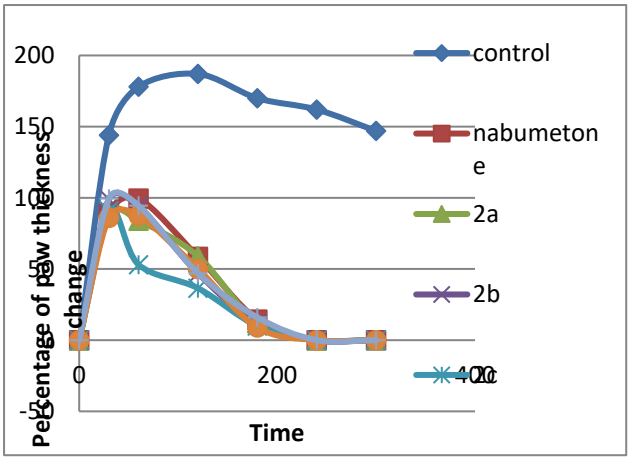

Figure 2: the relationship between the percentages of change in paw thickness with time for the control (propylene glycol), nabumetone, compounds (2a-e).

Table 3: The calculated area under the curve for Figure 2:

Area under the curve	compound
69930	control
11527.5	nabumetone
10710	2a
10740	2b
7905	2c
10057.5	2d
11017.5	2e

According to the above results, all the tested derivatives (2a-e) have more rapid onset of action than nabumetone especially (2c) and all of them have better anti-inflammatory outcome than nabumetone especially (2c and 2d).

4. Conclusion

1. The synthesis of the designed compounds has been successfully achieved.

2. Characterization and identification of the synthesized compounds were confirmed by determination of physical properties (melting point and description), FT-IR spectroscopy, ^{1}H-NMR spectra and ^{13}C-NMR.
3. The anti-inflammatory assessment of the final products indicates that the incorporation of pyrimidine pharmacophore into nabumetone improved its anti-inflammatory action.
4. The preliminary study of anti-inflammatory activity showed that all of the synthesized compounds have more rapid onset of action and better anti-inflammatory outcome than nabumetone especially (2c and 2d).

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References

(1)Kazemi S, Shirzad H, Rafieian-Kopaei M. Recent findings in molecular basis of inflammation and anti-inflammatory plants. Current pharmaceutical design. (2018). 24(14): 1551-1562.
(2)Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et.al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. (2018). 9(6): 7204.
(3)Munn L L. Cancer and inflammation. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. (2017). 9(2), e1370.
(4)Kumar D. Molecular biology of acute and chronic inflammation. InClinical Molecular Medicine 2020 (pp. 389-402). Academic Press.
(5)Woolbright BL, Pilbeam CC, Taylor III JA. Prostaglandin E2 as a Therapeutic Target in Bladder Cancer: From Basic Science to Clinical Trials. Prostaglandins & Other Lipid Mediators. 2020 Jan 10:106409.
(6)Muscella A, Cossa LG, Vetrugno C, Marsigliante S. Bradykinin stimulates prostaglandin E2 release in human skeletal muscular fibroblasts. Molecular and Cellular Endocrinology. 2020 Feb 27:110771.
(7)Piazza VG, Matzkin ME, Cicconi NS, Muia NV, Valquinta S, et.al. Exposure to growth hormone is associated with hepatic up-regulation of cPLA2α and COX. Molecular and Cellular Endocrinology. 2020 Apr 4:110802.
(8)Wang T, Fu X, Chen Q, Patra JK, Wang D, et.al. Arachidonic Acid Metabolism and Kidney Inflammation. International journal of molecular sciences. (2019). 20(15): 3683.
(9)Di Dato V, Ianora A, Romano G. Identification of Prostaglandin Pathway in Dinoflagellates by Transcriptome Data Mining. Marine Drugs. 2020 ;18(2):109.
(10)Altowyan MS, Barakat A, Al-Majid AM, Al-Ghulikah HA. Spiroindolone analogues bearing benzofuran moiety as a selective cyclooxygenase COX-1 with TNF-α and IL-6 inhibitors. Saudi Journal of Biological Sciences. 2020 Feb 26.
(11)Basumatary P, Das M, Barman P, Choudhury M. Molecular Docking Study of 2, 3-Dimethylmaleic Anhydride (3, 4-Dimethyl-2, 5-Furandione) as Anti-inflammatory Agent. Trends in Bioinformatics. (2018). 11(2): 56-63.
(12)Mishra CB, Kumari S, Prakash A, Yadav R, Tiwari AK, et.al. Discovery of novel Methylsulfonyl phenyl derivatives as potent human Cyclooxygenase-2 inhibitors with effective anticonvulsant action: Design, synthesis, in-silico, in-vitro and in-vivo evaluation. European journal of medicinal chemistry. (2018). 151: 520-532.
(13)Segelcke D, Reichl S, Neuffer S, Zapp S, Rüther T, et.al. The role of the spinal cyclooxygenase (COX) for incisional pain in rats at different developmental stages. European Journal of Pain. 2020 ;24(2):312-24.
(14)Sárosi MB. Binding of indomethacin methyl ester to cyclooxygenase 2. A computational study. Journal of molecular modeling. (2018). 24(7): 150.
(15)Doña I, Pérez-Sánchez N, Eguiluz-Gracia I, Muñoz-Cano R, Bartra J, et.al. Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Allergy. 2020 ;75(3):561-75.
(16)Wang H, Jin M, Mao W, Chen C, Fu L, et.al. Photosynthetic toxicity of non-steroidal anti-inflammatory drugs (NSAIDs) on green algae Scenedesmus obliquus. Science of The Total Environment. 2020; 707: 136176.
(17)Lichtenberger LM, Phan T, Fang D, Dial EJ. Chemoprevention with phosphatidylcholine non-steroidal anti-inflammatory drugs in vivo and in vitro. Oncology letters. (2018). 15(5): 6688-6694.
(18)Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. European urology. (2018). 73(4): 583-595.
(19)Cooper C, Chapurlat R, Al-Daghri N, Herrero-Beaumont G, Bruyère O, et. al. Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? Drugs & aging. (2019). 36(1): 15-24.
(20)Brown J, Crawford TJ, Allen C, Hopewell S, Prentice A. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database of Systematic Reviews. 2017(1).
(21)Bouck Z, Mecredy GC, Ivers NM, Barua M, Martin D, et.al. Frequency and associations of prescription nonsteroidal anti-inflammatory drug use among patients with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease. JAMA internal medicine. (2018). 178(11): 1516-1525.
(22)Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging and disease. (2018). 9(1): 143.
(23)Norkus CL. Non-Steroidal Anti-Inflammatory

Drugs. Textbook of Small Animal Emergency Medicine. (2018). 1258-1262.
(24)Capone ML, Tacconelli S, Patrignani P. Clinical pharmacology of etoricoxib. Expert opinion on drug metabolism & toxicology. (2005). 1(2): 269-282.
(25)Chaudhary S, Aqil M, Sultana Y, Kalam MA. Self-nanoemulsifying drug delivery system of nabumetone improved its oral bioavailability and anti-inflammatory effects in rat model. Journal of Drug Delivery Science and Technology. (2019). 51: 736-745.
(26)Bayach I, D'Aleó A, Trouillas P. Tuning optical properties of chalcone derivatives: a computational study. The Journal of Physical Chemistry A. (2018). 123(1): 194-201.
(27)Thirumurugan K, Lakshmanan S, Govindaraj D, Prabu DSD, Ramalakshmi N, et.al . Design, synthesis and anti-inflammatory activity of pyrimidine scaffold benzamide derivatives as epidermal growth factor receptor tyrosine kinase inhibitors. Journal of Molecular Structure. (2018). 1171: 541-550.
(28)Yousif OA, Mahdi MF, Raauf AM. Design, synthesis, preliminary pharmacological evaluation, molecular docking and ADME studies of some new pyrazoline, isoxazoline and pyrimidine derivatives bearing nabumetone moiety targeting cyclooxygenase enzyme. Journal of Contemporary Medical Sciences. 2019 ;5(1):41-50.
(29)Mosaa ZA. Synthesis and Characterization some Novel Heterocyclic Compounds of Pyrimidine and pyrazole from Chalcone derivatives. Al-Qadisiyah Journal of Pure Science. 2018 May 10;23(2):141-51.
(30)Abd El-Sattar NE, Badawy EH, Abdel-Mottaleb MS. Synthesis of some pyrimidine, pyrazole, and pyridine derivatives and their reactivity descriptors. Journal of Chemistry. 2018;2018.
(31)Adnan AM, Mahdi MF, kareem Khan A. Design, Synthesis, and Acute Anti-inflammatory Assessment of New 2-methyl Benzoimidazole Derivatives Having 4-Thiazolidinone Nucleus. Al-Mustansiriyah Journal of Pharmaceutical Sciences (AJPS). 2019 ;19(4):151-60.
(32)from some NSAID TD. Synthesis, Characterization and Preliminary Pharmacological Evaluation of Triazolothiadiazoles Derived from some NSAIDs and Thiocarbohydrazide Manar Serhan Ahmed*, Hayder Jafer Essa*, Ayad Kareem Khan*. AJPS. 2018;18(1).
(33)MAHDI MF, NASER NH, HAMMUD NH. Synthesis and preliminary pharmacological evaluation of new naproxen analogues having 1, 2, 4-triazole-3-thiol. Int J Pharm Pharm Sci. 2017;9(7):66-71.