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Review Article

DESIGN AND ANTIINFLAMATORY ACTIVITY OF SOME NOVEL OXADIAZOLE DERIVATIVES – AN OVERVIEW

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ABSTRACT

Oxadiazole derivates play vital role in biological field such as anti-microbial, anti-viral, anti-tubercular, anti-inflammatory and anti-convulsant activity. Therapeutic significance of these clinically useful drugs in treatment of inflammation encouraged the development of some more potent and significant compounds. oxadiazole derivatives are remarkably effective compounds for inflammation and analgesic activity. Extensive biochemical and pharmacological studies have confirmed that these molecules are effective in inflammation. This comprehensive overview summarizes the chemistry of different derivatives of substituted oxadiazole along with their anti-inflammatory activity.

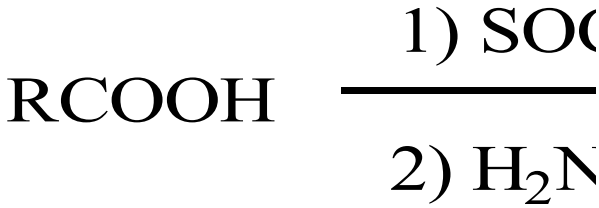
KEYWORDS: Oxadiazole derivatives, Chemistry, Design, Anti-inflammatory activity.

INTRODUCTION

Heterocyclic compounds containing the five-membered oxadiazole nucleus possess a diversity of useful biological effects. 1, 3, 4-Oxadiazole are important because of their versatile biological actions. In particular, compounds bearing the 1, 3, 4-oxadiazole nucleus is known to have unique antioedema and anti-inflammatory activities [1-4]. Differently substituted oxadiazole moieties have also been found to have other interesting activities such as analgesic [3-4], antimicrobial [5], antitubercular [6], anticonvulsant [7] and anti-hepatitis B viral activities [8]. Non-steroidal anti-inflammatory drugs NSAIDs form a class of therapeutic agents that are most widely used because of their anti-inflammatory, analgesic and antipyretic effects. The prevalent side effects of NSAIDs are the occurrence of gastrointestinal side effects like gastric upset, irritation and ulceration [9]. Substituted oxadiazole derivatives have been studied and proved to be potent CO/5-LO inhibitors [10-15]. This novel dual inhibitory activity of the enzyme pathways holds promise as anti-inflammatory agents with an improved efficacy and safety profile.

1. SYNTHESIS AND ANTIINFLAMATORY ACTIVITY OF SOME 1, 3, 4 OXADIAZOLE DERIVATIVES

A series of substituted 1, 3, 4-oxadiazole derivatives were synthesized as anti-inflammatory and analgesic agents. The target compounds were obtained by cyclodesulfurization of the corresponding thiosemicarbazides using either dicyclohexylcarbodiimide DCC, or I_2/NaOH. Intermediates thiosemicarbazides are readily accessible through conversion of the carboxylic acids to the respective hydrazides followed by treatment with appropriate isothiocyanate derivatives. The structures of the synthesized compounds were confirmed by elemental as well as spectroscopic analyses. The anti-inflammatory activity was investigated by determination of the inhibitory effects of the oxadiazole derivatives on histamine-induced edema in rat abdomen [10]



Synthesis of Substituted thiosemicarbazide derivatives (3)

To a solution of the acid hydrazide 2 (4.4 mmol) in hot ethanol (40 mL) was added equivalent amount of the appropriate isothiocyanate in ethanol (10 mL) and the

mixture was refluxed with stirring for 30 min. The products, which either precipitated during reflux or after cooling to room temperature, were-filtered and-crystallized from the proper solvent [10].

Synthesis of 2, 5-Disubstituted-1, 3, 4-oxadiazole derivatives (4)

To a stirred, cooled (0-5°C) solution of the respective thiosemicarbazide derivative (5 mmol) in ethanol (30 mL), was added 2N sodium hydroxide until the solution aquired pH 9. Iodine in potassium iodide solution (5%) was then added drop wise with stirring at room temperature until the yellow colour of iodine persisted. The solvent was removed under reduced pressure and the mixture cooled to precipitate the corresponding oxadiazole derivative. The products were then filtered, washed with water and carbon disulfide, dried and crystallized from the proper solvent [10].

Anti-inflammatory activity

The anti-inflammatory activity of the synthesized 1, 3, 4-oxadiazole derivatives 4a-4f was evaluated using Golikov's method [16]. Intradermally injected histamine was used as the phlogogenic substance and trypan blue (IV) as indicator. The increase in the time elapsed until the appearance of the blue colour at the site of injection of histamine v/s control was taken as a measure of the anti-inflammatory activity of the tested compounds and the reference standard drug (ibuprofen). Among the significantly active compounds, the oxadiazole derivatives 4a-4f were the most potent and exhibited higher anti-inflammatory activity than ibuprofen, the standard reference drug [10].

2. SYNTHESIS AND ANTIINFLAMATORY ACTIVITY OF SOME NOVEL 1, 3, 4 OXADIAZOLE DERIVATIVES

. Derivatization of the carboxylate function of some NSAIDs resulted in an increased anti-inflammatory activity with a reduced ulcerogenic effect. Hence, it is not irrelevant to speculate that replacing the terminal carboxylic function of 3-(4-bromobenzoyl) propionic acid by oxadiazole ring may enhance the anti-inflammatory activity of such compounds. Therefore, it was considered worthwhile to synthesize some new 3-(4-bromobenzoyl) propionic acid derivatives by incorporating the oxadiazolyl moiety to get better anti-inflammatory molecules [1]. A novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles (**4a-n**) have been synthesized from 3-(4-bromobenzoyl)propionic acid (**3**) with the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects (ulcerogenicity). Compound **3** was reacted with several aryl acid hydrazides (**2a-n**) in phosphorous oxychloride to obtain the title compounds.

Synthesis of 3-(4-Bromobenzoyl) propionic acid (Friedel-Craft's acylation reaction) (2)

To a solution of succinic anhydride (0.1mol) in bromobenzene (50 mL), anhydrous aluminium chloride (0.11mol) was added in small portions over a period of 2 h under stirring. The reaction mixture was then refluxed for two hours and after completion of the reaction, excess bromobenzene was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid so obtained was filtered, washed with cold water, dried and crystallized from methanol to give a cream colored product, which gave effervescence with sodium bicarbonate solution [1].

Synthesis of 2-[3-(4-Bromophenyl) propan-3-one]-5-(substituted phenyl)-1, 3, 4-oxadiazoles (3)

Appropriate aryl acid hydrazide (1 mmol) was dissolved in phosphorous oxychloride (5 mL) and 3-(4-bromobenzoyl) propionic acid (**2**) (1 mmol) was added. The reaction mixture, after refluxing for 5 h, was cooled to room temperature and poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20 %), a solid separated out and was filtered, washed with water and dried. It was crystallized from methanol to give 2-[3-(4-bromophenyl) propan-3-one]-(substituted phenyl)-1, 3, 4-oxadiazoles [1].

Anti-inflammatory activity

This activity was tested according to the Carrageenin-induced rat paw edema method on Wistar rats [17]. The rats were divided into thirteen groups of six animals each. Freshly prepared aqueous suspension of carrageenean (1 % *m*/*V*, 0.1 mL) was injected in the planta aponeurosis of the right hind paw of each rat. One group was kept as a control and the animals of other groups were pretreated with test

drugs (20 mg kg^{-1} body mass) given orally 30 minutes before carrageenean injection. The foot volume was measured before and 4 h after carrageenean injection with a plethysmograph. The mean increase in the paw volume in each group was calculated. Indomethacin and compound 3 were used as standard drugs for comparison. Two compounds, 2-[3-(4-bromophenyl)- propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole (3c) and 2-[3-(4-bromophenyl) propan-3-one]-5-(3,4-dimethoxy phenyl)-1,3,4-oxadiazole (3f) with anti-inflammatory activity of 59.5 and 61.9 %, respectively, were found to have comparable activity with that of indomethacin which showed 64.3 % activity at the same dose of 20 mg kg^{-1}.

3. SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF NOVEL S-SUBSTITUTED PHENACYL-1, 3, 4-OXADIAZOLE-2-THIOL

Synthetic approaches based upon chemical modification of NSAIDs have been taken with the aim of improving safety profile and in turn therapeutic window of this NSAID. Several studies have described the derivatization of the carboxylate function of representative NSAID with less acidic azoles, viz. 1, 3, 4-oxadiazole, Triazole, etc. which resulted in an increased anti-inflammatory activity with reduced ulcerogenicity. we have replaced the carboxylic acid group of diclofenac acid with less acidic heterocycle, 1,3,4-oxadiazole, in order to accentuate potency and reduce GI toxicities associated with the parent diclofenac due to its free –COOH group.

The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme prostaglandin endoperoxidase, popularly known as cyclo-oxygenase (COX) [18-20]. It was discovered that COX exists in two isoforms, COX-1 and COX-2, which are regulated and expressed differently [18, 21-23]. COX-1 provides cytoprotection in the gastrointestinal tract (GIT), whereas inducible COX-2 selectively mediates inflammatory signals [18, 24-25]. Since most of the currently available NSAIDs in the market show greater selectivity for COX-1 than COX-2 [18, 26]

Synthesis of 2-[(2, 6-dichloroanilino) phenyl] acetic acid (1)

Diclofenac sodium (0.101 mol) was dissolved in ethano (2.5 mol); to this solution conc.H_2SO_4 was added dropwise to hydrolyse the salt to acid. The acid obtained was filtered, dried mp 153–155 °C [18].

Synthesis of ethyl-[2-(2, 6-dichloroanilino) phenyl] acetate (2)

In a 500-ml round-bottomed flask place a mixture of 30 g (0.246mol) of diclofenac **1**, 80 g (101 ml, 2.5mol) of absolute methanol and 5 g (2.7 ml) of concentrated sulphuric acid. Add a few small chips of porous porcelain attach a reflux condenser and boil the mixture gently for 4 hours. Distil off the excess of alcohol on a water bath (rotary evaporator) and allow cooling. Pour the residue into about 250 ml of water contained in a separatory funnel and rinse the flask with a few ml of water which is also poured into the separatory funnel. If, owing to the comparatively slight difference between the density of the ester and of water, difficulty is experienced in obtaining a sharp separation of the lower ester layer and water, add 10-15 ml of carbon tetrachloride and shake the mixture in the funnel vigorously; upon standing, the heavy solution of methyl benzoate in the carbon tetrachloride separates sharply and rapidly at the bottom of the separatory funnel. Run off the lower layer carefully, reject the upper aqueous layer, return the methyl benzoate to the funnel and shake it with a strong solution of sodium hydrogen carbonate until all free acid is removed and no further evolution of carbon dioxide occurs. Wash once with water, and dry by pouring into a small dry conical flask containing about 5 g of magnesium sulphate. Stopper the flask, shake for about 5 minutes and allow standing for at least half an hour with occasional shaking. Filter the ethyl-[2-(2, 6-dichloroanilino) phenyl] acetate **2** through a small fluted filter paper directly into a round-bottomed flask fitted with a still-head carrying a 360 °C thermometer and an air condenser. Add a few boiling chips and distil from an air bath; raise the temperature *slowly* at first until all carbon tetrachloride has passed over and then heat more strongly. Collect the ethyl-[2-(2, 6-dichloroanilino) phenyl] acetate 2 (a colourless liquid) at 198-200 °C [27].

Synthesis of [2-(2, 6-dichloroanilino) phenyl] acetic acid hydrazide (3)

Compound **2** (0.01 mol) and hydrazine hydrate (0.02 mol) were refluxed in absolute ethanol (50 ml) for 20 h. The mixture was concentrated, cooled and poured in ice cold water. The solid thus separated out was filtered, dried and recrystallized from ethanol [28].

Synthesis of N-(4-Bromo benzylidenyl)-[2-(2, 6-dichloroanilino) benzyl carbazide (preparation of Schiff bases) (4)

A solution of 0.005mol of substituted benzaldehydes in ethanol was added a solution of 0.005mol of [2-(2, 6-dichloroanilino) phenyl] acetic acid hydrazide in 50 ml of ethanol. The mixture was refluxed on a water bath for 2–2.5 h. After cooling the mixture, the precipitate was filtered, dried and recrystallized from ethanol and purified by recrystallization from DMSO [29].

Synthesis of 5-[2-(2, 6-dichloroanilino) benzyl] 2-mercapto- 1, 3, 4-oxadiazole (5)

A mixture of **3** (0.005 mol), KOH (0.005 mol) and carbondisulphide (5 ml) in ethanol (50 ml) was refluxed on a steam bath for 12 h. The solution was then concentrated, cooled and acidified with dilute HCl. The solid mass that

separated out was filtered, washed with ethanol, dried and recrystallized from ethanol [18].

General procedure for the preparation of S-substituted phenacyl 1, 3, 4-oxadiazole-2-thiol (6a–d)

Substituted acetophenon and pyridine was taken in round bottom flask and refluxe for 5-8 hrs. The product was collected and recrystallized by suitable solvent [18].

Anti-inflammatory activity

Anti-inflammatory activity was evaluated using the well known Carrageenan induced rat paw oedema model [17] using groups of six animals each. A freshly prepared aqueous suspension of carrageenan (1.0% w/v, 0.1 ml) was injected in the sub-planter region of right hind paw of each rat. One group was kept as control and the animals of the other group were pretreated with the test drugs, 1 h before the carrageenan treatment. The volume was measured before and after carrageenan treatment at the 30 min. interval with the help of digital plethysmometer. Compounds 6a, 6b, 6c, and 6d exhibited very significant anti- inflammatory activity compared to standard drug diclofenac [18].

4. SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF FENBUFEN BASED 3-[5-(SUBSTITUTED ARYL)-1, 3, 4-OXADIAZOL-2-YL]-1-(BIPHENYL-4-YL) PROPAN-1-ONES

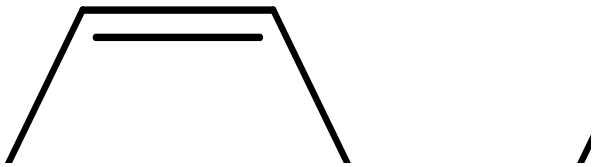
The synthesis of a series of 3-[5-(substituted aryl)-1, 3, 4-oxadiazol-2-yl]-1-(biphenyl-4-yl) propan-1-ones derived from 4-oxo-4-(biphenyl-4-yl) butanoic acid (fenbufen) is described. These compounds were tested for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation actions. Differently substituted oxadiazole moiety has also been found to have other interesting activities such as analgesic, antibacterial, antifungal, anticonvulsant, anticancer, etc. [30-35]. The carboxylic acid group of fenbufen has been replaced with an heterocyclic groups 1, 3, 4-oxadiazole [30].

Synthesis of 4-Oxo-4-(biphenyl-4-yl)butanoic acid (fenbufen) (2)

To a solution of succinic anhydride (0.1mol) in biphenyl (50 mL), anhydrous aluminium chloride (0.11mol) was added in small portions over a period of 2 h under stirring. The reaction mixture was then refluxed for two hours and after completion of the reaction, excess biphenyl was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid so obtained was filtered, washed with cold water, dried and crystallized from methanol to give a cream colored product, which gave effervescence with sodium bicarbonate solution [30].

General procedure for the synthesis of 3-[5-(substituted aryl)-1, 3, 4-oxadiazol-2-yl]-1-(biphenyl-4-yl) propan-1-ones (3a-3h)

Benzoic acid hydrazide derivatives (0.001 mol) were dissolved in phosphorous oxychloride (5 mL) and to it was added 3 (equimolar, 0.001 mol). The reaction mixture, after refluxing for 2–5 h, was cooled to room temperature and poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20% w/v) a solid mass separated out which was filtered, washed with water, dried and recrystallized from methanol to give 3a-3h [30].



Anti-inflammatory activity

Antiinflammatory activity test was performed by Carrageenan induced rat paw oedema model [17]. Freshly prepared suspension of carrageenan (0.05 mL, 1% w/v solution in 0.9% saline) was injected under the plantar aponeurosis of the right hind paw of each rat. Animals were divided in groups of six in each group. One groupwas kept as control and the animals of other groups were pre-treated with the test drugs suspended in 1% carboxymethylcellulose (CMC) given orally 30 min before carrageenan injection. The paw volume was measured before and after 4 h of carrageenan injection by plethysmograph. The percentage inhibition of inflammation was calculated by applying the following formula:

Antiinflammatory activity (% inhibition) = (Vc – Vt) /Vc X 100

Where Vc = edema volume in control group, Vt = edema volume in groups treated with test compounds.

Compounds 3a-3g was equipotent to fenbufen while 3h proved to be more potent than fenbufen, its anti-inflammatory activity being comparable with that of diclofenac. Data show that the presence of 2-naphtyloxymethyl, 4-methoxyphenyl or 3, 4-dimethoxy phenyl substitution at the 5 position of the oxadiazole ring can either maintain or improve the anti-inflammatory activity in this series of fenbufen derivatives [30].

5. SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 3-ARYL-5-DECAPENTYL-1, 2, 4-OXADIAZOLES

1, 2, 4-oxadiazoles having long fatty acid chain at C-5 have not been reported Therefore, it appeared attractive to undertake the synthesis of 1, 2, 4-oxadiazoles carrying a 15-carbon sidechain at C-5. In fact, these new heterocycles may be considered as isosters of palmitic acid esters and amides which possess interesting pharmacological properties. For example, *N*-(2-hydroxyethyl)palmitamide (PEA) helps to prevent acute respiratory diseases (ARD) in men [36-38]. It has also been shown that administration of PEA does not have any influence on the formation of antibodies [36, 39]. The production of palmitic acid ethyl ester (PAEE) in pregnant rat and its offspring was explored with interesting findings [36, 40]. Work on PEA considered this compound as a new class of anti-inflammatory agent and thought that PEA (an endogenous compound) is accumulated at the inflammation site and helps to suppress it [36, 41]. Very recently, identified the nuclear receptor peroxisome proliferator-activated receptor-a (PPAR) which secures the fatty acid amide (PEA) and causes the inflammation reduction[36, 42]. A recent publication also reports the anti-inflammatory activity of tri-terpene-fatty acid esters and free fatty acids [36, 43]. 1, 2, 4-Oxadiazoles with propyl and isopropyl functions at C-5 have been found to possess anti-inflammatory activity [36, 44-45]. The title compounds **4a–f** exhibited anti-inflammatory activity closely resembling to aspirin and ibuprofen.

Synthesis of 3-Aryl-5-decapentyl-1, 2, 4-oxadiazoles (4a–f)

An appropriate arylamidoxime 1 (1.0 mmol), palmitic acid 2 (1.0 mmol) and dicyclohexylcarbodiimide (1.25 mmol) were dissolved in dichloromethane (5.0 ml) and left under stirring for 6 h at room temperature under nitrogen atmosphere. TLC (cyclohexane/ethyl acetate, 9:1) confirmed the consumption of all arylamidoxime. Filtration of dicyclohexylurea and washing the solid with a little dichloromethane gave a transparent solution which contained largely the intermediate *O*-palmitoylbenzamidoxine (3a–f). Each intermediate was heated individually at 110 °C for about 6 h for complete cyclization. Further purification was achieved by passing the crude 1, 2, 4-oxadiazole through a column containing silica gel. The pure compound could be eluted with cyclohexane ethyl acetate (9.9:0.1). Thus, all Oxadiazoles 4a–f have been obtained in the pure form. The yields furnished below are of chromatographically pure compounds. Oxadiazoles 4a, d–f were crystallized and recrystallized from chloroform–*n*-hexane [36].

Anti-inflammatory activity

The anti-inflammatory activity was determined by Levy and Kerley method [46]. Three-month-old Swiss white mice with 25–30 g body weight were maintained with water and food. Ten groups, each containing 10 animals, were used separately for each experiment. Saline solution (0.9%) was administered to the control group. The drugs used for comparison purposes were aspirin and ibuprofen. All compounds were suspended in 1% carboxymethylcellulose (CMC) dissolved in water and a single dose of 250 mg kg^{-1} was administered intraperitoneally in the morning. Other animal group received 1% CMC only. Two positive and one negative anti-inflammatory test were done in three animal groups by intraperitoneal administration of 250 mg kg^{-1} of aspirin [47], in the first group, 250 mg kg^{-1} of ibuprofen in the second group and 0.9% of aqueous saline solution in the third group, respectively.. A 0.1 ml of 1% carrageenin in 0.9% aqueous NaCl solution was injected through the plantar tissue of the right hind paw of each mouse to produce inflammation. The test compounds were injected intraperitoneally 30 min later. After 4 h, their paws were cut and weighed. The results were analyzed according to the percentage of inflammation reduction.

All six compounds 4a–f are non-lethal in mice at four times the therapeutic dose (i.p., LD50 > 1 g kg^{-1}). Preliminary anti-inflammatory activity tests for compounds 4a–f exhibited positive results. Oxadiazoles 4a, 4e and 4f reduced carrageenan-induced edema in mice by 29, 33 and 34%, respectively. This result is significant ($P < 0.05$) compared to the control group treated with saline solution. However, compounds 4b, 4c and 4d, which have a *ortho*-, *meta*- and *para*-substituent in the phenyl ring did show a significant decrease in edema (55, 67 and 67%; $P < 0.001$) greater than the control animals treated with 0.9% saline or 1% CMC solution. Furthermore, the anti-inflammatory effect of compounds 4c and 4d were comparable with aspirin (68%) and ibuprofen (73%). Since compounds 4c and 4d gave the best acute anti-inflammatory activity, its dose–response curve was compared with ibuprofen which clearly shows that administration of 250 mg of compound 4c per kg of animal's body weight reduces the inflammation by 67%. This is closer to the value obtained by ibuprofen. Increasing the dose of 4c and 4d to 350 mg kg^{-1} of the animal's weight slightly improves the performance of these heterocycles and brings the activity very close to ibuprofen (70 and 73%).

6. SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF NOVEL 2-(1-ADAMANTYL)-5-SUBSTITUTED-1, 3, 4-OXADIAZOLES

Derivatives of adamantane have long been known for their antiviral activity against Influenza A [48-52] and HIV viruses [48, 53-55]. Anti-inflammatory and antimicrobial activities of novel series of 3-(1-adamantyl)-substituted-1, 2, 4-triazoline-5-thiones and 2-(1-adamantyl)-1, 3, 4-oxadiazolin-5-thiones, carrying an acetic or propionic acid moiety [48, 55]. Reaction of 1-adamantanecarbonyl chloride with certain carboxylic acid hydrazides in pyridine yielded the corresponding N-acyl adamantane- 1-carbohydrazide derivatives 3a-f, which were cyclized to the corresponding 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles 4a-f via heating with phosphorus oxychloride.

Synthesis of 2-(1-Adamantyl)-5-substituted-1, 3, 4-oxadiazoles

A mixture of 1-adamantanecarbonyl chloride 1 (1.99 g, 0.01 mol) and the appropriate carboxylic acid hydrazide 2 (0.01 mol), in dry pyridine (10 ml), was heated under reflux for 30 min. On cooling, the mixture was poured onto cold water (50 ml) and stirred for 10 min. The separated solid was filtered, washed thoroughly with cold water and dried to yield the N-acyl adamantane-1-carbohydrazide derivatives 3 in 90-95% yields. The products were pure enough to be used in the next step without further purification. The appropriate compounds 3 were added to phosphorus oxychloride (6 ml) and the mixture was heated under reflux for 1 h. On cooling, crushed ice (50 g) was added cautiously and the mixture was stirred for 30 min. The separated crude product was filtered, washed with water then with saturated sodium hydrogen carbonate solution and finally with water, dried and crystallized from ethanol to yield compounds 4a-f [48].

Anti-inflammatory activity

The acute anti-inflammatory activity of the synthesized compounds was determined following the carrageenin-induced paw oedema method in rats [26]. Each compound

was tested in three dose levels: 20, 40 and 60 mg/kg. The results of the anti-inflammatory activity of the synthesized compounds and the well-known anti-inflammatory drug Indomethacin (10 mg/kg). The majority of the oxadiazole derivatives 4a-f showed significant dose-dependent anti-inflammatory activity. The best activity was observed with the oxadiazole derivatives 4c, 4d, 4e and 4f which displayed strong dose-dependent inhibition of carrageenin-induced oedema producing >50% inhibition at 60 mg/kg dose. Meanwhile, the oxadiazole derivatives 4a, 4b were found moderately active producing <50% inhibition of carrageenin-induced oedema [48].

CONCLUSION

The oxadiazole ring is an important pharmacophore in modern drug discovery. In recent years, attention has increasingly been given to the synthesis of oxadiazole derivatives as a source of anti-inflammatory agents. The synthesis of novel oxadiazole derivatives remains a main focus of medicinal research. Since now, researchers have been attracted toward designing more potent oxadiazole derivatives having wide diverse of biological activity.

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