A critical review on synthesis and Biological Screening of 1,3,4-Oxadiazole based NSAIDs Derivatives

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Abstract: Oxadiazole is a five membered heterocyclic compound which is considered to be derived from furan by replacement of two methane (-CH²-) group by pyridine type nitrogen. In pharmaceutical chemistry various contaminations in now a day oxadiazole assume key role for the fix synthetic organic chemistry. Now a days, various types of irresistible illness caused by microorganisms compelled the researchers to find new antimicrobial agents that can control these irresistible diseases precisely. NSAIDs are non-steroidal anti-inflammatory drugs used for fever, pain, nausea, dyspepsia and inflammation. NSAIDs have some side effects like nausea, dyspepsia, bleeding, nephrotoxicity, renal injury and gastrointestinal ulceration. The major side effect of NSAIDs is gastrointestinal ulceration. The main cause of gastrointestinal ulceration is carboxylic group moiety which contains all types of NSAIDS. In future these side effects can be overcome by masking the carboxylic group with oxadiazole because oxadiazole has great pharmacological applications and oxadiazole based NSAIDs derivatives diverse biological activities like anti-inflammatory, anti-cancer, anti-convulsant, anti-tubercular, anti-microbial and anti-HIV. In this article, we have tried to accumulate some of the major researches carried out for 1,3,4- oxadiazole based NSAIDs derivatives.

Introduction

NSAIDs (non-steroidal anti-inflammatory drugs)

NSAIDs are the non-steroidal anti-inflammatory drugs which are used for different diseases like fever, pain, headache, nausea and inflammation (Woessner & Castells, 2013). NSAIDs has many beneficial effects as compared to the drugs which contain steroids therefore NSAIDs are used for the treatment of different types of diseases like joint pain, inflammation, and also use to control the body temperature. NSAIDs has some side effects like nausea, dyspepsia, bleeding, nephrotoxicity, renal injury and gastrointestinal ulceration (Surg et al., 2014). The main cause of gastrointestinal ulceration is carboxylic group moiety which contains all types of NSAIDs. These side effects can be overcome by masking the carboxylic group with oxadiazole because oxadiazole has great pharmacological applications.

History of NSAIDs

History of NSAIDs is very ancient because first NSAIDs aspirin was synthesized in 1897 but as the time passed many NSAIDs was prepared. Now mostly Aspirin, diclofenac, Ibuprofen, naproxen is used for the cure of different diseases like for the relieve of pain and inflammation different diseases are present in inflammation like hepatitis, cancer, tuberculosis, trauma injury, rheumatism because these can suppress the effect of COX II.

Properties of NSAIDs

NSAIDs use as analgesic (reduces pain)
Anti-pyretic (reduces fever)
Anti-inflammatory (reduce swelling)
Anti-platelet (retards blood clotting)
Analgesic (reduce pain)

Classification of NSAIDs

NSAIDs classifications are following:
1.2.1 Propionic acid derivatives

Ibuprofen is non-steroidal anti-inflammatory drug which is more beneficial than aspirin. This is first member of propionic acid which use for inflammation, back pain, toothache, menstrual pain, arthritis and minor injuries (Warner et al., 2011). Ibuprofen is salient properties like anti-pyretic, analgesic and anti-platelet but less anti-inflammatory activity than other non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen has some side effects such as bleeding, vomiting, nausea dyspepsia and gastrointestinal ulceration. Generally, in this drug fewer side effects than aspirin and indomethacin (Traversa et al., 1995). Naproxen is used for inflammation, chronic disease such as muscular pain. On the other hand, these side effects are including ibuprofen drugs such as anemia, gastrointestinal toxicity and ulceration (Wilkes et al., 2005). There are two steps in these side effects first step is carboxylic acid moiety in this drug which cause acidity and ulceration if remove the carboxylic acid in this drug and change the functional group then remove this side effect. Second step is cyclooxygenase inhibitors (COX) are main cause for prostaglandins (Wilson et al., 2006).

Acetic acid derivatives

Acetic acid derivatives in which indomethacin and diclofenac sodium is non-steroidal anti-inflammatory drugs are commonly used for fever, pain and stiffness and inflammation in swelling but while these are some side effects such as gastro toxicity, bleeding peptic ulceration (Shiri et al., 2006). In acetic acid derivatives in which different shapes and functional groups such as aceclofenac, tolmetin, sulindac, stodolac, ketorolac, diclofenac sodium, and nabumetone. On the other hand, some side effects are including in indomethacin such as bleeding gastrointestinal toxicity and ulceration (Thomas, 2000).
Enolic acid derivatives (Meloxicam)

Meloxicam is non-steroidal anti-inflammatory drugs in which enolic acid and show anti-pyretic and analgesic activities. It used to relieve the pain and inflammation and veterinary medicine but on the other hand this drug has many side effects such as cardiovascular effects and hypertension (Shionoiri, 1993).

Anthranilic acid derivatives

Anthranilic acid derivatives are known as mfenamic acid synthesize by 2-chlorobenzoic acid in the presence sodium acetate. Its common name is ponstan use for pain killer such as migraine headache and menstrual pain. On the other hand, some side effects in mfenamic acid such as vomiting, bleeding and diarrhea. Mfenamic acid analyzed by infra-red spectroscopy and nuclear magnetic resonance spectroscopy show analgesic and anti-inflammatory activities (Schjerning et al., 2011)

Salicylates

Aspirin 8 is use for treatment of cancer and different types of cancer such as liver cancer, breast cancer, colon cancer and colorectal cancer. It’s also uses for rheumatic arthritis and dilutes the human blood. There are many uses of aspirin due to cyclooxygenase inhibitors enzyme decrease the risk of heart attack after heart attack aspirin given that the heart patient due to control the blood pressure. On the other hand, some side effects are in aspirin such as gastrointestinal toxicity and create the peptic ulcer. When we prepared aspirin derivatives and change the functional group in these derivatives then remove these side effects from aspirin (Rouzer & Marnett, 2008). Salicyleamide 9 is use for treatment of cancer. There are many different biological activities. Salicylates show anti-inflammatory and analgesic activities due to cyclooxygenase inhibitors and paly main role in metabolism in metabolism change the embryonic proteins of fatty acid. Due to this quality this drug is use for tuberculosis (Rainsford, 2009). Sodium salicylate 10 is utilized for the fix of respiratory and stomach related illnesses because of it anti-inflammatory and pain-relieving impacts. It is additionally use for different purposes like for the rapid egg creation, worry because of warmth, variations from the norm in headway and for the egg shell thickness. It is likewise utilizing to create poultry medication Sodium salicylate additionally has numerous different uses like for the fix of Rheumatic illness and this is treated with sodium salicylates and this is the first run through presented non-steroid calming drug (Page & Henry, 2000)
Oxadiazole derivatives based on ibuprofen

Oxadiazole because of this substitution the reactions supplanted by the less acidic carboxylic acid functional group is practical. To maintain a strategic distance from this functional group is this ibuprofen and naproxen. One symptom identified with the fix of various infections are diclofenac sodium, distinctive carboxylic acid containing drugs use for various kinds of acids like phosphoric acid, sulfonic acid and hydroxamic acid. Carboxylic acid also utilizes in antimicrobial and use for the fix of a few ailments. Carboxylic acid additionally utilizes in various kinds of acids like phosphoric acid, sulfonic acid and hydroxamic acid (Machado et al., 2017). Distinctive carboxylic acid containing drugs use for the fix of various infections are diclofenac sodium, ibuprofen and naproxen. One symptom identified with this functional group is this reason GI poisonous quality. To maintain a strategic distance from every symptom carboxylic acid practical functional group is supplanted by the less acidic change of 1,3,4 Oxadiazole because of this substitution the reactions of GI danger is survived (Lim et al., 2016).

**Significance of functional group in medicine**

Functional group plays an important role in medicine. In this carboxylic acid utilized as a practical gathering. Carboxylic acids as a useful functional group present in numerous mixtures like prostanoids, triglycerides and in amino acid this functional group is available. Besides, carboxylic acid present in NSAIDs drugs which are anti-inflammatory, anticancer, antimicrobial medications and use for the fix of a few sorts of ailments. Carboxylic acid additionally utilizes in various kinds of acids like phosphoric acid, sulfonic acid and hydroxamic acid (Machado et al., 2017). Distinctive carboxylic acid containing drugs use for the fix of various infections are diclofenac sodium, ibuprofen and naproxen. One symptom identified with this functional group is this reason GI poisonous quality. To maintain a strategic distance from every symptom carboxylic acid practical functional group is supplanted by the less acidic change of 1,3,4 Oxadiazole because of this substitution the reactions of GI danger is survived (Lim et al., 2016).

**Oxadiazole derivatives based on ibuprofen**

NSAIDs additionally cause a few sorts of symptoms like distinctive kinds of wounds, GI poisonous quality, ulceration and draining when we utilize the medications consistently. Prostaglandin is mindful to control our basic homeostasis gastrointestinal and vascular homeostasis and PGs creation happen through COX-I significant symptom of NSAIDs is this restrains this COX-I compound. Significant reactions of NSAIDs are identified with renal, intestinal and gastric variations from the norm (Lee et al., 2001). These single reactions are because of dissatisfaction in - COOH bunch moiety. Researchers of whole world are attempting to integrate more compelling medications that beat these reactions (Kuritzky & Samraj, 2012). Consequently, Scientist arranged the NSAIDs derivatives these derivatives defeat the symptoms of carboxylic acid functional group of non-steroid calming drugs and has greater ability to diminish the allergenicity. These derivative drugs take care of the numerous issues identified with symptoms of various sorts of sicknesses. These plays better calming, pain relieving and antimicrobial exercises and can possibly battle unmistakable sorts of sicknesses (Kowalski et al., 2011).

**Heterocyclic chemistry**

Heterocyclic chemistry is the branch of chemistry which deals with synthesis chemical and physical properties of heterocycles are known as heterocyclic chemistry. In 1800s Italian chemist prepared first heterocyclic compound alloxan from uric acid. Heterocyclic compounds play an important role in nucleic acid, natural synthetic dyes, and different types drugs (Kearney et al., 2006). Heterocyclic might be helpfully grouped dependent on their electronic structure. The soaked heterocycles carry on like the non-cyclic derivative. Subsequently, Peppermint and tetrahydrofuran are customary amines and ethers, with adjusted steric profiles. In this manner, the analysis of heterocyclic chemistry centers particularly around un-saturated derivatives, and the dominance of work and applications include unstrained 5-and 6-membered rings. Included are pyridine, thiophene, pyrrole, and furan (Hinz & Brune, 2008). Another derivatives class of heterocycles is combined to benzene rings, which for pyridine, thiophene, pyrrole, and furan are quinolone, benzothiophene, indole, and benzo[furan, separately.
Combinations of two benzene rings offer a third extensive group of compounds, individually the acridine, dibenzo thiophene, carbazole, and dibenzofuran (Higuchi et al., 2009). These unsaturated rings can be grouped by the interest of the heteroatom in the conjugated and pi system. For the mixture of new compound due to their electronic assets, solubility, ophthalmic and these compounds display a great interest. Heterocyclic compounds show great biological activities such as oxadiazole are five member’s rings. Heterocyclic compounds play an important role in medicine and their rearrangements to derivatives occur. When these compounds react with medicine then synthesize bio active drugs prepared (Hamza & Dionne, 2009).

**Classification of heterocyclic compounds**

Due to essence of heteroatoms in ring these heterocyclic compounds are dispersed into three major classes. Because of these few kinds of molecules these compounds demonstrate a particular property and we can decide its structure (Guthrie et al., 2015). These are following categories are given below.

**Sulfur based heterocyclic compounds**

In this type of heterocyclic compounds in which sulfur present in the ring are known as sulfur-based heterocycles (Green, 2001). Sulfur based heterocycles are following:

![Figure 8. Sulfur based heterocyclic compounds](image)

Azole name was given to nitrogen containing heterocycles by Janssen assemble in 1960. These medicines additionally use to control the blood glucose level and have a large interest in obsessive pathological condition for the arrangement of new medicine that might be approved by FDA. In nitrogen containing drug we for the most part utilize indole this is generally utilized for the growth treatment and for the hindrance of tubulin polymerization (Gleason et al., 2011).

**Oxygen based heterocyclic compounds**

In this type of heterocyclic compounds in which oxygen present in the ring are known as oxygen based heterocyclic compounds (Gislason et al., 2009). Oxygen based heterocyclic compounds are following:

![Figure 11. Oxygen based heterocyclic compounds](image)

These heterocyclic compounds have great organic actions like as anti-fungal, anti-allergic, opposing- cancer and many others actions in human bodies such as kidney and breast cancer (Fowler, 2007).
of various component is very own significance and system however last result combination of oxadiazole. Each technique has its strategies have been outlined below for the Synthetic method of oxadiazole properties because of irresistible diseases to find new antimicrobial agents that can control researcher hence, microorganisms this was the huge test for the illness are expanding step by step which is caused by assume key role for the fix synthetic organic contaminants infection in nowadays oxadiazole pharmaceutical chemistry because of various present in oxadiazole is sp2 hybridization. In heterocyclic five membered compound which is gotten from furan by substitution of two (-CH=) compound by two nitrogen atoms called oxadiazole. This is additionally called cyclopentadiene and having general formula of C₈H₈ON₂ contain one oxygen and twofold nitrogen atoms. The hybridization present in oxadiazole is sp2 hybridization. In pharmaceutical chemistry because of various conditions infection in nowadays oxadiazole assume key role for the fix synthetic organic chemistry. The no of various types of irresistible illness are expanding step by step which is caused by microorganisms this was the huge test for the researcher hence, researcher feel this is essential need to find new antimicrobial agents that can control these irresistible diseases precisely. Other than these properties because of one-of-a-kind features in core of oxadiazole like antimicrobial anti-provocative, cancer prevention agent, antitumor and anticancer properties this is utilized for the combination of numerous new remedial medications and these properties demonstrate incredible fascination for researcher in light of the fact that these are interconnected with oxadiazole core. The other quality in oxadiazole is that the electrophilic substitution is happens on nitrogen molecule when contrasted with the carbon particle the fundamental reason is the electron thickness on carbon atom is not sufficient and like aliphatic compounds sp2 hybridization happens in oxadiazole and nucleophilic substitution occur on oxadiazole.

**Types of oxadiazole**

Many types of oxadiazole depends upon the course of action of nitrogen atom in ring structure. In oxadiazole same kinds of atoms are available however course of action of these molecules is extraordinary. In light of these atoms four kinds of oxadiazole can exist. 1,2,3-oxadiazole, 1,2,5-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole are available in these 1,3,4-oxadiazole has more significance as a result of various exceptional properties like metabolic movement, pharmacological chemistry, medicinal action, and organic activities.

![Figure 12. Oxygen based heterocyclic compounds](http://www.lifesciencesite.com)

**Synthetic method of oxadiazole**

Most essential synthetic development or strategies have been outlined below for the combination of oxadiazole. Each technique has its very own significance and system however last result of various component is a similar that is oxadiazole development these all are the best instruments for oxadiazole arrangement and have a great deal of significance from pharmaceutical perspective (Day & Graham, 2004). These are briefly described given below:

![Figure 13. Different types of oxadiazole](http://www.lifesciencesite.com)

![Figure 14. Synthetic method of oxadiazole](http://www.lifesciencesite.com)
By using ibuprofen

Oxadiazole based ibuprofen derivatives in which starting material are propionic acid. When propionic acid reacts with absolute ethanol in the presence of sulfuric acid then became ester produced further ester react by hydrazine in the existence of distilled ethanol then formed hydrazide. Hydrazide reacts by CS₂ in the existence of CH₃CH₂OH then formed oxadiazole. When oxadiazole react with dimethyl formide in the presence of lithium hydride then formed ibuprofen derivatives of oxadiazole (Danelich et al., 2015).

![Scheme 1. Oxadiazole derivatives prepared by ibuprofen](image)

By using diacyl hydrazine

In this reaction chemicals, reagent and is procedure is very simple and this reaction gain better yield than others. First of all, in this reaction starting material is diacylhydrazines react with distilled CH₃CH₂OH in the presence of ZnCl₂ used as catalyst. Due to catalyst this reaction occurs very fast as compare to other compounds (Cronstein & Sunkureddi, 2013).

![Scheme 2. By diacylhydrazines synthesis of 1,3,4-oxadiazole](image)

![Scheme 3. Synthesis of oxadiazole derivative by acetyl acetone](image)
By using acetyl acetone
These reactions in which we change the hydrazide into oxadiazole occur. In this reaction starting material is acetyl acetone, CS$_2$ and sulfur powder changed into hydrazide in the presence of distilled CH$_3$CH$_2$OH and NH$_2$NH$_2$ when reaction set on reflux then better yield of product gain (Buer, 2014).

By using naproxen

Oxadiazole based naproxen derivatives in which starting material are propionic acid. When propionic acid reacts with absolute ethanol in the presence of sulfuric acid then became ester produced further ester react by NH$_2$NH$_2$ in the existence of CH$_3$CH$_2$OH then formed hydrazide. Hydrazide reacts with CS$_2$ in the presence of ethanol then formed oxadiazole. When oxadiazole react with N, N dimethyl sulfoxide in the presence of lithium hydride then formed naproxen derivatives of oxadiazole (Brater et al., 2001).

By using Schiff bases
Oxadiazole might be prepared by carboxylic acid, cyclodehydration in the presence of FeCl$_3$. In Schiff bases reaction we synthesized only amine, aliphatic and aromatic compounds (Bombardier et al., 2000).

By using hydrazide
In this reaction starting material is hydrazide react by CS$_2$ in the presence of potassium hydroxide then formed oxadiazole. According to this method large quantity formed and large quantity of yield produced (Bleumink et al., 2003).
By Tetrazole acylation

Tetrazole containing four nitrogen atoms in the ring are known as tetrazole. When acid anhydride reacts with benzoic anhydride then formation of 1,3,5-oxadiazole occur. This method of preparation of oxadiazole is useful (Bleumink et al., 2003).

**Biological significance of Oxadiazole**

Oxadiazole show biological active compound since oxadiazole execute those activities such as:
- Anti-inflammatory
- Anti-oxidant
- Anti-fungal
- Anti-bacterial
- Anti-microbial
- Anti-fungal
- Anti-cancer
- Anti-tumor

**Figure 15.** Biological activities of ibuprofen based oxadiazole derivatives

**Oxadiazole as anticancer agent**

When we prepared oxadiazole derivatives and developed sea urchin embryo then we examine that these oxadiazole derivatives on its embryo so check the anti-cancer activity, hence oxadiazole derivatives performed anti-cancer agent stop the effect of cancer (Wallace and Soldato, 2003).

**Figure 16.** Oxadiazole as anti-cancer agent

**Oxadiazole as antimicrobial agent**

When prepared a series of oxadiazole derivatives by cyclic and hydrazone process then we examine that these derivatives are check on animal embryo after complete the reaction then check the anti-microbial activity then these derivatives most useful for micro-organism. These all derivatives characterized by infrared spectroscopy and nuclear magnetic resonance spectroscopy. So oxadiazole derivatives are helpful for micro-organism (Schenone et al., 2006).
Oxadiazole as antimicrobial agent

When synthesize oxadiazole derivatives then these derivatives present different activities such as anti-inflammatory activity. After the characterization all these derivatives contains choloroanilne piperazin, so C_{11}H_{15}N_{2}F show anti-inflammatory activity (Fiorucci & Distrutti, 2011).

Oxadiazole as antibacterial agent

Presently derivatives of oxadiazole by ibuprofen are demonstrate exceptionally valuable for antibacterial high-quality. After blend of this derivative these were tried against various bacterial maladies on various creatures and these demonstrates the incredible proficiency against bacterial sickness (Huguenin et al., 2005).
Oxadiazole as antioxidant agent

Oxadiazole ring which is shaped by ibuprofen acid or propionic acid show extraordinary activity against anti-oxidant and this is utilized for various purposes (Piazza et al., 2009).

Anti-tumor activity

Mannich bases are synthesized and act as great anti-tumor activity. Compound 56 exhibited the promising activity against the lung cell lines. Various 1,3,4-oxadiazole derivatives are prepared and show promising activities against tumor cell to stop the tubulin polymerization and mitotic division of tumor cell is blocked. Compound 57 and 58 shows potent activity. The compound 57 shows excessive pharmacokinetics profile. The nano concentration of 57 is enough to stop the mitotic division is breast carcinoma (Yadav et al., 2006).

Hemolytic activity

Different drugs that contain oxadiazole moiety in its structure is synthesize as well as its Hemolytic activity is assessed. Oxadiazole derivatives of 59 exhibited the promising hemolytic activity (Gul et al., 2014).
Anticonvulsant activity

Oxadiazole derivatives are showed that anti-convulsant activity and these are used for treatment of seizures and elliptic diseases. These are prepared by epileptic drug when introducing NH-group from this derivative then show anti-convulsant activity (Sharma & Mishra, 2006).

Insecticide activity

Oxadiazole derivatives on benzene ring in the presence of fluorine exhibits great insecticide action. Oxadiazole containing trifluoromethyl group 64 is synthesized via four steps synthetic process and these activities against the insecticide (Papadopoulou et al., 2005).

Conclusions

The review has concluded with biological activities of the 1,3,4-oxadiazole. Oxadiazole based NSAIDs derivatives has shown a wide range of therapeutic importance. This paper contains of all the major pharmacological activity of 1,3,4-oxadiazole and it can be used for further researches. The major activities of 1,3,4-oxadiazole are anti-microbial, anti-inflammatory, analgesic, anti-tumor, anti-convulsant, anthelmintic and ant hepatitis B viral activities. In future research to remove NSAIDs side effects such as gastrointestinal ulceration. The main cause of gastrointestinal ulceration is carboxylic group moiety which contains all types of NSAIDS. In future this side effect can be overcome by masking the carboxylic group with oxadiazole because oxadiazole has great pharmacological applications.
References


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