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An Overview on Ibuprofen Derivatives: Advancements in NSAIDs for Enhanced Anti-inflammatory and Analgesic Efficacy

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are widely used for pain relief and inflammation management. However, their clinical utility is often limited by gastrointestinal side effects arising from non-selective inhibition of both COX-1 and COX-2 enzymes. To address this issue, the ibuprofen derivatives with structural modifications aimed at enhancing COX-2 selectivity while minimizing COX-1 inhibition. The approach involved incorporating specific functional groups and substituents into the ibuprofen scaffold to modulate its binding affinity and selectivity for the COX-2 active site. These modifications were guided by computational modeling, molecular docking and structure-activity relationship (SAR) studies. The synthesis of the novel ibuprofen derivative such as ibuprofen amide and ibuprofen acyl hydrazide derivatives, ibuprofen quinoline conjugate, ibuprofen with hydroxyl group or hetero atoms has been investigate with the help of computational technology. The cucumis melo is also reported to posses anti-ulcer potential and study investigated the mechanism of underlying the anti-ulcer potential. All the molecule showed higher affinity towards Cox-2 enzyme as compared to traditional ibuprofen and also have cucumis melo showed ability to mitigate ulcer and posses anti- ulcer effect.

Keywords: NSAIDs, Ibuprofen Derivative, Computational Modeling, Molecular Docking, SAR, Cucumis Melo, Ulcer, Anti-Ulcer

1. Introduction

Ibuprofen or 2-[4(2-methyl)propyl phenyl]propionic acid is the imitative of propionic acid and associates to the paradigm of Non selective Cox inhibitors of a Non steroidal Anti-inflammatory Drug. It is a white crystalline powder with a molecular formula C13G18O2 and molecular weight of 206.29g/mol [1]. It is frequently remunerations both in prescription and over the counter forms. The typical over the counter dosage for drugs is 200mg to 400mg every 4-6 hours with a maximum daily limit of 1200mg. For prescription strength higher doses may be recommended under medical Supervision. It is effectual for ambit of conditions including headache, muscle cramps, toothache, menstrual cramps, arthritis, minor injuries, fever reduction etc. Ibuprofen is available in many forms comprising tablets, capsules, liquid suspension and topical gels. Ibuprofen have remain a popular choice for pain and inflammation relief due to it's effectiveness and availability.

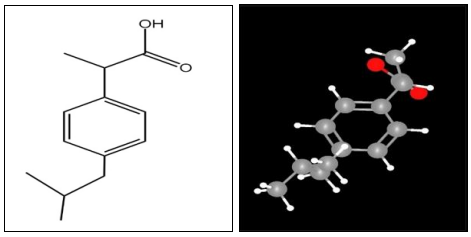

Fig 1: 2D and 3D structure of Ibuprofen

Mechanism of Action

Ibuprofen non-selectively inhibits both COX-1 and COX-2 enzymes. COX-1 is involved in the production of prostaglandins that protect the gastric mucosa, support kidney function, and regulate platelet aggregation. COX-2 is primarily induced during inflammation and produces prostaglandins that mediate pain and inflammatory responses. By inhibiting these enzymes, ibuprofen decreases the synthesis of prostaglandins, which are lipid compounds that play key roles in inflammation, pain signaling, and fever Regulations. The decrease in prostaglandin levels leads to a reduction in sensitization of pain receptors (nociceptors), which results in diminished pain perception as well as lower levels of prostaglandins reduce vasodilation and the permeability of blood vessels, which decreases the influx of immune cells and fluid to the site of injury, thus mitigating inflammation [2, 3]. Ibuprofen acts on the hypothalamus to lower elevated body temperature. By inhibiting prostaglandin E2 synthesis, which is elevated during fever, ibuprofen helps restore normal thermoregulation. The inhibition of COX-1 can also impact platelet aggregation since COX-1 is responsible for producing thromboxane A2, a promoter of platelet aggregation. This can lead to a temporary anti-platelet effect.

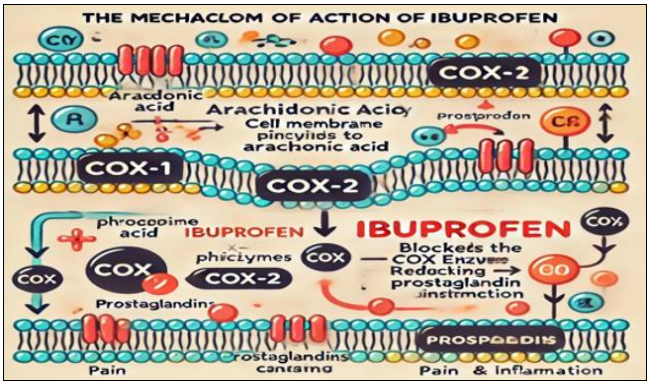

Fig 2: Mechanism of Action of Ibuprofen

Side effects

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) commonly used for pain relief, inflammation, and fever reduction. While it's generally safe when used as directed, it can have side effects, especially with long-term or high-dose use such as Stomach issues, nausea, heartburn, indigestion, or stomach pain. Headache or dizziness, Rash or itching. There can be some serious side effects as well which are less common but can occur, especially with high doses or prolonged use of drug. In Gastro intestinal can cause ulcers, bleeding, or holes in the stomach or intestine, which may cause black or tarry stools, Ibuprofen can increase the risk of heart attack or stroke, particularly with long-term useand may impair kidney function over time, especially in those with preexisting kidney conditions [3]. Liver issues are rarely observed but can lead to liver damage in some cases, indicated by jaundice. Some Allergic reactions can be seen in person with poor immune response including swelling, difficulty breathing, and severe skin reactions.

Ibuprofen Analogue

An ibuprofen analogue is a compound similar in structure or function to ibuprofen, typically used to relieve pain, reduce inflammation, and lower fever. These analogues share a similar chemical structure or mechanism of action but may vary slightly in molecular composition. They often belong to the class of nonsteroidal anti-inflammatory drugs (NSAIDs) and may be prescribed as alternatives when ibuprofen is unsuitable or when different properties, like potency or half-life, are desired [3]. The ibuprofen side effects are known by all and to overcome this problem various ibuprofen analogue are been designed with the aim of having desired changes in the structure so as to reduce the toxicity. The design, synthesis and evaluation of the different analogue can be time consuming and can be difficult as well as not economical, so to over come these molecular docking have shown the impressive role in the study of different drug analogue. It is a computational technique used to predict how a small molecule (ligand) will bind to a target macromolecule, typically a protein [4]. This approach is widely used in drug discovery and development to identify and optimize potential drug candidates. Docking helps understand the interactions between molecules at the atomic level and provides insights into the binding affinity and orientation of the ligand within the binding site. Molecular docking is an essential tool in structural biology and drug discovery that provides valuable insights into molecular interactions [5]. When combined with experimental and other computational methods, it can significantly accelerate the process of drug design and discovery [6].

The information related tosome of the ibuprofen analogue have been given below which have show better response when docking study have been done and compared to classical ibuprofen.

Analogue 1. Ibuprofen amide and Ibuprofen hydrazine derivative

The synthesis of the novel ibuprofen derivatives through their *in silico* and *in vitro* Cox-2 inhibitory activities was inquired. The ibuprofen amide and hydrazine derivatives have been synthesized to improve Cox-2 selectivity. The prostaglandin H synthase(PGHS) catalyses is the first step in the cyclic pathway of eicosanoid metabolism [7]. The Cox subunit within the PGHS is found on the opposite side of the heme and is located in the end of a long narrow hydrophobic to channel Arg120, Tyr 385 and Ser530 are important residues of the active site of Cox. Arg120 of also the great importance for inhibitor of Cox. Docking studies revealed interactions with COX-2, particularly involving Arg120, indicating strong hydrogen bonding and hydrophobic interactions [8]. Molecule N-(4,4-diethoxybutyl)-2-(4-isobutylphenyl) propanamide showed the highest affinity, with binding energies close to that of arachidonic acid.

In Vitro COX-2 Inhibition: CompoundN'-(1H-indol-3-ylmethylene)-2-(4-isobutylphenyl)propanehydrazide demonstrated the most effective COX-2 inhibition compared to ibuprofen, with inhibition rates higher than the parent compound's [9, 10].

These findings suggest the potential of these both derivatives, has improved COX-2 selective inhibitors suitable for *in vivo* studies. The study focused on synthesizing novel ibuprofen derivatives with enhanced selectivity toward cyclooxygenase-2 (COX-2), an enzyme involved in inflammation pathways. Due to the non-selective inhibition of COX-1 and COX-2 by traditional NSAIDs (including ibuprofen), side effects like gastrointestinal and cardiovascular issues often arise.

Targeting COX-2 selectively can help reduce these adverse effects [11, 12].

The modifications targeted the ibuprofen carboxyl group to improve COX-2 selectivity by promoting specific binding interactions within the COX-2 active site, especially with key amino acids [13, 14, 15].

Molecule N-(4,4-diethoxybutyl)-2-(4-isobutylphenyl)propanamide demonstrated the highest docking affinity with COX-2, registering a binding energy of -65 kJ/mol, similar to arachidonic acid (the natural COX substrate) [16].

Affinity scores of N-(4,4-diethoxybutyl)-2-(4-isobutylphenyl)propanamide, which showed binding affinities that suggested strong interactions with COX-2's Arg120 and Tyr355 residues [17]. These docking scores highlight these compounds' ability to mimic arachidonic acid's hydrophobic interactions within the enzyme's binding pocket, particularly through their hydrocarbon chains.

In Vitro COX-2 Inhibition, N'-(1H-indol-3-ylmethylene)-2-(4-isobutylphenyl)propanehydrazide exhibited the highest COX-2 inhibition, achieving 21.5% inhibition at a concentration of 50 µM, surpassing ibuprofen's inhibition rate of 9.7% [17].

The increased inhibition efficiency of these compounds correlates with the strong docking interactions observed *in silico*, where these molecules could effectively interact with COX-2's hydrophobic and active-site residues, stabilizing their binding and blocking arachidonic acid's access to the enzyme. The increased selectivity and binding affinity are attributed to modifications that enhance interactions with COX-2 specific residues, especially Arg120 [18]. The bulky and hydrophobic characteristics of the synthesized derivatives help them occupy the active site effectively, thus blocking COX-2 selectively. These interactions exploit the larger binding channel of COX-2 compared to COX-1, improving affinity and inhibition without impacting COX-1 as strongly, which is likely to reduce the gastrointestinal side effects commonly associated with classical ibuprofen.

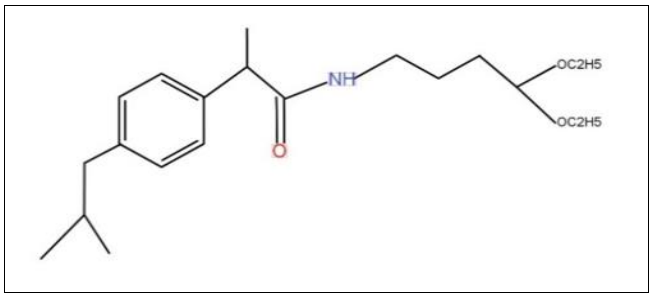

Fig 3: N-(4,4-diethoxybutyl)-2-(4-isobutylphenyl) propanamide

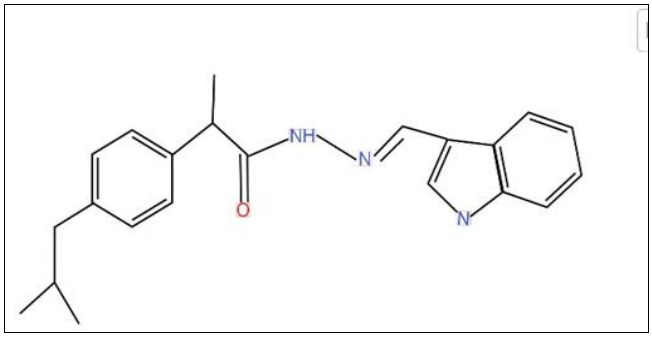

Fig 4: N'-(1H-indol-3-ylmethylene)-2-(4-isobutylphenyl) propanehydrazide

Analogue 2: Ibuprofen with Cucumismelo derivative

The use of NSAIDs class of drugs have cause major problem of peptic ulcer. Peptic ulcer is a discontinuation or abrasive of the stomach/intestinal mucus or upper part of the small intestine by digestive juice or intestinal secretion. It is usually in the fundis part of the stomach or lower esophageal sphincter or the upper part of duodenum. Ibuprofen, a commonly used NSAID, can cause gastric ulcers by reducing prostaglandin levels, which protect the stomach lining. The study investigate the melon extract can mitigate these effects, focusing on its bioactive compoundsreduce ulcer severity and inflammation.The study Involved administering different concentrations of Cucumis melo extract to male Wistar rats before inducing ulcers with ibuprofen. The extract significantly reduced ulcer severity by lowering total gastric acidity, decreasing ulcer scores, and improving antioxidant activity. Key measurements included levels of oxidative stress indicators and the activity of H+/K+ ATPase [19, 20], an enzyme linked to acid secretion in the stomach. Furthermore, the study utilized molecular docking to assess how specific compounds in Cucumis melo, such as folic acid and certain phytosterols, interact with the prostaglandin E2 receptor, potentially enhancing mucosal protection.

The molecular docking was conducted to investigate compounds in Cucumis melo interact with the prostaglandin E2 receptor (PGE2), which plays a role in gastric protection. Out of 66 compounds screened, five compounds demonstrated notable binding affinity with the PGE2 receptor [21], which suggests a potential for anti-ulcer activity by enhancing mucosal defense.

The top compounds based on their docking scores were:

Folic acid – Showed the highest docking score (-9.965 kcal/mol), suggesting strong binding potential. Folic acid formed multiple interactions with the PGE2 receptor, including hydrogen bonds with residues like THR 206, ARG 333, and TYR 114, which are crucial for receptor binding [22].

Delta7-avenasterol – Had a docking score of -9.181 kcal/mol and formed hydrogen bonds with TYR 114, alongside several hydrophobic interactions.

Codisterol – With a docking score of -8.976 kcal/mol, codisterol also showed hydrogen bonding and hydrophobic interactions with key receptor sites.

Stigmasta-5,7,22-trien-3-ol, (3beta) – Docking score of -8.879 kcal/mol, indicating moderate binding affinity.

24-Methylenecholesterol – Scored -8.82 kcal/mol, also indicating notable binding interactions [22].

These compounds interacted with the same binding site as misoprostol (a standard anti-ulcer drug), which enhances PGE2 receptor activity. This similarity suggests that the bioactive components in Cucumis melo may exhibit protective effects on the gastric mucosa by mimicking or supporting prostaglandin activity, thereby reducing acid secretion and increasing mucosal defense,overall the findings indicate that Cucumis melo extract can effectively reduce gastric ulceration, possibly by increasing protective prostaglandins and reducing oxidative damage in the stomach. This suggests that Cucumis melo could be a natural alternative to mitigate ibuprofen-induced gastric ulcers.

Analogue 3: Ibuprofen derivative towards Cox and interleukin site

Theibuprofen derivatives aimed at improving anti-inflammatory efficacy and minimizing adverse effects associated with ibuprofen, such as gastrointestinal irritation. Ibuprofen is widely used as an NSAID, but side effects, especially gastrointestinal issues, necessitate improved derivatives. This research focuses on the design, synthesis, and evaluation of ibuprofen analogs, emphasizing Compound 2-(2-(4-isobutylphenyl) propanoyl)hydrazine-1-carboxamide, which shows promising activity against COX-2 and Interleukin (IL)-6, suggesting potential for reduced inflammatory response without the typical side effects [23, 24].

The synthesis of derivatives through chemical modifications to ibuprofen, notably masking the carboxylic acid group to reduce ulcerogenic potential. Compound 2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide, which shows variation in molecular structure that impact the ibuprofen bioactivity.

Molecular Docking studies were conducted using AutoDock Vina to predict binding affinities of the compounds to COX-1, COX-2, and IL-6 protein targets [25]. Compound 2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide showed selective binding affinity towards COX-2 and IL-6, attributed to specific electrostatic interactions and hydrogen bonds that enhanced stability in binding sites.

To confirm stability, Molecular Dynamic simulations of the above ibuprofen derivative with IL-6 were performed over 150 ns, highlighting stable interactions and minor fluctuations, indicating a strong and consistent binding.

ADMET stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity. These are key pharmacokinetic properties studied in drug development to predict a compound's behavior in the body, including how well it is absorbed, how it is distributed to tissues, how it is metabolized, how it is excreted, and its potential toxicity.The ibuprofen derivative was assessed for pharmacokinetic properties using SwissADME [26, 27]. Compound 2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide demonstrated favorable drug-likeness, high gastrointestinal absorption, and no blood-brain barrier penetration, suggesting minimal toxicity and improved safety.

In Vitro Anti-inflammatory Activity the ibuprofen derivative showed 90.8% inhibition of RBC hemolysis in membrane stability tests, indicating strong anti-inflammatory potential.The Compound 2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide emerged as the lead candidate due to its high binding affinity for COX-2 and IL-6, stable interactions, favorable [28] ADMET properties, and promising anti-inflammatory effects. It presents a potential NSAID with reduced adverse effects and may be useful in treating inflammatory diseases and conditions with IL-6 involvement [29], such as COVID-19 and depressive disordersthus suggests compound2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamideas a promising ibuprofen analogue.

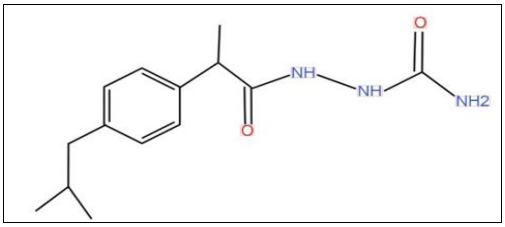

Fig 5:-2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide

Analogue 4: Ibuprofen-quinoline conjugates

Thedesign, synthesis, and biological evaluation of ibuprofen-quinoline conjugates as potential anti-inflammatory and analgesic agents have been done. These conjugates combine a quinoline moiety with ibuprofen through an alkyl chain, aiming to enhance anti-inflammatory effects while reducing gastrointestinal side effects commonly associated with NSAIDs. The compounds were tested for anti-inflammatory, analgesic, and ulcerogenic properties, showing promising results.In molecular docking, the study involved computational docking to validate the binding affinities of these conjugates towards COX-2, an enzyme targeted to reduce inflammation, and interleukin-6 (IL-6) [30], a cytokine associated with inflammatory responses. The docking studies demonstrated strong interactions between the synthesizedcompound2-[4-(2-propyl-6-chloroquinoline-4-ylmethoxylphenyl]propanoicacid and the active sites of COX-2 and IL-6 [30], supporting ibuprofen-quinoline conjugate potential as selective COX-2 inhibitors with reduced gastrointestinal risks compared to traditional NSAIDs like ibuprofen.

Thedesign of ibuprofen-quinoline conjugates as derivatives of ibuprofen are synthesized by linking the ibuprofen moiety with a quinoline ring through alkyl chains of varying lengths. This design leverages the anti-inflammatory properties of ibuprofen and the COX-2 selectivity of quinoline-based structures, aiming to enhance anti-inflammatory efficacy while minimizing gastrointestinal side effects. These explores different substituents on the quinoline ring, including fluoro and chloro groups, to optimize the anti-inflammatory and analgesic properties of the conjugates [31, 32]. QSAR models were developed to understand the relationship between the structural properties of the compounds and their observed biological activities. The QSAR analysis highlighted the importance of charge-related descriptors and linker length, providing insights into the structure-activity relationships (SAR).QSAR analysis confirmed that three-carbon linkers and halogenated (fluoro or chloro) substituents on the quinoline ring enhanced anti-inflammatory and analgesic activities [33, 34].The successfull synthesize of a series of ibuprofen-quinoline conjugates, which demonstrated significant anti-inflammatory and analgesic properties with a favorable safety profile. Compounds with three-carbon alkyl linkers and specific substituents on the quinoline ring (fluoro or chloro) were identified as the most promising candidates.

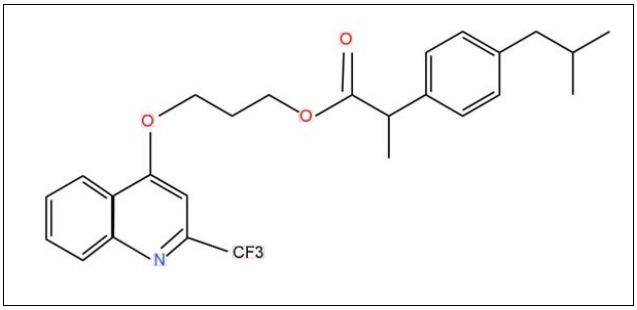

Fig 6: 2-[4-(2-propyl-6-chloroquinoline-4-ylmethoxylphenyl]propanoic acid

These conjugates exhibited COX-2 selectivity, reduced gastric toxicity, and additional anti-inflammatory effects through suppression of pro-inflammatory cytokines, making them promising drug candidates for further development.

Conclusion

All the new ibuprofen derivatives has been successfully demonstrated anti-inflammatory activity. The molecular docking study of new compounds were investigated against Cox isoenzyme and interleukin 6 and effective action against peptic ulcer. The molecules N-(4,4-diethoxybutyl)-2-(4-isobutylphenyl)propanamide, N'-(1H-indol-3-ylmethylene)-2-(4-isobutylphenyl)propanehydrazide, 2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide, 2-[4-(2-propyl-6-chloroquinoline-4-ylmethoxylphenyl]propanoic acid showed binding energies closest to that of arachidonic acid by interacting with Cox-2, particularly involving Arg120 and exhibited the highest Cox-2 inhibition achieving 21.5% inhibitionsurpassing ibuprofen rate 9.7%. The extract of Cucumis melo significantly protect the integrity of gastric acidity. It also increase the percentage inhibition antioxidants activity and prostaglanfin synthesis. The 2-(2-(4-isobutylphenyl) propanoyl) hydrazine-1-carboxamide demonstrated strong binding affinity towards the selected protein site in molecular docking analysis including the IL target site which serves on the key protein site, which may be useful in somewhat lowering pro-inflammation and depression. The molecule – 2-[4-(2-propyl-6-chloroquinoline-4-ylmethoxylphenyl]propanoic acid, a ibuprofen quinoline conjugate exhibited potent anti-inflammatory properties compared to classical ibuprofen. The furthermore understanding for biological effects of the ibuprofen derivatives research is going on.

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Conflict of Interest

The authors declare that no conflict of interest of any financial or other issues.

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