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SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY EVALUATION OF SOME NEW 2-(3-FLUOROBIPHENYL-4-YL) PROPANOIC ACID DERIVATIVES

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Keywords:

Flurbiprofen, *In vivo* evaluation. NSAIDs, Anti- inflammatory

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ABSTRACT: Different new compounds derived from 2-(3-flourobiphenyl-4-yl) propanohydrazide [2] as starting material were synthesized. Reaction [2] with maleic anhydride, succinic anhydride and phthalic anhydride gave the corresponding cyclicimides [3a-c]. The hydrazone derivatives [4a-d] were obtained by condensation of compound [2] with 2,4-dimethoxybenzaldehyde, 4-(N,N-dimethylamino)benzaldehyde, 3-hydroxybenzaldehyde and 2-hydroxybenzaldehyde. The cyclization of [2] with CS_2 in presence potassium hydroxide and hydrazine hydrate gave 1,2,4-triazole compound [5], that condensation either with 2,4-dimethoxybenzaldehyde, 4-(N,N-dimethyl amino) benzaldehyde, 3-hydroxybenzaldehyde and 2-hydroxybenzaldehyde to give the corresponding Schiff-bases [6a-d]. The cyclization of hydrazone derivatives [4a-d] with phenyl isocyanate, maleic anhydride, succinic anhydride and phthalic anhydride gave the corresponding aza-β-lactams [7a-d], oxazepine [8,9,10 a-d]. The structures of new compounds are supported by FT-IR, ^{1}H-NMR and ^{13}C-NMR. Compounds [3c], [4c], [8d], [7d] and [4b] were evaluated *in vivo* for their anti-inflammatory activity comparable to the standard drug flurbiprofen. Compound 2-(2-hydroxyphenyl)-3-[2-(3-fluorobiphenyl-4-yl)] propan- amido-2,3-dihydro-1,3-oxazepine-4,7-dione [8d] showed anti-inflammatory activity more than the standard drug flurbiprofen, in the egg-albumin induced paw edema in rats.

INTRODUCTION: Flurbiprofen, a non-steroidal anti-inflammatory drugs (NSAIDs) is a phenyl alkanoic acid derivative 2-(3-fluorobiphenyl-4-yl) propanoic acid [1], which has an anti-inflammatory, antipyretic and analgesic agent, used in the treatment of pain or inflammation, in humans [2, 3]. Flurbiprofen tablets are used in the management of acute or longterm treatment of osteoarthritis, rheumatoid arthritis, joint stiffness and dysmenorrhea gout, ankylosing spondylitis, periodontitis, reduction postoperative pain, and in initially treated pain induced from cancer [4-7].

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The compound efficiently works in pain management and has, therefore, gained wide use in the preparation of anti-inflammatory medicines [8, 9]. Flurbiprofen exerts their therapeutic action by inhibiting two isoforms of cyclooxygenase (COX-1, the constitutive enzyme and COX-2, the inducible enzyme) [10, 11]. Cyclooxygenase also known as prostaglandin endoperoxide synthase or PGH synthase, which is the rate-limiting enzyme responsible for the biosynthesis of the prostaglandins (PGs) from arachidonic acid (AA), and thereby modulating pain transmission, attenuating inflammation, and reducing fever [12, 13].

They also produce their undesirable side effects such as gastrointestinal (GI) bleeding, ulcerations, or renal impairments by blocking the same cyclooxygenases responsible for synthesizing PGs that modulate platelet activity, gastric acid

secretion and cytoprotection, and renal blood flow [14-16]. The α-CH3 substituent present in the flurbiprofen increases cyclooxygenase inhibitory activity and reduces the toxicity of the flurbiprofen [17, 18]. Among the many methods used for screening and evaluation of anti-inflammatory drugs, one of the most commonly employed techniques is based upon the ability of such agents to inhibit the edema produced in the hind paw of the rat by injection of a phlogistic agent such as egg-albumin [19-21].

MATERIALS AND METHODS: All chemicals were purchased from Fluka, BDH, CDH and Merck. 2 - (3-fluorobiphenyl - 4 -yl) propanoic acid (flurbiprofen) was received from FDC limited (India). Melting points were recorder using electrothermal melting point apparatus. Fourier transform infrared (FT-IR) spectra were run on a Shimadzu FT-IR-8400S spectrophotometer. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectrum were recorder on Bruker Ultra Shield, 400MHz, using dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard.

Synthesis of cyclicimides derivatives [3a-c]: A mixture of 2-(3-fluorobiphenyl-4-yl) propane hydrazide [2] [22] (0.004 mole, 1 gm.) and the appropriate acid anhydride, namely maleic anhydride, succinic anhydride and phthalic anhydride (0.004 mole) in (15ml) acetic acid, were refluxed for 24 hours. The formed precipitate was filtered, dried and recrystallized to give compounds [3a-c] respectively.

2-(3-Fluorobiphenyl-4yl)propanamidomaleimide [3a]: Red solid, m.p. 122-124 ℃, yield 60%. FT-IR (ν cm^{-1}): 1739 (C=O imide), 1367 (C-N), 3382 (-NH-)

2-(3- Fluorobiphenyl - 4yl) propaneamidosuccinimide [3b]: White solid, m.p. 118-120 ℃, yield 64%. FT-IR (ν cm^{-1}):1716 (C=O imide), 1325 (C-N), 3222 (-NH-)

2-(3-Fluorobiphenyl-4-yl) propaneamidophthalimide [3c]: White solid, m.p. 120-122 ℃, yield 75%, FT-IR (ν cm^{-1}): 1741(C=O imide), 1361 (C-N), 3271 (-NH-)

Synthesis of hydrazone derivatives [4a-d] [23]: 2-(3- Fluorobiphenyl – 4 - yl) propanehydrazide [2] (0.004 mole, 1 gm.) was dissolved in boiling absolute ethanol. Aromatic aldehyde namely 2,4-dimethoxybenzaldehyd, 4 - (N, N - dimethylamino) benzaldehyde, 3-hydroxybenzaldehyde and 2-hydroxybenzaldehyde (0.004 mole), (2-3) drops of glacial acetic acid were added and refluxed for 6 hours. The formed precipitate after cooling was filtred, dried and recrystallized from ethanol, to give compounds [4a-d].

N-(2, 4-dimethoxybenzalidene) - 2- (3-fluorobi phenyl - 4-yl) propanamide [4a]: Yellow solid, m.p. 106-108℃, yield 75%. FT-IR (ν cm^{-1}): 1658 (C=O amide), 1602 (C=N), 1269 (C-O ether), 3197 (N-H), ^{1}H-NMR (DMSO-d_6) δ(ppm): 11.25 (s, 1H, NH), 10.23 (s, 1H, CH=N), 6.64-8.26 (m, 11H, Ar-H), 3.76-3.96 (q, 1H, CH-CH_3), 3.4 (s, 6H, 2CH_3O), 1.46 & 1.50 (d, 3H, CH_3-CH), ^{13}C-NMR δ(ppm): 187 (C=O amide), 173 (C=N imine), (98-168) aromatic ring carbons, 55(-OCH_3), 43(CH-CH_3) and 18(CH_3-CH).

N-(4-(N,N-dimethylamino) benzalidene) – 2 - (3-fluorobiphenyl-4-yl) propanamide [4b]: Red solid, m.p. 124-126℃, yield 70%. FT-IR (ν cm^{-1}): 1645 (C=O amide), 1598 (C=N), 1369 (C-N amine), 3186 (N-H), ^{1}H-NMR (DMSO-d_6) δ(ppm): 11.15 (s, 1H, NH), 9.72 (s, 1H, CH=N), 6.76-8.12(m, 12H, Ar-H), 3.7-4.1 (q, 1H, CH-CH_3), 3.1 (s, 6H, N(CH_3)$_2$), 1.46 & 1.50 (d, 3H, CH_3-CH), ^{13}C-NMR δ(ppm): 189 (C=O amide), 173 (C=N imine), 111-168 aromatic ring carbons, 43 (CH-CH_3) and 18 (CH_3-CH).

N-(3-hydroxybenzalidene)-2-(3 - fluorobiphenyl-4-yl) propanamide [4c]: Brown solid, m.p. 110-112℃, yield 65%. FT-IR (ν cm^{-1}): 1668 (C=O amide), 1581 (C=N), 3107 (O-H), 3207 (N-H)

N-(2-hdroxybenzalidene)-2- (3-fluorobiphenyl-4-yl) propanamide [4d]: Brown solid, m.p. 120-132℃, yield 60%. FT-IR (ν cm^{-1}): 1662 (C=O amide), 1620 (C=N), 3190 (O-H), 3221 (N-H)

Synthesis of 1-(3-flurobiphenyl - 4 - yl) - 1-(3-mercapto-4-amino-1,2,4-triazole-5-yl)ethane [5]: A mixture of 2-(3-fluorobiphenyl-4-yl) propane hydrazide [2] (0.004 mole, 1 gm.), potassium hydroxide (0.0045 mole, 0.25 gm.) and (0.0045

mole, 0.3 ml.) carbon disulfide was dissolved in absolute ethanol (30 ml) and refluxed for 1 hour in a water bath. After that excess carbon disulfide was removed by distillation. Hydrazine hydrate (80%) (5 ml.) was added to the solution and refluxed for 4 hours. After cooling, acidification the solution by 20% HCl, the formed precipitate was filtered and recrystallization from ethanol to give compound [5]. White solid, m.p 140-142℃, yield 80%. FT-IR (ν cm^{-1}): 2773 (S-H), 1612 (C=N), 698 (C-S), 3414 & 3480 (-NH_2) ^{1}H-NMR (DMSO-d_6) δ(ppm): 14.29 (s, 1H, SH), 7.23-8.07 (m, 8H, Ar-H), 4.47-4.54 (q, 1H, CH-CH_3), 3.41 (s,2H, NH_2), 1.61 & 1.66 (d, 3H, CH_3-CH), ^{13}C-NMR δ(ppm): 165 (C=N imine), (115-160) aromatic ring carbons, 34 (CH-CH_3) and 18 (CH_3-CH).

Synthesis of Schiff-bases [6a-d] derived from compound [5]: Compounds [6a-d] was prepared by the same method described for the preparation of compounds [4a-d].

1-(3-fluorobiphenyl-4-yl)-1-[3-mercapto-4- (2, 4-dimethoxybenzalidene)- 1, 2, 4 – triazole – 5 -yl] ethane [6a]: Yellow solid, m.p. 130-132℃, yield 76 %. FT-IR (ν cm^{-1}): 1678 (C=S), 1597 (C=N), 3429 (-NH-)

1-(3-fluorobiphenyl-4-yl)-1-[3-mercapto- 4 - (4-(N,N-dimethylaminobenzalidene))-1,2,4-triazole-5-yl]ethane [6b]: Red solid, m.p. 116-118℃, yield 70 %. FT-IR (ν cm^{-1}): 1658 (C=S), 1612 (C=N), 3545 (-NH-), ^{1}H-NMR (DMSO-d_6) δ(ppm): 14.10 (s, 1H, SH), 9.68 (s, 1H, CH=N), 6.77-8.57 (m, 12H,Ar-H), 4.45-4.65 (q,1H, CH-CH_3), 1.15& 1.22 (d, 3H, CH_3-CH), ^{13}C-NMR δ(ppm): 154 ppm due to (C=N imine), 111-141 aromatic ring carbons, 35 (CH-CH_3) and 18 (CH_3-CH) respectively

1-(3-fluorobiphenyl-4-yl)-1-[3- mercapto - 4 - (3-hydroxybenzalidene)-1, 2, 4-triazole-5-yl] ethane [6c]: Yellow solid, m.p. 124-126℃, yield 72 %. FT-IR (ν cm^{-1}): 1670 (C=S), 1614 (C=N), 3313 (-NH-), 3186 (O-H)

1-(3-fluorobiphenyl-4-yl) - [3- mercapto - 4 - (2-hydroxybenzalidene)-1, 2, 4-triazole-5-yl] ethane [6d]: Brown solid, m.p. 132-134℃, yield 75 %. FT-IR (ν cm^{-1}): 1662 (C=S), 1616 (C=N), 3402 (-NH-), 3248 (O-H)

Synthesis of 1, 3-diazetidine – 2 - one (Aza - β-lactam) derivatives [7a-d]: A mixture of hydrazone derivatives [4a-d] (0.004 mole) and phenyl isocyanate (0.004 mole) in chloroform (15ml) was refluxed for 6 hours. The solvent was removed and the residue treated with a mixture of (1:1) ethyl acetate and petroleum ether. The resultant precipitate was filtered and dried to give compounds [8a-d] respectively.

N-[2-oxo-3-phenyl-4-(2,4-dimethoxyphenyl)-1, 3-diazetidin-1-yl] - 2- (3 – fluorobiphenyl – 4 - yl) - propane amide [7a]: Brown solid, m.p. 150-152℃, yield 70%. FT-IR (ν cm^{-1}): 1735 (C=O ring), 1662 (C=O amide), 3236 (-NH-)

N-[2-oxo-3-phenyl-4-(4 - (N, N dimethyamino) phenyl)-1,3-diazetidin-1-yl]-2-(3-fluorobiphenyl-4-yl)-propane amide [7b]: Red solid, m.p. 130-132℃, yield 75%. FT-IR (ν cm^{-1}): 1728 (C=O ring), 1658 (C=O amide), 3309 (-NH-)

N-[2-oxo-3-phenyl - 4 - (3-hydroxyphenyl) - 1, 3-diazetidin-1-yl] – 2 - (3- fluorobiphenyl – 4 - yl) propane amide [7c]: Brown solid, m.p. 142-144℃, yield 77%. FT-IR (ν cm^{-1}): 1745(C=O ring), 1691 (C=O amide), 3323 (-NH-)

N-[2-oxo-3-phenyl - 4-(2-hydroxyphenyl) - 1, 3-diazetidin-1-yl] – 2 - (3-fluorobiphenyl - 4 - yl)-propane amide [7d]: Brown solid, m.p. 148-150℃, yield 73%. FT-IR (ν cm^{-1}): 1708(C=O ring), 1662 (C=O amide), 1226 (C-O ether), 3228 (-NH-), ^{1}H-NMR (DMSO-d_6) δ(ppm): 11.87 (s, 1H, OH), 11.11 (s, 1H, NH), 6.92-8.46 (m,12H, Ar-H), 4.74 (s, 1H, CH ring), 3.41-4.73 (q, 1H, CH-CH_3), 1.50 & 1.52 (d, 3H, CH_3-CH), ^{13}C-NMR δ(ppm): 173 (C=O amide), 168 (C=O ring), 114-160 aromatic carbons, 43 (CH-CH_3) and 18 (CH_3-CH).

Synthesis of oxazepine derivatives [8a-d], [9a-d] and [10a-d]: A mixture of hydrazone derivatives [4a-d] (0.004 mole) and the appropriate acid anhydride, namely maleic anhydride, succinic anhydride and phthalic anhydride (0.004 mole) in (20ml) tetrahedrofuran (THF), were refluxed for 24 hours. After cooling the formed precipitate was filtered, dried and recrystallized from ethanol, to give oxazepine derivatives.

2-(2,4-Dimethoxyphenyl)-3-[2-(3-fluoro biphenyl -4-yl)] propanamido-2,3-dihydro-1,3 - oxazepine -4,7-dione [8a]: Red solid, m.p.122-124℃, yield 75%. FT-IR (ν cm^{-1}): 1733 (C=O ring), 1677 (C=O amide), 1602 (C=C), 3240 (-NH-).

2-[4-(N, N- Dimethylaminophenyl)] - 3 - [2 - (3-fluorobiphenyl-4-yl)]propanamido-2,3- dihydro-1,3-oxazepine-4,7-dione [8b]: Red solid, m.p. 146-148℃, yield 68%. FT-IR (ν cm^{-1}): 1730 (C=O ring), 1660 (C=O amide), 1595 (C=C), 3419 (-NH)

2-(3-Hydroxyphenyl)-3-[2- (3 - fluorobiphenyl-4-yl)] propanamido - 2, 3-dihydro-1, 3-oxazepine-4,7-dione [8c]: Yellow solid, m.p. 130-132℃, yield 71%. FT-IR (ν cm^{-1}): 1714 (C=O ring), 1660 (C=O amide), 1591 (C=C), 3168 (O-H), 3409 (-NH-)

2-(2-Hydroxyphenyl)-3-[2-(3-fluorobiphenyl - 4 -yl)] propanamido - 2, 3 - dihydro-1,3-oxazepine-4,7-dione [8d]: Brown solid, m.p.128-130℃, yield 64%. FT-IR (ν cm^{-1}): 1703 (C=O ring), 1666 (C=O amide), 1620 (C=C), 3186 (O-H), 3215 (-NH-)^{1}H-NMR (DMSO-d_6) δ(ppm): 12.23 (s, 1H, OH), 11.87 (s, 1H, NH), 6.87-8.43 (m, 12H, Ar-H), 3.58-3.91 (q, 1H, CH-CH_3), 1.42 & 1.79 (d, 3H, CH_3-CH), ^{13}C-NMR δ(ppm): 173 (C=O amide), 168 (C=O ring), (114-160) aromatic ring carbons, 78(C=C), 45(CH ring), 28(CH-CH_3) and 18 (CH_3-CH).

2-(2,4-Dimethoxyphenyl)- 3-[2-(3-fluorobiphenyl -4-yl)] propanamido-2, 3, 5, 6-tetrahydro - 1, 3-oxa zepine-4,7-dione [9a]: Yellow solid, m.p. 110-112℃, yield 74%. FT-IR (ν cm^{-1}): 1730 (C=O ring), 1681 (C=O amide), 3236 (-NH-)

2-[4-(N,N-Dimethylaminophenyl)]-3-[2-(3-fluoro biphenyl-4-yl)]propanamido-2,3,5,6- tetrahydro-1,3-oxazepine-4,7-dione [9b]: Yellow solid, m.p. 122-124℃, yield 70%. FT-IR (ν cm^{-1}): 1691(C=O ring), 1645 (C=O amide), 3188 (-NH-)^{1}H-NMR (DMSO-d_6) δ(ppm): 11.05 (s, 1H, NH), 6.69-8.05 (m, 12H, Ar-H), 4.75 (s, 1H, CH ring), 3.91-4.05 (q, 1H, CH-CH_3), 3 (s, 6H, N(CH_3)$_2$), ^{13}C-NMR δ(ppm) 173 (C=O amide), 143 (C=O ring), (110-134) aromatic ring carbons, 28 (CH-CH_3), 43(CH ring) and 18 (CH_3-CH).

2-(3-Hydroxyphenyl)-3-[2-(3-fluorobiphenyl - 4-yl)] propanamido - 2, 3, 5, 6-tetrahydro-1, 3-oxazepine-4,7-dione [9c] Brown solid, m.p. 138-140℃, yield 71%. FT-IR (ν cm^{-1}): 1693 (C=O ring), 1660 (C=O amide), 3176 (O-H), 3205 (-NH-)

2-(2-Hydroxyphenyl)-3-[2-(3-fluorobiphenyl - 4-yl)]propanamido-2, 3, 5, 6- tetrahydro- 1, 3-oxa zepine-4,7-dione [9d]: White solid, m.p. 140-142℃, yield 69%. FT-IR (ν cm^{-1}): 1691 (C=O ring), 1662 (C=O amide), 3184 (O-H), 3245 (-NH)^{1} H-NMR (DMSO-d_6) δ(ppm):11.89 (s, 1H, OH), 11.34 (s, 1H, NH), 6.59-8.41 (m, 12H, Ar-H), 4.66 (s, 1H, CH ring), 3.75-4.06 (q, 1H, CH-CH_3), ^{13}C-NMR δ(ppm): 173 ppm due to (C=O amide), 169 (C=O ring), (118-160) aromatic ring carbons, 43(CH ring), 28(CH-CH3) and 18(CH_3-CH).

2-(2,4-Dimethoxyphenyl)-3-[2-(3-fluorobi phenyl -4-yl)]propanamido-2,3-dihydro(5,6,e)benzo-1,3-oxazepine-4,7-dione [10a]: Yellow solid, m.p. 116-118℃, yield 76%. FT-IR (ν cm^{-1}): 1677 (C=O ring), 1660 (C=O amide), 3236 (-NH-

2-[4-(N,N-Dimethylaminophenyl)]-3-[2-(3-fluoro biphenyl-4-yl)]propanamido-2, 3-dihydro (5,6,e) benzo -1,3-oxazepine-4,7-dione [10b]: Yellow solid, m.p. 130-132℃, yield 69%. FT-IR (ν cm^{-1}): 1720 (C=O ring), 1658 (C=O amide), 3402 (-NH-)

2-(3-Hydroxyphenyl) - 3 - [2-(3-fluorobiphenyl-4-yl)]propanamido-2,3-dihydro(5,6,e)benzo-1, 3-oxazepine-4,7-dione [10c]: Brown solid, m.p. 118-120℃, yield 74%. FT-IR (ν cm^{-1}): 1683 (C=O ring), 1650 (C=O amide), 3100 (O-H), 3155 (-NH-)

2-(2-Hydroxyphenyl)-3-[2-(3-fluorobiphenyl - 4-yl)] propanamido-2,3-dihydro(5,6,e)benzo - 1, 3-oxazepine-4,7-dione [10d]: solid, m.p. 118-120℃, yield 71%. FT-IR (ν cm^{-1}): 1724 (C=O ring), 1620 (C=O amide), 3417 (-NH-)

Evaluation of the anti-inflammatory activity of the synthesized compounds [3c], [4c], [8d], [7d] and [4b]: Albino rats of both sexes their weight (180-220 g), were supplied by the Animal House of the College of Pharmacy, University of Baghdad, and housed in the same location under standardized condition. Animals were fed standard and drinking water ad libitum. They were allocated into seven groups (six rats each) as follows:

Group I: Six rats that received an appropriate volume of dimethyl sulfoxide (DMSO) (according to the body weight of each rat). This group served as negative control.

Group II: Six rats treated with flurbiprofen as reference substance in a dose of 9mg/kg, dissolved in dimethyl sulfoxide (DMSO).

Group III-VII: Six rats/group treated with the tested compounds (3c, 4c, 8d, 7d or 4b), in dose 9mg/kg and each dissolved in dimethyl sulfoxide (DMSO).

The anti-inflammatory activity of the tested compounds was studied using the egg-albumin induced-edema model. Acute inflammation was induced by a subcutaneous (S.C.) injection of undiluted egg-albumin (0.05 ml) into the planter side of the left hand paw of the rats 30 minutes after intraperitoneal (I.P.) administration of each compound, drugs or the vehicle. The paw thickness was measured by means of vernea at five-time intervals (30, 60, 120, 180 and 240 min.) after drug administration. The data were expressed as the mean ± SEM.

Statistical Analysis: The significance of differences between the mean value was calculated using unpaired Student t-test. Comparison among multiple groups was made by using analysis of variance (ANOVA). *P*-value less than 0.05 were considered significant for all data showed in the study part of anti-inflammatory activity. The percent of anti-inflammatory activity was calculated according to the following equation:

$$\text{Percentage of inhibition (\%)} = 100 \times [1-(x/y)]$$

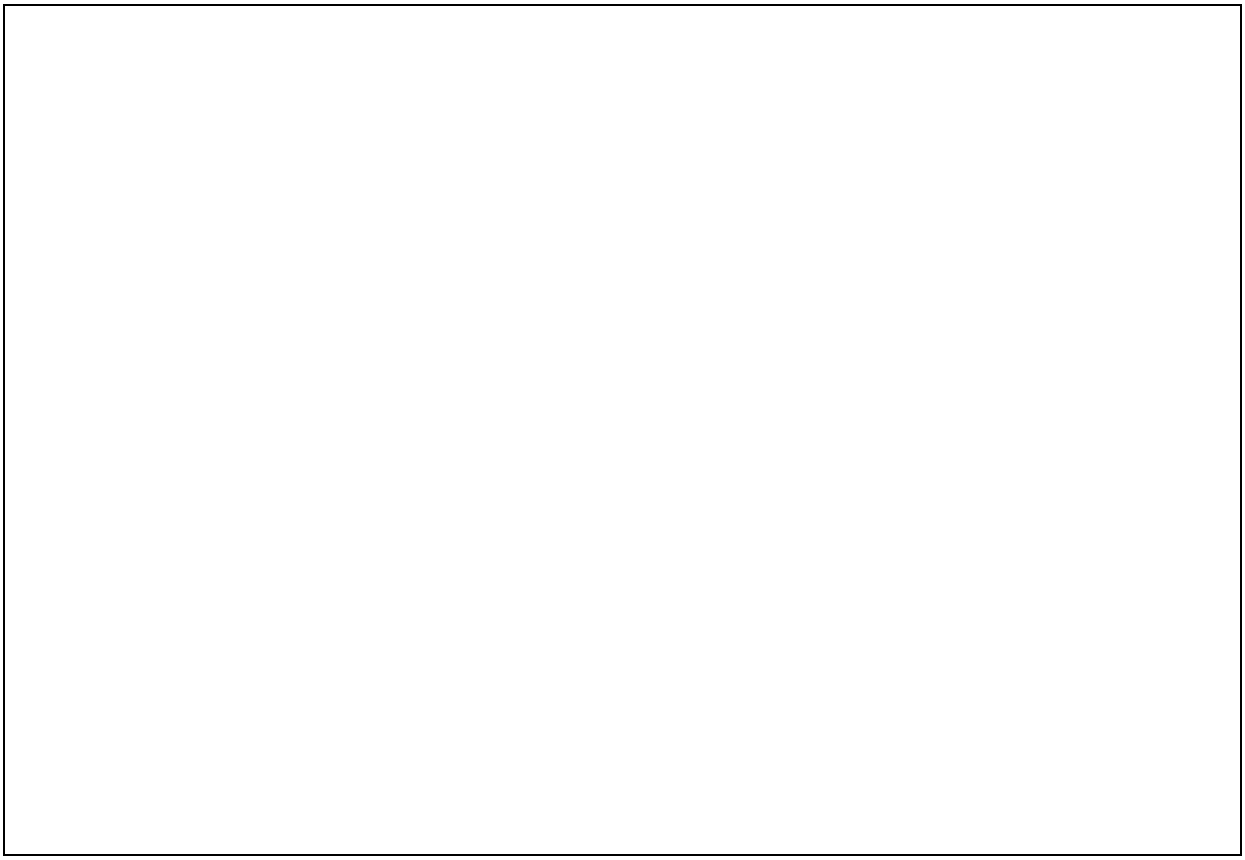
Where:
x= mean increase in paw volume, the thickness of treated rats of either (group II, III, IV, V, VI, VII).
y= mean increase in paw volume, the thickness of group I rats (negative control).

RESULTS AND DISCUSSION: 2-(3-Flourobiphenyl-4-yl)propanohydrazide [2] was chosen as a starting material for the synthesis of all derivatives [3a-c] - [10a-d]. It was reacted with a different acid anhydride namely maleic anhydride, succinic anhydride and phthalic anhydride in presence acetic acid to get N-cyclicimide derivatives [3a-c] (**Scheme 1**). The disappearance of (NH_2) stretching band at (3313 cm^{-1}) and the appearance of stretching band of (C=O cyclicimide) is attributed to the formation of cyclic imide derivatives. Hyrazone derivatives [4a-c] were prepared by condensation of [2] with some aromatic aldehydes namely: 2,4-dimethoxy benzaldehyde, 4-(N,N-dimethylamino) benzal dehyde, 3-hydroxybenzaldehyde and 2-hydroxy benzaldehyde with few drops of glacial acetic acid. The FT-IR and ^{1}H-NMR spectrum of formed hydrazone derivatives showed the presence of (C=N) band at (1581-1620) cm^{-1}, singlet signal for azomethine (CH=N) at 9.72-10.23 ppm. Cyclization [2] with carbon disulfide in presence potassium hydroxide and hydrazen hydrate gave the corresponding 1,2,4-triazole compound [5]. The disappearance of the absorption bands at (3184-3404) cm^{-1} (-NH-NH_2), (1637) cm^{-1} (C=O amide) and appearance absorption bands of (-SH) at (2773) cm^{-1} and at (1612)cm^{-1} for (C=N) were confirm the structure of the compound [5], while the ^{1}H-NMR spectrum showed singlet signals at (14.5) ppm and (3-5)ppm assigned to thiol (-SH) and (-NH_2) groups respectively.

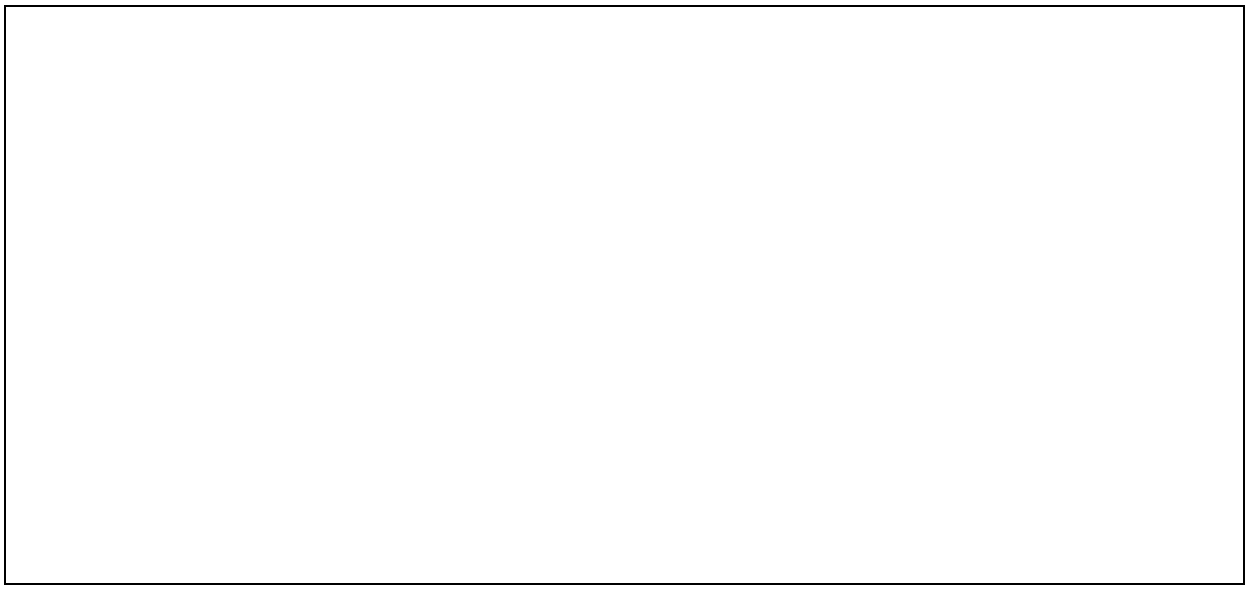
The refluxing of [3a-d] with some acid anhydride namely maleic anhydride, succinic anhydride and phthalic anhydride gave the corresponding oxazepine derivatives [8a-d], [9a-d] and [10a-d]. The absence of stretching absorption band at (1581-1620) cm^{-1} for izomethain group (CH=N) and appearance of absorption band which is due to (C=O ring) at (1662-1733) cm^{-1}, while ^{1}H-NMR spectrum showed singlet signal at (3.90-4.69) ppm for (C-H oxazepine ring) gave a good evidence for the formation of oxazpine derivatives. Hydrazone derivatives [4a-d] that reacted with phenylisocyanate via a [2+2] cycloaddition reaction [24] to give corresponding aza-β-lactam derivatives [7a-d].

The FT-IR spectrum of formed diazetidinone derivatives showed the presence of β-azalactam carbonyl absorption band at (1685-1745) cm^{-1}, while the ^{1}H-NMR spectrum showed a single signal at (4.74) ppm assigned to (C-H) azalactam ring at position (4). Compounds [3c], [4c], [8d], [7d] and [4b] *in vivo* tested for their anti-inflammatory activities compared to the standard drug flurbiprofen.

Table 1 and **Fig. 1** showed the effect of prior treatment with various compounds against egg albumin-induced acute inflammation compared to group I (negative control), and group II (flurbiprofen 9mg/kg) -treated animals. Percent inhibition (%) compared to the negative control (group I) was shown in table 1. All tested compounds effectively limited the increase in paw edema, where, their effect started at 60 minutes and continues until the end of the experiment except the compound **[3c]**, which its effect was only appearing on 180 minutes. Tested compounds showed weak anti-inflammatory except compound **[8d]**, which showed anti-inflammatory activity more than standard drug (flurbiprofen).



SCHEME (1): SYNTHETIC ROUTE OF COMPOUNDS [3a-c], [4a-d], [5] AND [6a-c]



SCHEME (2): SYNTHETIC ROUTE OF COMPOUNDS [7a-d], [8a-d], [9a-d] AND [10a-d].

TABLE 1: THE EFFECT CONTROL, FLURBIPROFEN AND COMPOUNDS [3c], [4c], [8d], [7d] AND [4b] ON EGG-ALBUMIN INDUCED PAW EDEMA IN RATS

Group	Mean increase in paw thickness (mm)					% of inhibition				
	30 Min.	60 Min.	120 Min.	180 Min.	240 Min.	30 Min.	60 Min.	120 Min.	180 Min.	240 Min.
GI Negative control (DMSO)	4.95± 0.11	5.17± 0.06	5.06± 0.11	4.87± 0.09	4.67± 0.11	---	---	---	---	---
GII Flurbp.	4.67± 0.12*A	5.21± 0.22A	5.53± 0.25*A	4.53± 0.16*A	4.67± 0.14A	5.66	---	---	6.98	---
GIII 3c	5.49± 0.14*B	5.76± 0.19*B	5.07± 0.17B	4.67± 0.13*B	4.89± 0.19*B	---	---	---	4.11	---
GIV 4c	5.02± 0.17C	5.3± 0.1C	4.99± 0.15*C	4.46± 0.11*C	4.19± 0.12*C	---	---	3.29	8.42	10.28
GV 8d	4.79± 0.16D	5.06± 0.23D	4.59± 0.211*D	4.24± 0.19*D	4.21± 0.19*D	3.23	2.12	9.28	12.9	9.8
GVI 7d	5.24± 0.078E	5.65± 0.11*E	5.19± 0.07E	4.69± 0.13B	4.39± 0.1*E	---	---	---	3.69	5.99
GVII 4b	5.25± 0.12*E	5.48± 0.09*C	5.08± 0.1C	4.54± 0.09*C	4.37± 0.08*E	---	---	---	6.77	6.42

-Data were expressed as mean ± SEM
-*P<0.05: significant difference compared to the negative control group.
-Values with non-identical subscripts (A, B, C, D and E) among different groups are considered significantly different (P<0.05) in each time column.
-Percent inhibition (%) compared to the negative control (group I).
-Number of animals= 6/ group.

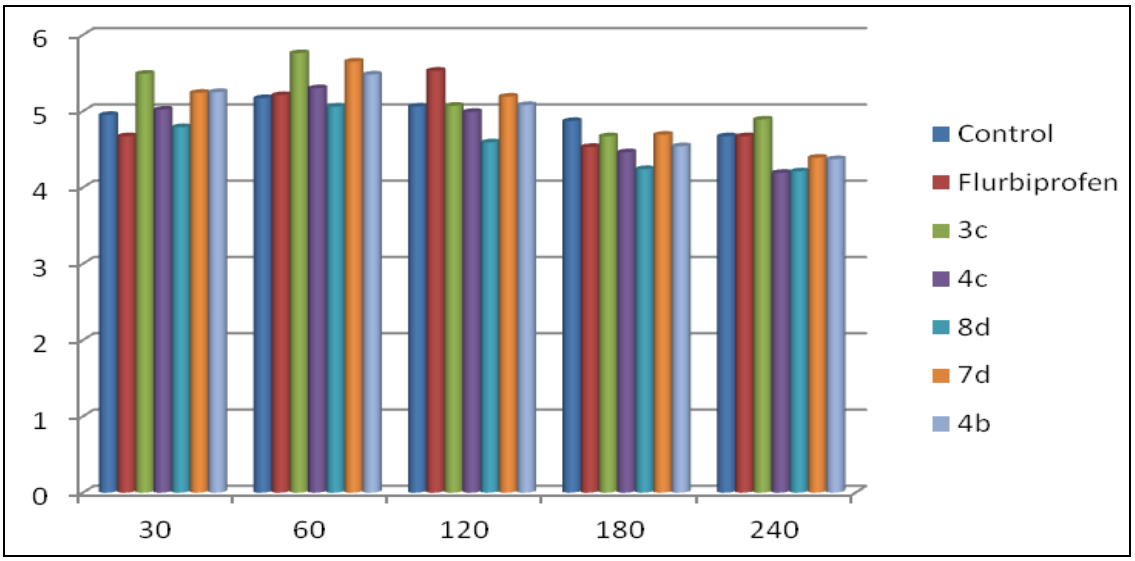


FIG. 1: THE EFFECT CONTROL, FLURBIPROFEN AND COMPOUNDS (3c, 4c, 8d, 7d AND 4b) ON EGG-ALBUMIN INDUCED PAW EDEMA IN RATS

CONCLUSION: Some new 2-(3-fluorobiphenyl-4-yl) propanoic acid derivatives were synthesized from starting material 2-(3-Fluorobiphenyl-4-yl) propanehydrazide [2]. Compounds [3c], [4c], [8d], [7d], [4b] were *in vivo* evaluated for their anti-inflammatory activities compared to the standard drug flurbiprofen. Tested compounds possessed weak anti-inflammatory activities except the compound [8d], where, it has better anti-inflammatory activity than flurbiprofen.

For future work; perform dose-response curve for [8d] compound against inflammation-induced by egg-albumin.

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