Research Article **www.ijcps.com**

International Journal of
Chemical and Pharmaceutical Sciences
2014, Dec., Vol. 5 (4)

ISSN: 0976-9390
IJCPS

Synthesis of novel diflunisal carboxamide derivatives to enhance anti-inflammatory activity

[1] Sadik AlMekhlafia[*] and [2] Muhanned Shehab.

[1] Department of Medicinal Chemistry, Faculty of Pharmacy, Sana'a University, Yemen

[2] Department of Pharmacology, Faculty of Medicine, Sana'a University, Yemen

[*] **Corresponding Author:** E-Mail: ahmedsarhan1966@gmail.com

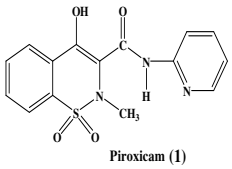
ABSTRACT

The aim of this work was to synthesis and preliminary pharmacological evaluation of target compounds that derived from the conversion of the carboxyl group in diflunisal into carboxamide derivatives of different heterocyclic rings including 2- aminothiazole, 2-amino-5-methyl-2- thiazole, 3-amino-5-methylisoxazole, and 2-amino-5- methylthio-1,3,4-thiadiazole in order to enhance anti-inflammatory activity and to decrease gastric side effects. The synthetic steps involve esterification of the phenolic group in diflunisal, followed by activation of the carboxyl group of the esterified difluninal by N,N-dicyclohexylcarbodiimide (DCC) as coupling agent to form difluninal anhydride,that coupled with heterocyclic rings yielded an intermediate compounds (6-9). Removal of the acetate moiety generated the final compounds (10-13). The anti-inflammatory activity of these compounds was tested using the % inhibition of granuloma. The results were 61.1059%, 50.536%, and 57.227% for compound 13, Roficoxib and Indomethacin respectively. The ulcerogenic potential of tested compounds indicate that compound 13 in this novel series showed better anti-inflammatory activity with least ulcerogenic side effect relatively to Rofecoxib and Indomethacin.

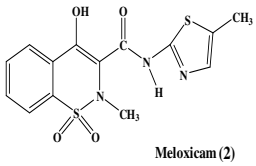
Keywords: Anti-inflammatory, Diflunisal derivatives, Craboxamide derivatives.

1. INTRODUCTION

Cyclooxygenase (COX) enzymes which catalyze the formation of prostaglandins (PGs) from arachidonic acid, PGS play an important role in various types of inflammation and ulceration [1-3]. COX exists at least in two mammalian isoform, COX_1 and COX_2. Constitutive COX_1 has housekeeping function including gastro protective PGs, whereas COX_2 is induced in inflammation [4-6]. Traditional nonsteroidal anti-inflammatory drugs (TNSAIDs), inhibit both COX_1 and COX_2. Inhibition of COX_1 is associated with reduction in gastro protection, while selective COX_2 inhibitors such as Valdecoxib, Rofecoxib, Celecoxib exert their anti–inflammatory, and analgesic effect with less GI toxicity than traditional NSAIDs but suffer from cardiovascular, renal and even GI irritation or ulceration with long term use or at higher doses [7-9]. These clinical observations associated with nonselective or selective COX2 inhibitors necessitated the need for new selective, potent COX_2 inhibitors with no or reduce risk of side effects. An increasing in the number of studies indicate that the structural modification of commercially available traditional NSAIDS such as Piroxicam, lead to improvement their specificity for COX–2 enzyme selectivity with less GIT side effects as in Meloxicam [10-12].



Piroxicam (1)



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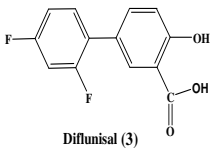
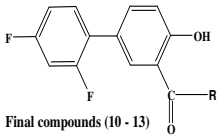


Diflunisal (3)



Final compounds (10 - 13)

Where R = 2-aminothiazole, 2-amino-5-methylthiazole, 3-amino-5-methylisoxazole, and 2-amino-5- methylthio-1,3,4-thiadiazole **.**

A novel of compounds generated from coupling of nonselective COX inhibitors as represented by Diflunisal and the side chain analogous found in meloxicam as represented by 2-aminothiazole, 2-amino-5-methylthiazole, 3-

amino-5-methylisoxazole, and 2-amino-5-methylthio-1,3,4-thiadiazole resulting in the formation of the target compounds (10-13).

2. EXPERIMENTAL

2. 1. Materials

Diflunisal powder was kind gift from Ram Pharmaceutical Industry Jordan. Indomethacin and Rofecoxib were kind gift from National Drug Quality Control laboratory, Yemen. 2-aminothiazole, 2-amino-5-methylthiazole, 3-amino-5-methylisoxazole, and 2-amino-5-methylthio-1,3,4-thiadiazole were purchased from Aldrich, Germany. N, N–Dicyclohexylcarbodiimide was purchased from Acros, USA. Dicholromethane AR 99.5% was purchased from PTV, Italy. Zinc dust and thin layer chromatography (TLC) were purchased from Merck, Germany. Acetic anhydride was purchased from Synchemica Hopking and Williams ChaDwell Health Essex, England. Sodium carbonate, petroleum ether 60-80%, ether, propylene glycol 50%, ethanol and dioxane were purchased from Scharlab, Spain. HCI was purchased from Unichem, India. Glacial acetic acid was purchased from Himedia, India .

2.2. Instruments

Thin layer chromatography (TLC) is performed with precoated silica gel plates (60F-254 with iodine as developing compound. (^{1}H–NMR) spectra were carried out on, mercury 300 MHz spectrometer (Aldenmark), using tetramethylsilane as the internal reference. Melting points (MP) were determined by using a calibrated Thomas–Hoover melting apparatus and uncorrected. IR spectra were recorded using Shimadza FT- (8101 IR) spectrophotometer (Japan). Elemental Microanalyses CHN(CE–440 ,Germany. Rotary evaporator(R-210 V-700 V-850, Buchi, Switzerland).

2.3. Methodology

2.3.1. Synthesis and identification of diflunisal derivatives

2.3.1.1. 5–(2,4–Difluorophenyl) acetylsalicylic acid (4)

A dry Diflunisal **3**, (10 g, 40 mmol) was placed in 200 ml round conical flask. Acetic anhydride (25 mL, 262 mmol) was added, and 5 drops of sulfuric acid was added dropwise, mixing the contents by rotating the conical flask for 5 minutes, warm in water bath to about 50-60 °C, with stirring for 20 minutes. The reaction mixture was allowed to cool with occasional stirring, and then cold distilled water was added until precipitate was formed, and filtered by using suction pump, washed with cold distilled water several times, and the crude product was collected [13,14]. Recrystallization was carried out by using ethanol 95%, the crystals were collected and dried to give compound **4** in 89 % yield as a white crystals. Mp. 175–176 °C, (KBr, Cm^{-1}): 3250 – 2500 (COOH, ArH), 1760 (C=O, ester), 1650 (C=O, COOH), 1600, 1550, 1450 (C=C,Ar). ^{1}H – NMR (DMSO-d6) δ ppm: 2.2(s, 3H, $COCH_3$),11.23(s,1H,COOH), 7.25 - 7.50 (m, 3H, ArH), 7.75, (m, 2H, $ArHF_2$), 8.08 (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{15}H_{10}F_2O_4$; C, 61.60; H, 3.45. Found: C, 61.68; H, 3.43%.

2.3.1.2. 5–(2,4–Difluorophenyl)–acetyl salicylic acid anhydride(5)

Compound **4**, (10 g, 34.22 mmol) was dissolved inmethylene chloride(160 mL), dicyclohexylcarbodimide (3.53 g, 17.11 mmol) was added. The reaction mixture was continuously stirred at room temperature for about 3 hrs. A white precipitate of dicyclohexylurea was formed and removed by filtration. The solvent was evaporated under vacuum; a solid product was obtained to yield the desired known anhydride compound **5** [15].

2.3.1.3. 5–(2,4–Difluorophenyl)–N–(2–thiazolyl) acetyl salicylamide (6)

Compound 5, (5 g , 8.8 mmol), 2-aminothiazole(0.883 g , 8.82 mmol), zinc dust (0.008g), glacial acetic acid (0.85 ml, 14.864 mmol), dioxane (50 mL) were placed in 100 ml round bottom flask, equipped with reflux condenser, and boiling stones were added. The reaction mixture was refluxed for about 1 hr with continuous stirring. The reaction was checked with TLC to make sure of the completion of the reaction. The solvent was evaporated under vacuum; the residue was dissolved in ethyl acetate, washed by (20mL) with NaHCO3 (10%,3 times), HCL (IN,3 times) and 3 times with distilled water (20 ml used), and filtered over anhydrous sodium sulphate. The filtrate was evaporated and the residue was redissolved in ethyl acetate and filtered. The recrystallization was carried out by adding petroleum ether (60 – 80 °C) on the filtrate until turbidity occurred and kept in cold place over-night. Then the mixture was filtered while it was cold and the precipitate was collected to give compound **6** in 51% yield as faint reddish powder. Mp. 85 °C, decompose: IR, (KBr, Cm^{-1}) 3220 (NH, amide), 1620, 1560, 1520 (C=C,Ar),3040(ArH), 1765 (C=O, ester).^{1}H – NMR (DMSO-d6) δ ppm: 2.2 (s, 3H, $COCH_3$), 5.5 (br, 1H, CONH), 7.35- 7.70 (m, 3H, ArH), 7.85, (m, 2H, $ArHF_2$), 8.12 (s, 1H, $ArHF_2$). Anal. Calcd. for: $C_{18}H_{12}N_2F_2O_3S$; C, 57.75; H, 3.20; N, 7.48. Found: C, 57.68; H, 3.20; N, 7.5%.

2.3.1.4. 5–(2,4–Difluorophenyl)–N–(5–methyl–2– thiazolyl)– acetyl salicylamide (7)

Compound 5, (5 g , 8.82 mmol), 2– amino– 5– methylthiazole (1.00 g , 8.82 mmol), zinc dust (0.008 g), glacial acetic acid (0.85 mL , 14.864 mmol), dioxane (50 mL), were prepared as described before in **6**, to generate compound 7 in 56 % yield as a faint yellow powder. Mp.94- 96 °C. The IR (KBr, Cm^{-1}): 3450 (NH, amide),3040 (ArH), 1750 (C=O, ester), 1650 (C=O, amide), 1610, 1550, 1450 (C=C,Ar), 1110 (5- CH_3, thiazolyl). ^{1}H–NMR (DMSO-d6) δ pmm: 2.2 (s, 3H, $COCH_3$), 2.45 (s, 3H, 5-CH_3, thiazolyl), 5.25 (br, 1H, CONH), 7.15 (s, 1H, thiazolyl), 7.20- 7.40 (m, 3H, ArH), 7.5-7.7 (m, 2H, ArH_2F_2), 8.20 (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{19}H_{14}N_2F_2O_3S$; C, 58.76; H, 3.60; N, 7.21. Found: C, 58.55; H, 3.6; N, 7.11%.

2.3.1.5. (2,4–Difluorophenyl)–N–(5–methyl–3–isoxazolyl)– acetyl salicylamide (8)

Compound 5, (5 g , 8.82 mmol), 3- amino-5- methylisoxazole (0.865 g , 8.82 mmol), zinc dust (0.008 g), glacial acetic acid (0.85 mL , 14.864 mmol), dioxane(40 mL), were prepared as described before in compound **6** to give compound **8** in 50% yield as a faint yellow powder. Mp.150–152 °C. The IR (KBr, Cm-1): 3255 (NH, amide), 3050 (,ArH), 1745 (C=O, ester), 1630 (C=O, amide), 1605, 1560, 1450 (C=C,Ar), 1120 (5-CH_3, isoxazolyl). ^{1}H– NMR (DMSO-d6) δ ppm: 2.2 (s, 3H, $COCH_3$), 2.5 (s, 3H, 5- CH_3, isoxazole), 5.65 (br, 1H, CONH), 7.15 (s, 1H, isoxazole), 7.20 -7.35 (m, 3H, ArH), 7.45-7.65 (m, 2H, ArH_2F_2), 8.15 (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{18}H_{14}N_2F_2O_4$; C, 61.29; H, 3.76; N, 7.52. Found: C, 61.10; H, 3.8; N, 7.54%.

2.3.1.6. 5–(2,4–Difluorophenyl)–N–(5–(methylthio)–2–(1,3,4–thiadiazolyl)–acetylsalicylamide (9)

Compound 5, (5 g, 8.82 mmol), 2–amino-5-(methylthio)–1,3,4–thiadiazole (1.298 g , 8.82 mmol), zinc dust (0.008 g), glacial acetic acid (0.85 mL , 14.864 mmol), dioxane (60 mL), were prepared as described before in compound **6** to give Compound **9** in 57% as a faint yellow powder. Mp.164-167 °C. The IR (KBr, Cm^{-1}) 3450 (NH, amide), 3030 (ArH), 1750 (C=O, ester), 1650 (C=O, amide), 1610, 1550, 1450, (C=C,Ar). ^{1}H – NMR (DMSO-d6) δ ppm:2.2 (s, 3H, $COCH_3$), 2.5 (s, 3H, S-CH_3), 5.65 (br, 1H, CONH), 7.20-7.35, (m, 3H, ArH), 7.45 -7.60 (m, 2H, ArH_2F), 8.20 (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{18}H_{13}N_3F_2O_3S_2$; C, 51.35; H, 3.08; N, 9.97. Found: C, 51.22; H, 3.1; N, 9.95%.

2.3.1.7. 5–(2,4–Difluorophenyl)–N–(2–thiazolyl) salicylamide(10)

Compound **6**, (5.67 g, 10 mmol) was dissolved in minimum volume of ethanol (95%). The solution was cooled to 18 °C, and then sodium hydroxide (6 mL, 12 mmol) was added dropwise, with continuous stirring at 18 °C, during which the reaction mixture was checked by TLC, until the disappearance of methyl ester group in compound **6**, indicating a complete alkaline hydrolysis. Then the reaction mixture was acidified with HCL (6 mL, 12 mmol,), excess of cold water was added and the crude phenolic compound was precipitated. TLC showed a single spot. The recrystallization was carried out by using ethanol and water to liberate compound **10** in 63 .4 % yields as white crystalline powder [16]. Mp. 251-253 °C. IR (KBr, Cm^{-1}), 3600 – 3350 (OH, phenolic), 3250 (NH, amide), 3035 (ArH), 1675 (C=O, amide), 1600, 1550, 1500, 1450 (C=C,Ar), 1325, 1200 (C-O). ^{1}H–NMR (DMSO-d6) δ ppm: 5.65 (br, 2 H, OH, CONH, exchangeable with D_2O), 7.2 -7.40, (m, 3H, ArH), 7.45 (m, 2H, ArH_2F_2), 8.20 (s,1H, $ArHF_2$). Anal. Calcd. for $C_{16}H_{10}$ $N_2F_2O_2S$; C, 57.77; H, 3.00; N, 8.42. Found: C, 57.78; H, 3.08; N, 8.4%.

2.3.1.8. 5–(2,4–Difluorophenyl)–N–(5–methyl–2–thiazolyl– salicylamide (11)

Compound 7 was treated through the same condition for the synthesis of compound **10** afforded compound **11** in 53% yields as white crystals. Mp. 297–299 °C. IR (KBr, Cm^{-1}) 3350 (OH), 3150 (NH, amide), 1675 (C=O, amide), 1600, 1550, 1450 (C=C, Ar). ^{1}H–NMR (DMSO-d6) δ ppm: 2.55 (s, 3H, 5-CH_3, thiazolyl), 5.65 (br, 2H, OH, CONH, exchangeable with D_2O), 7.15 (s, 1H, thiazolyl), 7.2 -7.45, (m, 3H, ArH) 7.60-7.65,(m, 2H, ArH_2F_2), 8.15 (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{17}H_{12}N_2F_2O_2S$; C, 58, 89; H, 3.46; N, 8.08. Found: C, 58.87; H, 3.45; N, 8%.

2.3.1.9. 5–(2,4–Difluorophenyl)N–(5–methyl–3–isoxazolyl)– salicylamide (12)

Compound **8** was treated as described for **10** to afford compound **12** in 55% yields as white crystals. Mp. 230-232 °C. IR (KBr, Cm^{-1}) 3350 (OH), 3200 (NH, amide), 1680 (C=O), 1610, 1550, 1450, (C=C,Ar). 1H–NMR(DMSO-d6) δ ppm: 2.50 (s, 3H, 5-CH_3, isoxazolyl), 5.60 (br, 2 H, OH, CONH, exchangeable with D_2O), 7.0 (s, 1H, isoxazolyl), 7.20 -7.40(m, 3H, ArH), 7.65 (m, 2H, ArH_2 F_2), 8.2 (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{17}H_{12}N_2F_2O_3$; C, 61.75; H, 3.63; N, 8.47. Found: C, 61.79; H, 3.65; N, 8.35%.

2.3.1.10. 5–(2,4–Difluorophenyl)–N–(5–methylthio–2–(1,3,4– thiadiazolyl)-salicylamide (13)

Compound **9** was treated as described for compound**10** to generate compound **13** in 57% yields as a white crystalline powder. Mp. 281–282 °C. IR (KBr, Cm^{-1}) 3500 (OH), 3150 (NH, amide), 3050(CH, ArH), 1650(C=O), 1610, 1540, 1450 (C=C,Ar). ^{1}H–NMR (DMSO-d6) δ ppm: 2.5 (s, 3H, 5-CH_3, thiadiazolyl), 5.65 (br, 2H, OH, CONH,

exchangeable with D_2O), 7.45, 7.33 (m, 3H, ArH), 7.50 7,69 (m, 2H, ArH_2F_2),8.1, (s, 1H, $ArHF_2$). Anal. Calcd. for $C_{16}H_{11}N_3F_2O_2S_2$): C, 50.60; H, 2.89; N, 11.06. Found: C, 50.49; H, 2.81; N, 11%.

2.4. Preliminary pharmacological evaluation

2. 4. 1. Animals

Adult male guinea pigs weighing 400±50 gm were used throughout the study. These were fed fresh plants, and provided with water ad libitum.

The animals were divided into 7 different groups as follows:

Group 1: 6 animals served as control received propylene glycol 50% v/v only.

Group 2: 6 animals received 2.55 mg/400 gm body weight of Indomethacin.

Group 3: 6 animals received Rofecoxib (in a dose based on the equimolecular dose to that of Indomethacin).

Group 4: 6 animals received test compound **no. 10**.

Group 5: 6 animals received test compound **no.11**.

Group 6: 6 animals received test compound **no.12**.

Group 7: 6 animals received test compound **no.13**.

Note: All other prepared compounds were pharmacologically inactive.

2.4.2. Route of schedule of treatment

The compounds and Rofecoxib were given (I.P.) as single daily doses for 7 days. Indomethacin was given twice daily (every 12 hours) for 7 days. Control animals were given propylene glycol 50% v/v for 7 days.

2.4.3. Experimental design

A model of chronic inflammation was induced in all animals by S.C. implantation of cotton pellets of fixed weight (35±1 mg) according to the method described in. [17,18]. After 7 days administration of drug (references) and tested compounds (10-13) , all animals were sacrificed by decapitation cotton pellets were removed, dried and weighed. The increase in the weight of cotton pellet is considered as an indication of inflammatory response by implanted cotton pellets.

2.4.4. Anti-inflammatory effect

The effect of test compounds is inversely proportional to the increasing in the weight of cotton pellets. The presence of compound-induced gastric ulceration was examined both macroscopically and microscopically. The confirmed ulceration indicates the inhibition of COX-1 enzyme, and the non-selectivity of the test compounds.

2.4.5. Statistical calculation

The processing of the results by using the T-test to show the differences among all groups, the highly significance is considerable, in which ($P< 0.01$). To conform that the result obtained by T-test using ANOVA test, in which ($P< 0.01$).

3. RESULTS AND DISCUSSION

3.1. Determination of the anti-inflammatory activity of test compounds

Table (1) shows the biological evaluation of the test compounds as indicated by changing the weight of granuloma induced by S.C. implantation of cotton pellets. According to the method, the most potent anti-inflammatory compound was compound 13, followed by compounds 11 and 12, and Indomethacin, then compound10 and Rofecoxib. The respective values for granuloma reduction (%inhibition) were 61.1059%, 59.09%,57.486%,57.227%, and 50.536% for compounds 13, 11, 12 and indomethacin, and Rofecoxib, respectively.

3.2. Determination of ulcerogenic effect of test compounds:

Macroscopic examination of the possible ulcerogenic effects of the equimolar dose of test compounds, indomethacin and rofecoxib using method described in [19]. It found that compound 10 had the most marked diffused hyperemia but less than indomethacin. The microscopic examination showed results parallel to those of macroscopic evaluation. Higher doses of test compound and indomethacin (ulcerogenic dose) showed marked diffuse, thinning and diffuse hyperemia with numerous and deep ulceration, some of them perforated (e.g. indomethacin),others are not perforated (e.g. compound 10 and 12). Compound 11 caused hyperemia without ulceration, while compound 13 was not toxic to gastric mucosa at all.

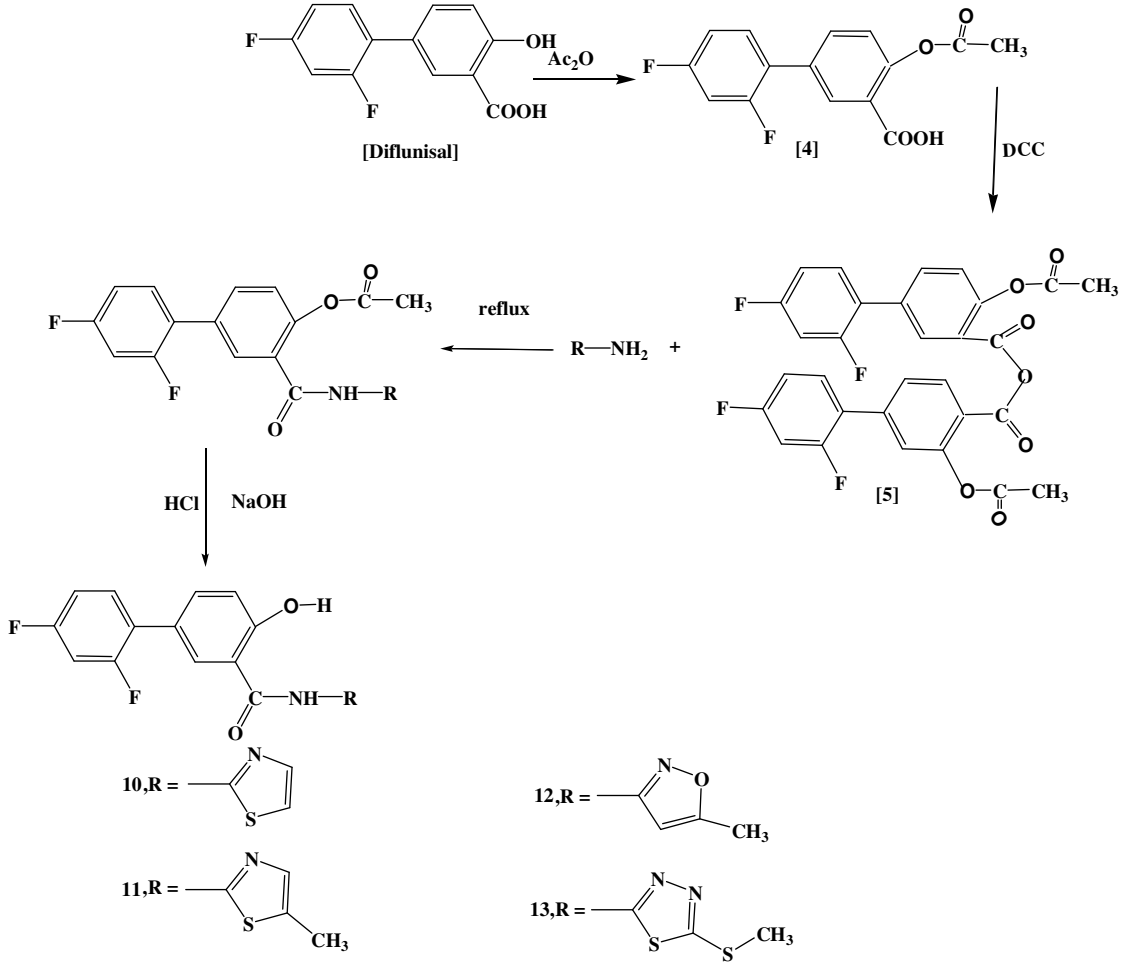
3.3. Chemistry

The synthetic routes for preparation of the desired compounds are outlined in scheme 1. Diflunisal carboxamide derivatives (10- 13) were prepared by acylation of the phenolic group of diflunisal with acetic anhydride as protecting group to prevent the interference of phenolic group with carboxyl group in subsequent reactions. Compound (4) was converted to its

Table - 1: The effect of compounds 10, 11, 12, 13, Indomethacin and Rofecoxib on changing the weight of Granuloma, induced by S.C. implantation of cotton pellets.

Group	Dose (mg/kg)	Mean weight of dry granuloma(mg)*	S.D.	% inhibition	P*	P**
Vehicle	(7.5ml/kg)	31.25	1.2145	-	<0.01	-
Indomethacin	6.375	13.333	1.4376	57.227	<0.01	<0.01
Rofecoxib	5.575	15.416	1.1143	50.536	<0.01	<0.01
Compound 10	5.885	15.0833	1.5218	50.3025	<0.01	<0.01
Compound 11	5.900	12.75	1.8371	59.09	<0.01	<0.01
Compound 12	6.075	13.25	1.2942	57.486	<0.01	<0.01
Compound 13	6.750	11.00	0.7071	61.1059	<0.01	<0.01

*The mean of granuloma of 6 animals (right and left body sides)



Scheme 1

corresponding anhydride as very reactive intermediate (5) upon treatment with (DCC) in methylene chloride. The acylated diflunisal anhydride coupled with various selected aminosubstituted heterocyclic rings in the presence of Zn dust as catalyst to accelerate the formation of compounds (6 -9) amide derivatives of acylated diflunisal. Deprotection by removal of the acetate group in compounds (6-9) resulted in the diflunisal derivative compounds (10-13) as final products [16].

IR, H– NMR and Elemental analysis were consistent with the assigned structures as described in the experimental part.

3.4. Pharmacology

The anti-inflammatory activity of the proposed compounds indicate that 5–(2,4–difluorophenyl)–N–[5– methylthio–2–(1,3–4–thiadiazolyl)] salicylamide compound (13) is the most active one among the active synthesized salicylamide derivatives (10- 13) and to indomethacin and rofecoxib as reference drugs. The least activity was showed by compound 10 in our series compared to compounds 13, 11 and 12 may be attributed to the absence of methyl group at position-5 of heterocyclic ring of salicylamide. However the prepared compounds showed higher anti-inflammatory activity than references compounds this may be due to ,the presence of 2,4-difluorophenyl group at the p-position of salicylamide, which is required for effective overlap with COX enzyme, and this is in agreement with what is seen with many anti – inflammatory drugs such as mefenamic acid, ketoprofen, nabumetone and many others [20,21] . Comparison of the activity of compounds 13, 12 and 11 can recognize the importance of the substituent on the heterocyclic ring; methylthio contributes more than methyl and least in unsubstituted heterocyclic ring (see compound 10). However, this cannot rule out the contribution of the heterocyclic ring as seen in compound 13.

Early reports indicated that indomethacin showed effective anti–inflammatory activity with profound ulcerogenic side effects while rofecoxib showed less potent anti–inflammatory effect with mild toxicity on gastric mucosa. This property of rofecoxib was attributed to COX2 selectivity [22]**.** Accordingly, the microscopic and macroscopic examinations of ulcerogenic effect of the newly synthesized compounds 10- 13, indomethacin and rofecoxib indicate that indomethacin showed greater ulcerogenic effect as characterized by marked diffuse, thinning and diffuse hyperemia with numerous and deep ulceration, some of which with perforation. Compounds 10 and 12 showed similar effect to indomethacin but no sign of perforation; compound 11 caused hyperemia without ulceration, while compound 13 was not toxic to gastric mucosa.

4. CONCLUSION

A novel anti-inflammatory agents have been synthesized and preliminary pharmacological evaluation was performed and compared with reference drugs (Rofecoxib and Meloxicam).

The synthesized compounds being having carboxamid group and heterocyclic rings, which characterized by sufficient size in position -5 that closely related to Meloxicam which is preferential selective COX-2 inhibitor (except compound 10).

The result presented in the pharmacological section suggest that compound 13 in this novel series possess a profound anti–inflammatory activity with no or negligible ulcerogenic activity. The above observations indicate selectivity to inhibit COX2 enzyme.

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