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An Overview of New Acetamide Derivatives in COX-II Inhibitors

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) have long been recognized as one of the most commonly used agents. However, their adverse effects on various organs are well-documented. This review focuses on the development of acetamide derivatives that retain their anti-inflammatory effects while selectively inhibiting COX-II. Several literature sources emphasize the importance of these heterocyclic compounds in the treatment of inflammatory conditions, recognizing their therapeutic value in this pharmacological class. COX-II inhibitors, through the prodrug approach, offer a wide range of applications and have significantly contributed to drug development. Researchers have designed numerous prodrugs using acetamide molecules to improve pharmacokinetic properties, enhance sensory attributes, or optimize chemical properties. A wide array of amide derivatives, across different classes of compounds, has been identified as effective COX-II inhibitors, primarily used for conditions such as arthritis, pain, menstrual cramps, and colonic polyps, helping to alleviate symptoms such as pain, fever, swelling, and tenderness. In addition, COX-II inhibitor nanoparticles have been investigated to improve the efficacy of the treatment.

Keywords: Acetamide derivatives, NSAIDs, Prodrug, COX-II inhibitors

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Introduction

Inflammation is a complex physiological response that has been implicated in various diseases, including rheumatoid arthritis, a serious condition. Finding effective anti-inflammatory agents that can address the degenerative effects of inflammation while minimizing adverse reactions has been a significant challenge. Inflammation is also linked to several other health conditions, such as cancer [1], diabetes [2], obesity [3], asthma [4], fatty liver [5], microbial infections [6], and Alzheimer's disease [7]. The enzyme cyclooxygenase (COX) plays a crucial role in converting arachidonic acid (C20AA), a product of the intricate prostaglandin pathway, into prostaglandin H2 (PGH2), as illustrated in **Figure 1**.

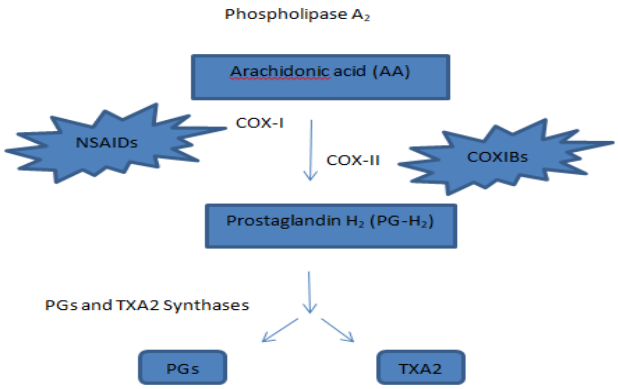


Figure 1. A diagram of the prostaglandin synthesis.

Among the most potent anti-inflammatory agents are cyclooxygenase I and II (COX-I and COX-II) [8], nitric oxide donors (NOs), and inducible nitric oxide synthetase (iNOS) [9], all of which are organic synthetic compounds. COX-II, an enzyme that plays a major role in pathological inflammation, is often targeted for its strong anti-inflammatory effects. Acetamide derivatives are crucial structural components found both in nature and within approved small-molecule drugs.

A quick overview of acetamide derivatives highlights their extensive biological activities, including antimicrobial [10], anti-inflammatory [11], anti-tumor [12], anti-HIV [13], antiviral [14], anticonvulsant [15], analgesic [16], anti-cancer [17], anti-allergic [18], sedative-hypnotic [19], and antihypertensive [20] effects. The flexibility in synthesizing quinazolinone derivatives has expanded the range of biological activities that these compounds can exhibit [21]. The structural differences between these COX-II inhibitors and classic NSAIDs are notable, primarily because they lack the traditional amide structure.

This review will explore the importance of different structural modifications of acetamide derivatives, focusing on their relevance to COX-II inhibition and drug and peptide synthesis. The role of acetamide compounds in medicinal chemistry is significant, with amide bond formation being a key process in both organic and synthetic medicinal chemistry.

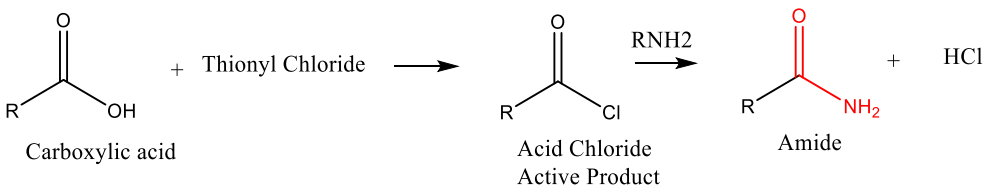
Results and Discussion

Synthesis of amides

Several methods are available for synthesizing amides.

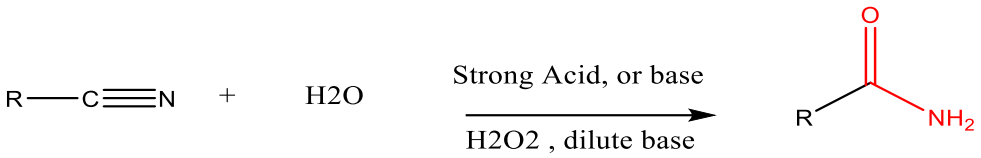
Via acid chlorides

Carboxylic acids or esters are not reactive enough to form amides directly, so they must first be activated to acid chlorides, where the halogen serves as a suitable leaving group [22].



Hydrolysis of nitriles

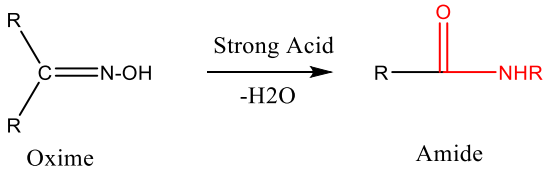
The nitrile group is notably reactive and can be easily hydrolyzed under both acidic and basic conditions [23].



This technique has been applied in the hydrolysis of harmful compounds containing cyanide groups.

Beckmann rearrangement of oximes

When a ketone reacts with hydroxylamine, it produces a ketoxime (oxime), which is not stable and can undergo a rearrangement in the presence of a strong acid, resulting in the formation of an amide [24].



Modern approaches in green chemistry for amide synthesis now include reactions conducted under environmentally friendly conditions such as in water [25], via microwave heating [26], using ultrasound [27], or through electrochemical synthesis [28].

Peptide synthesis in the liquid phase

Various coupling agents are commonly used in the formation of amides during peptide synthesis, both in liquid and solid-phase processes. Examples of these agents include N,N′-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), and 1,1′-carbonyldiimidazole (CDI), as illustrated in **(Figure 2)**. These reagents are typically applied when synthesizing macromolecules in solution, while different strategies are utilized in solid-phase synthesis [29].

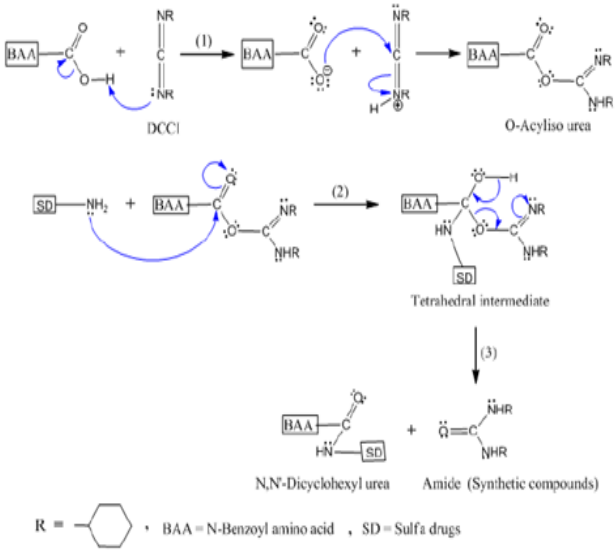


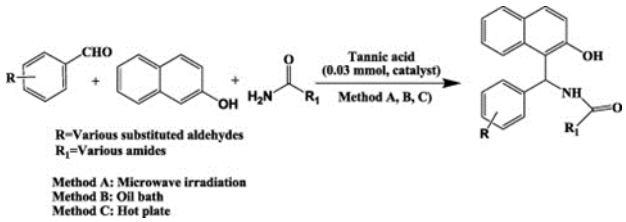
Figure 2. Mechanism preparation of amide derivatives using DCCI

Amide formation reactions constitute approximately 16% of all chemical reactions involved in the development of new pharmaceuticals, making them one of the most frequently performed reactions in the industry.

Greener approaches for acetamide synthesis

Green chemistry education, particularly at the introductory level, aims to establish a robust understanding of key principles related to process efficiency, biocatalysis, solvent and reagent selection, equipment usage, and operational excellence [26].

A novel, simple, cost-effective, and environmentally sustainable method for synthesizing acetamide derivatives has been reported. This approach employs thermal (using hot plates and oil baths) and microwave irradiation techniques, eliminating the need for solvents and utilizing tannic acid as a catalyst [30].



Cyrene has been suggested as a more sustainable alternative to traditional coupling solvents like DMF and NMP for amide bond formation, particularly when starting from acid chlorides [22] and carboxylic acids [31], yielding remarkable outcomes. Bousfield *et al*. proposed a straightforward method for amide synthesis from acid chlorides using a bio-compatible solvent, as illustrated in **Figure 3** [31].

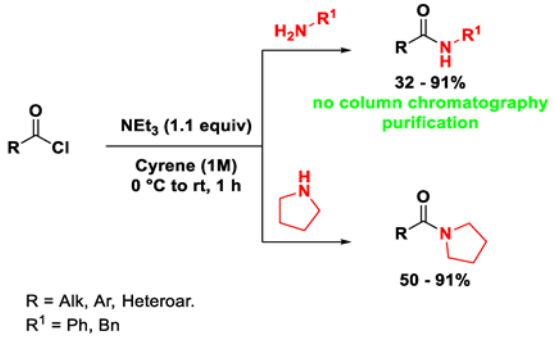
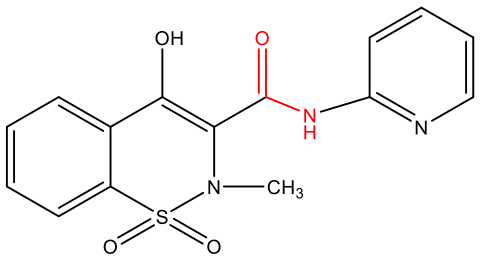


Figure 3. Two methods for amide formation reactions utilizing Cyrene as a catalyst.

Classification of amides in selective COX-II

Amides are categorized into three groups based on their naming conventions: primary amines, secondary amines, and tertiary amines, where R can be either aliphatic or aromatic. Secondary amides are commonly found in NSAIDs, peptides, and polymers. For instance, piroxicam contains a secondary amide as its pharmacophore, stabilized through hydrogen bonding. This amide acts as a linker between the pyridine ring and the benzothiazine nucleus, making it a cyclooxygenase-2 (COX-2) inhibitor. Importantly, piroxicam does not contain a carboxylic acid moiety, setting it apart as a modified NSAID with enhanced COX-2 selectivity [32].



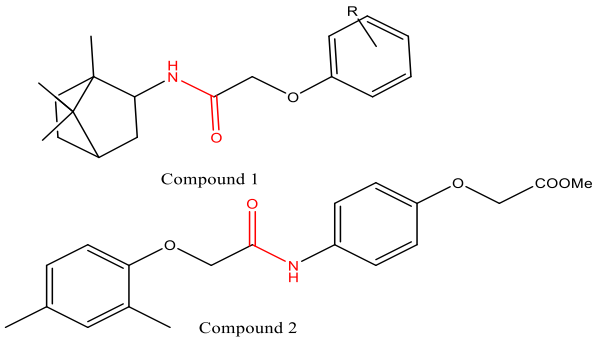
4-Hydroxy-2-methyl-N-(2-pyridinyl)-2H-1,2 benzothiazine-1,1-dioxide (piroxicam)

These compounds are effective in managing conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA).

Chemistry and pharmacology of new acetamide derivatives as COX-II inhibitors

Compounds containing a phenoxy acetamide group

Rani *et al*. [33] developed substituted phenoxy acetamide derivatives, specifically compounds 1 and 2. These compounds were tested for their analgesic, anti-inflammatory, and antipyretic properties using various methods: carrageenan-induced rat paw edema, Eddy's hot plate test, and the brewer's yeast-induced pyrexia method for compounds I and II, respectively [33].



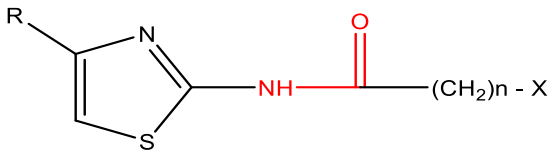
The chemical structures of methyl 2-(4-(2-(2,4-dimethylphenoxy)acetamido) phenoxy)acetate (I) 2-(substituted phenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide (II) derivatives

Compounds containing a phenol acetamide group

Cheng's research team assessed the anti-inflammatory properties of two phenol-based compounds, determining their IC50 values of 0.768 and 0.616 mol/L in vitro, compared to Celecoxib, whose IC50 was recorded at 0.041 mol/L as a reference [34].

Compounds containing a thiazole acetamide group

Thiazole derivatives have been identified as selective inhibitors for COX-II.



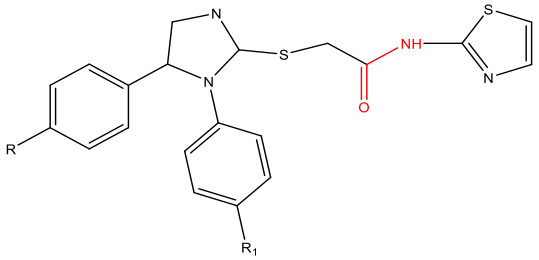
The general structure of thiazolyl-N- substituted amide derivatives.

A regression analysis was performed to investigate if there is a correlation between the anti-inflammatory activity, represented by CPE% (percentage inhibition of carrageenan-induced paw edema in mice, in log-transformed form) [10].

$$\log CPE\ \% = -0.001(0.036)\ clog\ D\ 7.6 + 0.0002(0.01) clog\ D7.42 + 1.672(0.032)$$
$$n = 26,\ r = 0.067,\ r2 = 0.005,\ s = 0.124,\ F = 0.052,\ p = 0.949 \quad (1)$$

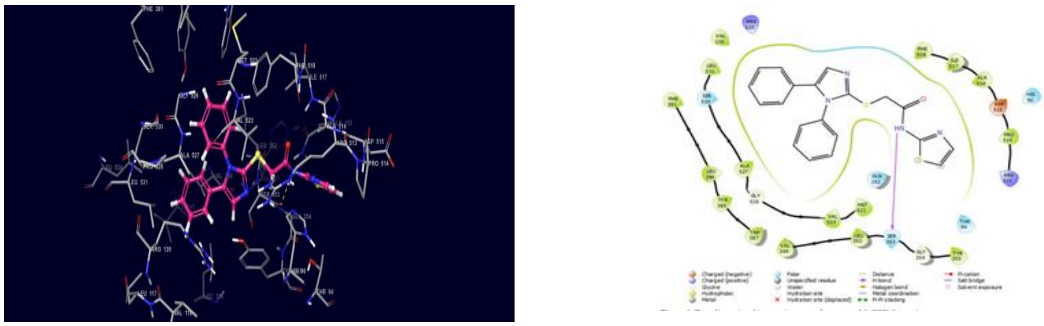
Various physicochemical factors, including lipophilicity, polarizability, and both steric and electronic characteristics, play a significant role [10].

Compounds having an imidazole acetamide group



[(1,5-disubstituted phenyl-1H-imidazol-2-yl) thio] -N-thiazol-2-yl acetamide derivatives

In molecular docking studies, interactions between the functional groups of the compound—such as the ring nitrogen, carbonyl, phenyl, and secondary amine—and the active site amino acids of COX-II were observed [35]. The acetamide nitrogen interacts through hydrogen bonding with amino acids Trp 387 and Ser 353, suggesting a strong theoretical link to the compound's practical anti-inflammatory effects **(Figure 4)** [35].

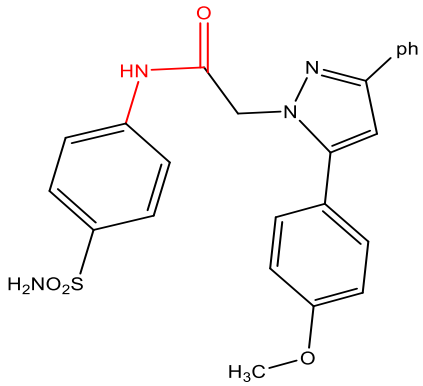


a) b)

Figure 4. The 3D and 2D docking of the thiazole acetamide derivatives with COX-II

Compounds having a pyrazole acetamide group

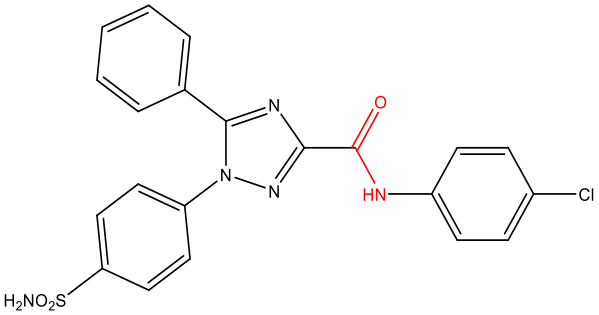
Pyrazole, a prominent pharmacophore in medicinal chemistry, shows significant promise as a basis for developing anti-inflammatory agents, especially COX-II inhibitors [36]. One such compound, 2-(5-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl) acetamide, which includes an acylamino linker, has demonstrated notable anti-inflammatory potential.



2-(5-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)-N-(4-sulfamoylphenyl)acetamide.

Compounds having a triazole acetamide group

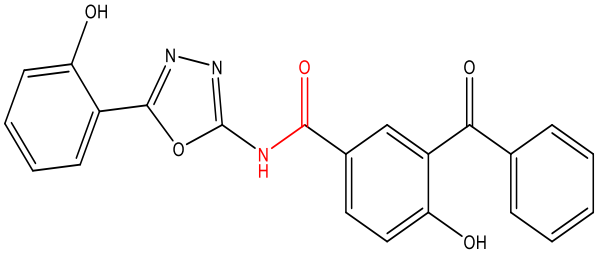
The COX-2 inhibitory effectiveness and selectivity of triazole acetamide derivatives are primarily influenced by the characteristics and size of the substituents located at the C-3 and C-4 positions. Recent developments have led to the synthesis of novel compounds with enhanced COX-2 selectivity, incorporating 4-NH2SO2Ph and amide groups, which are critical for their biological activity [37].



N-(4-chlorophenyl)-5-phenyl-1-(4-sulfamoylphenyl)-1H-1,2,4-triazole-3-carboxamide

Compounds having an oxadiazole acetamide group

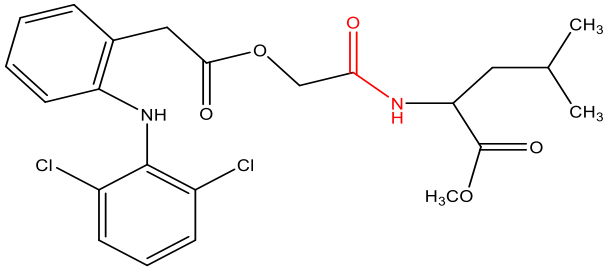
The use of the 1,3,4-oxadiazole moiety as a bioisosteric replacement in drug development has been well-established. Recently, three research teams synthesized COX-II inhibitors incorporating oxadiazole derivatives. One such compound, 3-benzoyl-N-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-4-(1-oxidaneyl) benzamide, combines an amide bond with the oxadiazole group of benzophenone, demonstrating potential anti-inflammatory properties [38].



3-benzoyl-4-hydroxy-N-(5-(2-hydroxyphenyl)1,3,4-oxadiazole-2-yl)benzamide.

Prodrugs of COX-II acetamide inhibitors

COX-2 selective inhibitors were developed to avoid the gastrointestinal side effects commonly associated with traditional NSAIDs, although they still carry risks such as elevated serum potassium and potential liver toxicity. Prodrugs derived from aceclofenac, a drug containing an amino acid, were designed to enhance solubility, maintain stability at acidic pH, and undergo hydrolysis at physiological pH 7.4. To mitigate some of the drawbacks, the amino acid acetamide linkage in aceclofenac was synthesized using DD [39].



methyl (2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)acetyl)leucinate

Methyl(2-(2-(2-((2,6-dichlorophenyl)amino) phenyl)acetyl) leucinate.

Mutual prodrugs

Mutual prodrugs are defined as two active pharmaceutical compounds that are chemically joined, allowing each drug to serve as a functional group for the other. The acetamide group is suitable for the design of prodrugs targeting COX-II inhibitors, where amidase acts as the enzyme responsible for hydrolysis in vivo [33].

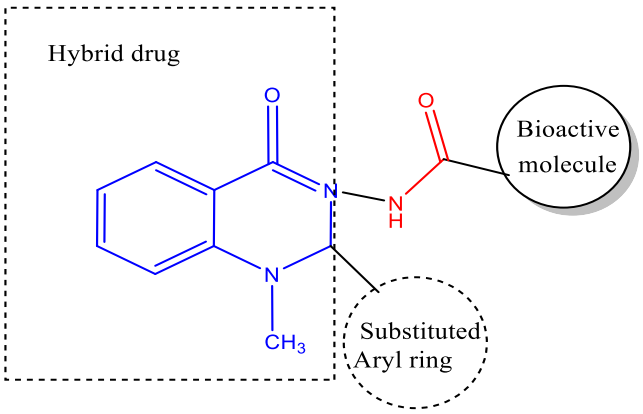


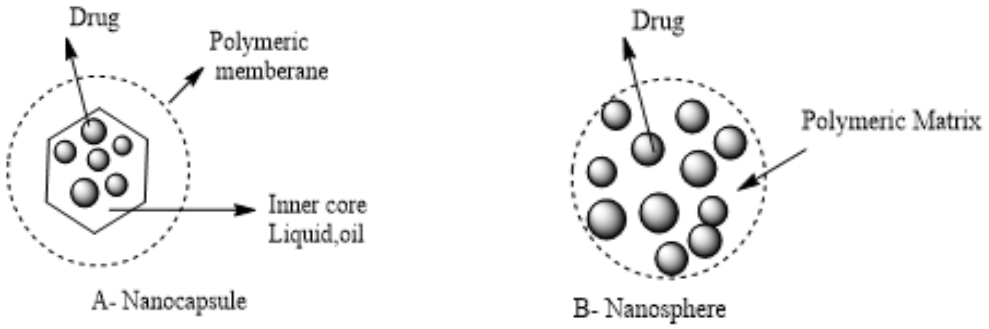
Figure 5. Molecular design for hybrid bioactive acetamide compounds selective for COX-II.

By exhibiting cyclooxygenase-2 inhibitory activity, new benzophenone-linked oxadiazole compounds were developed and shown to be effective in reducing inflammatory paw edema [38]. Additionally, a novel hybrid drug, combining bioactive molecules with various substituted aryl compounds, is currently under development as a mutual prodrug **(Figure 5)** [40, 41].

Reactive oxygen species (ROS), generated by COX-2, play a key role in inhibiting the production of pro-inflammatory cytokines such as NO, PGE2, IL-6, and TNF-α18. Inhibition of COX-2 leads to a significant reduction in ROS levels, preventing the activation of NF-κB and maintaining it in its inactive state by binding to P-IκB [42].

Nanoparticles of NSAIDs

Nanoparticle-mediated drug delivery systems have been utilized in the development of anti-inflammatory medications. The underlying mechanisms of inflammation contribute significantly to diseases like rheumatoid arthritis, inflammatory bowel disease, and osteoarthritis. Recently, a variety of hybrid nanoparticles (NPs) have been studied for their potential in treating inflammation [43]. Recent advancements highlight the synthesis of multiple materials into nanostructures, maximizing the properties of each material to enhance biocompatibility and targeting precision. These nanoparticles possess distinct characteristics that enable targeted delivery to specific tissues. For NP-based drug delivery systems, manufactured nanoparticles serve as carriers, loaded with anti-inflammatory agents **(Figure 6)** [43].



a) b)

Figure 6. Two polymeric nanostructures of drugs; A) nanocapsule, and B) nanosphere.

Polymeric nanoparticles, such as nanospheres and nanocapsules, serve as highly effective drug delivery platforms. These systems often use acetamide linkages to bind the polymer to the drugs, similar to liposomes and micelles. For targeted drug delivery, lipid-based nanostructures and phospholipids are particularly advantageous. The rapidly advancing field of nanomedicine, especially nano delivery systems, utilizes COX-II inhibitors at the nanoscale, not only as diagnostic tools but also to deliver therapeutic agents directly to specific regions in a controlled manner [44].

Conclusion

The design of new pharmacological agents has been a key focus for medicinal chemists. This review emphasizes the role of spacer acetamide linkages in potent COX-II inhibitors, including a variety of aromatic and heterocyclic compounds, as well as nano-NSAIDs, aimed at reducing the adverse effects associated with these treatments.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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