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Review Article

1, 3, 4-Oxadiazole: A Versatile Compound With Potent Analgesic Activity

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ABSTRACT

Oxadiazole is a heterocyclic ring with 5 members that has 1 oxygen atom, 2 nitrogen atoms, 2 double bonds, and 2 carbons. In furan, they are created by placing two methylene groups (=CH) for two nitrogen (-N=) atoms. The aromaticity was reduced by the substitution of these groups. There were four different isomer of oxadiazole that were identified: 1,3,4-oxadiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, and 1,2,4-oxadiazole. Because of their vast array of chemical and biological characteristics, 1,2,4-oxadiazoles and 1,3,4-oxadiazoles are One of them that scientists are more familiar with oxadiazole and have studied more extensively. The 1,3,4-oxadiazole has grown in importance as a synthon. Non-steroidal anti-inflammatory drugs, like diclofenac (DCF), is generally prescribed to reduce pain. Through cyclooxygenase (COX) inhibition, prostaglandin synthesis can be inhibited. Important adverse effects include cardiovascular, gastrointestinal, liver and renal damage are displayed. Diclofenac's center contains a carboxylic group (COOH), which harm gastrointestinal Tract. By employing the retro-synthetic method, which reduces gastrointestinal side effects while increasing chemical and biological activity, the hydroxyl (OH) component of COOH was replaced with new functional groups i.e methyl, methoxy, CH_2NH_2, NH_2, $NHCOCH_3$, $NHCONH_2$, Chlorine, CF_3..

INTRODUCTION

Pain and Pain Management: Acute discomfort experienced by the body, a sign of a physical injury or illness, or even emotional suffering. One of the most important components of the body's defense mechanisms is pain, which serves as immediate warnings that give instructions to motor neurons in the CNS to reduce Damage to the body (1).

Sensing potential or actual harm to the body is one of the most significant functions of pain in the nervous system. It's a visceral and emotional experience. impacted by psychological elements like fear and anxiousness, as well as by prior experiences and beliefs regarding pain. An overview of the major pain pathways and the physiological mechanisms underlying pain is given in this article. It talks about pain receptors,

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how pain signals reach the spinal cord, and how pain travels through the spinal cord. In addition to discussing the various forms of pain, such as visceral and neuropathic pain, it also examines how pain can be modulated at various levels along the pathway and the sites of action of analgesic medications(2).

Reason Behind Pain

- The activation of free nerve endings called pain receptors results in pain.
- Nocireceptors are pain receptors that are called after how they appear at their sensory ends. They are located in the dorsal root ganglion, which is present outside the spinal column. These sensory ends resemble tiny bush branches.
- Pain is experienced when these receptors are activated because signals are transmitted from the sensory neurons in the spinal cord to the central nervous system (3).

Nociceptors

The specific sensory receptors known as nociceptors are responsible for detecting noxious, or unpleasant, stimuli. By activating the primary afferent nociceptors, which are commonly the first structures turned on during nociceptive processes, potentially damaging stimuli e.g., thermal, mechanical, or chemical stimuli cause discomfort on the skin.There are many nociceptors in the skin, muscles, blood vessels, connective tissues, and viscera. The dorsal root ganglion (DRG) contains the cell body of primary afferent nociceptors, which are pseudo-unipolar neurons (4).

Pathways of pain

The brain receives information from them via stimuli that are electrical, mechanical, biological, chemical and thermal. Pain appears when stimuli reach the spinal cord and subsequently the brain's central regions. after their attachment to neurons in the substantia gelatinosa to form synapses, impulses travel to the dorsal horn of the spine and then enter the nervous system. The thalamus is where pain is initially perceived. The limbic system, which is the psychological center, and the cerebral cortex both perceive and interpret pain. Nociciceptors are fundamental structures because they are found at the extremities of nerve fibersThe 2 types of fibers involved in the transmission of pain are Aδ and C. Sharp, clearly defined pain is produced by the large Aδ fibers and is typically triggered by a cut, electrical shock, or physical blow. Due to their myelinated nature, an action potential can travel through them at a speed of about 20 meters per second before entering the central nervous system. The body reacts to pain stimuli more quickly than through Aδ fiber transmission because of their rapidity. The affected body part retracts as a result, preventing the person from feeling pain. This makes it possible to act quickly and either "escape" or get ready to "fight." Pain receptors at the ends of these fibers are always ready to respond, but there are essentially no opioid receptors in them. The ability to pharmacologically alter these receptors is restricted. Analgesic medications can effectively suppress chronic, "slow" pain, but they have little effect on "sharp," "fast," pain. The smaller C fiber convey dull, aching, or burning sensations that are referred to as a "second pain" after the so-called first pain (4,5)(6).C fibers are incredibly fragile and susceptible to breaking. Due to their lack of myelin sheath, they experience extremely slow conduction of painful stimuli, ranging from 0.5 to 2 m/s. A "net" made up of several C fibers is assembled; (6,7). Because of this, the region that branching C-fibres cover is typically wide, and the patient can only pinpoint the exact location of the pain. C fibers respond to stimuli that are mechanical, thermal, and chemical. They respond to both pain and pruritic stimuli (a fiber type that is particularly histamine-sensitive) (8)When C fibers become involved, patients describe their pain as rapid, twitchy, and pulsating. These nerve fiber ends are the location to a variety of receptors,

the most important of which are the opioid receptors. The ganglion cells produce the proteins that make up these receptors, and its axon carry them into the synapses at the corners of the spinal cord and towards the peripheral tissues' nerve endings. The cell membrane of nerve endings contains "sleeping receptors," which are inactive types of receptors (9). Inflammation may "awaken" them. Inflammatory cells produce a range of cytokines that can enter damaged perineurium and activate the receptors. In this manner, endogenous and exogenous opioids can trigger a response from the opioid receptors, which are then activated and sensitized. Prostaglandin and other mediators also "sensitize" C-fiber nerve endings. Prostaglandin synthesis inhibition, which is treated with a non-steroidal anti-inflammatory medication, and corticosteroid inflammation inhibition both lower fiber nerve sensitivity and raise the threshold for pain. The immune and nervous systems working together is the foundation of this fundamental defense mechanism (3).

Types of Pain

Acute Pain - The body uses acute pain as a cautionary sign for addressing illness or tissue damage. It is frequently sudden, severe, and followed by unbearable pain. Either acute pain or pain with a definite cause is present.

Chronic pain - "Chronic pain" describes pain that lasts much longer than it would after particular injuries. Compared to chronic pain, which can be infrequent or constant, acute pain is simpler to treat. Different types of pain can also be classified according to their source and the associated pain-detecting neurons, such as cutaneous, somatic, visceral, and neuropathic pain (10).

Mechanism of action of Analgesic: Prostaglandin endoperoxide-H synthase (PGHS), a bifunctional enzyme bearing cyclooxygenases, transforms arachidonic acid (AA) into prostaglandin H2 (PGH2). In POX activity, PGG2 is reduced to PGH2.The tissue enzymes TXA2 and TXB2, respectively, further convert prostaglandin H into prostaglandins of the PGE2, PGD2, and PGF2 series, prostacyclin PGI2, and thromboxanes B2 and A2 (11).

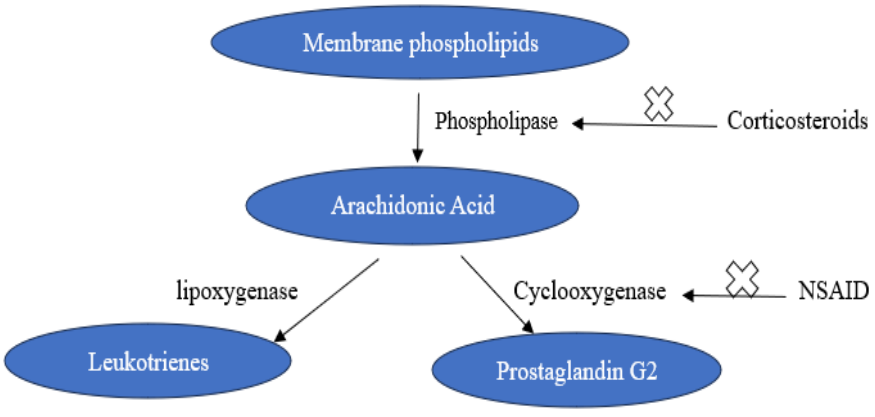


Fig.1: Mechanism of action of NSAIDs

Introduction of 1,3,4-oxadiazole:

The most prevalent heterocyclic compounds have fused rings with five or six members and heteroatoms that are nitrogen, oxygen, or sulphur (12). Heteroatoms such as silicon, phosphorus, and boron can occasionally be used. Chemical researchers in the fields of medicine and pharmaceuticals are interested in heterocyclic compounds that contain nitrogen atoms, such as oxadiazole moieties (13). With single oxygen atom, a pair carbons, the two nitrogen atoms, and 2 double bonds, oxadiazole is a heterocycle ring

with 5 members (14).Other names for this type of ring system are furadiazole, furoxans, diazoxole, biozole, azomes, and oxybiazole. Ainsworth created oxadiazole in 1965 by thermolyzing hydrazine. It is soluble in water and has the molecular formula $C_2H_2ON_2$ and molecular mass of 70.05 g/mol (15)According to calculations, oxadiazoles have a resonance energy of 167.4 kJ/mol and are thermally stable compounds. The substitution at the second position increases the thermal stability of oxadiazoles (14)1,3,4-oxadiazole Because of its many biological applications, One of among the most essential heterocyclic moieties is the heterocyclic ring(16). These derivatives of furan consist of two nitrogen atoms in place of the two methylene groups. When 2 nitrogen atoms are added to 2 methylene groups, the ring becomes less aromatic and takes on the characteristics of a conjugated diene (17).A second heteroatom acts as a weak base for the oxadiazole due to the inductive effect (16).Nucleophiles were substituted for hydrogen atoms in a nucleophilic substitution reaction.

The oxadiazole ring contains nitrogen atoms at four different positions. These positions can result in four different isomers of oxadiazole, which are shown in Fig. 1 as (a) 1,2,4-oxadiazole (b) 1,3,4-oxadiazole (c) 1,2,5-oxadiazole (d) 1,2,3-Oxadiazole (18).

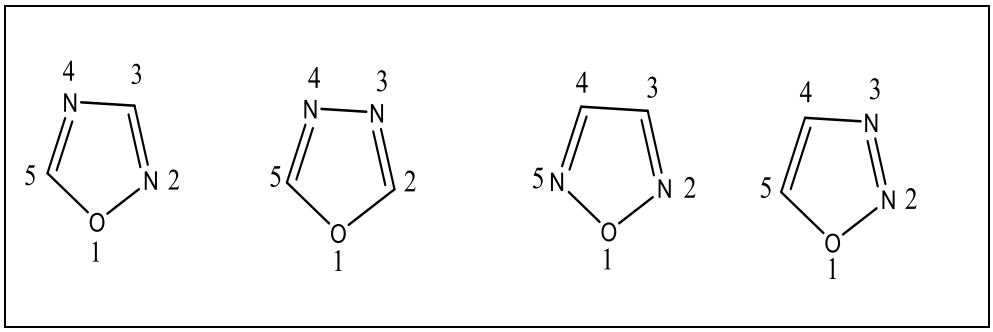


Fig.2: Oxadiazole isomers (18)

Among the different isomers, the literature states that the 1,3,4-oxadiazole isomer has a wide range of therapeutic uses, such as antimicrobial properties. (19), anticonvulsant (20), cancer-fighting (21), low blood sugar, antipyretic, anti-tubercular (22), antiviral in nature (23), immune-suppressive, spasmolytic, antioxidant (23), anti-inflammatory in nature (24), insecticide (25), CNS stimulant, antiamoebic, antiemetic, antidepressants, anthelmintic activities, vasodilator activity, antimycotic, anti-allergic, anti-Alzheimer, ulcerogenic, and cardiovascular activities, among other properties. In light of this, we have looked into a number of oxadiazole derivatives that contain amide, sulphonamide, and amide groups in order to evaluate their antimicrobial, antioxidant, and antiviral qualities (26)

The potent pharmacological effects of 1,3,4-oxadiazole may stem from its toxophoric –N=C–O– linkage. Among them are substituted 1,3,4-oxadiazoles, which have important medicinal applications. More stable than their corresponding 2,5-dialkyl derivatives are 2,5-diaryl-1,3,4-oxadiazoles in particular. Derivatives of 2,5-disubstituted-1,3,4-oxadiazole exhibit stability. Medicinal chemists are tenacious in their pursuit of safer and more sophisticated antitumor agents. The EGFR family of tyrosine kinases is essential for the development of cancer. Thus, drugs that block tyrosine kinase activity are important in the treatment of cancer. In order to investigate the novel compounds' mode of binding to the EGFR tyrosine kinase active site, therefore tyrosine kinases (EGFR family) were chosen (27).

Uses of Oxadiazole:

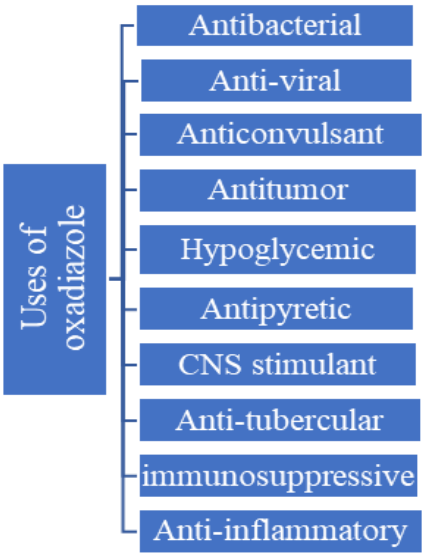
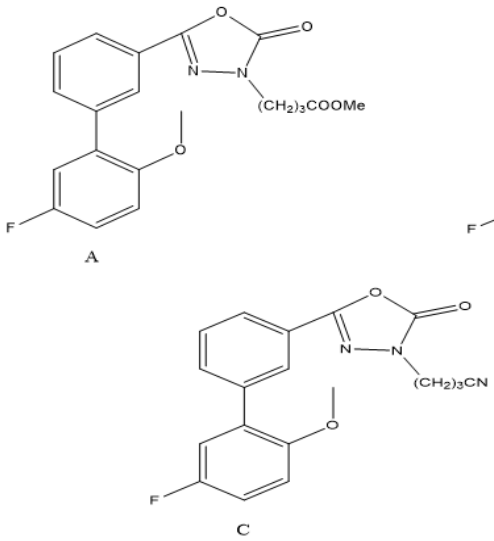


Fig.3: Different uses of oxadiazole

Use of Oxadiazole as potent Analgesic:

With RCOOR'(Ester), F(fluorine), and RCN (nitrile) functional groups in the aliphatic side cha in, oxadiazole derivatives have been shown in thi s study to have good analgesic and anti-inflammatory activity. The compound which show good analgesic activity is mention below the compound name is A,B,C (28).



According to the study of substituted oxadiazole revels that oxadiazole derivatives possess analgesic activity as well as other activity such as anti-inflammatory properties, anti-bacterial, anti-tubercular properties. The chemical compounds were then examined for their analgesic property. Acetic acid-induced writhing was used to test the analgesic effect in male Swiss albino mice (25–35 g) chosen at random for the experiment. Diclofenac (5 mg/kg) was utilized as the reference medication (29).

Add compound name (Acetic acid-induced writhing was used to test the analgesic effect in Swiss albino mice (25–35 g) chosen at random for the experiment. Diclofenac (5 mg/kg) was utilized as the reference medication.

Synthesis Scheme 1:

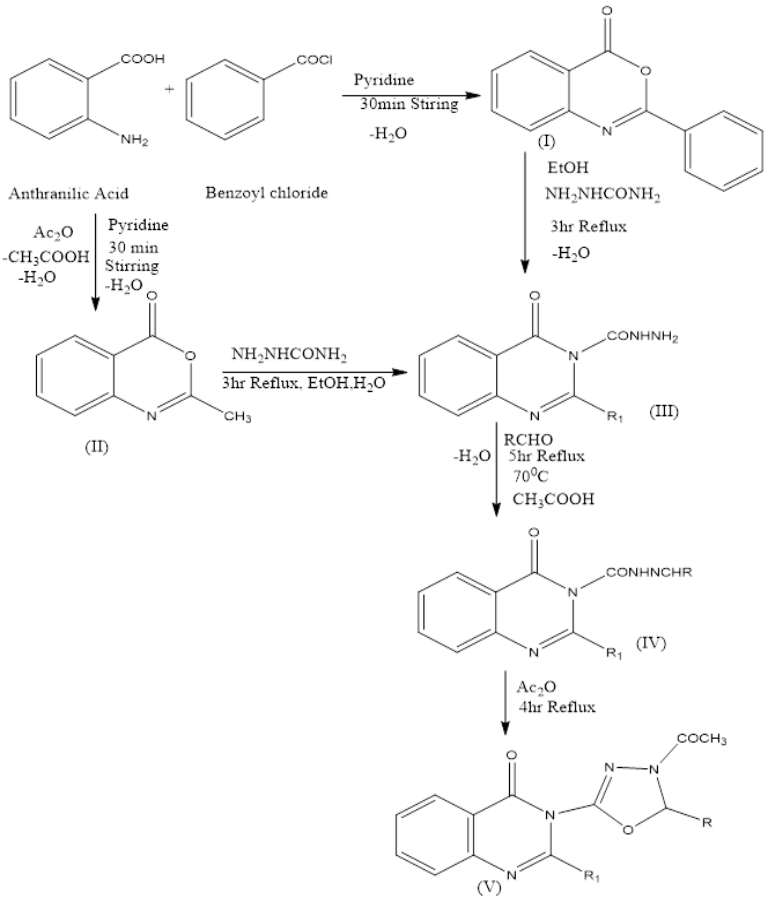


Table-1

Derivatives Name	R_1	R
A	$-C_6H_5$	$-2OHC_6H_4$
B	$-CH_3$	$-2OHC_6H_4$
C	$-C_6H_5$	$-3OH-4OCH_3C_6H_3$
D	$-CH_3$	$-C_6H_5N$
E	$-C_6H_5$	$-2NH_2C_6H_4$
F	$-CH_3$	-SH

As per this article synthesis 22 compound from that eight compound having good analgesic activity ranging from 55% -48%.

According to the Study, the substituted oxadiazole derivatives possess anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities. Compound A, B, C, D derivatives demonstrated excellent analgesic activity in the acetic acid-induced writhing test along with minimal ulcerogenic activity in comparison with diclofenac (30).

SYNTHETIC SCHEME- 2:

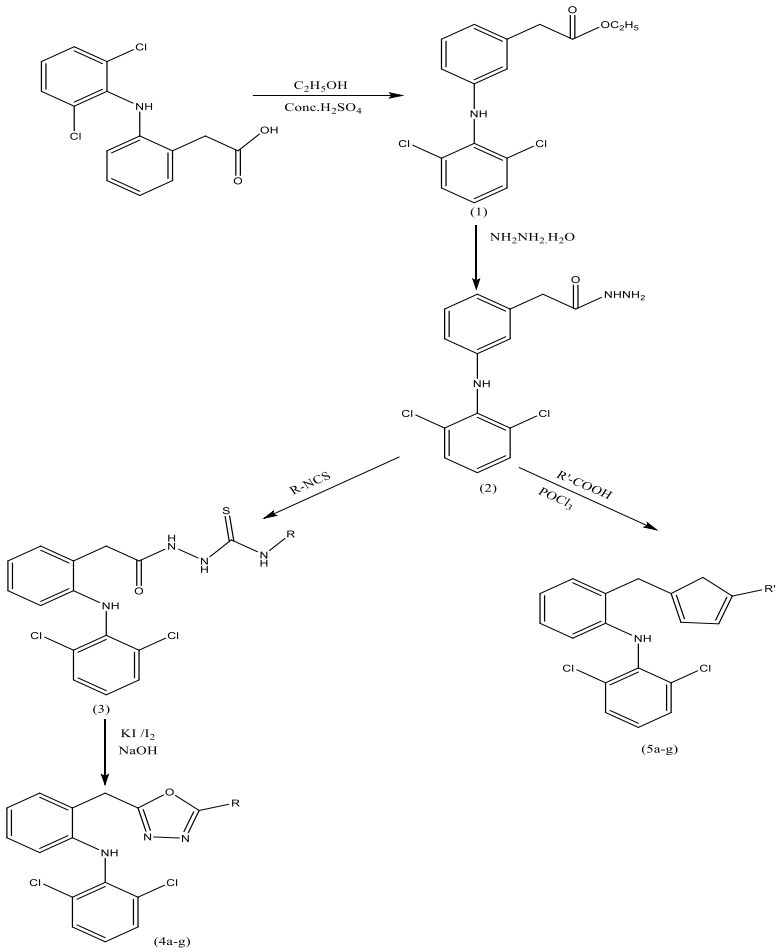
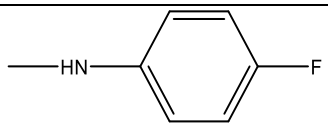
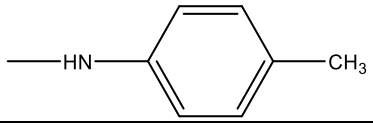
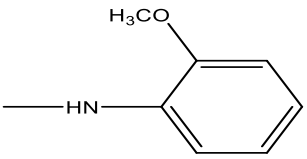


Table-2

Derivatives	R
A	–NH–CH2–CH2–CH2–CH3
B	
C	
D	

As per this article synthesis eight compound from out of the eight compound 4 having showed good Analgesic activity ranging from 78%- 82%, better than the diclofenac (70%).

The study indicates that when Oxadiazole combine with Benzothiazole nucleus have analgesic and anti-inflammatory properties. Compound A, B derivatives showed potent analgesic property in Eddy's hot plate method (31).

SYNTHETIC SCHEME 3:

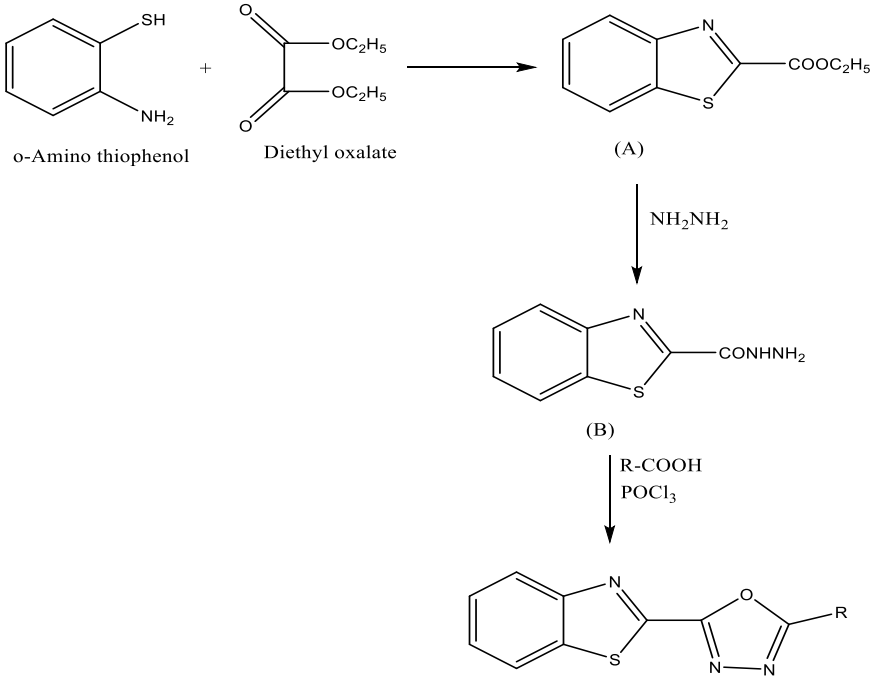
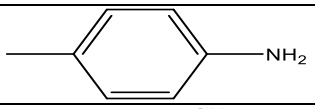
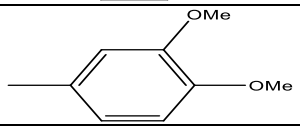
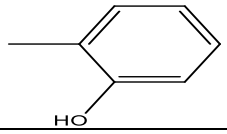
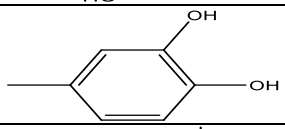
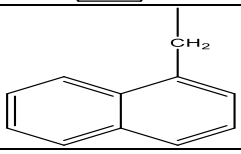


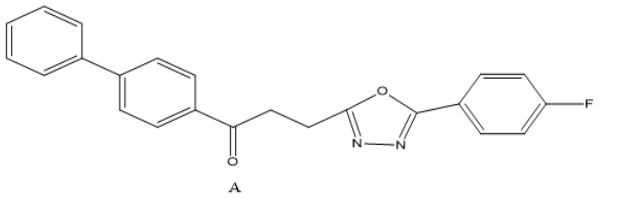
Table-3

Derivatives Name	R
A	
B	
C	
D	
E	

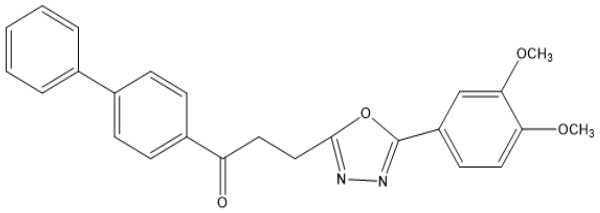
The compound a and compound b have potent analgesic activity, as well as compound C,D and E have moderate analgesic activity.

We obtain the oxadiazole derivative from this article, which has ulcerogenic properties and having analgesic anti-inflammatory and

properties. The derivative's structure of compound A and B shown below (32).



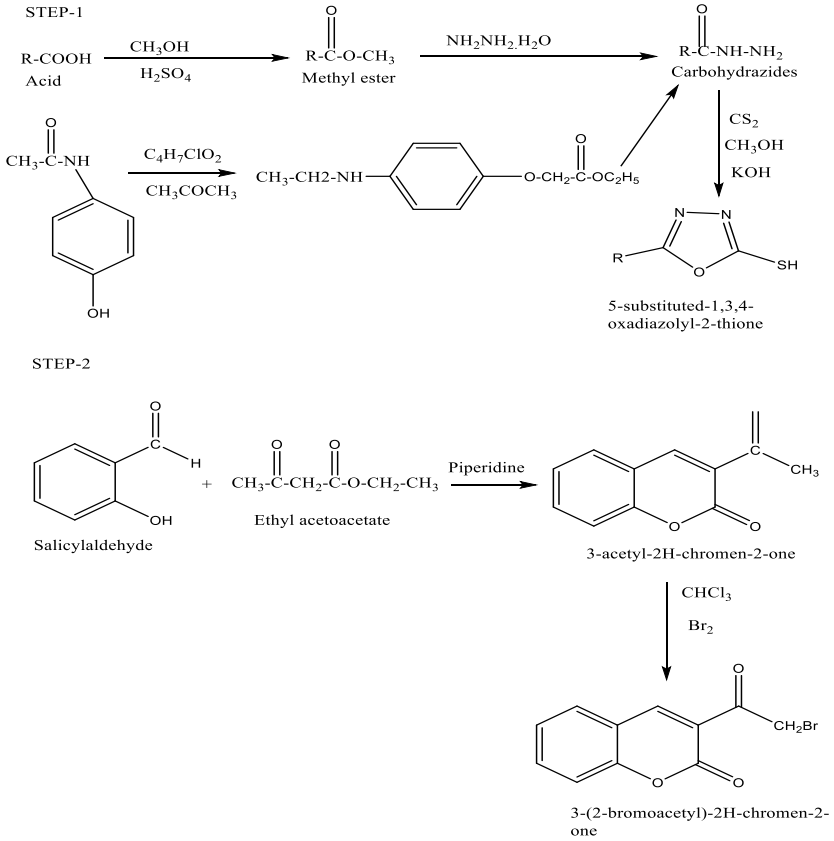
A



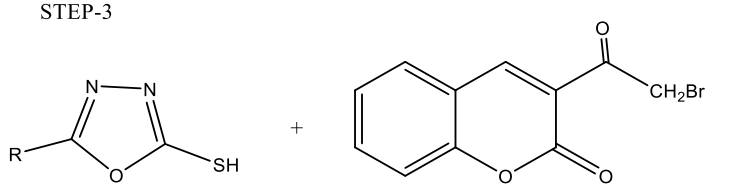
B

3-[(5-substituted-1,3,4-oxadiazol-2-yl-thio) acetyl] is a novel series. 2H-chromen-2-one was produced by refluxing 3-(2-bromoacetyl)- 2H-chromen-2-one in the presence of sodium ethoxide and appropriately 5-substituted-1,3,4-oxadiazolyl-2-thione that was obtained from different NSAIDs that were already on the market. With the aid of spectral data, elemental analysis, and physicochemical information, the structure of the synthesized compounds was established. A 200 mg/kg dose of the title compounds was used to screen for their acute anti-inflammatory and analgesic effects in vivo. Four compounds in the series were discovered to have a notable profile of analgesic and anti-inflammatory activity (33,34).

SYNHETIC SCHEME 4:



STEP-3

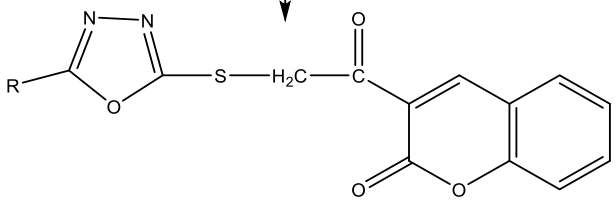


5-substituted-1,3,4-oxadiazolyl--2-thione

3-(2-bromoacetyl)-2H-chromen-2-one

CH_3CH_2ONa

CH_3CH_2OH



3-[(5-substituted-1,3,4-oxadiazol-2-yl-thio)acetyl]-2H-chromen-2-on

A novel series of 3-[(5-substituted-1,3,4-oxadiazol-2-yl-thio)acetyl] has analgesic properties.derivatives of -2H-chromen-2-one through the acetic acid-induced writhing technique.

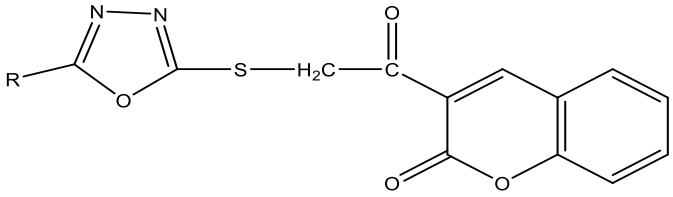
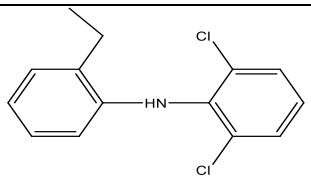
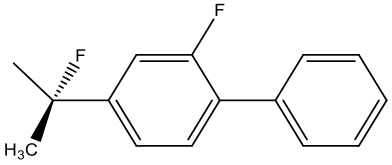
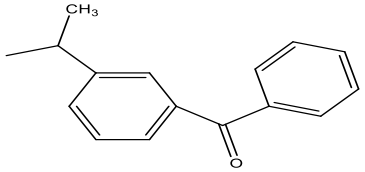
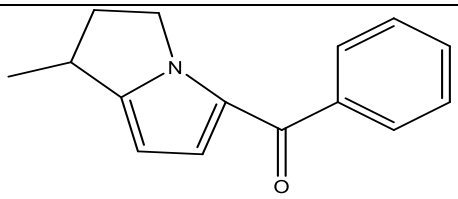
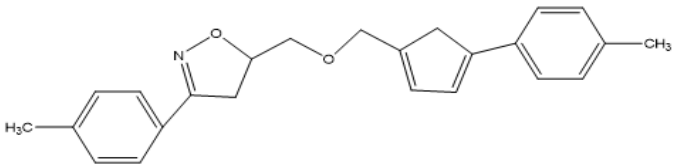


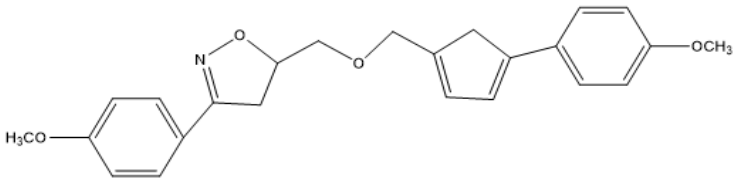
Table-4

Derivatives	R
A	
B	
C	
D	

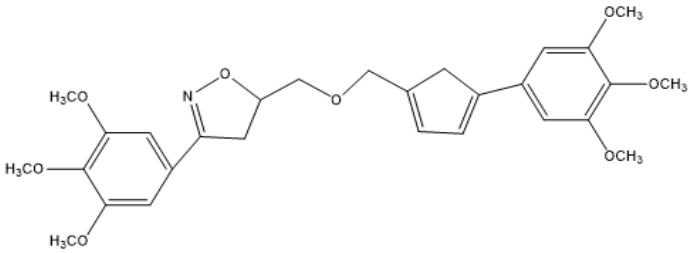
According to this literature, nitrile oxide and allyl alcohol [3 + 2] have been cycloadditionally combined to create novel ether-linked bis(heterocycles]. This is followed by the intramolecular 1,3-diploar cycloaddition of nitrile imine with carbonyl group. We assessed each newly synthesized compound's analgesic and anti-inflammatory qualities. Among the list of substances that were investigated, several showed outstanding efficacy at dosages that were comparable to ibuprofen and aspirin. The compounds having good analgesic property are listed below (35,36).



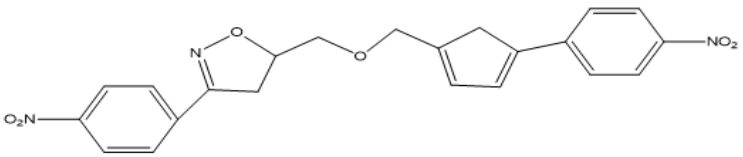
A



B

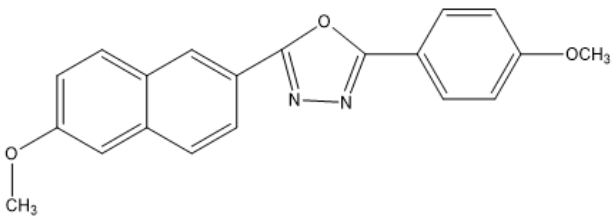


C

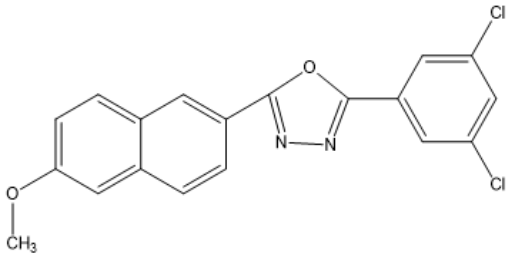


D

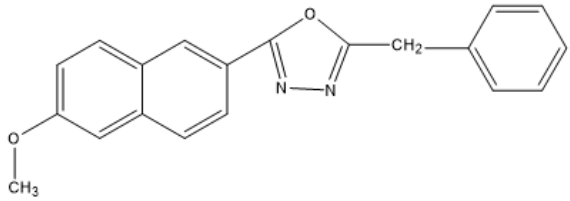
The last ten years have seen a great deal of interest in The chemical structure of 1,3,4-oxadiazoles that have been substituted and their derivatives as possible analgesics, CNS stimulants, Anti-convulsives, Anti-carcinoma, and Anti-hypertensive drugs. Recent studies have looked closely into the effects of 1,3,4-oxadiazole derivatives as analgesics and anti-inflammatory agents. In addition, the analgesic and anti-inflammatory qualities of 1,3,4-Oxadiazole with a naphthalene ring have been synthesized and studied. The analgesic property studies indicated that most of the compounds showed good analgesic activity at a dose of 50 mg/kg when compared to the standard medication, Diclofenac sodium (2.5 mg/kg). The compound that has analgesic effects is listed below (37, 38).



A



B



C

At C-5, A containing the 4-methoxy phenyl moiety exhibited the greatest analgesic activity. The compound C, which has a benzyl moiety as a substituent, has the least analgesic effect, while compound B, which contains dichlorophenyl, exhibited moderate analgesic activity. The compound B demonstrated strong anti-inflammatory and moderate analgesic properties(39).

Structure Activity Relationship of Oxadiazole for Analgesic Activity:

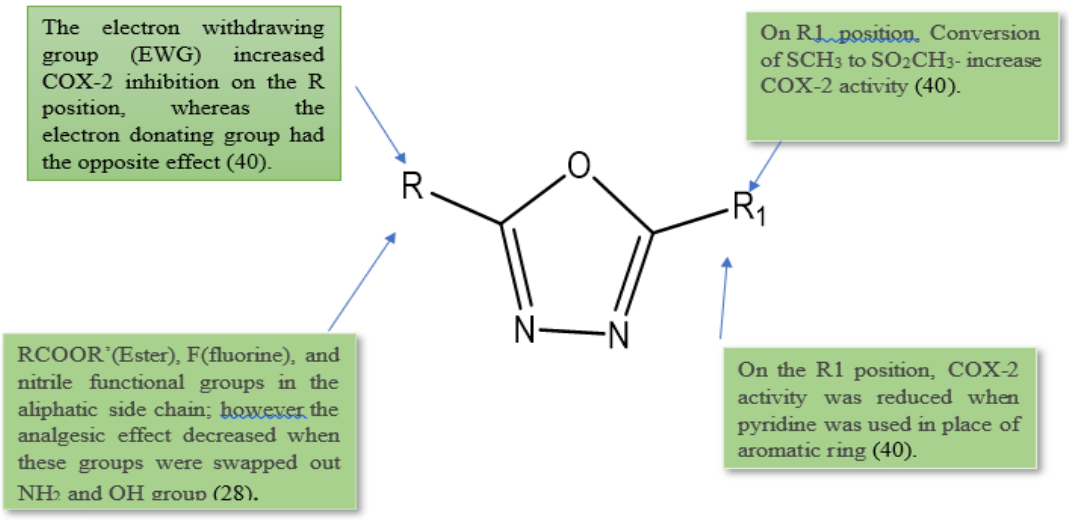


Fig.4: SAR of oxadiazole

CONCLUSION

The review article shows that there are multiple synthetic pathways that can be used to synthesise molecules containing 1,3,4-oxadiazole. In addition to their strong analgesic effects, these compounds show an extensive Several different biological processes, such as Antioxidant, Antitubercular, Anticancer, Antibacterial, and Antiviral effects. This review paper states that 1,3,4-oxadiazole can be further changed or derivatized to produce compounds that are physiologically active and have higher potency. The two primary side effects of long-term NSAID use are gastrointestinal irritation and ulcerogenic activity. Oxadiazole derivatives mainly act as COX-2 inhibitors, and they have fewer adverse effects than NSAIDs that are available on the market. It was demonstrated that an aliphatic side chain containing ester, fluoro, and nitrile functional groups was linked to strong analgesic action; on the other hand, an aliphatic side chain containing NH_2 and OH groups was linked to a reduction in analgesic activity. The effectiveness of additional sulfonamide molecules was limited.

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