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Synthesis and Pharmacological Evaluation of Fenamate Analogues: 1,3,4-Oxadiazol-2-ones and 1,3,4- Oxadiazole-2-thiones

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Abstract

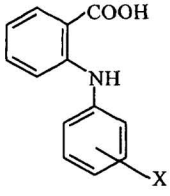
A series of fenamate pyridyl or quinolinyl analogues of 1,3,4-oxadiazol-2-ones **5a-d** and **6a-r,** and 1,3,4-oxadiazole-2-thiones **5e-g** and **6s-v,** respectively, have been synthesized and evaluated for their analgesic (hot-plate) , antiinflammatory (carrageenin induced rat's paw edema) and ulcerogenic effects as well as plasma prostaglandin E_2 (PGE_2) level. The highest analgesic activity was achieved with compound **5a** (0.5 ,0.6 ,0.7 mmol/kg b.wt.) in respect with mefenamic acid (0.4 mmol/kg b.wt.). Compounds **6h, 6l and 5g** showed 93, 88 and 84% inhibition, respectively on the carrageenan-induced rat's paw edema at dose level of 0.1mmol/kg b.wt, compared with 58% inhibition of mefenamic acid (0.2mmol/ kg b.wt.). Moreover, the highest inhibitory activity on plasma PGE_2 level was displayed also with **6h, 6l** and **5g** (71, 70, 68.5% respectively, 0.1mmol/kg b.wt.) compared with indomethacin (60%, 0.01 mmol/kg b.wt.) as a reference drug. In addition **6i, 6k, 6p, 6r, 6t** and **6v** were devoid of any ulcerogenicity.

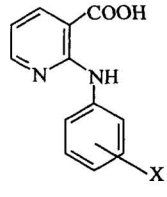
Keywords:

Analgesics; nonsteroidal antiinflammatories; 1,3,4-oxadiazol-2-ones and 2-thiones; fenamate analogues

Introduction

Many nonsteroidal antiinflammatories (NSAIDs) are now widely used in the treatment of inflammatory disorders. However , despite their wide spread use , none of the presently available agents are ideal , each has its shortcoming [1]. The need for more effective and safer agents for treating inflammatory conditions is reflected in the growing list of new compounds undergoing clinical trials.The fenamates represent a class of NSAIDs that share as their common structural feature an N-arylanthranilic acid [2]. Their mechanism of action is inhibtion of cyclooxygenase (COX) activity and thereby the production of prostaglandins [3]. The fenamates are differentiated by their aryl substituents as shown by meclofenamic acid (**1a**) [4], mefenamic acid (**1b**) [5] and flufenamic acid (**1c**) [6]. The most active derivatives have substituents at positions 2 , 3 and 6 of the ring attached to the anthranilic acid nitrogen atom . Also, the pyridyl moiety of clonixin (**2a**) [7] and niflumic acid (**2b**) [8] can be considered isosteric to the aryl one of fenamic acid derivatives.

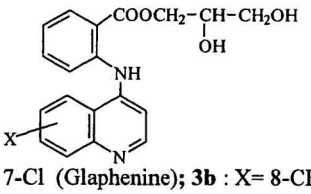




1a: X=2,6-Cl_2, 3-CH_3 (Meclofenamic acid)
1b: X= 2,3-$(CH_3)_2$ (Mefenamic acid)
1c: X=3-CF_3 (Flufenamic acid)

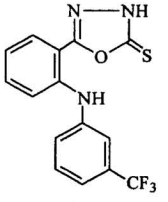
2a: X=2-CH_3, 3-Cl (Clonixin)
2b:X= 3-CF_3 (Niflumic acid)

Despite the significant potency exhibited by these fenamates, they display various side effects as gastrointestinal disturbances, ulcerogenicity [9] and renal toxicity [10]. Thus, among the attempts to achieve safer agents is the esterification of the carboxylic function. This is well represented by glaphenine (**3a**) [11] and floctaphenine (**3b**) [11], in which the N-aryl ring of fenamic acid is replaced by the substituted heterocylic quinolinyl moiety.

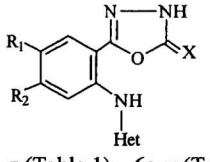


3a : X= 7-Cl (Glaphenine); **3b** : X= 8-CF_3 (Floctaphenine

Further development in this area is extended through search for other active heterocylic biological isosteres of N-arylanthranilic acid. Thus, the replacement of the carboxylic acid functionality of several fenamates with acidic heterocyles e.g. 1,3,4-oxadiazole-2-thione **4** provided dual inhibitor of cylooxygenase and 5-lipooxygenase enzymes [12].



4

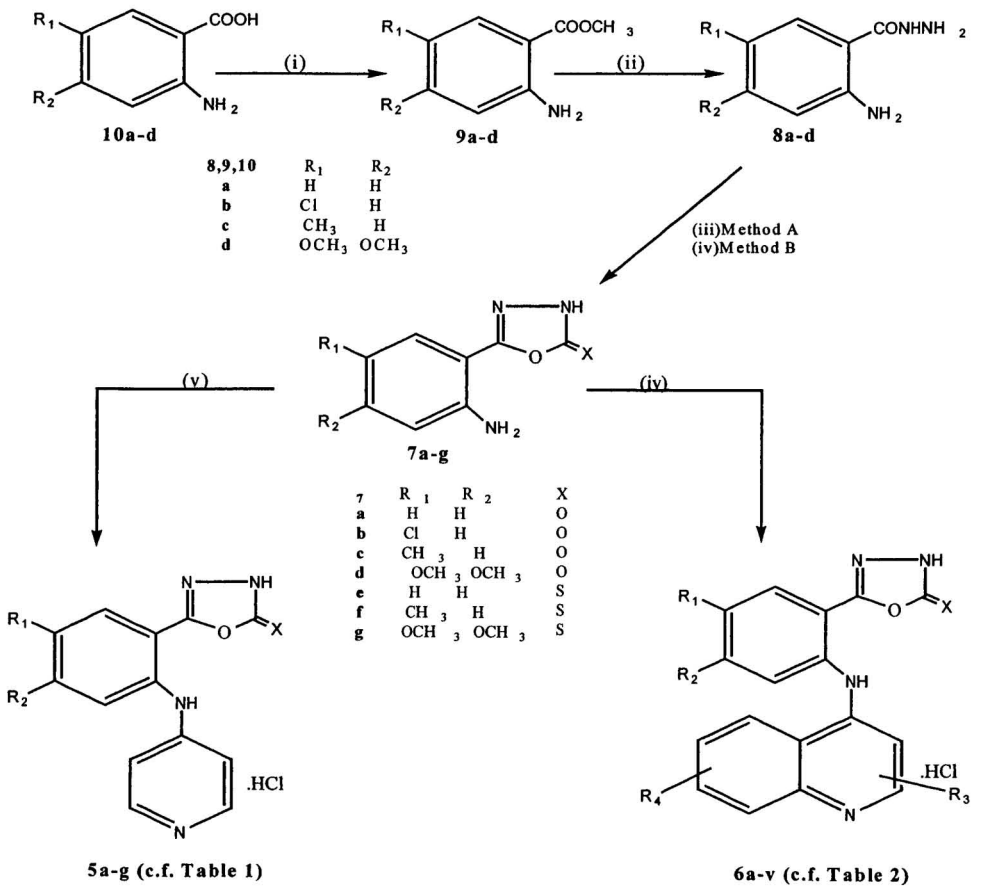


5a –g (Table 1), **6a-v** (Table 2)
X = O or S R_1R_2 = H, Cl, CH_3, OCH_3
Het = 4-pyridyl (**5a-g**), 4-quinolinyl (**6a-v**)

All these premises focused the intense interest for the search of novel analgesic and antiinflammatory agents that belong to the class of fenamates having the general framework **5** and **6** in order to modulate the biologic effects and abolish others.

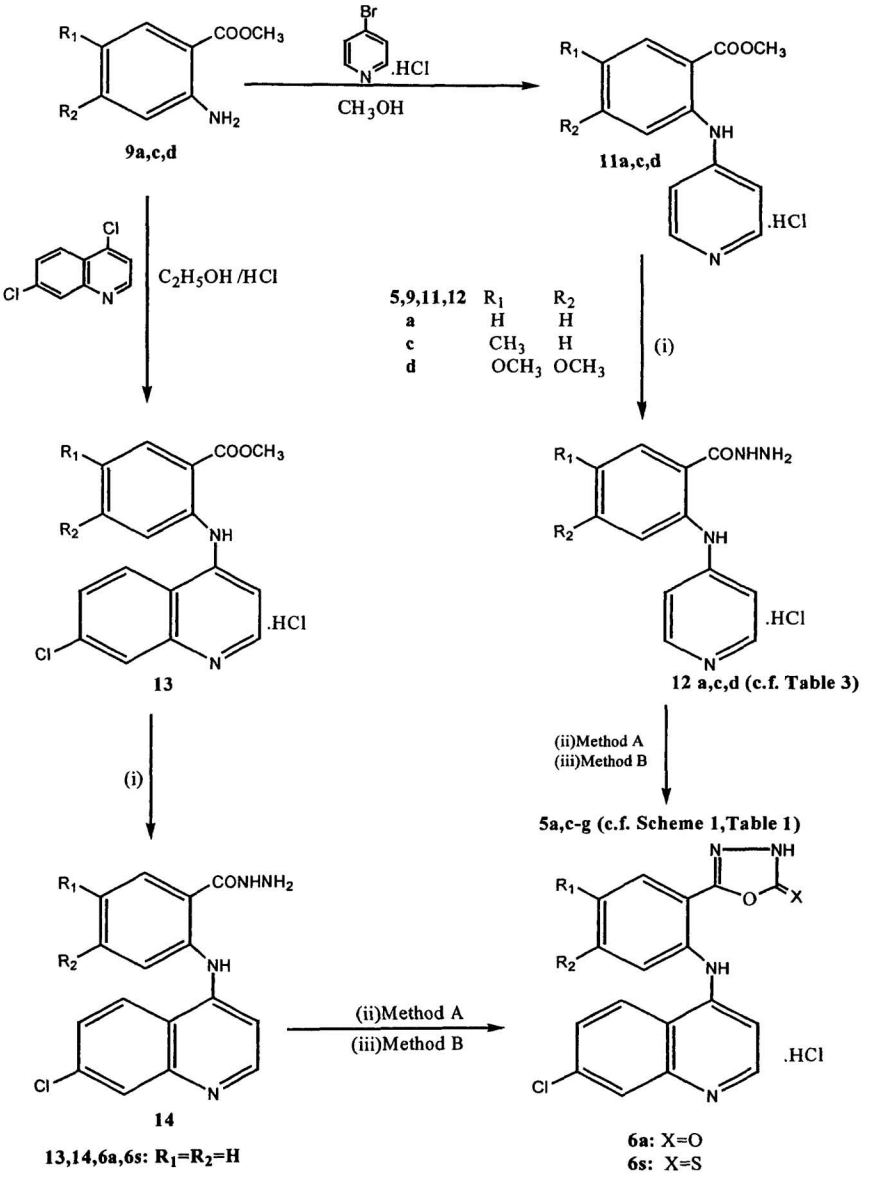
The synthesis and pharmacological screening of the analgesic, antiinflammatory activities, as well as the ulcerogenic effect of series of: a): 5-[2-(4-pyridyl) aminoaryl]-1,3,4-oxadiazol- 2(3H)-ones **(5a-d)** and–2(3H)-thione analogues **(5e-g)** ; b):5-[2-(4-quinonalinyl) aminoaryl] 1,3,4-oxadiazol- 2(3H)-ones **(6a-r)** and –2(3H)-thione analogues **(6s-v),** have been carried out. The synthetic pathways are illustrated in Schemes1 and 2.

Scheme 1[a]



[a]Reagents:(i) $CH_3OH/SOCl_2$; (ii) NH_2NH_2(80%);(iii) Method A:carbonyldiimidazole , THF, X=O; (iv) Method B: CS_2, KOH/H_2O, ethanol ,X=S; (v) 4-bromopyridine HCl, ethanol, compounds **5a-d** when X=O, compounds **5e-g** when X=S; R_1=H, Cl, CH_3, R_2=H,OCH_3; (vi) 4-chloroquinoline derivatives, ethanol/HCl, compounds **6a-r** when X=O, compounds **6s-v** when X=S; R_1=H, Cl, CH_3, OCH_3; R_2=H, OCH_3; R_3= 2-CH_3, 3-$COOC_2H_5$; R_4= 7-Cl, 7-CF_3, 8-CH_3, 8-CF_3

Scheme 2 [a]



[a]Reagents:(i) NH_2NH_2(80%); Method A:carbonyldiimidazole , THF, **5a,c,d**; (ii) Method B: CS_2, KOH/H_2O, ethanol , **5e -g** .

Experimental

Chemistry:

All Melting points were determined with electrothermal capillary melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded as KBr pellets with Philips PU 9712-IR and FTIR spectrometers (300E Jasco Ishikawa-Cho, Tokyo, Japan) and values are presented in cm^{-1}. ^{1}H-NMR spectra were run on a Jeol Ex-270 MHz instrument (Jeol Ltd, Tachikawa, Tokyo, Japan) as solutions in DMSO-d_6, using tetramethylsilane (TMS) as an internal standard and chemical shift values are recorded in ppm on δ scales (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). The mass spectra were run on Finnigan Mat SSQ-7000 spectrometer, 70 eV. Elemental analyses were determined in the Microanalytical Centre, Cairo University,.

The methyl anthranilates 9b-d[13] (Scheme 1), were obtained according to the procedure cited in ref. [12]. A methanolic solution of the corresponding anthranilic acid derivative was refluxed for 14 h with thionyl chloride.

2-Aminobenzoic acid hydrazides 8a-d [14](Scheme 1).

To 0.032 mol of each of the methyl anthranilate esters **9a-d** was added 11ml (0.07 mol) of 80% hydrazine hydrate. The reaction mixture was refluxed overnight. After cooling, the required hydrazides **8a-d** were precipitated and purified by crystallization from 2-propanol. **8d:** m.p.129 °C, yield 95%, elemental analysis, calcd. for $C_9H_{13}N_3O_3$; C: 51.18; H: 6.20; N: 19.90. Found: C: 51.35; H: 6.41; N: 19.97.

General procedure for synthesis of 5-(2-aminoaryl)-1,3,4-oxadiazol-2(3H)-ones 7a-d [14]. **Method A** (Scheme 1)

A solution of 0.01 mol of each ofthe 2-aminobenzoic acid hydrazides **8a-d** in 30 ml of tetrahydrofuran, was heated under stirring to 40-50 °C, followed by portionwise addition of 1.78 g (0.011 mol) of carbonyldiimidazole during 15 min. Then, the reaction mixture was refluxed for 14h. Most of the organic solvent was distilled under reduced pressure, then water was added to precipitate **7a-d**, which were filtered and purified by crystallization from 2-propanol: water.**7d:**m.p.263 °C, yield 62%, elemental analysis, calcd. for $C_{10}H_{11}N_3O_4$: C: 50.63; H: 4.76; N: 17.71. Found: C: 50.76; H: 4.92; N: 17.54.

General procedure for the synthesis of 5-(2-Aminoaryl)-1,3,4-oxadiazole-2(3H)-thiones 7e-g [15]**. Method B** (Scheme 1)

To a solution of 1.4 g (0.025 mol) of potassium hydroxide in 5 ml water and 25 ml ethanol was added dropwisely under stirring and cooling (5 °C) a solution of 0.025 mol of the hydrazide **8a** or **8c-d** in 75 ml of ethanol. Carbon disulfide (0.55 ml, 0.027mol) was added to the previous mixture and the temperature was raised to 50-60°C during 1h and heating was continued overnight. The residual solid after concentration under reduced pressure was dissolved in water, neutralized with 2N hydrochloric acid to precipitate **7e-g**, filtered and purified by cystallization from methanol. **7g**: m.p.262 °C, yield 57 %, elemental analysis, calcd. for $C_{10}H_{11}N_3O_3S$: C: 47.42; H: 4.38; N: 16.59. Found: C: 47.53; H: 4.12; N: 16.76.

General procedure for synthesis of 5-[2-(4-Pyridyl) aminoaryl]-1,3,4-oxadiazol-2(3H)-ones (5a-d) and/or -2(3H)-thione analogues (5e-g) hydrochlorides, Scheme 1.

To a stirred solution of 0.01 mol of either **7a-d** or **7e-g** in 30 ml of absolute ethanol was added in portions 1.92 g (0.01 mol) of 4-bromopyridine hydrochloride. The reaction mixture was refluxed for 3h. The organic solvent was concentrated and the residual solid of either **5a-d** or **5e-g,** respectively, was crystallized from 2-propanol (c.f. Table 1).

General procedure for synthesis of 5-[2-(4-quinolinyl) aminoaryl]-1,3,4-oxadiazol-2(3H)-ones (6a-r) and/or -2(3H)-thione analogues (6s-v) hydrochlorides, Scheme 1.

A stirred solution of 0.01 mol of either **7a-d** or **7e-g** in 30 ml of absolute ethanol containing 1 drop of concentrated hydrochloric acid was heated gradually to 60 °C. The appropriate 4-chloroquinoline derivative (0.01mol) was added at once to the previous mixture, then refluxed for 3h. The formed yellow precipitate of either **6a-r** or **6s-v** was filtered and crystallized from 2-propanol: ethanol (c.f. Table 2).

2-(4-Pyridyl)aminobenzoic acid methyl ester hydrochlorides (11a,c,d) were synthesized according to the procedure cited in ref. [16] in 60-70% yields, (c.f. Scheme 2). **11c:** m.p.65 °C, yield 58%, elemental analysis, calcd. for $C_{14}H_{14}N_2O_2$.HCl : C: 60.33; H: 5.42; N: 10.05. Found : C: 60.47; H: 5.61; N: 10.17. **11d** : m.p.101 °C, yield 68%, elemental analysis, calcd. for $C_{15}H_{16}N_2O_4$.HCl: C: 55.48; H: 5.28; N: 8.63. Found : C: 55.57; H: 5.42; N: 8.80.

Hydrazides of 2-(4-Pyridyl) aminobenzoic acids (12a,c,d).

A mixture of 0.01 mol of the appropriate 2-(4-pyridyl) amino benzoic acid methyl ester **11a,c,d** and hydrazine hydrate (80%, 10 ml, 0.07 mol) was heated to reflux overnight. After cooling, the appropriate hydrazide **12a,c,d** was precipitated, filtered and crystallized from 2-propanol (c.f. Table 3 , Scheme 2).

5- [2- (4-Pyridyl) aminoaryl] - 1,3,4- oxadiazol- 2(3H) - ones (5a,c and d), Method A (Scheme2) were prepared as described under **7a-d** starting from the appropriate hydrazide **12a,c,d** (c.f. Table 1).

5- [2- (4-Pyridyl) aminoaryl] - 1,3,4- oxadiazole – 2(3H) - thiones (5e-g), Method B (Scheme2), were prepared as described under **7e-g** starting from the appropriate hydrazide **12a,c,d** (c.f. Table 1).

Pharmacology:

1.Analgesic activity:

The analgesic effect of the prepared compounds **5a-g** and **6a-v** was investigated using the hot-plate method[17]. The method depends on observing the normal response to a pain stimulus in untreated animals and comparing it with the response to the same stimulus after the administration of the tested compound at definite time intervals. The mouse response to heat is a convenient application of this principle. The mice were dropped gently in a dry glass beaker of one litre capacity maintained at 55-55.5°C. The normal reaction time in seconds for all animals was determined. The tested compounds **5a-g** and **6a-v** in doses of 0.5,0.6 and 0.7 mmol/kg b.wt. as well as mefenamic acid in a dose of 0.4 mmol/kg b.wt. as reference drug were subcutaneously (s.c.) administered in groups of mice (n=6) as an aqueous suspension in 7% tween-80 and the reaction time was re-determined at 10,20, 30,45 and 60 minutes intervals. Thereafter, the relative potency as well as the duration of action of the test compounds was compared with that of the standard drug.

2.Antiinflammatory activity:

The inhibitory activity of the tested compounds on carrageenan-induced rat's paw edema were determined according to the method of Winter *et al*[18]. Groups of adult male albino rats (120-160 g) of 6 animals each were fasted for 18 h before beingorally dosed with the tested compounds **5a-g** and **6a-v** in a dose of 0.1 mmol/kg b.wt.[19] (as aqueous suspension in 7% tween 80) one hour before carrageenan challenge. Foot paw edema was induced by subplanter injection of 0.05ml of 1% suspension of carrageenan in saline into the plantar tissue of one hind paw. An equal volume of saline was injected into the other hind paw and served as control. Four hours after compound administration, the animals were decapitated, blood samples were collected and the paws were rapidly excised. The average weight of edema was estimated for the treated as well as the control groups and the percentage inhibition of weight of edema was also evaluated [20]. Mefenamic acid (0.2 mmol/kg b.wt.)[21] was employed as standard against which the tested compounds were compared.

3.Estimation of Plasma Prostaglandin E_2 (PGE_2):

Plasma was separated from heparinized blood collected from rats (n=6) by centrifugation at 12000g for 2 minutes at 4°C and immediately stored frozen at -20°C until assayed. The Assay Designs'Correlate-EIA Prostaglandin E_2 (PGE_2) Kit is a competitive immunoassay for the quantitative determination of PGE_2 in biological fluids [22]. The kit uses a monoclonal antibody to PGE_2 to bind, in a competitive manner, the PGE_2 in the sample. After simultaneous incubation at room temperature, the excess reagent was washed away and substrate was added. After a short incubation time, the enzyme reaction was stopped and the yellow colour generated was read on a microplate reader (DYNATECH, MR 5000) at 405 nm. The intensity of the bound yellow colour is inversely proportional to the concentration of PGE_2 in either standards or samples.

4-Ulcerogenic effect in rats:

Groups of adult male albino rats of six animals each (120-160 g), were fasted overnight, then orally given the tested compounds (0.1 mmol/kg b.wt.).Four hours later, animals were killed, their stomachs were removed, opened along the greater curvature, and

the number of ulcers were assessed by adopting the method of Corell *et al*[23].The results were compared with that of mefenamic acid (0.2 mmol/kg b.wt.) as reference drug.

Statistical and data analysis:

Data are expressed as means ± s.e.m. Statistical comparison between different groups was done using one way analysis of variance (ANOVA), followed by multiple comparison test (post hoc LSD). Significance was accepted at $p < 0.05$.

Results and Discussion

1. Synthesis:

In Scheme 1, the methyl anthranilate esters **9a-d** were prepared from their corresponding anthranilic acid derivatives **10a-d** by treating with $SOCl_2$ in methanol [13], which were converted to the corresponding hydrazides **8a-d** [14] by heating with hydrazine hydrate in methanol. Compounds 5-(2-aminophenyl)-1,3,4-oxadiazol-2(3H)-ones **7a-d** [14] were obtained in 60-83% yields by reaction of the hydrazides **8a-d** in THF with 1,1-carbonyldiimidazole (Method A). On the other hand, treatment of the hydrazides **8a,c** or **d** with carbon disulfide under basic condition (Method B) afforded the corresponding 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3H)-thiones **7e-g** [15] in 58-65% yields. The target compounds **5a-g** (Table 1) and **6a-v** (Table 2) were achieved by refluxing either 4-bromopyridine hydrochloride or 4-chloroquinoline derivatives with **7a-g** in an ethanolic solution, respectively; while catalytic amount of HCl was added in case of **6a-v** (Scheme1). Several trials failed to convert the N-(7-chloroquinoline) anthranilic acid hydrazide **(14)** to the target compounds **6a** or **6s** *via* Methods A or B, respectively, (Scheme 2), due to the difficulty of solubility of **14** in various solvents. On the other hand, the desired 2-(4-pyridyl) aminophenyl-1,3,4-oxadiazol-2(3H)-ones **5a** and thiones **5c-g** were achieved in good yields (Scheme 2 ,Table 1) through the reactions of 2-(4-pyridyl) aminobenzoic acid hydrazides **(12a,c,d** , Table 3) either with 1,1-carbonyldiimidazole in THF (Method A) or carbon disulfide in ethanolic aqueous KOH (Method B). The IR spectra of 1,3,4-oxadiazol-2(3H)-ones **5a-d** and **6a-r** showed a strong C=O absorption bands near 1790 cm^{-1}, while the 2(3H)-thiones **5e-g** and **6s-v** exhibited C=S absorption

bands at 1125 –1140 cm^{-1}. Furthermore, the ^1H NMR data of **5** and **6** (Tables 4 and 5) showed the NH signal of 1,3,4-oxadiazol–2(3H)-ones and 2(3H)-thiones at δ 12.00-12.80 and δ 14.25- 14.55 ppm, respectively (and were exchangeable with D_2O). The mass spectra of **5** and **6** revealed compatible molecular ion peaks (Tables 4 and 5).

2.Pharmacology:

2.1. Analgesic activity

The data presented in Table 6 revealed the analgesic activity of both the pyridyl **5a-g** and quinolinyl **6 a-v** series. Compound 2-(4-pyridyl) aminophenyl-oxadiazol-2(3H)-one **(5a)** was the most active one in the pyridyl series **5a-g** (Fig. 1). The analgesic activity of the pyridyl oxadiazol-2-ones **5a-d** was arranged in the following decreasing order :**5a>5b>5d**, while compound **5c** lacked the analgesic activity. Concerning the pyridyl oxadiazole-2-thiones **5e-g,** the 5-methylphenyl substituent **5f** displayed the highest analgesic activity. The analgesic potential was arranged in the following decreasing order: **5f >5g >5e.** Regarding the analgesic activity of the quinolinyl oxadiazol-2-ones **6a-r**, it was found that compound **6i** was the most active one, where both the phenyl and quinolinyl rings are substituted with 5-Cl and 7-CF_3, respectively. Meanwhile, compounds **6k** and **6o** were devoid of any activity. The analgesic effect of the different congeners of this group was arranged in the following decreasing order: **6i> 6q> 6p> 6e=6c> 6r=6d> 6a =6l=6n> 6m=6f> 6h> 6b> 6j.** Concerning the quinolinyl oxadiazole - 2- thiones **6 s-v,** compound 8 - trifluoromethyl-quinolinyl oxadiazole-2-thione **6v** was the most active one. The analgesic activity of the other congeners was arranged in the following order: **6v>6s>6u>6t.** Conclusively, analgesic activity was augmented by the pyridyl oxadiazol-2-one and 2-thione moieties, in addition to the trifluoromethyl quinolinyl one as achieved with compounds **5a > 5f >6i >6v,** respectively at a dose level of 0.6 and 0.7 mmol/kg b.wt. , 30 to 45 min from compound administration. Their analgesic activities were higher than that of mefenamic acid (0.4 mmol/kg b.wt.) used as reference drug.

2.2. Antiinflammatory activity

The evaluation of the antiinflammatory activity of the pyridyl **5a-g** and quinolinyl **6a-v** series was illustrated in Table 7. In the pyridyl oxadiazol-2-ones **5a-d,** compound 5-[4,5-dimethoxy-2-(pyridin-4-ylamino)-phenyl]-3H-[1,3,4]-oxadiazol-2-one (**5d**) was the most active one and showed higher inhibitory activity (76%, 0.1 mmol/kg b.wt.) compared with mefenamic acid as reference drug (58%,0.2 mmol/kg b.wt.).The antiinflammatory activity of the other congeners was arranged in the following decreasing order: **5d >5a >5c >5b.** Regarding the pyridyl oxadiazole-2-thiones **5e-g,** the 4,5-dimethoxy substituent of the phenyl moiety in **5g** augmented the inhibitory activity (84%, 0.1 mmol/kg b.wt.) compared with mefenamic acid. The other congeners showed decrease in the antiinflammatory activity in the following order: **5g > 5f >5e.** On the other hand, in the quinolinyl oxadiazol-2-ones **6a-r,** both the 5-chloro phenyl and the 7-chloro, 3-ethoxycarbonyl quinolinyl moieties of **6h** potentiated the inhibitory effect (93%, 0.1 mmol/kg b.wt.) compared with mefenamic acid value. Moreover, compounds **6a-r** significantly decreased the edema of the rat's paw in the following order: **6h >6l >6d >6o >6b >6f >6e >6i >6a >6p >6k >6r >6n >6m >6g >6c >6j >6q.** Concerning the quinolinyl oxadiazole-2-thiones **6s-v,** compound **6t** was the most effective analogue, where the quinolinyl moiety is substituted with ethoxycarbonyl and chloro groups in the 3 and 7 positions, respectively. It exhibited inhibitory activity (67%, 0.1 mmol/kg b.wt.) superior to mefenamic acid value as reference drug .The antiinflammatory activity was arranged in the following decreasing order : **6t > 6s > 6u > 6v.** Conclusively, the highest antiinflammatory activity was achieved with compounds **6h, 6l, 5g, 6d** (93, 88, 84 and 81%), respectively (c.f. fig. 2) using mefenamic acid as reference standard.

2.3. Plasma prostaglandin E_2 (PGE_2) level

The data presented in Table 8, illustrate the effect of compounds **5a-g** and **6a-v** on plasma PGE_2 level. In the pyridyl oxadiazol-2-ones **5a-d,** compound 5-[4,5-dimethoxy-2-(pyridin-4-ylamino) -phenyl] -3H-[1,3,4]-oxadiazol-2-one (**5d**) was the most active one, and possessed inhibitory activity 64% of control value. The effect of the analogues of this

group on plasma PGE_2 level was arranged in the following order: **5d>5a>5c>5b.** Concerning the pyridyl oxadiazole-2-thiones **5e-g,** compound 5-[4,5-dimethoxy-2-(pyridin-4-ylamino)-phenyl]-3H-[1,3,4]-oxadiazole-2-thione (**5g**) exhibited the highest inhibitory effect. It reaches 68% at a dose level of 0.1mmol/kg b.wt of control value, while indomethacin (0.01mmol/kg b.wt.), as reference drug, exhibited an inhibitory effect on plasma PGE_2 60% of control value. The different congeners of this group showed a decreased effect on plasma PGE_2 level as follows: **5g>5f>5e.** In the quinolinyl oxadiazole-2-ones **6a-r,** compound 5-[2-(7-chloro-3-ethoxy carbonyl -quinolin-4-ylamino)-phenyl]-3H-[1,3,4]-oxadiazol-2-one analogue (**6h**), showed the highest activity (71% at a dose level of 0.1 mmol/kg b.wt.) of control value, which was also superior to that of indomethacin (60%,0.01 mmol/kg b.wt.) as reference drug. The plasma PGE_2 level of **6a-r** was arranged in the following decreasing order: **6h> 6l> 6d> 6o> 6b> 6f> 6e> 6i> 6a> 6p> 6k> 6r> 6n> 6m> 6g> 6c> 6j> 6q**. Concerning the quinolinyl oxadiazole-2-thiones **6s-v** , the highest activity was achieved by 5-[2-(7- chloro-3-ethoxycarbonyl-quinolin-4-ylamino)-phenyl]-3H-[1,3 ,4]- oxadiazole -2-thione (**6t**), which induced an inhibitory effect about 62% at a dose level of 0.1 mmol/kg b.wt. of positive control value. Moreover, the plasma PGE_2 level in this group was arranged in the following decreasing order: **6t>6s>6u>6v**. In general, the highest inhibitory effect on plasma PGE_2 level was achieved with compounds **6h>6l>5g** (0.1 mmol/kg b.wt.) in the previous decreasing order (Fig. 3).

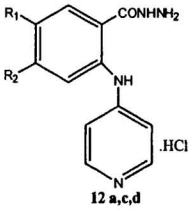
2.4. Ulcerogenic effect

The data presented in Table 7 showed the ulcerogenic effect of the pyridyl **5a-g** and the quinolinyl **6a-v** series compared with mefenamic acid as reference drug. In the pyridyl oxadiazol-2-ones **5a-d**, compound 5-[4,5- dimethoxy -2- (pyridin-4-ylamino)-phenyl]-3H-[1,3,4] oxadiazol-2-one (**5d**) exhibited the highest ulcerogenic effect. Moreover, **5a** and **5c** both had similar ulcerogenicity. Their ulcerogenic effect was arranged in the following decreasing order: **5d>5a=5c>5b**. Concerning the pyridyl oxadiazole-2-thiones **5e-g,** compound 5-[4,5-dimethoxy-2-(pyridin-4-ylamino)-phenyl]-3H-[1,3,4]-oxadiazole-2-thione (**5g**) possessed the highest ulcerogenicity .The different congeners showed a decrease in the ulcerogenic effect in the following order : **5g > 5f >5e**. Regarding the quinolinyl oxadiazol-2-ones **6a-r**, compound 5-[2-(7-trifluoromethyl-quinolin-4-ylamino)-phenyl]-3H-[1,3,4]-

oxadiazol-2-one (**6d**) exhibited the highest ulcerogenic effect. Furthermore, compounds **6l** and **6n** both had similar effects. Also compounds **6e, 6f, 6g** and **6o** possessed the same ulcerogenicity, as well as, **6b, 6j, 6m** and **6q** exhibited similar effects. On the other hand, compounds **6i, 6k, 6p** and **6r** were devoid of any ulcerogenic effect. The different congeners of this series showed a decrease in the ulcerogenic effect in the following decreasing order: **6d>6a>6l=6n>6h>6e= 6f=6g=6o>6b=6j=6m=6q=6c>6i=6k=6p=6r.** In the quinolinyl oxadiazole-2-thiones **6s-v**, the 5-[2-(7-chloro-quinolin-4-ylamino)-phenyl]-3H-[1,3,4]-oxadiazole-2-thione (**6s**) exhibited the highest ulcerogenic effect. On the otherhand, **6t** and **6v** were devoid of any ulcerogenic effect .The ulcerogenicity was arranged in the following decreasing order: **6s>6u>6t=6v.** Conclusively, compounds **6i, 6k, 6p, 6r, 6t** and **6v** were devoid of any ulcerogenicity, while mefenamic acid, (as reference drug) exhibited an ulcerogenic effect superior to that of the tested compounds.

In conclusion, the highest analgesic activity was achieved with the pyridyl oxadiazol-2-one **5a** (0.5, 0.6 and 0.7 mmol /Kg b.wt.). Also, the replacement of both the N-phenyl and carboxylic acid functions of mefenamic acid, with either substituted quinolinyl and oxadiazol-2-one moieties as represented with **6h** and **6l** or with pyridyl and oxadiazole-2-thione such as **5g,** augments the antiinflammatory activity compared with mefenamic acid as reference drug. Regarding the ulcerogenic effect of **5a, 6h** and **6l**, it was much less than that of mefenamic acid, while the same effect was observed with **5g**. Since the mechanism of action of the fenamates is inhibtion of cyclooxygenase (COX) activity and thereby the production of prostaglandins [3] and since carrageenan in the paw edema model, increases COX-2 and PGE2 level [1,24] and inflammation could be blocked by a selective COX-2 inhibitor [25, we can deduce from the present results that the most potent compounds under investigation may act through inhibition of COX-2.

Table 3: Hydrazides of 2-(4-pyridyl)aminobenzoic acids (12a,c,d) .



12 a,c,d

Compd. No.	R_1	R_2	m.p. °C	Yield %	Mol. Formula mol. mass	Analysis% Calc. (Found) C	H	N
12a	H	H	141	98	$C_{12}H_{12}N_4O$ 228.253	63.15 (63.26)	5.30 (5.42)	24.55 (24.34)
12c	CH_3	H	163	96	$C_{13}H_{14}N_4O$ 242.280	64.45 (64.64)	5.82 (5.79)	23.12 (23.33)
12d	OCH_3	OCH_3	190	90	$C_{14}H_{16}N_4O_3$ 288.305	58.33 (58.42)	5.59 (5.48)	19.43 (19.67)

Table 4: Spectroscopic data of compounds 5a-g

Compd. No.	IR(cm^{-1})	^1H NMR δ (ppm) (DMSO-d_6)	MS(m/z)
5a	3350(NH), 1790(C=O), 1610(C=C)	6.90-8.35(m ,8H[a]),10.46(s ,1H,NH[b]),12.73 (s ,1H,NH-hetero[b])	254 (M^+,$C_{13}H_{10}N_4O_2$, 88%)
5b	3345(NH), 1785(C=O), 1615(C=C)	6.90-8.35(m ,7H[a]),10.42(s ,1H,NH[b]),12.70 (s ,1H,NH-hetero[b])	288(M^+,$C_{13}H_9ClN_4O_2$, 22%)
5c	3340(NH), 1790(C=O), 1610(C=C)	2.21(s ,3H,CH_3),6.90-8.35(m ,7H[a]),10.46 (s ,1H,NH[b]), 12.73 (s ,1H,NH-hetero[b])	268(M^+,$C_{14}H_{12}N_4O_2$, 100%)
5d	3355(NH), 1790(C=O), 1610(C=C)	3.80(s ,3H,OCH_3),3.83(s ,3H,OCH_3),6.82-8.35 (m ,6H[a]), 10.43 (s ,1H,NH[b]),12.70 (br s ,1H,NH-hetero[b])	314(M^+,$C_{15}H_{14}N_4O_4$, 100%)
5e	3340(NH)),1610(C=C), 1130((C=S)	6.52-8.25(m ,8H[a]),10.45(s ,1H,NH[b]),14.38 (br s ,1H,NH-hetero[b])	270(M^+,$C_{13}H_{10}N_4OS$, 75%)
5f	3343(NH)),1610(C=C), 1125((C=S)	2.22(s ,3H,CH_3),6.90-8.35(m ,7H[a]),10.45 (s ,1H,NH[b]), 14.25(br s ,1H,NH-hetero[b])	284(M^+,$C_{14}H_{12}N_4OS$, 28%)
5g	3300(NH)),1615(C=C), 1140((C=S)	3.80(s ,3H,OCH_3),3.85(s ,3H,OCH_3),6.92-8.18(m ,6H[a]), 10.45 (s ,1H,NH[b]),14.36 (br s ,1H,NH-hetero[b])	330(M^+,$C_{15}H_{14}N_4O_3S$, 65%)

a: Aromatic protons
b: D_2O exchangeable

Table 5: Spectroscopic data of compounds 6a-v.

Compd. No.	IR (Cm^{-1})	1H NMR δ (ppm) (DMSO-d_6)	MS (m/z)
6a	3350 (NH), 1790 (C=O), 1610 (C=C)	6.50-8.85(m, 9H[a]), 11.21 (s, 1H, NH[b]), 12.60 (s, 1H, NH-hetero [b])	338 (M^+, $C_{17}H_{11}ClN_4O_2$, 100%)
6b	3358 (NH), 1790 (C=O), 1620 (C=C)	2.20(s, 3H, CH_3),2.61 (s, 3H, CH_3) , 6.42-8.55 (m, 8H[a]), 11.22 (s, 1H, NH[b]), 12.60 (s, 1H, NH-hetero [b])	332 (M^+, $C_{19}H_{16}N_4O_2$, 25%)
6c	3345 (NH), 1792 (C=O), 1735 (C=O, ester), 1610 (C=C)	1.33 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 7.31-9.10 (m, 8H[a]), 11.45 (s, 1H, NH[b]), 12.80 (s, 1H, NH-hetero [b])	410 (M^+, $C_{20}H_{15}ClN_4O_4$, 95%)
6d	3355 (NH), 1790 (C=O), 1615 (C=C)	6.65-9.30 (m, 9H[a]) 11.32 (s, 1H, NH[b]), 12.62 (s, 1H, NH-hetero [b])	372 (M^+, $C_{18}H_{11}F_3N_4O_2$, 93%)
6e	3352 (NH), 1790 (C=O), 1610 (C=C)	6.74-9.10 (m, 9H[a]), 11.32 (s, 1H, NH[b]), 12.61 (s, 1H, NH-hetero [b])	372 (M^+, $C_{18}H_{11}F_3N_4O_2$, 100%)
6f	3385 (NH), 1790 (C=O), 1610 (C=C)	6.81-8.93 (m, 8H[a]), 11.32 (s, 1H, NH[b]), 12.61 (s, 1H, NH-hetero [b])	373 (M^+, $C_{17}H_{10}Cl_2N_4O_2$, 21%)
6g	3350 (NH), 1792 (C=O), 1615 (C=C)	2.70 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 6.92-8.25 (m, 7H[a]), 11.31 (s, 1H, NH[b]), 12.78 (s, 1H, NH-hetero [b])	366 (M^+, $C_{19}H_{15}ClN_4O_2$, 30%)
6h	3355 (NH), 1792 (C=O), 1740 (C=O, ester), 1615 (C=C)	1.30 (t, 3H, CH_3), 4.31 (q, 2H, CH_2), 6.81-9.15 (m, 7H[a]), 11.00 (s, 1H, NH[b]), 12.80 (s, 1H, NH-hetero [b])	444 (M^+, $C_{20}H_{14}Cl_2N_4O_4$, 75%)
6i	3360 (NH), 1790 (C=O), 1610 (C=C)	6.94 -9.13 (m, 8H[a]), 11.32 (s, 1H, NH[b]), 12.73 (s, 1H, NH-hetero [b])	406 (M^+,$C_{18}H_{10}ClF_3N_4O_2$, 27%)
6j	3350 (NH), 1790 (C=O), 1625 (C=C)	6.50 -9.15 (m, 8H[a]), 11.25 (s, 1H, NH[b]), 12.65 (s, 1H, NH-hetero [b])	406 (M^+,$C_{18}H_{10}ClF_3N_4O_2$, 18%)
6k	3352 (NH), 1790 (C=O), 1620 (C=C)	2.45 (s, 3H,CH_3), 6.41-9.11(m, 8H[a]), 11.13 (s, 1H, NH[b]), 12.65 (s, 1H, NH-hetero [b])	352 (M^+, $C_{18}H_{13}ClN_4O_2$, 100%)
6l	3368 (NH), 1790 (C=O), 1735 (C=O, ester), 1610 (C=C)	1.30 (t, 3H,CH_2CH_3), 2.45 (s, 3H, CH_3), 4.31 (q, 2H, CH_2), 7.10-9.15 (m, 7H[a]), 11.15 (s, 1H, NH[b]), 12.71 (s, 1H, NH-hetero [b])	424 (M^+, $C_{21}H_{17}ClN_4O_4$, 92%)
6m	3350 (NH), 1790 (C=O), 1610 (C=C)	2.45 (s, 3H, CH_3), 6.65-9.21 (m, 8H[a]), 11.33 (s, 1H, NH[b]), 12.62 (s, 1H, NH-hetero [b])	386 (M^+, $C_{19}H_{13}F_3N_4O_2$, 100%)

Table 5: (cont.).

Compd. No.	IR (Cm^{-1})	1H NMR δ (ppm) (DMSO-d_6)	MS (m/z)
6n	3340 (NH), 1790 (C=O), 1615 (C=C)	2.45 (s, 3H, CH_3), 6.65-9.22 (m, 8H[a]), 11.26 (s, 1H, NH[b]), 12.63 (s, 1H, NH-hetero [b])	386 (M^+, $C_{19}H_{13}F_3N_4O_2$, 100%)
6o	3350 (NH), 1790 (C=O), 1620 (C=C)	3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.60-8.85 (m, 7H[a]), 11.25 (s, 1H, NH[b]), 12.26 (s, 1H, NH-hetero [b])	398 (M^+, $C_{19}H_{15}ClN_4O_4$, 100%)
6p	3340 (NH), 1790 (C=O), 1735 (C=O, ester), 1618 (C=C)	1.30 (t, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.31 (q, 2H, CH_2), 6.60-8.85 (m, 6H[a]), 11.32 (s, 1H, NH[b]), 12.25 (s, 1H, NH-hetero [b])	424 (M^+, $C_{22}H_{19}ClN_4O_6$, 100%)
6q	3355 (NH), 1790 (C=O), 1610 (C=C)	3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.60-8.85 (m, 7H[a]), 11.30 (s, 1H, NH[b]), 12.25 (s, 1H, NH-hetero [b])	432 (M^+, $C_{20}H_{15}F_3N_4O_4$, 25%)
6r	3350 (NH), 1790 (C=O), 1615 (C=C)	3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.65-8.80 (m, 7H[a]), 11.26 (s, 1H, NH[b]), 12.35 (s, 1H, NH-hetero [b])	432 (M^+, $C_{20}H_{15}F_3N_4O_4$, 17%)
6s	3345 (NH), 1610 (C=C), 1140 (C=S)	6.60-8.85 (m, 9H[a]) 11.32 (s, 1H, NH[b]), 14.13 (br s, 1H, NH-hetero [b])	354 (M^+, $C_{17}H_{11}ClN_4OS$, 100%)
6t	3380 (NH), 1735 (C=O ester), 1620 (C=C), 1140 (C=S)	1.30 (t, 3H, CH_3), 4.31 (q,2H, CH_2), 6.60-8.85 (m, 8H[a]), 11.40 (s, 1H, NH[b]), 14.32 (br s, 1H, NH-hetero [b])	426 (M^+,$C_{20}H_{15}ClN_4O_3S$, 24%)
6u	3355 (NH), 1615 (C=C), 1140 (C=S)	6.60-8.85 (m, 9H[a]) 11.32 (s, 1H, NH[b]), 14.13 (br s, 1H, NH-hetero [b])	388 (M^+, $C_{18}H_{11}F_3N_4OS$, 36%)
6v	3350 (NH), 1610 (C=C), 1140 (C=S)	6.61-8.85 (m, 9H[a]) 11.22 (s, 1H, NH[b]), 14.25(br s, 1H, NH-hetero [b])	388 (M^+, $C_{18}H_{11}F_3N_4OS$, 33%)

a : Aromatic protons
b : D_2O exchangeable

Table 6: Analgesic activity of compounds 5a-g and 6a-v in adult male albino mice after the respective time from compound administration.

Compd[b] No.	Time of administration in minutes[d]					
	0	10	20	30	45	60
Control	7.39 ± 0.73	7.67 ± 0.71[a]	7.78 ± 0.63[a]	7.76 ± 0.91[a]	7.75 ± 0.75[a]	7.79 ± 0.84[a]
Mefenamic acid[c]	7.50 ± 0.96	9.58 ± 0.71**	10.83± 0.62**	12.80± 0.76**	14.40 ± 1.00**	11.80± 0.73**
5a	7.85 ± 1.06	10.71± 1.04**	14.50±1.19**[a]	16.00±1.17**[a]	10.17 ± 1.08**[a]	10.00 ± 1.15**[a]
	8.89 ± 1.18	11.85± 1.12**	14.67±1.07**[a]	18.68± 1.13**[a]	15.00 ± 1.14**	13.25 ± 1.17**[a]
	8.17 ± 0.59	14.67± 1.38**[a]	18.76±1.38**[a]	22.00± 1.07**[a]	16.00 ± 1.15**	14.17 ± 1.19**[a]
5b	7.00 ± 0.56	8.80 ± 0.46	9.80 ± 0.79**	11.80± 1.08**	10.74 ± 1.09**[a]	8.47 ± 0.79[a]
	7.17 ± 0.62	9.20 ± 0.87*	12.14± 1.05**	14.40± 1.15**[a]	13.50 ± 1.13**	10.65 ± 1.09**
	7.88 ± 0.71	10.98± 0.98**[a]	14.00±1.17**[a]	16.35± 1.13**[a]	15.08 ± 1.28**	13.18 ± 1.11**
5c	7.40 ± 0.52	7.30 ± 0.48[a]	7.60 ± 0.68[a]	7.00 ± 0.67[a]	7.60 ± 0.59[a]	7.40 ± 0.66[a]
	8.50 ± 0.85	8.20 ± 0.68	8.40 ± 1.00[a]	8.20 ± 0.71[a]	8.50 ± 0.75[a]	8.40 ± 0.63[a]
	7.80 ± 0.74	7.60 ± 0.81[a]	7.40 ± 0.81[a]	7.43 ± 0.67[a]	7.60 ± 0.89[a]	7.60 ± 0.82[a]
5d	8.00 ± 0.87	10.00 ± 0.71**	11.17±0.99**	12.50 ± 0.92**	12.42 ± 0.97**[a]	11.60 ± 0.93**
	7.98 ± 0.76	11.00 ± 0.98**	12.00±1.03**	13.68 ± 1.17**	13.00 ± 1.14**	12.42 ± 0.97**
	8.95 ± 0.71	12.67 ± 1.05**[a]	14.00±1.26**[a]	14.67 ± 1.27**	14.35 ± 1.20**	13.00 ± 1.14**[a]
5e	7.52 ± 0.68	7.88 ± 0.85[a]	8.20± 0.79[a]	9.00 ± 0.71[a]	8.11 ± 0.60[a]	7.74 ± 0.63[a]
	7.71 ± 0.75	8.30 ± 1.12	9.60± 1.04**	10.59 ± 1.16**[a]	9.31 ± 1.07*[a]	8.33 ± 1.03[a]
	8.20 ± 0.78	9.98 ± 0.78**	11.00± 0.90**	12.98 ± 1.06**	10.51 ± 1.03**[a]	9.00 ± 0.88[a]
5f	7.31 ± 0.93	10.00 ± 0.85**	11.83 ± 1.22**	13.82 ± 1.33**	13.10 ± 1.19**	11.67 ± 1.18**
	8.57 ± 0.79	11.27 ± 1.33**[a]	13.85 ± 1.12**[a]	16.89 ± 1.18**[a]	14.29 ± 1.03**	11.83 ± 0.96**
	8.85 ± 0.83	13.80 ± 1.26**[a]	15.27 ± 1.37**[a]	20.17 ± 1.34**[a]	17.00 ± 1.27**[a]	15.50 ± 1.04**[a]
5g	7.93 ± 0.81	9.83 ± 0.87**	10.83 ± 0.70**	10.88 ± 0.84**	11.50 ± 0.64**[a]	11.00 ± 0.56**
	8.63 ± 0.69	10.83± 0.79**[a]	11.67 ± 1.02**	12.60 ± 1.04**	12.17 ± 1.04**[a]	11.33 ± 0.81**
	8.81 ± 0.75	12.67± 0.96**[a]	13.64 ± 0.48**[a]	14.83 ± 0.79**	14.00 ± 1.06**	13.10 ± 1.03**
6a	7.89 ± 0.78	8.83 ± 1.08	9.51 ± 0.89*	10.00 ± 0.89**[a]	11.90 ± 0.77**[a]	9.33 ± 0.63[a]
	8.13 ± 0.70	9.96 ± 1.01*	10.90 ± 1.05**	11.00 ± 0.93**	12.50 ± 1.09**	10.00 ± 1.03*
	8.41 ± 1.01	10.66± 1.13**	11.85 ± 1.08**	12.00 ± 0.77**	14.33 ± 1.18**	11.66 ± 1.16**
6b	7.20 ± 0.63	6.99± 0.63[a]	7.50 ± 0.61[a]	8.60 ± 0.60[a]	8.91 ± 0.11[a]	8.00 ± 0.69[a]
	8.19 ± 1.06	8.00± 0.64	8.80 ± 1.07[a]	9.42 ± 0.66[a]	10.00 ± 0.76*[a]	8.90 ± 0.77[a]
	6.89 ± 0.45	7.01± 0.90[a]	9.98 ± 0.86*[a]	11.00 ± 1.04**	11.80 ± 1.01**[a]	9.71 ± 0.86*[a]
6c	8.31 ± 0.78	9.33± 0.84*	9.83 ± 0.89**	11.17 ± 0.91**	12.00 ± 1.03**[a]	11.33 ± 0.96**
	7.98 ± 0.59	9.38± 0.82*	11.00 ± 0.73*	12.07 ± 0.89**	13.95 ± 1.09**	12.00 ± 0.82**
	8.33 ± 0.69	12.33± 0.78**[a]	14.00 ±1.15**	15.17 ± 0.91**[a]	16.50 ± 1.06**[a]	14.83 ± 1.08**
6d	8.17 ± 0.79	9.67± 0.89*	9.99 ± 0.78**	10.00 ± 0.52**[a]	10.50 ± 0.72**[a]	10.33 ± 0.76**[a]
	8.67 ± 0.80	10.00± 0.82**	11.17 ± 0.63**	11.50 ± 1.11**	13.00 ± 1.04**	11.95 ± 1.05**
	7.91 ± 0.64	11.17± 0.94**	12.17 ± 1.01**	13.50 ± 1.07**	15.00 ± 1.02**	13.67 ± 0.98**
6e	7.88 ± 0.71	9.67± 1.05	10.32 ± 0.92	11.18 ± 1.03**[a]	13.60 ± 0.89**	12.33 ± 1.03*
	8.31 ± 0.76	10.50± 1.05	11.83 ± 0.93**	12.97 ± 1.14**[a]	15.83 ± 1.06**	14.50 ± 0.85*[a]
	8.41 ± 0.64	11.00 ± 1.03**	13.00 ± 0.95**	14.33 ± 1.08**	16.67 ± 1.13**[a]	15.00 ± 1.13*[a]
6f	8.12 ± 0.76	9.21 ± 1.04*	9.80 ± 1.04**	10.17 ± 1.08**[a]	11.83 ± 0.99**[a]	9.58 ± 0.80*[a]
	8.51 ± 0.69	9.67 ± 0.87*	10.87 ± 0.66**	12.08 ± 0.99**	13.80 ± 1.03**	11.17 ± 1.03**
	7.92 ± 0.72	11.33 ± 1.05**	12.33 ± 0.64**	13.08 ± 0.40**	13.08 ± 1.07**	13.00 ± 1.08**
6h	7.33 ± 0.72	7.67 ± 0.96	8.50 ± 0.43[a]	9.00 ± 0.78[a]	9.83 ± 0.83*[a]	8.33 ± 0.62[a]
	8.50 ± 0.54	8.98 ± 0.87	9.00 ± 0.61*[a]	9.25 ± 0.96[a]	10.50 ± 0.81**[a]	8.83 ± 0.78[a]
	8.25 ± 0.99	9.38 ± 0.68*	9.58 ± 0.82**	10.67 ± 1.01**	12.50 ± 1.03**	10.83 ± 1.02*

Table 6 (cont.):

Compd[b] No.	Time of administration in minutes [d]					
	0	10	20	30	45	60
6i	8.31 ± 0.80 7.86 ± 0.63 8.00 ± 0.73	8.85 ± 0.47 8.96 ± 0.71 9.75 ± 0.71*	9.11 ± 0.74*[a] 10.67 ± 0.86** 11.95 ± 0.99**	10.00 ± 0.56*[a] 12.00 ± 1.05** 13.33 ±1.02**	13.87 ± 1.12** 14.88 ± 1.09** 18.17 ± 1.05**[a]	11.00 ± 1.05** 12.15 ± 1.07** 15.00 ± 0.86**[a]
6j	7.63 ± 0.87 7.58 ± 0.65 7.49 ± 0.59	7.37 ± 0.58[a] 7.92 ± 0.49[a] 8.83 ± 0.53	8.17 ± 0.58[a] 8.54 ± 0.61[a] 8.89 ± 0.53[a]	8.53 ± 0.73[a] 8.88 ± 0.63[a] 9.53 ± 0.78[a]	9.50 ± 0.72*[a] 9.83 ± 0.63*[a] 10.08 ± 0.69**[a]	8.17 ± 0.55[a] 8.43 ± 0.53[a] 9.07 ± 0.63[a]
6k	7.78 ± 0.49 7.28 ± 0.65 8.00 ± 0.68	7.29 ± 0.58[a] 7.80 ± 0.66[a] 8.60 ± 0.52	7.63 ± 0.48[a] 7.42 ± 0.51[a] 8.50 ± 0.63[a]	7.81 ± 0.68[a] 8.43 ± 0.55[a] 9.00 ± 0.81[a]	7.45 ± 0.71[a] 8.80 ± 0.62[a] 9.20 ± 1.01[a]	7.81 ± 0.44[a] 7.92 ± 0.66[a] 8.40 ± 0.59[a]
6l	8.00 ± 0.70 8.51 ± 0.62 8.24 ± 0.56	8.51 ± 0.59 9.17 ± 0.59* 10.00 ± 0.85**	9.68 ± 0.64* 10.10 ± 0.68** 10.83 ± 0.75**	10.33 ± 0.54*[a] 11.00 ± 0.71* 12.83 ± 0.98**	10.33 ± 0.53**[a] 12.51 ± 0.75** 14.33 ± 1.03**	8.59 ± 0.68[a] 10.00 ± 0.58* 11.75 ± 1.12**
6m	7.85 ± 0.49 8.36 ± 0.64 8.51 ± 0.71	8.17 ± 0.73 9.51 ± 0.82* 10.13 ±0.90*	8.45 ± 0.63[a] 10.53 ± 0.52** 11.50 ± 1.06**	8.60 ± 0.69[a] 11.25 ± 0.82** 12.00 ± 1.04**	9.17 ± 0.63*[a] 11.67 ± 0.76**[a] 13.33 ± 0.82**	8.67 ± 0.62[a] 10.50 ± 0.62** 11.08 ± 1.01**
6n	8.13 ± 0.83 8.08 ± 0.68 8.66 ± 0.54	8.70 ± 0.67 9.66 ± 0.71* 9.98 ± 0.86*	9.00 ± 0.68[a] 9.59 ± 0.89* 11.51 ± 1.03**	9.58 ± 0.78*[a] 10.33±1.03**[a] 12.00±1.08**	10.18 ± 0.98**[a] 12.50 ± 1.08** 14.16 ± 1.06**	9.14 ± 0.83[a] 10.00 ± 0.91* 11.69 ± 1.06**
6o	8.14 ± 0.71 7.68 ± 0.69 8.54 ± 0.78	7.93 ± 0.57 7.67 ± 0.56[a] 8.17 ± 0.79	8.33 ± 0.67[a] 7.71 ± 0.54[a] 8.67 ± 0.62[a]	8.67 ± 0.54[a] 7.91 ± 0.68[a] 8.81 ± 0.63[a]	8.83 ± 0.68[a] 8.17 ± 0.62[a] 9.00 ± 0.63[a]	7.96 ± 0.61[a] 7.65 ± 0.57[a] 8.33 ± 0.72[a]
6p	8.13 ± 0.71 7.99 ± 0.61 8.36 ± 0.90	9.00 ± 0.72 9.08 ± 0.81 10.67 ± 1.08**	10.10 ± 0.93** 11.13 ± 1.05** 11.83 ± 1.09**	11.33 ± 1.02** 12.17 ± 1.03** 14.67 ± 1.16**	12.33 ± 1.03**[a] 14.33 ± 0.87** 17.00 ± 1.07**[a]	11.83 ± 1.01** 12.00 ± 1.03** 14.50 ± 1.13**[a]
6q	8.50 ± 0.76 8.13 ± 0.65 8.34 ± 0.78	9.58 ± 0.80* 10.50 ± 1.03** 11.66 ± 0.80**[a]	9.98 ± 0.92* 11.85 ± 0.84** 12.76 ± 1.21**	11.80 ± 1.03** 12.66 ± 1.14** 15.75 ±1.09**[a]	12.00 ± 0.89**[a] 14.33 ± 1.15** 17.50 ± 1.14**[a]	10.50 ± 0.68** 12.33 ± 0.94** 13.50 ± 1.18**
6r	7.67 ± 0.65 8.33 ± 0.69 7.83 ± 0.78	9.26 ± 0.77* 10.00 ± 0.90** 10.98 ± 1.02**[a]	10.01 ± 1.01** 11.33 ± 0.61** 12.66 ± 0.85**	12.00 ± 1.01** 13.33 ± 0.88** 15.16 ± 1.17**[a]	12.33 ± 1.03**[a] 13.66 ± 1.06** 15.16 ± 1.17**	11.00 ± 0.90** 12.33 ± 1.00** 13.50 ± 1.07**
6s	8.67 ± 1.15 7.89 ± 1.14 8.78 ± 0.79	9.00 ± 1.08 11.33 ± 0.99**[a] 12.50 ± 1.13**[a]	9.50 ± 1.18* 12.33 ± 1.09** 15.83 ±1.11**[a]	10.67 ± 0.77**[a] 13.50 ± 1.16**[a] 16.17 ±0.91**[a]	9.50 ± 1.16*[a] 12.33 ± 1.10** 13.17 ± 0.87**	8.83 ± 0.70[a] 11.58 ± 1.18** 12.47 ± 1.08**
6t	6.80 ± 0.58 7.40 ± 1.16 8.60 ± 1.20	7.20 ± 0.85[a] 8.30 ± 0.78 10.10 ± 0.75**	8.80 ± 0.50[a] 9.20 ± 0.83* 10.40 ± 1.03**	9.00 ± 1.03[a] 9.60 ± 1.14*[a] 10.60± 1.06**	8.00 ± 0.58[a] 9.20 ± 1.13*[a] 10.00 ± 0.95**[a]	7.50 ± 0.55[a] 7.40 ± 0.25[a] 9.60 ± 0.51[a]
6u	7.10 ± 0.61 7.80 ± 1.02 8.20 ± 0.73	7.80 ± 0.62*[a] 8.00 ± 0.67 9.20 ± 0.80*	8.10 ± 0.70[a] 9.80 ± 0.81* 11.10 ± 1.11**	9.50 ± 0.72*[a] 10.80 ± 0.86** 13.61± 1.03**	9.00 ± 0.80[a] 10.60 ± 0.75**[a] 12.30 ± 1.04**	8.90 ± 0.69[a] 9.40 ± 1.01[a] 10.41 ± 1.21**
6v	8.30 ± 0.65 7.81 ± 0.59 8.60 ± 0.73	9.17 ± 1.05 11.33 ± 1.16**[a] 12.00 ± 1.18**[a]	10.51 ± 1.18** 12.67 ± 1.02**[a] 14.17 ±1.16**[a]	12.83 ± 1.19** 14.33 ± 1.15** 17.00± 1.14**[a]	11.17 ± 1.12 * 13.00 ± 1.07** 15.33 ± 1.13**	11.60 ± 1.21** 12.67 ± 1.01** 14.75 ± 1.22**[a]

* p<0.05 ** p < 0.01 compared with control value.

a p<0.05 å p< 0.01 compared with mefenamic acid (0.4 mmol / kg b.wt.) value

b At a dose level of 0.5, 0.6 and 0.7 mmol/ kg b.wt.

c Mefenamic acid at a dose level of 0.4 mmol/ kg b.wt.

d Each value represents the mean reaction time in seconds ±s.e.of the number of animals in each group (n=6).

Table7: Antiinflammatory activity and ulcerogenic effect of compounds 5a-g and 6a-v .

Compd[b] No.	Antiinflammatory Activity		Ulcerogenic effect
	%Increase in weight [d] of paw edema (g) $\bar{x}$±s.e.m.	% Inhibition	Ulcer number [e]
Control	60.59 ± 3.75	----------	0 ± 0 [å]
Mefenamic acid[c]	25.17 ± 2.58**	58.46	1.80 ± 0.18**
5a	20.10 ± 2.90**	66.82	0.83 ± 0.48*[a]
5b	35.14 ± 3.05**[å]	42.01	0.33 ± 0.21 [å]
5c	31.19 ± 3.29**	48.53	0.83 ± 0.22*[a]
5d	14.58 ± 2.17** [å]	75.93	1.40 ± 0.39*
5e	29.70 ± 3.63**	50.98	0.50 ± 0.22 [å]
5f	28.63 ± 3.58**	52.75	1.50 ± 0.66**
5g	9.44 ± 1.85** [å]	84.41	1.80 ± 0.58**
6a	28.58 ± 2.59**	52.83	1.00 ± 0.26**[a]
6b	16.49 ± 2.48**[a]	72.78	0.33 ± 0.21 [å]
6c	35.19 ± 2.74** [a]	41.91	0.17 ± 0.16 [å]
6d	10.97 ± 1.89** [å]	81.89	1.33 ± 0.42**
6e	24.63 ± 2.39**	59.24	0.50 ± 0.34 [å]
6f	22.29 ± 2.24**	63.21	0.50 ± 0.31 [å]
6g	34.98 ± 3.11** [å]	42.27	0.50 ± 0.28 [å]
6h	4.17 ± 2.26** [å]	93.12	0.67 ± 0.33* [å]
6i	27.93 ± 2.46**	53.91	0 ± 0 [å]
6j	37.25 ± 2.41** [å]	38.53	0.33 ± 0.21 [å]
6k	29.35 ± 2.29**[a]	51.56	0 ± 0 [å]
6l	7.24 ± 2.28** [å]	88.05	0.83± 0.31* [a]
6m	34.62 ± 3.72**[a]	42.87	0.33 ± 0.21 [å]
6n	32.37 ± 2.56** [å]	46.58	0.83 ± 0.30* [a]
6o	12.65 ± 1.79** [å]	79.13	0.50 ± 0.34 [å]
6p	28.91 ± 3.55**	52.28	0 ± 0 [å]
6q	37.86 ± 3.50** [å]	37.51	0.33 ± 0.21 [å]
6r	30.85 ± 3.64**	49.08	0 ± 0 [å]
6s	20.68 ± 2.62**	65.87	0.67 ±0.21* [å]
6t	20.09 ± 2.54**	66.85	0 ± 0 [å]
6u	23.12 ± 3.64**	61.84	0.17 ± 0.16 [å]
6v	29.39 ± 2.53**[a]	51.49	0 ± 0 [å]

* p< 0.05 ** p<0.01 compared with control value.
a p<0.05 å p<0.01 compared with mefenamic acid value.
b- At a dose level of 0.1 mmol/ kg b.wt.
c Mefenamic acid at a dose level of 0.2 mmol/ kg b.wt.
d Each value represents the mean ± s.e.m. of the number of animals in each group (n=6).
e Each value represents the mean (ulcer number) ± s.e.m.of the number of animals in each group (n=6).

Table 8: Effect of compounds 5a-g and 6a-v on plasma prostaglandin E_2 (PGE_2) level in adult male albino rats.

Compd[c] No.	PGE_2 (pg/ml)[d]	%Inhibition
Control	7.43 ± 1.03 [å]	-------
Indomethacin	2.94 ± 0.46**	60.43
5a	2.84 ± 0.37**	61.78
5b	3.78 ± 0.42**[a]	49.13
5c	3.60 ± 0.59**	51.55
5d	2.67 ± 0.45**	64.07
5e	3.53 ± 0.66**	52.49
5f	3.42 ± 0.58**	53.97
5g	2.34 ± 0.37**	68.51
6a	3.47 ± 0.50**	53.29
6b	2.79 ± 0.32**	62.45
6c	3.76 ± 0.41**[a]	49.39
6d	2.39 ± 0.39**	67.83
6e	3.21 ± 0.47**	56.79
6f	3.09 ± 0.55**	58.41
6g	3.76 ± 0.48**[a]	49.39
6h	2.13 ± 0.25**	71.06
6i	3.36 ± 0.42**	54.78
6j	4.13 ± 0.51** [å]	44.41
6k	3.52 ± 0.44**	52.62
6l	2.23 ± 0.39**	69.99
6m	3.68 ± 0.41**	50.47
6n	3.64 ± 0.45**	51.01
6o	2.46 ± 0.36**	66.89
6p	3.50 ± 0.47**	52.89
6q	4.37 ± 0.64** [å]	41.18
6r	3.58 ± 0.58**	51.82
6s	2.91 ± 0.40**	60.83
6t	2.84 ± 0.32**	61.78
6u	3.15 ± 0.58**	57.60
6v	3.52 ± 0.43**	52.62

** $p < 0.01$ compared with control value.

a $p<0.05$ å $p<0.01$ compared with indomethacin (0.01 mmol/kg. b.wt.) value

c At a dose level of 0.1 mmol /kg. b.wt.

d Each value represents the mean plasma PGE_2 (pg/ml) ± s.e.m.of the number of animals in each group (n=6)

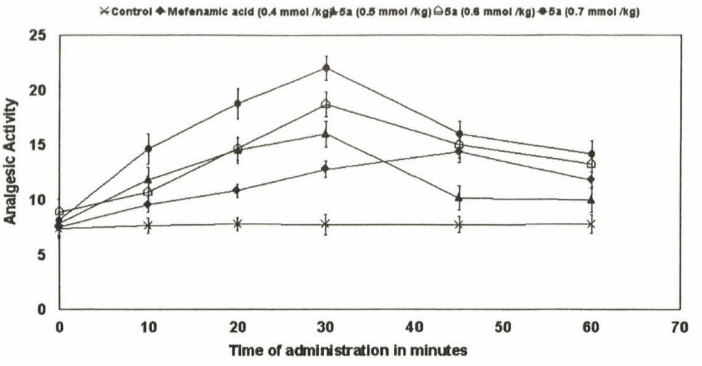


Fig.(1) : Analgesic activity of the most potent compound 5 a (0.5, 0.6, 0.7 mmol /kg b.wt.) after the respective time from compound administration.

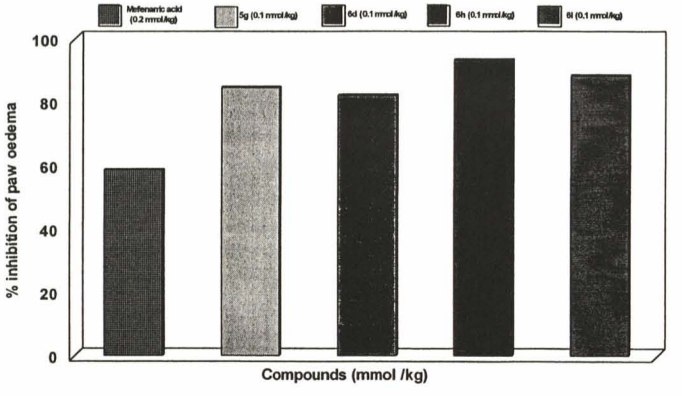


Fig.(2) :Antiinflammatory effect of the most potent compounds 6h,6l,5g and 6d(0.1 mmol/kg b.wt.).

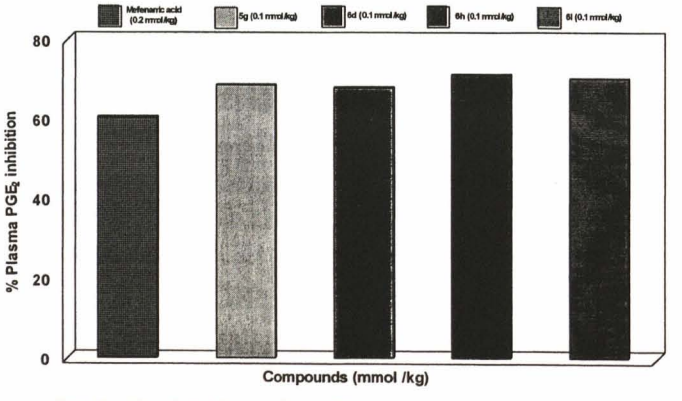


Fig.(3) : The inhibitory effect of the most potent compounds 6h,6l,5g and 6d(0.1 mmol/kg b.wt.) on plasma PGE_2 level.

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