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Recent Advances in the Synthesis and Pharmacological Evaluation of Naproxen Derivatives: A Review

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ABSTRACT

Naproxen is a medication classified as a non-steroidal Anti-Inflammatory Drug (NSAIDs) utilized for its anti-inflammatory properties. The principal functional group in naproxen is the carboxyl group, prompting numerous researchers to modify this group to synthesize novel derivatives of naproxen and investigate their pharmacological efficacy, to discover more effective molecules than naproxen. This review examines the methodologies for synthesizing derivatives, with an emphasis on notable molecules exhibiting unique biological activity and the key techniques employed in these investigations. Modification involves introducing a triazole 5n moiety via transformation of the carboxyl group which has been found to enhance the efficacy of the derivative and constitute a potential treatment for prostate cancer. Some pyrazole and pyrazoline derivatives have shown anti-inflammatory and anti-proliferative activity, like derivative 9c which demonstrated high antioxidant activity due to the presence of a methoxy group (an electron-donating group), which increased its potency. It also exhibited vigorous anti-proliferative activity against MCF-7 cells, with an IC_{50} value of 1.49 µM. Research has also found that modifying the carboxyl group of naproxen to derivatives containing sulfur-containing heterocyclic rings, such as thiazole and thiadiazole 14a and 22q, whether as single or fused rings, enhances its anti-inflammatory and analgesic activity. Amines and amino acids 26a, 26b, 29b, 32b, and 33b have also been observed to enhance their anti-inflammatory and analgesic activity. These compounds exhibited high oral absorption and were not carcinogenic or toxic in rodent studies, showing safety and minimal ulceration. The most prominent derivatives that inhibit the Cyclooxygenase-2 (COX-2) enzyme are hydrazone derivatives that contain the functional group (-NH-N=CH-), and the substituted *m*-chlorophenyl 35c emerged as the most inhibitory derivative. Structural modification at the carboxyl group of naproxen yields diverse derivatives with enhanced pharmacological profiles and potential safety advantages over the parent compound.

Keywords: Naproxen, Derivatives Synthesis, Structure–Activity Relationship (SAR), Anti-inflammatory Activity, Analgesic Activity, COX-2 Inhibition, Pharmacological Evaluation

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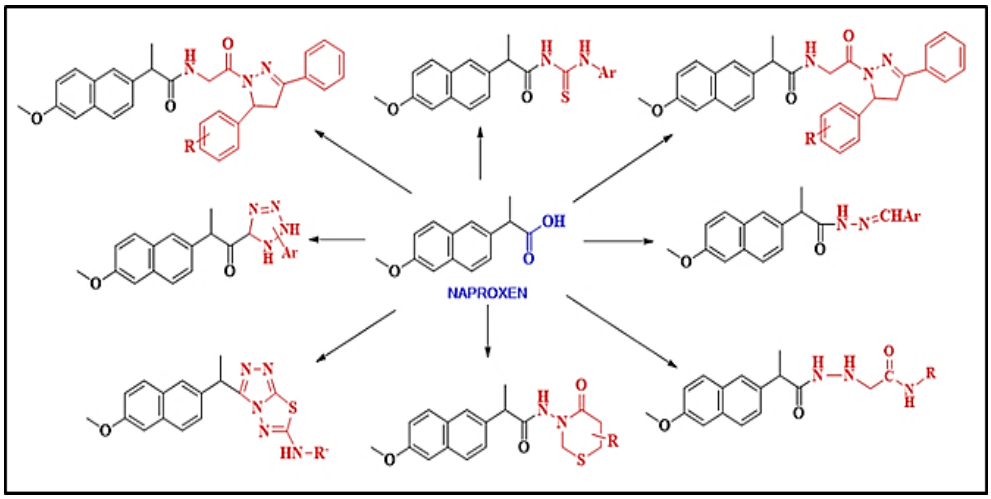
Graphical Abstract



(Prepared by Authors, 2025).

1. Introduction

Modifying the composition of drugs is one of the most critical research fields through which new compounds with significant pharmaceutical activities can be discovered that are superior to the original compounds. The most prominent of these modifications is the addition of new functional groups to pharmaceutical compounds or the introduction of heterocyclic groups that exhibit significant biological and pharmaceutical activities, thereby enhancing the effectiveness of the drug when incorporated into the structure (1).

Naproxen, IUPAC name: 2-(6-methoxynaphthalen-2-yl) propionic acid, molecular formula is $C_{14}H_{14}O_3$, is categorized as a non-steroidal Anti-Inflammatory Drug (NSAIDs). Naproxen alleviates pain, mitigates inflammation, and decreases fever, so it is employed to address the following conditions (1, 2): Prevalent types of pain include: dysmenorrhea, cephalalgia, odontalgia, myalgia, lumbago, osteoarthritis, rheumatoid arthritis, acute gout episodes, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, muscle strains and sprains, tendinitis, bursitis, and pyrexia. Naproxen undergoes significant hepatic metabolism. Approximately 95% of the naproxen is removed through urine. The half-life of naproxen ranges from 12 to17 hours (3). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) exhibit analgesic and antipyretic properties at standard dosages and possess anti-inflammatory effects at elevated dosages. They are differentiated from other analgesics by their non-narcotic nature, therefore preventing addiction (4). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), both non-selective and selective COX-2 inhibitors, are associated with a serious and potentially fatal increase in several cardiovascular problems. However, naproxen is considered the least likely of these drugs to cause cardiovascular problems, such as myocardial infarction. According to the American Heart Association, naproxen is considered safer compared to diclofenac, which has recently been warned of its severe heart risks, as dangerous as selective Cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and etoricoxib (Arcoxia). Studies link increased COX-2 selectivity to an increased risk of heart disease. Naproxen, like other NSAIDs, can cause gastrointestinal problems such as heartburn, gastritis, constipation, diarrhea, and peptic ulcers at high doses. Therefore, it is recommended to use it in conjunction with proton pump inhibitors, such as lansoprazole or omeprazole (5, 6).

2. Naproxen Structure

Naproxen consists of three groups: naphthalene, a methoxy group, and a propanoic acid group linked to position 2 with naphthalene. The propanoic acid group plays a key role in the mechanism of COX-2 inhibition. The presence of the carboxyl group in naproxen enables it to undergo various electrophilic and nucleophilic reactions. Therefore, many researchers have modified the carboxyl group to prepare a variety of pharmaceutical derivatives. The goal of changing the carboxyl group is to add new organic groups to naproxen to create derivatives with higher pharmaceutical activity than the original drug (naproxen).

3. Preparation of Naproxen

Syntex's industrial production of naproxen began with 2-naphthol as follows (Figure 1):

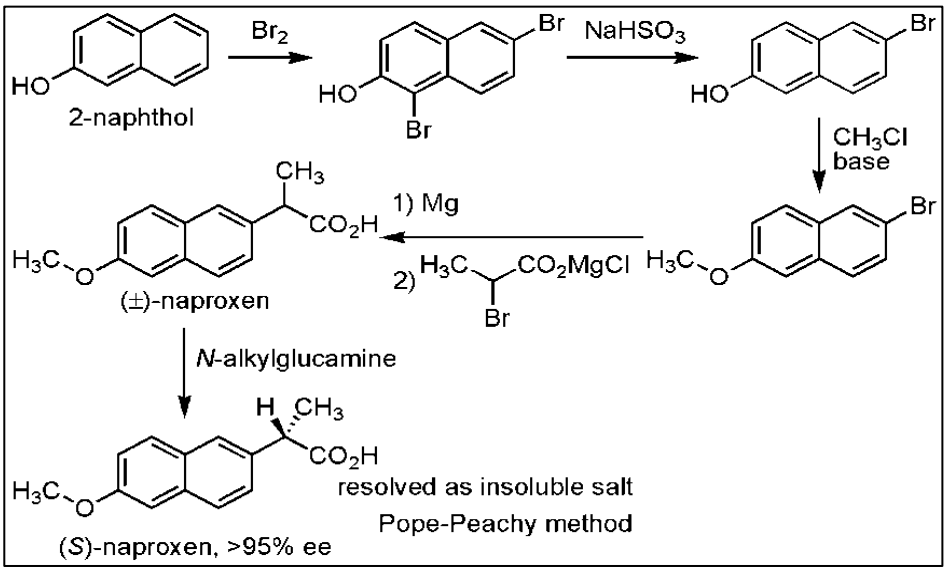


Figure 1. Industrial synthesis of naproxen (**Dilekoglu and Yapici (7)**).

4. Mechanism of Naproxen's Action

The mechanism of naproxen's action entails the inhibition of cyclooxygenase enzymes COX-1 and COX-2, predominantly COX-2, hence diminishing the synthesis of prostaglandins **(7, 8)**. COX-1 and COX-2 are enzymes that catalyze the transformation of arachidonic acid into prostaglandin G (PGG), the preliminary phase in the biosynthesis of prostaglandins and thromboxanes implicated in rapid physiological responses **(9)**. Prostaglandins are endogenous molecules that play critical roles in the body, including the perception of pain, suppression of stomach acid secretion, promotion of intestinal mucosal secretion, and mediation of inflammation and pyrexia. COX-1 is present in the majority of tissues, while COX-2 is found in the brain, kidneys, bones, reproductive organs, and some cancers **(10-12)**.

5. Naproxen Derivatives

5.1 Naproxen-triazole Derivatives

Triazole, or pyrrolidazole, is a heterocyclic organic molecule characterized by a five-membered unsaturated ring structure including three nitrogen atoms and two carbon atoms **(13)**. Triazole derivatives are compounds that have made exceptional contributions to the treatment of human diseases, exhibiting excellent pharmacokinetics, minimal toxicity, and a positive therapeutic effect in pharmaceutical research and development.

Birgül et al **(14)**. A study was conducted to synthesize novel derivatives of (S)-naproxen, specifically a series of thiosemicarbazides (3a-d), 1, 2, 4-triazoles (4a-c), and triazole-thioether hybrids (5a-p). These compounds were rationally designed to target and inhibit methionine aminopeptidase-2 (MetAP2), an enzyme relevant to prostate cancer progression. The hybrid compounds (5a-p) were evaluated for their cytotoxic effects on both androgen-independent (PC-3, DU-145) and androgen-dependent (LNCaP) prostate cancer cell lines using an MTS assay. The results identified specific compounds with notable activity: for instance, 5a, 5b, 5d, and 5e were active against PC-3 cells, while 5n emerged as a particularly potent agent against LNCaP cells. As a result, compounds 5e and 5n exhibited the most potent activities against androgen-dependent and independent prostate cancer cell lines of these results. Researchers noted that compound 5n has high pharmacological activities, which necessitated additional studies and analyses of the compound, including investigating the activation of the mitogen-activated protein kinase (MAPK) pathway, AKT (protein kinase B) phosphorylation, and the activation of androgen receptors in LNCaP cells, which was done by Western blot. Various biological and pharmaceutical analyses as well as molecular docking simulations, were conducted for compound 5n, revealing that it is a potential candidate for treating prostate cancer.

5.2 Naproxen- Perhydrothiazin-4-one Derivatives

Perhydrothiazin-4-one is a class of heterocyclic characterized by their formation from a saturated six-membered ring containing nitrogen, sulfur, and a carbonyl group. Perydrothiazines are characterized by their high biological effectiveness due to their nitrogen and sulfur atom content, which makes them essential derivatives added to drug compounds to increase therapeutic effectiveness **(15)**.

Seyfimoghaddam et al **(16)** synthesized new perhydrohiazin-4-one derivatives (7a-f) derived from naproxen, and studied their applications as non-steroidal anti-inflammatory drugs (NSAIDs) and as anti-epileptic agents. The newly synthesized compounds demonstrated moderate to good effectiveness against Gram-negative Escherichia coli and Staphylococcus aurous, as well as Gram-positive bacteria, in biological studies. The prepared compounds exhibited good activity when studied for their biological properties.

5.3 Naproxen- tetrazole Derivatives

A tetrazole is a type of organic molecule with a five-atom ring structure, where four of the atoms are nitrogen and one is carbon. Tetrazole is a viable alternative to the carboxyl group in drug design to improve pharmacological properties and reduce side effects (17).

Mahmood et al (18), synthesized new tetrazole derivatives 8a-j, derived from Naproxen; this is done by preparing naproxen-hydrazide derivatives with aromatic substituents and then reacting the hydrazone with sodium azide (NaN_3) in the presence of dried benzene.

5.4 Naproxen- pyrazole Derivatives

Pyrazole is a heterocyclic organic compound characterized by a five-atom ring structure containing three carbon and two adjacent nitrogen atoms. This core structure is the building block for a vast array of significant compounds used in technology, agriculture, and particularly medicine. Its derivatives are recognized for their diverse biological activities, such as acting as antibacterial, antifungal, anticancer, antidepressant, and antiviral agents. Because of these compelling pharmacological properties, pyrazole biomolecules are receiving growing interest in scientific research (19, 20).

Al-Sehemi et al (21) synthesized five new naproxen derivatives 9a-e, by linking naproxen with pyrazole and then conducting a computer study of the prepared compounds. The newly prepared derivatives contain electron-withdrawing groups (–Br and $–NO_2$), and some of them contain electron-donating groups (-CH_3 and -OCH_3). Time-dependent DFT was used to determine the key transitions, oscillator strengths, and absorption wavelengths. The study observed a transparent interconnection between the HOMOs and LUMOs of naproxen derivatives. Electron-withdrawing groups raise the energy levels of the HOMOs and LUMOs, while electron-repelling groups lower them. The examination of molecular docking studies revealed that pure hydrophobic substitution at position 4 of the aldehyde portion is more advantageous than hydrophilic substitution. Among the new compounds, 9c was the most potent, strongly inhibiting the growth of MCF-7 breast cancer cells (IC50 = 1.49 μM), while 9d showed a more moderate effect. Although the overall activity of the series was weak to moderate, all compounds were more effective than the parent drug, naproxen. Furthermore, their low Polar Surface Area (PSA) values suggest they could be developed as orally administered drugs that can also reach the brain.

5.5 Naproxen- pyrazoline Derivatives

Pyrazoline is a heterocyclic compound consisting of a five-membered ring containing two adjacent nitrogen atoms. Unlike pyrazole, which contains two double bonds, pyrazoline contains one double bond. It is widely used in pharmaceutical chemistry due to its diverse biological properties, including anticancer, anti-inflammatory, antimicrobial, and other activities (22).

Mahdi et al (23), synthesized six new pyrazoline ring derivatives as a pharmacophore inserted into naproxen and preliminarily analyzed them as anti-inflammatory drugs with anticipated selectivity toward the COX-2 enzyme. The in vivo acute anti-inflammatory properties of the final compounds (12a-f) were assessed in rats using the egg-white-induced edema model of inflammation. The evaluated substances and the reference medication resulted in a considerable decrease in paw edema compared to the control group (propylene glycol 50%, v: v). While compounds 12a, 12b, and 12c had a much lower inhibitory effect than naproxen at time 120–240 minutes, compounds 12d and 12e exhibit an effect that is comparable to naproxen at all trial durations. Moreover, compound 12f demonstrated a significantly greater reduction in paw edema compared to naproxen at 60-240 minutes. When compared to dimethyl sulfoxide as a control group, all investigated substances exhibit strong antibacterial activity against both Gram-positive and Gram-negative bacteria, especially *Bacillus, Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli*. Compound 12e may be considered the best evaluated chemical in terms of antibacterial activity, while compound 12c may be viewed the least effective.

5.6 Naproxen- thiadiazole Derivatives

Thiadiazole derivatives are a class of heterocyclic organic compounds characterized by a five-membered ring containing two nitrogen atoms, one sulfur atom, and two carbon atoms. Thiadiazole derivatives have many important pharmacological activities and have therefore been the subject of extensive research. Biological Activity: A variety of pharmacological effects are displayed by derivatives of thiadiazole, such as anticancer, antibacterial qualities against bacteria and fungus, anti-inflammatory, analgesic, antiviral, and other medicinal substances (24-26).

Mahdi and Dakhel (27) prepared new 1, 3, 4-thiadiazol-2-thiol derivatives of naproxen, and studied their pharmacological activity as anti-inflammatory agents. The compounds were found to maintain their anti-inflammatory activity even after modification of the carboxyl group of the parent naproxen compound, with a significant reduction in side effects, which are often attributed to the carboxyl group in naproxen. Notably, compound 14a demonstrated greater anti-inflammatory activity than the parent drug naproxen after five hours of testing in rats. The researchers' findings provide hope for new naproxen derivatives with minimal or no side effects and similar or even greater activity.

5.7 Naproxen-condensed triazole-thiadiazole

Condensed triazole-thiadiazole is a molecule composed of a 1, 2, 4-triazole ring and a 1, 3, 4-thiadiazole ring fused. This fused ring structure is a prevalent characteristic in many physiologically active substances, with varied pharmacological effects (28).

Amir et al (29) Synthesized some 6-substituted-1, 2, 4-triazolo [3, 4-b]. -1, 3, 4-thiadiazole derivatives 17a-f and 18a-d by the cyclization of 16 with different substituted

aromatic carboxylic acids and aryl/alkyl isothiocyanates R-NCS in a single-step synthesis. Compound 17a exhibited strong anti-inflammatory and analgesic properties in addition to the greatest reduction in severity index with the least amount of lipid peroxidation and no liver cell necrosis or degeneration. Based on their results, the researchers concluded that fused triazolo-thiadiazole derivatives may offer a safer alternative to naproxen for the treatment of inflammatory diseases and pain.

5.8 Naproxen-condensed triazole-thiazole

Condensed triazole-thiazole is a molecule composed of a 1, 2, 4-triazole ring and a 1, 3-thiazole ring fused together. This fused ring structure is a prevalent characteristic in many physiologically active substances, with varied pharmacological effects **(30)**.

Sarigol et al **(31)**, synthesized a series of new thiazolo[3,2-b]-1,2,4-triazoles (compounds 22a-t derived from naproxen by using 3-Substituted-1,2,4-triazole-5-thiones as intermediates since they contain two reactive sites: thiocarbonyl and amine nitrogen (N1/N4) 21, and then study their analgesic and anti-inflammatory activities. When compared to a naproxen control, the study discovered that all of the recently produced derivatives reduce inflammation and nociception. Compared to the common medications naproxen and indomethacin, all of the produced compounds showed a significantly decreased risk of ulcers. Selected compounds exhibiting notable analgesic and anti-inflammatory properties, alongside low ulcer scores, were subsequently assessed for them in vitro inhibitory effects on COX-1 and COX-2. Assay for prostaglandin production catalyzed by COX. In pharmacological investigations, compounds modified with biphenyl 22j, 1-naphthyl 22k, and 5-substituted heteroaromatic moieties, including 5-methylfuran 22n, 5-methyl thiophene 22q, and 5-bromo thiophene 22s at the fifth position of the ring, exhibited notable analgesic and anti-inflammatory properties. Compound 22q, which was determined by calculating the in vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}), had the greatest selectivity index (SI) of 4.87 among the examined compounds. Docking studies were utilized to forecast the binding modes of various tested chemicals to cyclooxygenase (COX) enzymes.

5.9 Naproxen- sulfanilamide derivatives

4-aminobenzenesulfonamide derivatives are commonly referred as sulfanilamide derivatives. This fundamental structure is well recognized for its applicability in several biological and pharmacological fields **(32)**. These compounds demonstrate varied characteristics and are employed in research and clinical applications, including anti-inflammatory, particularly those that integrate the sulfanilamide moiety into established anti-inflammatory medications such as mefenamic acid, ibuprofen, and indomethacin **(33)**. Anticonvulsant properties have been investigated for their capacity to inhibit particular isoforms of carbonic anhydrase (CA) **(34)**. Anticancer effects, including the activation of apoptosis, modification of cellular signaling pathways, and prevention of cancer cell migration **(35, 36)**.

Naser et al **(37)** prepared a new sulfanilamide derivative, 4-aminobenzenesulfonamide, by attaching it to the alpha carbon of naproxen. Unlike most studies that rely on modifying the carboxyl group, this study aimed to add a large group to the alpha carbon to increase the derivative's selectivity for the COX-2 enzyme over COX-1, thereby reducing the drug's gastrointestinal side effects.

5.10 Naproxen- heterocyclic amine derivatives

Heterocyclic amines are compounds that contain at least one atom other than carbon, which is nitrogen, and may contain other heteroatoms such as nitrogen, and may be single or fused rings. Heterocyclic amines are extremely prevalent, and many possess critical biological properties. A few examples include heme, the oxygen carrier in blood, sildenafil (Viagra), a well-known pharmaceutical, and pyridoxal phosphate, a coenzyme **(38)**.

Naser **(39)**, synthesized three new naproxen derivatives 26a-c by linking naproxen with heterocyclic amine named 2-aminothiazole, 2-aminobenzimidazole, and 2-aminobenzothiazole. Wistar albino rats with fresh egg white-induced paw edema were used to test the target compound's in vivo anti-inflammatory properties. Researchers discovered that while compound 26c exhibits activity similar to naproxen, compounds 26a and 26b are noticeably more active than naproxen.

5.11 Naproxen- amino Acid Derivatives

Amino acids are organic compounds characterized by containing two functional groups: the carboxyl group (-COOH) and the amino group ($-NH_2$). Amino acid derivatives play a crucial role in pharmaceuticals, forming the foundation for several medicines and therapeutic agents. L-DOPA, a derivative of the amino acid tyrosine, is a notable example utilized in the treatment of Parkinson's disease **(40)**. Amino acid derivatives serve as enzyme inhibitors in pharmaceutical development **(41)**. Angiotensin-converting enzyme (ACE) inhibitors, used for hypertension management, are amino acid derivatives that inhibit the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor **(42)**.

Elhenawy et al **(43)** prepared a peptide derivative by linking naproxen with amino acids and studied the compounds computationally. An investigation of chemical reactivity was conducted, providing a potential explanation for the reactivity of ligands with receptors. The docking results demonstrated that the binding relationship intensified following the incorporation of an acidic fragment into the parent molecule. Carboxyl 28-31 and phthalyl 34a-d derivatives were less electrophilic than methoxy 32a-d and hydrazide 33a-d. Therefore, these compounds may assault the receptor's hydrophilic portion. Molecular docking revealed that tyrosine residues 29,32d, and 33d had the greatest MOE scores, whereas adding β-amino acid to the original molecule had the lowest binding energies. The presence of serine and

alanine residues moderated binding potency. Free acids 28-31 were stronger than methyl esters 32a-d and hydrazide derivatives 33a-d. Increasing ligand hydrophobicity boosted binding interactions. These derivatives are likely to have adequate oral bioavailability, with minimal or no cancer or significant health consequences based on rodent toxicity profiles and ADMET in silico. The anti-inflammatory potency of compounds 29 and 33d was significantly greater than that of naproxen and the tested compounds. The analgesic potency of compounds 29, 32b, and 33b was the highest among the other prepared compounds. All compounds demonstrated minimal ulcerogenic effects and may be regarded as safer alternatives to naproxen for the treating of inflammatory conditions.

5.12 Hydrazide-hydrazone derivatives of Naproxen

Organic compounds are characterized by containing the (-CO-NH-N=CH-) functional group. Numerous studies and sources have indicated that they possess a wide range of biological activities, including antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, analgesic, antiplatelet, antimalarial, anticancer, antifungal, antituberculosis, antiviral, anticardiovascular, and others. Therefore, many researchers have modified drug structures to incorporate the hydrazone group, aiming to design and discover new drugs with enhanced pharmaceutical activity **(4, 44, 45)**.

Tok et al **(46)**, synthesized a series of *N*-acylhydrazone derivatives 35a-p by reacting naproxen with a variety of substituted aldehydes. The derivatives were prepared using two methods: the conventional method and the microwave method, to know the difference between them. According to the synthesis of *N*-acylhydrazone derivatives, microwave irradiation outperformed the traditional method in terms of yields while reducing reaction time and environmental impact. The new derivatives were prepared as potential COX-2 inhibitors, and the interactions between these derivatives and COX-2 were studied with computer applications, including molecular modeling using Gaussian 09 and Discovery Studio 3.5. Authors found that *N*-acylhydrazone compounds exhibited a distinct mechanism compared to SC-558 as COX-2 inhibitors by interacting with different active sites of the COX-2 protein. The results of molecular modeling indicate that compound 35c is a potential inhibitor of COX-2.

Abbas et al **(47)**, synthesized new substituted hydrazide-hydrazone 36a-g derived from naproxen, by react naproxen hydrazide 2 with seven natural and synthetic aldehydes and ketones a-g using glacial acetic acid as a catalyst and then study their anti-inflammatory activities. The anti-inflammatory activity of the produced compounds was tested in vivo using the egg-white-induced edema paradigm in rats. The researchers found that derivatives 36b, 36c, 36e, and 36f gave anti-inflammatory activity comparable to that of the original drug (naproxen), while compounds 36a, 36d, and 36g gave activity higher than naproxen. Here, it becomes clear that the type of aldehyde or ketone plays an important role in determining the effectiveness of the prepared drug.

Azizian et al **(48)**, synthesized a series of new arylhydrazone derivatives 37a-l derived from naproxen and studied their pharmacological activities, such as analgesic and anti-inflammatory. The researchers used to electron-donate and electron-withdrawing substituents, and concluded that electron-withdrawing substituents at the para position enhance the analgesic and anti-inflammatory activities. A molecular modeling study of the prepared compounds revealed greater selectivity in binding to the active site of COX-2 compared to COX-1. The findings suggest that the selectivity of ligands for COX-2 is attributable to three primary factors: 1- The reduced steric hindrance of valine residues at positions 523 and 89, 2- The capacity of tyrosine at position 115 for hydrogen-bonding interactions, and 3- The presence of para substituents in arylidenehydrazone derivatives of naproxen, particularly the bulkier variants, in addition to their electronic properties. The most notable finding in the study conducted by the researchers is the discovery of the high analgesic efficacy of the 37j derivative. It was also found that the compound 37g had higher anti-inflammatory activity than the original drug (naproxen). The results also indicated that the compound 37g had higher selectivity for the COX-2 enzyme ($R_{COX\text{-}2/COX\text{-}1}$ = 1.94) and higher affinity compared to naproxen for the active site of the COX-2 enzyme ($R_{COX\text{-}2/naproxen}$ = 1.28).

Nakka et al **(49)**, synthesized several new arylhydrazones derived from naproxen and studied their cytotoxicity. All compounds 38a-i were found to be active when tested in vitro against the PC-3 cell line, a human prostate cancer cell type. Additionally, numerous compounds were found to be potent in the same assay.

5.13 Naproxen- thiourea Derivatives

Thiourea derivatives are a class of organic compounds characterized by their (-NH-CS-NH-) functional group. They have numerous applications, most notably their high pharmaceutical activity and their inclusion in the composition of numerous drugs. Their most prominent pharmaceutical activities include Enzyme inhibition, antimicrobial activity, antifungal properties, and antitumor activity as anticancer agents **(50-52)**.

Nedeljković et al **(53)**, prepared seven new thiourea derivatives of naproxen 40a-b and 41a-e, with five aromatic amines and two aromatic amino acid esters, and then evaluated their anti-inflammatory and cytotoxic properties. Certain derivatives, such as compound 41a, had the most potent anti-inflammatory activity. The dose used was found to be highly correlated with the anti-inflammatory effect in vivo, with the greatest reduction in foot edema occurring at the highest dose of all the prepared derivatives. The in vivo anti-inflammatory activity study showed that the prepared compounds 41a and 41b showed the highest anti-inflammatory activity among the other derivatives with an inhibition rate of 44.83% and 49.29%, respectively. Conversely, derivatives 41b, 41c, 41e, and 41b exhibited mild

cytotoxicity against the HCT 116 cell line, whilst compound 41a displayed pronounced cytotoxicity on HeLa cells, indicating their participation in the extrinsic apoptotic pathway and G0/G1 phase arrest in HeLa cells. It is possible that the presence of unsubstituted, *m*-substituted and *p*-substituted aromatic amines in the side chain of the investigated thiourea derivatives of naproxen is associated with potent anti-inflammatory and cytotoxic activity. Compound 41a is among the most potent cytotoxic agents.

5.14 Naproxen-Salicylate Derivatives

Schlecht et al **(54)**, created and Evaluated Naproxen-Salicylate Derivatives as Possible Dual-Targeted Dihydrofolate Reductase Inhibitors. DHF is converted to THF by dihydrofolate reductase (DHFR). Competitive inhibition of DHFR by methotrexate inhibits cancer cell nucleotide synthesis. In addition to inhibiting cyclooxygenase enzymes, nonsteroidal anti-inflammatory drugs (NSAIDs) compete with dihydrofolate reductase (DHFR). This interaction affects the enzymatic conversion of dihydrofolate to tetrahydrofolate, blocking the folate metabolism pathway needed for nucleotide synthesis and cell proliferation. This is due to their structural similarities to folate's p-aminobenzoyl-l-glutamate (pABG), a DHFR substrate. Salicylic NSAIDs such as diflunisal have increased DHFR-binding affinity, according to research. Salicylate derivatives of naproxen were prepared to test their DHFR inhibitory capability. The interactions between these substances and human DHFR were revealed by biochemical, biophysical, and structural methods. The salicylate derivatives' binding affinity and inhibitory activity against DHFR were tested using PAGE, enzymatic assays, and quantitative ELISA. This study suggests that salicylate derivatives of naproxen may inhibit DHFR, potentially opening up novel therapies for controlling inflammation.

Table 1. The anti-inflammatory effect of control, naproxen and compounds 5a-f on egg-white induced paw edema in rat (**Mahdi et al (23)**).

Compounds		Time (mm)						
		0	**30**	**60**	**120**	**180**	**240**	**300**
Paw Thickness (mm) / n=6	Control	4.85±0.05	5.83±0.06	6.58±0.06	6.96±0.03	6.81±0.06	6.71±0.02	5.39±0.01
	Naproxen	4.82±0.04	5,72±0.05	6,51±0.05	5.81±0.05 *a	5.44±0.06 *a	5.14±0.06 *a	4.93±0.02 *
	12a	4.87±0.06	5.74±0.02	6.56±0.06	6.31±0.01 *b	5.72±0.03 *b	5.43±0.02 *b	5.06±0.04 *
	12b	4.81±0.03	5.75±0.06	6.51±0.01	6.21±0.04 *b	5.76±0.06 *b	5.51±0.02 *b	4.99±0.05 *
	12c	4.81±0.02	5.75±0.01	6.50±0.03	6.17±0.06 *b	5.73±0.05 *b	5.47±0.06 *b	5.03±0.06 *
	12d	4.78±0.01	5.79±0.06	6.49±0.04	5.84±0.03 *a	5.46±0.02 *a	5.16±0.05 *a	5.06±0.06 *
	12e	4.82±0.06	5.74±0.02	6.49±0.03	5.91±0.02 *a	5.41±0.04 *a	5.15±0.01 *a	4.99±0.06 *
	12f	4.84±0.01	5.82±0.02	5.77±0.04 *	5.43±0.05 *c	5.08±0.06 *c	4.86±0.03 *c	4.94±0.08 *

Non-identical superscripts (a, b and c) among different tested compounds are considered significantly different ($p < 0.05$).

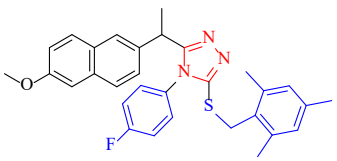
* Significantly different compared to control ($p < 0.05$). Data are expressed in mm paw thickness as mean ± SEM. n= number of animals. Time (0) is the time of i.p. injection of naproxen, tested compounds and propylene glycol. Time (30) is the time of injection of egg white (induction of paw edema).

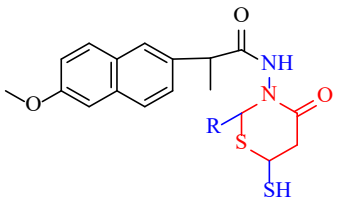
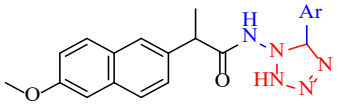
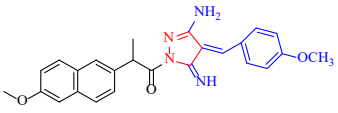
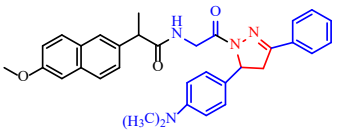
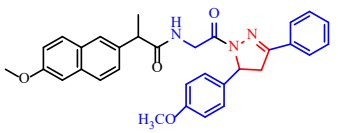
Table 2. Anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of the synthesized compounds (17a–f and 18a–d) (**Amir et al (29)**).

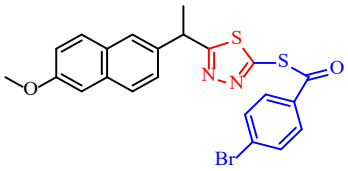
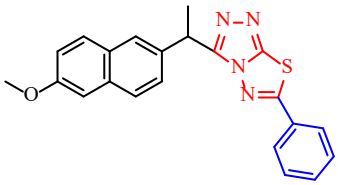
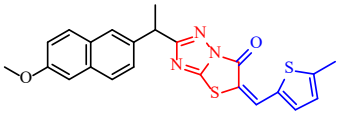
Compound	Anti-inflammatory activity (% inhibition ± SEM)[#]	Analgesic activity[##]			Ulcerogenic activity (severity index ± SEM)[#]	nmol MDA content ± SEM/ 100 mg tissue[#]
	After 4 h	Pre-treatment (0 h)	Post-treatment (4 h)	% inhibition		
4a	81.05 ± 2.17	1.57 ± 0.210	2.98 ± 0.225[c]	89.5	0.500 ± 0.00[b]	4.86 ± 0.10[b]
4b	80.30 ± 0.96	1.28 ± 0.084	1.62 ± 0.148	26.7	0.583 ± 0.00[b]	5.27 ± 0.26[b]
4c	68.93 ± 1.40[a]	1.80 ± 0.076	2.47 ± 0.174[d]	37.2	0.750 ± 0.11[b]	5.63 ± 0.35[b]
4d	78.02 ± 1.82	1.43 ± 0.146	2.58 ± 0.156[d]	80.3	0.667 ± 0.16[b]	5.38 ± 0.25[b]
4e	54.54 ± 3.32[b]	XX	XX	XX	XX	XX
4f	78.02 ± 1.82	1.36 ± 0.104	2.15 ± 0.142[d]	58.1	0.833 ± 0.21[b]	5.85 ± 0.22[b]
5a	40.90 ± 3.52[b]	XX	XX	XX	XX	XX
5b	43.93 ± 3.03[b]	XX	XX	XX	XX	XX
5c	40.14 ± 4.90[b]	XX	XX	XX	XX	XX
5d	76.51 ± 2.17	1.44 ± 0.156	1.92 ± 0.222	33.3	0.833 ± 0.21[b]	6.11 ±0.40[b]
Naproxen	81.81 ± 2.65	1.17 ± 0.086	2.03 ± 0.039[c]	73.5	2.250 ± 0.11	9.04 ± 0.24
Control	-	-	-	-	0.00	3.25 ± 0.05

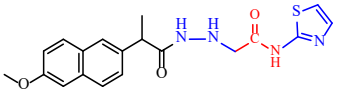
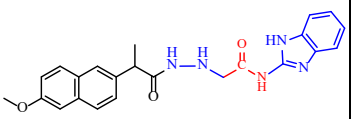
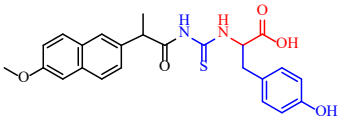
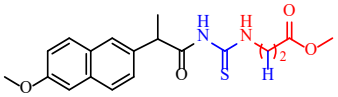
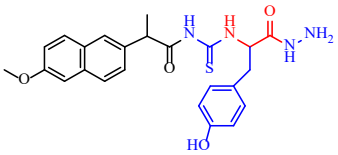
[XX]Not tested. [#] Relative to standard and data were analyzed by ANOVA followed by Dunnett's multiple comparison test for n = 6; a $p < 0.05$; b $p < 0.01$. [##]Relative to normal (pre-treatment) and data were analyzed by paired Student's t test for n = 6; c $p < 0.0001$, d $p < 0.005$.

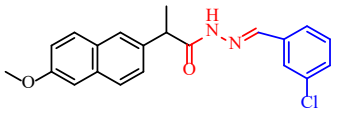
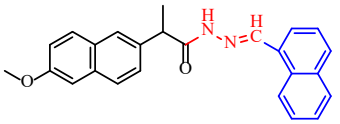
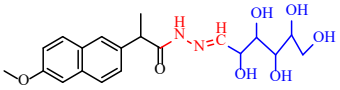
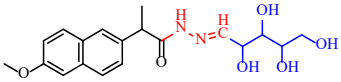
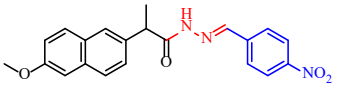
Table 3. Summary of the Naproxen Derivatives and Their Related Pharmacological Activities.

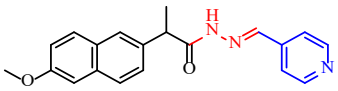
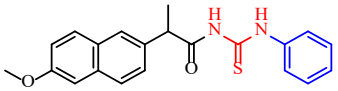
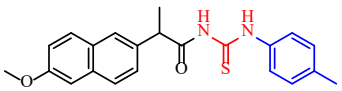
Modification	Authors	Methods	Aim	Results/Finding	
Naproxen-triazole derivatives	Birgül et al (14)	• Synthesis triazole derivatives and triazole-thioether • Molecular docking study • In vivo study and anticancer activities	Anti-Prostate Cancer	 **Comp. 5n**	• Highly effective pharmaceutical and potential treatment for prostate cancer

Naproxen-Perhydrothiazin-4-one derivatives	Seyfimoghaddam et al (16)	• Synthesis of thiazin-4-one • Evaluation of antibacterial activity against E. coli and S. aureus	Antibacterial	 **Comp. 7a-f**	• Good inhibition against Gram positive bacterias, S. aureus, and E. coli Gram negative bacteria
Naproxen-tetrazole derivatives	Mahmood (18)	• Synthesis naproxen-hydrazide derivatives • Synthesis naproxen-tetrazole	Synthesis new tetrazole	 **Comp. 8a-j**	• Tetrazole derivatives were prepared with good yields and could be used for pharmaceutical testing in the future.
Naproxen-pyrazole derivatives	Al-Sehemi et al (21)	• Synthesis pyrazole derivatives • In vitro evaluation of the anti-proliferative activity • Computational studies of the new derivatives	Anti-proliferative activity	 **Comp. 9c**	• Hydrophobic substitution at position 4 of aldehyde is preferable to hydrophilic one. • Compound **9c** showed significant anti-proliferative activity against MCF-7 cells, with an IC_{50} of 1.49 µM. • Computational studies suggest these compounds may be an orally active and brain-penetrating drug.
Naproxen-pyrazoline derivatives	Mahdi et al (23)	• Synthesis pyrazoline derivatives • Evaluation of in vivo anti-inflammatory • Evaluation antibacterial activity against tested Gram-positive and	Anti-inflammatory	 **Comp. 12f**  **Comp. 12e**	• Compound **12f** demonstrates a much greater reduction in paw edema compared to naproxen • Compound **12e** demonstrated high activity against both Gram-positive

		Gram-negative bacteria			and Gram-negative bacteria.
Naproxen-thiadiazole derivatives	Mahdi and Dakhel (27)	• Synthesis new 1,3,4-thiadiazol-2-thiol derivatives • Evaluation of In vivo anti-inflammatory	Anti-inflammatory	 **Comp. 14a**	• Compound **14a** demonstrated greater anti-inflammatory activity than naproxen. • The derivatives showed minimal or no side effects.
Naproxen linking with condensed triazole-thiadiazole	Amir et al (29)	• Synthesis new condensed triazole-thiadiazole • Evaluated anti-inflammatory and analgesic	Anti-inflammatory & analgesic	 **Comp. 17a**	• Compound **17a** demonstrated significant anti-inflammatory and analgesic activity without causing liver cell damage. • Condensed triazolo-thiadiazole derivatives are promising compounds for creating safer alternatives to naproxen for treating inflammation and pain.
Naproxen linking with condensed triazole-thiazole	Sarigol et al (31)	• Synthesis new condensed triazole-thiazole form 1,2,4-triazole-5-thiones. • Evaluation of in vivo analgesic and anti-inflammatory properties in acute experimental pain and	Anti-inflammatory & analgesic	 **Comp. 22q**	• Substituting the free carboxylic acid group in NSAIDs with a thiazolo[3,2-b]-1,2,4-triazole ring leads to reduced gastrointestinal toxicity in vivo. • Compound (**22q**), which was determined by calculating the in vitro COX-2

		inflammation models.			selectivity index (COX-1 IC_{50}/COX-2 IC_{50}), had the greatest selectivity index (SI) of 4.87 among the examined compounds
Naproxen-amine derivatives	Naser (39)	• Linking heterocyclic amine with parent drug naproxen • Evaluation of anti-inflammatory activity using paw edema model	Anti-inflammatory	 **Comp. 26a**  **Comp. 26b**	• Combination of heterocyclic amines with naproxen increases the anti-inflammatory efficacy of the derivative depending on the type of amine. • Compared to naproxen, the **26a** and **26b** compounds were significantly more efficacious as anti-inflammatory agents.
Naproxen-amino acid derivatives	Elhenawy et al (43)	• Linking naproxen with amino acids • Computational studies and molecular docking • Evaluation of anti-inflammatory activity using paw edema model	Anti-inflammatory & analgesic	 **Comp. 29**  **Comp. 32b**  **Comp. 33d**	• The anti-inflammatory effectiveness of compounds **29** and **33d** was substantially higher than naproxen. • Compounds **29, 32b**, and **33b** outperformed the other produced compounds in analgesia. • Docking experiments showed that adding an acidic fragment to the parent molecule boosted binding.

					• The compounds have high oral absorption and no carcinogenic or rodent-toxic effects. • It has been demonstrated that the nonsteroidal anti-inflammatory drug based on peptide derivatives is safe and has little ulcerogenic effects.
Naproxen-hydrazone derivatives	Tok et al (46)	• Synthesis hydrazone by conventional and microwave method • Structure-activity relationships and molecular docking were done with Gaussian 09 and Discovery Studio 3.5.	COX-2 inhibitors	 **Comp. 35c**	• N-acylhydrazones inhibit COX-2 by binding to distinct protein active sites than SC-558. • COX-2 inhibitor compound **35c** is promising in preclinical trials.
	Abbas et al (47)	• Synthesis hydrazone by use natural and synthetic aldehydes and ketones • Egg-white-induced edema in rats was used to assess anti-inflammatory efficacy.	Anti-inflammatory	 **Comp. 36a**  **Comp. 36d**  **Comp. 36g**	• Compounds **36a, 36d**, and **36g** had more anti-inflammatory activity than naproxen. • The type of aldehyde or ketone used in the preparation significantly affects the biological activity of the products.
	Azizian et al (48)	• Synthesis arylhydrazone	Anti-inflammatory & analgesic	 **Comp. 37g**	• Electron withdrawing groups increase

		• In vivo evaluation of anti-inflammatory and analgesic • Molecular modeling study of the new derivatives		 **Comp. 37j**	pharmaceutical activity. • Compound **37j** is a highly effective analgesic. • Compound **37g** is a highly effective anti-inflammatory with high selectivity for the COX-2 enzyme.
Naproxen-thiourea derivatives	Nedeljkovic et al (53)	• Synthesis thiourea using five aromatic amines and two aromatic amino acid esters • In vivo evaluation of anti-inflammatory and cytotoxic	Anti-inflammatory and cytotoxic	 **Comp. 41a**  **Comp.41b**	• The greatest reduction in inflammation occurred at the highest dose. • Compounds **41a** and **41b** had the highest in vivo anti-inflammatory activity with 44.83% and 49.29% inhibition rates, respectively. • Compound **41a** are among the most potent cytotoxic agents. • Aromatic amines may exhibit powerful anti-inflammatory and cytotoxic properties.

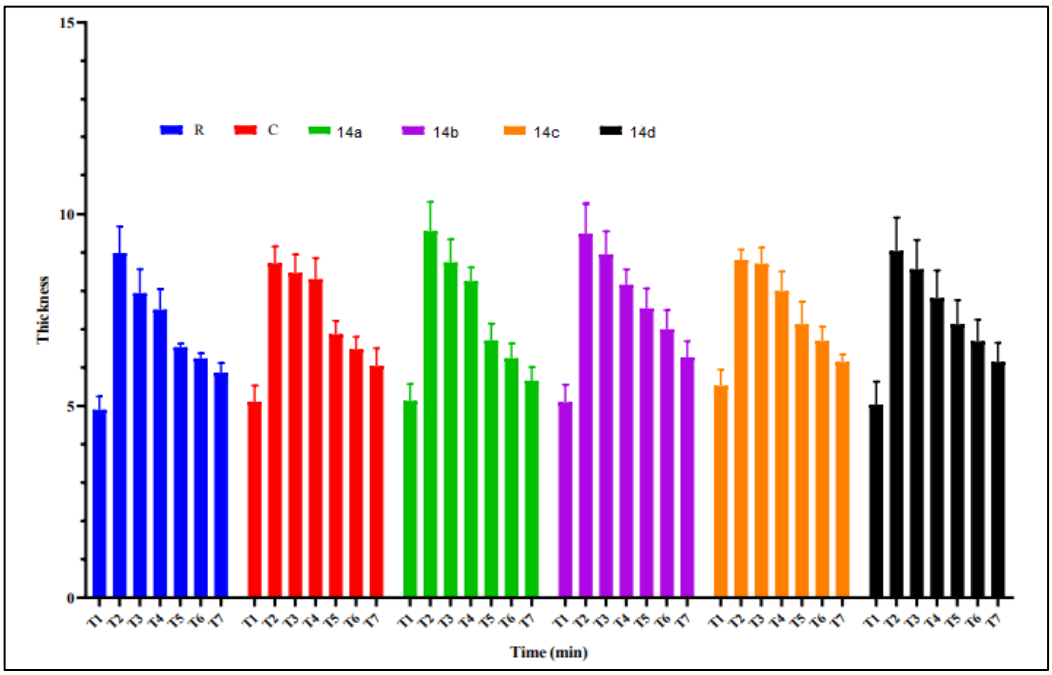


Figure 2. The impact of naproxen, dimethyl sulfoxide (DMSO), and substances 14a, 14b, 14c, and 14d on egg whites caused paw edema in rats. The findings are presented as mean ± SEM and percentage (**Mahdi and Dakhel (27)**).

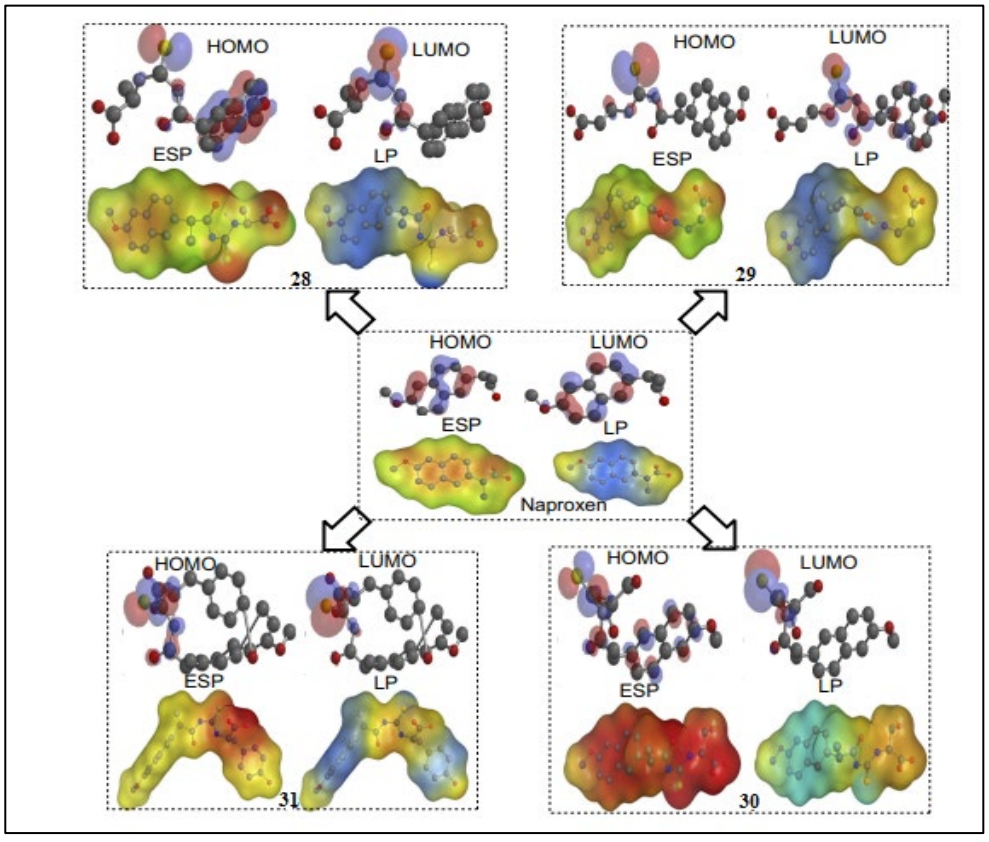


Figure 3. Design of initial hit molecules (26-29) compared with naproxen structure (**Elhenawy et al (43)**).

6. Conclusion

This review article focuses on the most prominent modifications that can be made to the carboxyl group of naproxen and summarizes the most important substitute groups with high efficacy or near-efficacy to the original drug, thus making it easier for future researchers to select highly effective groups for preparing pharmaceutical derivatives.

7. Declarations

7.1 Acknowledgments

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7.2 Ethical Considerations

Not applicable.

7.3 Authors' Contributions

All authors contributed equally to the preparation of this review article. All authors reviewed, edited, and approved the final version of the manuscript.

7.4 Conflict of Interest

The authors declare no conflict of interest.

7.5 Fund or Financial Support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

7.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

8. Publisher's Note

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