RESEARCH ARTICLE ISSN: 2349-2678

Contents lists available at www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

Volume 4 Issue 6; November-December; 2016; Page No.01-09

SYNTHESIS, CHARECTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF SUBSTITUTED 5-(5-SULFANYL-1,3,4 - OXADIAZOL-2-YL)BENZENE- 1,2,3-TRIOL DERIVATIVES

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ABSTRACT

All solvents were redistilled before use. Reactions were routinely monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour or UV light. A solution of propyl gallate(0.01 mol) in ethanol and hydrazine hydrate (0.01 mol) was refluxed for 4 hours. The excess solvent was distilled off under reduced pressure. The cooled residual mass was washed with distilled water. It was filtered and dried. The crude product was recrystallised from methanol to yield galloylhydrazide, Carbon disulfide (2 ml) was added drop wise to an ice cooled solution of KOH (2g) in ethanol (20 ml) containing the acid hydrazide 4 (0.02 mole), then the reaction mixture was stirred at room temperature 2h . After dilution with ethanol the solid precipitated was washed twice with ether. To the solid obtained (1 g), 10% KOH (20 ml) was added then the reaction mixture was refluxed for 4 hr, cooled, acidified with conc. HCl. The resulting solid was filtered washed with water, dried and crystallized. A mixture of (0.97g, 0.005mol) of 5-(5-sulfanyl- 1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol and (0.005mol) of different aryl or alkyl halides were refluxed in 25ml of pyridine solution for 3.5 hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol. Synthesized derivatives purity were checked by TLC, Melting point & characterized by FT-IR, Mass, NMR spectroscopic techniques. Synthesized derivatives were evaluated for anti-inflammatory activity.

Key words: Oxadiazole, Oxadiazole derivatives, convulsion, Anti-Inflammatrory activity.

1. INTRODUCTION:

Inflammation—" **Inflammation** (Latin, i*nflammo*,"I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.[1]

Inflammation is a protective immunovascular response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.[2]

Inflammation is tightly regulated by the body. Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (eg. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as ever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g.gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body.

Inflammation can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as *chronic inflammation*, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

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Various biological activities like antimicrobial, anti-tubercular, anti-inflammatory, Anticonvulsant[2], Hypnotic , Anesthetic activity[3].1,3,4-oxadiazoles showed antibacterial properties similar to those of well-known sulfonamide drugs. The oxadiazole nucleus with N=C-S linkage exhibits a large number of pharmacological activities.[4]Sulfone derivatives containing heterocyclic moiety are known for their interesting antifungal bioactivities and have attracted considerable attention in pesticide and medicinal formulation. A large number of report on their synthesis and biological activities have appeared during the last three years[5]

1.1 Causes of inflammation:[15]

Physical:

-Burns

-Frostbite

-Physical injury, blunt or penetrating

-Foreign bodies, including splinters, dirt and debris

-Trauma

-Ionizing radiation

Biological:

-Infection by pathogens

-Immune reactions due to hypersensitivity

-Stress

Chemical:

-Chemical irritants

-Toxins

-Alcohol

1.2 Anti-inflammatory:

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation or swelling. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system.

Non-steroidal anti-inflammatory drugs (NSAIDs):

Non-steroidal anti-inflammatory drugs (NSAIDs), alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own, COX enzyme synthesizesprostaglandins, creating inflammation. In whole, the NSAIDs prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain.

Some common examples of NSAIDs are: aspirin, ibuprofen, and naproxen. The newer specific COX-inhibitors are not classified together with the traditional NSAIDs even though they presumably share the same mode of action.

On the other hand, there are analgesics that are commonly associated with anti-inflammatory drugs but that have no anti-inflammatory effects. An example isparacetamol, called acetaminophen in the U.S. and sold under the brand name of Tylenol. As opposed to NSAIDs, which reduce pain and inflammation by inhibiting COX enzymes, paracetamol has as early as 2006 been shown to block the reuptake of endocannabinoids,[3,4] which only reduces pain, likely explaining why it has minimal effect on inflammation.

1.3 Mechanism of action:

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)isoenzymes. This inhibition is competitively reversible (albeit at varying degrees of reversibility), as opposed to the mechanism of aspirin, which is irreversible inhibition.[10]

2. MATERIAL & METHODS:

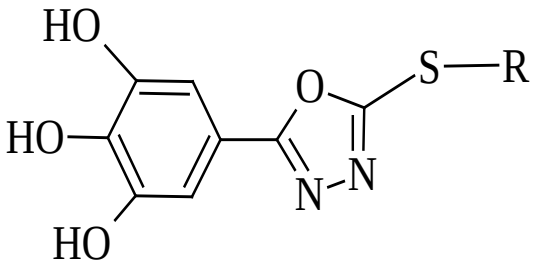
from literature review studies: the following requirement must be essential for anti-inflammatrory activity.

1. Oxadiazole Moiety.

2. Substituted Phenyl Ring at 2nd Position.

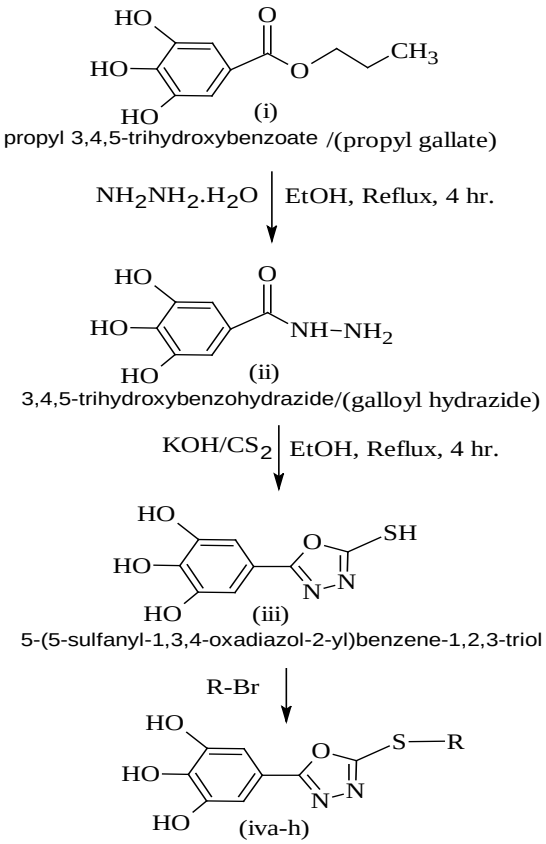
3. Substituted phenyl ring at 5th position (substitution)

4. Sulphur bridge



(Fig. 1 Target Molecule)

3. SYNTHETIC SCHEME:



Where **R**=
iva=Ar-CH_3**ivb**=Ar-OCH_3**ivc**=Ar-OH
ivd=Ar-NO_2**ive**=Ar-C_2H_5 **ivf**=CH_3**ivg**= -C_2H_5
ivh= C_3H_7 **ivi**=Ar-NH_2**ivj**=Phenyl

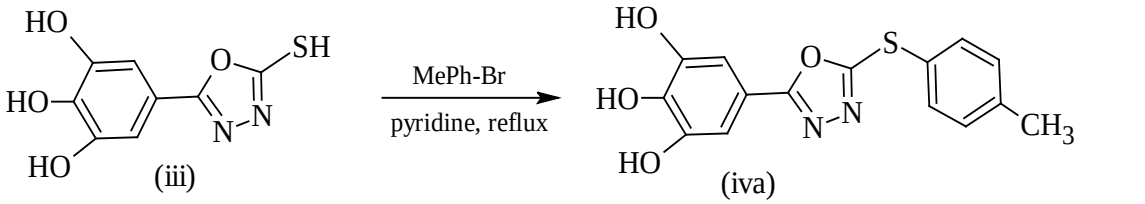
4. SYNTHETIC PROCEDURE:

4.1 General procedure for preparation of 5-[5-(substitutedsufanyl)-1,3,4-oxadiazole-2-yl]benzene-1,2,3-triol (iva-j)

A mixture of (0.97g, 0.005mol) of 5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol and (0.005mol) of different aryl or alkyl halides were refluxed in 25ml of pyridine solution for 3.5 hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol.

Step: 4.2 Synthesis of 5-{5-[(4-methylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl} benzene-1,2,3-

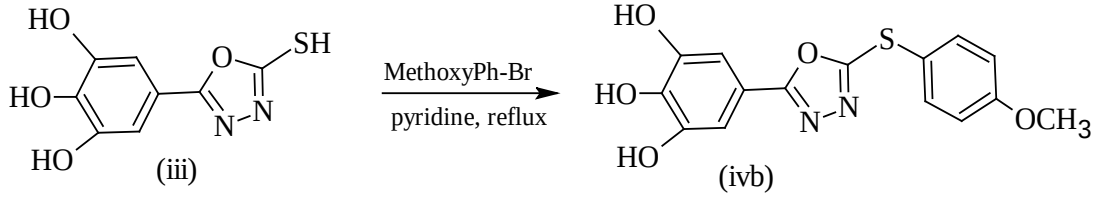
triol **(iva)** for procedure refer step 3, aryl halide (4-methylbromo-benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-methylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl} benzene-1,2,3-triol

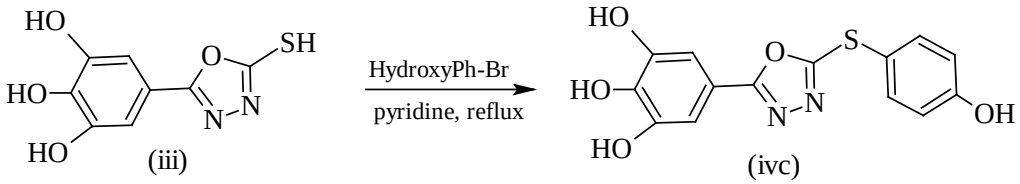
Step: 4.3 Synthesis of 5-{5-[(4-methoxyphenyl) sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol**(ivb)** for procedure refer step 3, aryl halide (4-methoxylbromo benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-methoxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl} benzene-1,2,3-triol

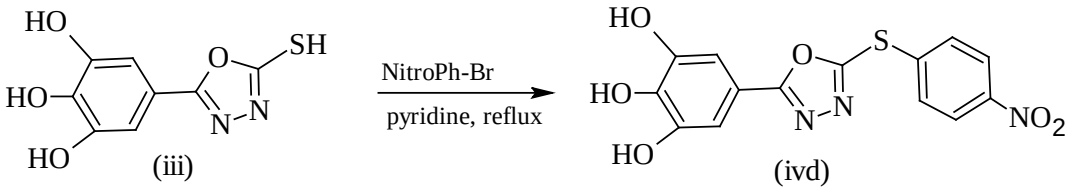
Step: 4.4 Synthesis of 5-{5-[(4-hydroxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene -1,2,3-triol**(ivc)** for procedure refer step 3, aryl halide (4-hydroxy bromo benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-hydroxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

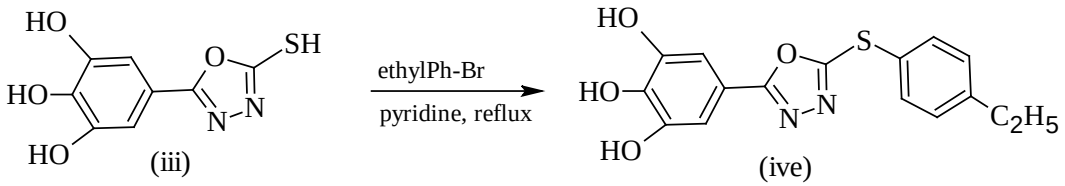
Step: 4.5 Synthesis of 5-{5-[(4-nitrophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol **(ivd)** for procedure refer step 3, aryl halide (4-nitro-bromobenzene) was used



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-nitrophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

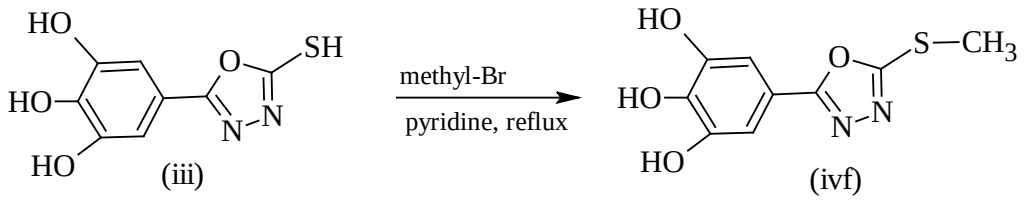
Step: 4.6 Synthesis of 5-{5-[(4-ethylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol **(ive)** for procedure refer step 3, aryl halide (4-ethyl-bromo benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-ethylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

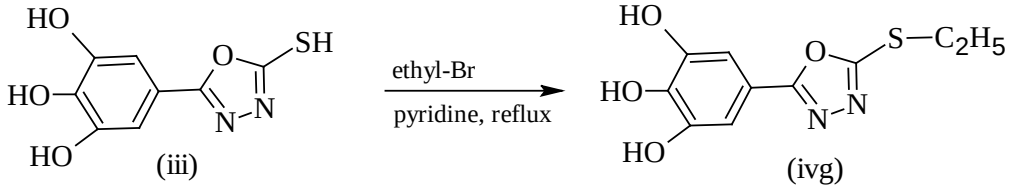
Step: 4.7 Synthesis of 5-[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol **(ivf)** for procedure refer step 3 alkyl halide (methyl-bromo) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

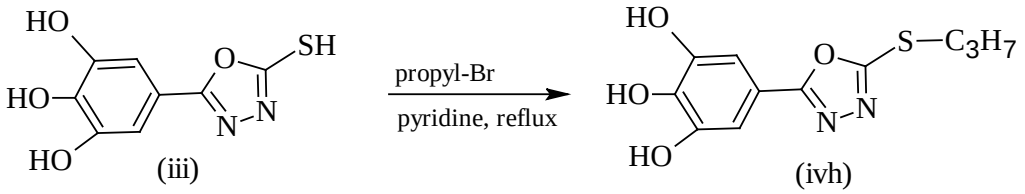
Step: 4.8 Synthesis of 5-[5-(ethylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol (ivg) for procedure refer step 3 alkyl halide (ethyl-bromo) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-[5-(ethylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

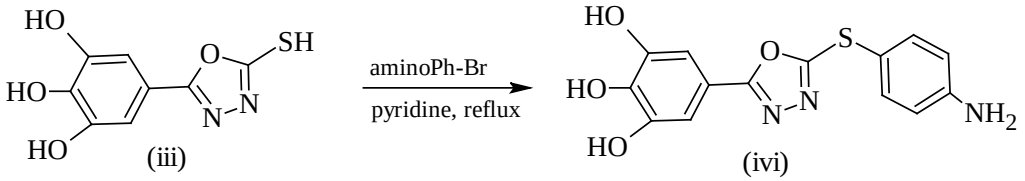
Step: 4.9 Synthesis of 5-[5-(propylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol (ivh) for procedure refer step 3 alkyl halide (propyl-bromo) was used



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-[5-(propylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

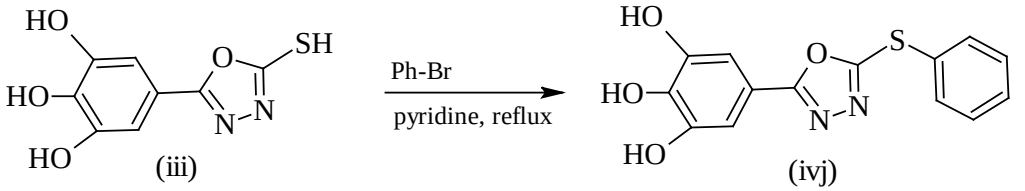
Step: 4.10 Synthesis of 5-{5-[(4-aminophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol**(ivi)** for procedure refer step 3, aryl halide (4-amino-bromo benzene) was used



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-aminophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

Step: 4.11 Synthesis of 5-[5-(phenylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol **(ivj)** for procedure refer step 3, aryl halide (bromo benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-[5-(phenylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

Table 1 physiochemical data of synthesized compound (iva-j)

Compound	% yield	Rf value	Mol. formula	Mol. weight
iva	81.64	0.63	$C_{15}H_{12}N_2O_4S$	316.33
ivb	73.27	0.82	$C_{15}H_{12}N_2O_5S$	332.33
ivc	77.33	0.74	$C_{14}H_{10}N_2O_5S$	318.30
ivd	61.01	0.79	$C_{14}H_{19}N_3O_6S$	347.30
ive	69.82	0.81	$C_{16}H_{14}N_2O_4S$	330.35
ivf	78.62	0.58	$C_9H_8N_2O_4S$	240.23
ivg	76.23	0.68	$C_{10}H_{10}N_2O_4S$	254.26
ivh	65.73	0.66	$C_{11}H_{12}N_2O_4S$	268.28
ivi	71.98	0.85	$C_{14}H_{11}N_3O_4S$	317.31
ivj	91.82	0.71	$C_{14}H_{10}N_2O_4S$	302.30

Solvent system for TLC- ethyl acetate: n-hexane (65:35)

5. PHARMACOLOGICAL SCREENING:

5.1 Anti-Inflammatory Activity

Animals

For the biological evaluation Albino wistar rats, (200-300 g), were used. The animals were kept in colony cages (6 rats each), maintained on a standard pellet diet with water, and left for 2 days for acclimatization before the experimental session. They kept on fast for 16 hour before the experiment, but free access to water. Experiments were carried out according to the ethical guidelines for the care of laboratory animals.

Selection of experimental animals: - Healthy Albino wistar male rats weighing between 200-300 g. were used for the evaluation of anti-inflammatory activity. The animals were obtained from Zydus research centre, Ahmedabad.

Laboratory conditions: - The rats were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its top. Environmental room should be 22°C (± 3°C) relative humidity was at least 30 % and preferably not exceed 70 % other than during room cleaning the aim was to maintain between 50-60%. Lighting was to be artificial, the sequence being 12 hours light and 12 hours.

Food and water: - All animals had free access to water and standard palletized laboratory animal diet.

Bedding: - In the present study animals were provided with clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic conditions. [25]

Acute toxicity studies

The acute toxicity of indole derivatives was determined by using Albino wistar rats (200-300 g) before taking the anti-inflammatory activity. The animals were fasted for 24 hours prior to the experiment and up and down procedure (OECD Guideline no.425) method of CPCSEA was adopted for acute toxicity studies. Newly synthesized compounds suspended in tween-80 was administered to the group of rats (n=3) up to dose level of 10 mg/kg. Animals were placed in individual plastic cage and observed at least once daily for the first 30 minutes and periodically for 24 hours to observe for sign of toxicity.[25]

Principle:-

Inflammation is defined classically as a protective reaction by the body, in response to some physical or chemical injury. Inflammation is a protective reaction by the body. It is a part of the host defense mechanism. There are several tissue factors or mechanisms that are involved in the inflammatory reactions such as release of histamine, prostaglandins, and bradykinin. There are many diseases which are produced due to inflammation such as arthritis, fever etc. Now, there are many medicines are also available for the treatment of the inflammation. Recently many novels Non steroidalanti inflammatory drugs are available in the market. In rats the inflammatory reaction is produced in form of paw edema with the help of some chemicals, some chemicals which are used are carrageenan, bradykinin, histamine, formalin, 5-hydroxytryptamine and mustard or egg white. When this type of compound are injected into the plantar tissue of the right hind footpad of the rats, the paw edema was produced within a few minutes of the injection. Carrageenan-induced paw edema is the most commonly used method in experimental pharmacology for the anti inflammatory activity. Carrageenan is a sulphated polysaccharide, obtained from sea weed (Rhodophyceae). It produces edema by releasing the histamine, 5-HT, bradykinin and prostaglandins in the body.[26]

Anti-inflammatory activity

The anti-inflammatory activity of synthesized indole derivatives were carried out using carrageenan induced rat hind paw edema method.

Method: - carrageenan induced paw edema.

Animals used:-Albino wistar rats

No. of animals used per group:-6 rats

Dose of test compound:-3 mg/kg

Dose of standard drug:-3 mg/kg (Indomethacin)

Route of administration:-Intra peritoneal (suspended in 1% tween-80 solution)

Requirements:-

Instruments:-Mercury displacement plethysmometer.

Inflammation inducing agent:-carrageenan solution (1%w/v) in saline solution was prepared and injected (0.1ml) in sub planter region to induce paw edema.

Chemicals:-Tween-80

Standard drug:-Indomethacin (3 mg/kg) aqueous suspension was prepared using solution of tween-80 as a suspending agent.

Test compounds:-suspension of compounds were prepared and administered intra peritoneal similar to that of standard drug.

Apparatus: -Syringes (1 ml, 2 ml), sample tubes (to prepare suspension of test compounds).

Experimental design and procedure:-

Weigh the animals and number them. Mark the animals with picric acid for individual animal identification. Divide rats into 5 groups of 6 rats each. Note the initial paw volume of each rat by dipping just beyond tibio-tarsal junction by mercury displacement method, so that every time the paw is dipped in the mercury column up to the fixed mark to ensure constant paw volume. The animals were deprived of food overnight (allowed free access to water) and synthetic compounds were administered once before 30 minutes the injection of carrageenan. Dose volume not exceeding 0.5ml/100gm intra peritoneal was administered.

Group I:-The solvent control received normal saline.

Group II:-Positive control received Indomethacin (3 mg/kg).

Group III:-Received indole derivative-4.7 at a dose of 3 mg/kg suspended in 1%w/v tween-80

Group IV:-Received indole derivative-4.8 at a dose of 3 mg/kg suspended in 1%w/v. tween-80

Group V:-Received indole derivative-4.9 at a dose of 3 mg/kg suspended in 1%w/v tween-80.

Group VI:-Received indole derivative-4.10 at a dose of 3 mg/kg suspended in 1%w/v tween-80.

After 30 minutes of test compound administration, 0.1ml of 1%w/v of carrageenan in normal saline was injected in to the sub planter region of the left hind paw of rat. Immediately after the carrageenan injection, the volume of its displacement was measured using plethysmometer.[27,28,29]

The reading was recorded at 0, ½, 1, 2, 3 hrs.

The % inhibition of edema was calculated at the end of 3 hrs by using the formula.[30]

Percent (%) inhibition = 1 – Vt**/**Vc X 100,

Where Vt: - edema volume in test group,

Vc: -edema volume in control group

Results were expressed as mean ± standard deviation.

6. RESULT & DISCUSSION:

6.1 Screening of Anti-inflammatory activity

Table 2:-Screening of Anti-inflammatory activity in Albino wistar rat

Compound code	Inhibition of inflammation in cm					% inhibition			
	0 hr	1 hr	2 hr	3 hr	4 hr	1 hr	2 hr	3 hr	4 hr
Control	0.36±0.02	0.33±0.02	0.31±0.02	0.30±0.02	0.29±0.02				
Standard (Indome thacin)	0.33±0.02	0.30±0.02	0.26±0.02	0.23±0.02	0.20±0.18	09.09	16.13	41.33	42.45
Comp-Iva	0.33±0.02	0.28±0.02	0.26±0.02	0.22±0.02	0.18±0.02	15.15	16.12	26.66	37.93
Comp-Ivb	0.31±0.02	0.27±0.02	0.17±0.02	0.14±0.09	0.11±0.009	18.18	16.12	53.33	62.06
Comp-Ivc	0.34±0.07	0.30±0.02	0.21±0.008	0.17±0.08	0.21±0.01	09.09	32.19	43.33	27.58
Comp-Ivd	0.32±0.02	0.31±0.1	0.21±0.02	0.14±0.02	0.10±0.01	12.12	19.09	53.33	65.51
Comp-ive	0.32±0.02	0.32±0.02	0.25±0.01	0.15±0.007	0.13±0.02	13.13	20.13	27.77	37.58
Comp-ivf	0.31±0.02	0.31±0.02	0.21±0.02	0.21±0.01	09.09	12.12	18.18	26.66	38.98
Comp-ivg	0.31±0.02	0.27±0.02	0.17±0.02	0.14±0.02	0.10±0.01	12.12	19.09	49.11	51.12
Comp-ivh	0.32±0.02	0.32±0.02	0.25±0.01	0.17±0.08	0.21±0.01	09.09	32.19	43.33	47.12
Comp-ivi	0.31±0.02	0.27±0.02	0.17±0.02	0.14±0.02	0.10±0.01	12.12	18.18	26.66	38.54
Comp-ivj	0.33±0.02	0.28±0.02	0.26±0.02	0.22±0.02	0.21±0.01	09.09	32.19	42.84	46.55

No. of animals used in each Group (n) = 6, Values are expressed as Mean ± SEM
Dose of test compound = 3 mg/kg, Dose of Indomethacin = 3 mg/kg

- The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 27.58 to 65.51 % inhibition of rat paw edema volume after 3 hours, whereas the standard drug Indomethacin showed 42.45 % inhibition of rat paw edema volume after 3 hours.
- The compound –ivb, ivd,ivg and ivj were found to be nearly more potent then indomethacin which is used as standard drug. A Compounds iva, ivc, ive, ivf and ivi has shown less activity then indomethacine.

7. CONCLUSION:

The present work, which has undertaken is bonafied, and novel for the synthesis of oxadiazole derivatives. In this view we have made an attempt in reviewing the literature on substituted oxadiazolefor their medicinal significance with help of chemical abstract, journals and internet sites.

The compound –ivb, ivd,ivg and ivj were found to be nearly more potent then indomethacin which is used as standard drug. A Compounds iva, ivc, ive, ivf and ivi has shown less activity then indomethacine.

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