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Synthesis and Antimicrobial Evaluation of Etodolac-Based Derivatives

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ABSTRACT
Etodolac, a non-steroidal anti-inflammatory drug (NSAID) with selective cyclo-oxygenase 2 inhibition, is known for its anti-inflammatory properties and reduced gastrointestinal side effects. Recent studies have highlighted its potential for modification to develop derivatives with antimicrobial activity. This study aimed to synthesize and evaluate etodolac derivatives for enhanced antimicrobial efficacy. Specific chemical modifications were introduced to the etodolac structure to investigate their inhibitory effects on medically relevant bacterial and fungal strains. The findings suggest that these derivatives exhibit promising antimicrobial properties, offering potential as alternative therapeutic agents in addressing antimicrobial resistance.

Keywords: Etodolac, Etodolac derivatives, cyclic anhydrides, biological activity, heterocyclic compound

INTRODUCTION

It has been found that etodolac (used in osteoarthritis, rheumatoid arthritis, and postoperative pain) is a commonly used nonsteroidal anti-inflammatory drug (NSAID) used generally to prevent the production of prostaglandin and inflammation by blocking the COX-2 enzyme [1, 2].
Etodolac is a gastrointestinal safe NSAID, that selectively inhibits COX-2 compared to other NSAIDs. In recent years various studies have demonstrated that etodolac derivatives are potential anticancer agents in prostate and colorectal cancer cell lines [3]. The studies also demonstrate antimicrobial activity against Pseudomonas aeruginosa and Streptococcus pneumoniae [4].Also, its antioxidant properties help further reducing oxidative stress concentrated on the increased therapeutic value of etodolac, a point established by Fernandes et al[5]. Further, it has also shown effectiveness against chronic inflammation models [6] and against macrophage migration, inflammatory responses. In animal models, research shows a possible ability to decrease cartilage and bone damage in arthritis [7]. Etodolac has been advanced in drug delivery in the microbeads of chitosan to increase the bioavailability time of drug and reduce release time to minimize the side effects [8]. New formulations, with reduced gastrointestinal risk, have further anti-inflammatory action [9]. Therapeutic scope of etodolac in pain management and disease treatment [1] then slowly widens yet further. Etodolac derivatives and modulation of its therapeutic efficacy with improved drug delivery systems and target specific actions is driven by reduced side effects [10]. Recent evidence indicates that emulsomes and emulgels can improve novel sustained and prolonged drug delivery with increased patient compliance [11].
Recently, etodolac derivatives have been explored as potential inhibitors of key enzymes to cancer, including eEF2K, in which they have been found to inhibit cancer in vitro[12].

Materials and Reagents

For the synthesis portion of the work, methanol and ethanol served as solvents and concentrated sulfuric acid (H_2SO_4) as the catalyst for the esterification reactions. Neutralization and pH adjustments (during purification) employed sodium bicarbonate ($NaHCO_3$). We synthesized desired derivatives using several organic anhydrides, including maleic anhydride, phthalic anhydride, and succinic anhydride. Synthesized intermediates were converted to hydrazides using hydrazine hydrate.

Synthesis of etodolac derivatives

The compilation of etodolac derivatives started with generating critical intermediates; these were then transformed into the compounds we were searching for.

Synthesis of Etodolac Ester (Compound 1)

Etodolac powder (0.0235 moles, 6 g) was placed in a round-bottom flask, followed by the addition of 20 mL of methanol with stirring to achieve a clear solution. The mixture was then cooled to 0°C using an ice bath. Subsequently, 5 mL of concentrated sulfuric acid (H_2SO_4) was added dropwise with continuous stirring. The resulting mixture was subjected to reflux for 6 hours under stirring. Upon completion of the reaction, TLC verified its progress. The mixture was then allowed to return to room temperature and subsequently neutralized with a 5% w/v sodium bicarbonate solution. The precipitate was filtered, collected, washed with distilled water, and dried. Finally, the product underwent recrystallization using absolute ethanol, yielding etodolac methyl ester crystals.

Synthesis of Etodolac Hydrazide (Compound 2)

To synthesize etodolac hydrazide, we started with etodolac methyl ester. Etodolac methyl ester (1.7 g, 0.006 moles) was dissolved in 35 mL of ethanol, and the suspension was stirred until the ester completely dissolved. Once the solution was clear, we added hydrazine hydrate (3 mL, 0.06 moles, 80% concentration) dropwise to the mixture, while stirring continuously at room temperature. We then allowed the mixture to stir for 6 hours at ambient conditions to ensure the reactants had a good opportunity to interact.

The reaction was allowed to complete for 24 hours while being heated under reflux. Thin-layer chromatography (TLC) was used to monitor the reaction and to verify that the methyl ester was converted into the hydrazide. After 24 hours, the mixture was allowed to cool to room temperature and was then poured into a beaker containing crushed ice. This step caused the desired product to precipitate out of solution.

The etodolac hydrazide was collected as a precipitate by vacuum filtration, washed well with cold water to remove any remaining impurities, and left to air dry. The next step was to purify the etodolac hydrazide through recrystallization. This process is detailed as follows in the result section. Despite the materials being a product of a laboratory synthesis, the process resembles the purification of minerals. After the imposing structure of etodolac hydrazide was fashioned, molecules were tightly packed in an orderly manner, and any impurities or defects found in the etodolac hydrazide were byproducts of synthesis or alternate routes taken in the purification steps.

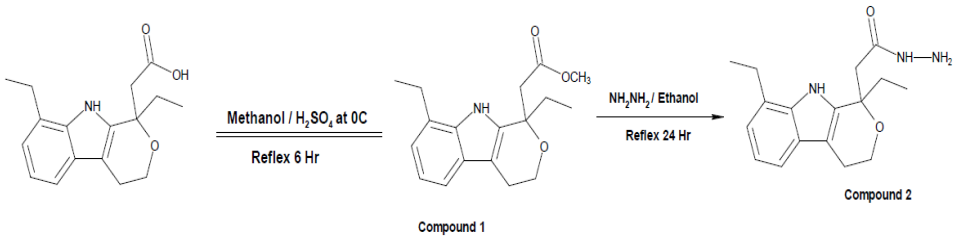

Figure1. Synthesis of Etodolac intermediate

Synthesis of Etodolac-Maleic Anhydride Derivative (Compound I)

To make the etodolac-maleic anhydride derivative, we used glacial acetic acid as a solvent for the starting material, etodolac hydrazide. We then added maleic anhydride—previously weighed—to the solution. The next step was to heat the mixture under reflux at 118°C for 8–10 hours. We monitored the progress of the reaction using thin-layer chromatography (TLC). After the reaction was complete (as indicated by TLC), we allowed the mixture to cool to room temperature. Upon cooling, we filtered the mixture to remove any insoluble material. We then evaporated the solvent under reduced pressure. The residue was washed with sufficient water to remove residual acetic acid (we knew that acetic acid is insoluble in n-hexane and is readily soluble in water). Finally, after we dried the product, we used the recrystallization technique to purify the compound.

Synthesis of Etodolac-Phthalic Anhydride Derivative (Compound II)

The etodolac-phthalic anhydride derivative was prepared in much the same way as the maleic anhydride derivative. Etodolac hydrazide was dissolved in glacial acetic acid, and phthalic anhydride was added. Again, we heated the mixture under reflux, this time at 118 °C for 8 to 10 hours. We monitored the reaction by TLC and allowed it to cool when it was done. After filtration, we evaporated the solvent under reduced pressure and washed the residue with distilled water. Finally, the product was purified via the recrystallization technique

Synthesis of Etodolac-Succinic Anhydride Derivative (Compound III)

The etodolac-succinic anhydride derivative was synthesized following a protocol similar to that of the first derivative. Etodolac hydrazide was dissolved in glacial acetic acid, and succinic anhydride was added. The reaction mixture was refluxed for 8 to 10 hours at a temperature of 118°C. TLC was used to monitor the progress of the reaction. When the reaction was complete, the mixture was cooled, filtered, and the solvent evaporated. The residue was washed with distilled water to remove impurities. The product was purified using the recrystallization from ethanol.

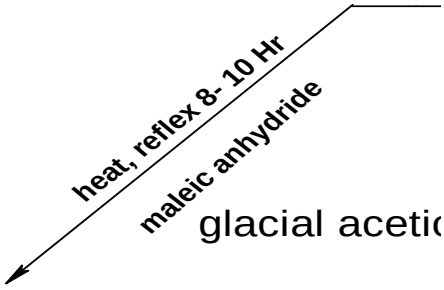

Figure 2. Synthesis of Etodolac derivatives

Purification Methods

In this study, purification was achieved through recrystallization, and the method was crucial for obtaining pure compounds from mixtures of crude reactions. Upon completion of a compound's synthesis, that compound was first dissolved in a minimal amount of hot ethanol. The solution was then gently but thoroughly heated to ensure that the compound fully melted, creating a clear solution—obviously, just before it could "refight" the covalent bonds that had allowed it to exist in a crystalline form. Afterward, the solution was allowed to cool slowly to room temperature; as it did, the formation of a solid through the nutation of the hydrogen bonds in the compound was facilitated.

The compounds were dissolved in the minimum amount of hot ethanol. The solutions were then allowed to cool to room temperature. The solutions continued to cool in a cold-water bath to ensure complete crystallization. Crystals were collected by vacuum filtration and washed once with cold ethanol. After the ethanol wash, crystals were air-dried and stored in a desiccator. The integrity of the crystals was never compromised, and the method was safe, simple, and effective.

Detection of Melting Points and Rf Values

The melting points of the synthesized etodolac derivatives were determined using a standard melting point apparatus. Samples were gradually heated, and the temperature range at which melting was observed was recorded. This provided a useful indication of the compound's purity and consistency with expected chemical structures.

Thin-layer chromatography (TLC) was employed to determine the retention factor (Rf) values of each compound. TLC was performed on silica gel plates, and appropriate solvent systems were used to ensure the separation of the compounds. The Rf values were calculated by measuring the distance traveled by the compound relative to the solvent front. This technique allowed for the monitoring of the synthesis process and the purity of the derivatives. Both melting point and Rf value determinations were carried out to confirm the identity and purity of the synthesized derivatives and to compare them with known standards.

Biological Assays

Antibacterial Activity Testing

We evaluated the antibacterial activity of the synthesized etodolac derivatives by two methods: the microdilution method and agar inhibition zone measurement. For the microdilution method, we prepared serial dilutions of the compounds in sterile 96-well plates using Mueller-Hinton broth. We then added various strains of bacteria, including Streptococcus, Staphylococcus, Pseudomonas, and Neisseria, to each well. After incubating the plates for 24 hours at 37°C, we observed the wells for bacterial growth. The lowest concentration of the compound that showed no visible growth (i.e., the MIC) was recorded.To confirm the results from our first method, we also used the second method—the agar diffusion test. We inoculated plates of Mueller-Hinton agar with different strains of bacteria and placed sterile paper discs soaked in various concentrations of the compounds onto the surface of the agar. After 24 hours of incubation at 37°C, we measured the inhibition zone diameters to assess the antibacterial activity.

Antifungal Activity Testing

The antifungal activity was assessed similarly. Candida species were tested using the microdilution method in Sabouraud dextrose broth. The MIC was determined after 48 hours of incubation at 30°C. Additionally, the inhibitory zones were measured on Sabouraud dextrose agar plates following the same disc diffusion method used for bacteria.

Preparation of Culture Media

For the antibacterial and antifungal activity tests, standard culture media were prepared under sterile conditions. Nutrient agar was used for the bacterial strains, and Sabouraud dextrose agar was used for the fungal strains. The powdered nutrient agar and Sabouraud dextrose agar were first weighed and then mixed with the appropriate volume of distilled water, according to the manufacturer's instructions. The mixtures were stirred to ensure complete dissolution. The media underwent sterilization in the autoclave. Contaminants would be eliminated when the media was held at the autoclave's temperature of 121°C for 15 minutes. After this time, the agar was removed from the autoclave and placed into a sterile environment to cool to about 45-50°C. It was poured with care into the Petri dishes, reaching the edge without introducing air bubbles. The media was allowed to solidify at room temperature. After that, the prepared plates were then stored in an incubator; the bacteria plates at 37°C and the fungi plates at 30°C. The culture media would provide the necessary nutrients and environment for the growth of the microbial strains to be used to test the antibacterial and antifungal activities of the synthesized etodolac derivatives.

Minimum Inhibitory Concentration Reagent

A colorimetric reagent known as resazurin (Alamar Blue) was prepared for the determination of the synthesized compounds' minimum inhibitory concentrations (MICs). A vortex mixer was used to dissolve 0.015 g of resazurin in 100 mL of sterile distilled water. The complete dissolution of the resazurin was ensured, and the prepared solution was stored at 4ºC to be used within a week. The selection of resazurin for our assays was based on its color change capacity. When it is reduced by viable bacteria, it changes from blue (the color of 0.8 g/L solution) to pink, which is the color of the 0.08 g/L solution and can be seen with the naked eye.

Determination of Minimum Inhibitory Concentration (MIC)

The MIC of the synthesized etodolac derivatives was determined using the microdilution method. Serial double dilutions of the compounds (ranging from 1 to 64 µg/mL) were prepared from a stock solution (10 mg/mL) in Mueller-Hinton broth. The dilutions were set up in sterile 96-well microtiter plates. Each well, except for the negative control, was inoculated with 20 µL of bacterial suspension, standardized to match McFarland standard 0.5, equivalent to 1.5×10^8 CFU/mL.

The plates were incubated at 37°C for 18-20 hours. Following incubation, 20 µL of resazurin dye was added to each well, and the plates were incubated for an additional 2 hours. The MIC was visually determined as the lowest concentration at which the resazurin color remained blue, indicating no bacterial growth. A change from blue to pink signified bacterial activity, helping to assess the antimicrobial potency of the compounds.

Antibacterial Activity of Synthesized Compounds Against Isolates

The agar well diffusion method was used to evaluate the antibacterial activity of thesynthesized etodolac derivatives against various bacterial isolates, including Streptococcus, Staphylococcus, Pseudomonas, and Neisseria. After preparing a bacterial suspension from nutrient broth cultures (incubated at 37°C for 18-24 hours), the concentration was adjusted to match 1.5×10^8 CFU/mL.Using sterile cotton swabs, the bacterial suspension was evenly spread over the surface of Mueller-Hinton agar plates, which were allowed to rest for 10 minutes. Wells (5 mm in diameter) were made in the agar using a sterile borer. 50 µL of the synthesized compounds (at their MIC concentrations) were added to each well. The plates were then incubated at 37°C for 18 hours.

After incubation, the diameter of the zones of inhibition around each well was measured to determine the antibacterial efficacy of the compounds. These results were compared against standard antibiotics to assess the relative effectiveness of the synthesized derivatives.

RESULTS AND DISCUSSION

Table 1: Melting Points and Rf Values for Etodolac Derivatives

Physical Appearance	Rf Value	Melting Point (°C)	Compound
Orange precipitate	0.33	133-136	Etodolac Hydrazide + Phthalic Anhydride
White precipitate	0.66	115-119	Etodolac Hydrazide + Succinic Anhydride
White precipitate	0.45	130-135	Etodolac Hydrazide + Maleic Anhydride
White powder	0.56	145-148	Etodolac
Yellow powder	0.78	128-130	Etodolac Ester
White powder	0.41	187-189	Etodolac Hydrazide

Table 2: Minimum Inhibitory Concentration (MIC) and Sub-MIC Values of Synthesized Etodolac Derivatives Against Bacterial and Fungal Isolates

ISOLATES	etodolac-maleic anhydride		etodolac-phthalic anhydride		etodolac-phthalic anhydride		Ciprofloxacin	
	Mic	Sub	mic	Sub	mic	Sub	mic	Sub
STAPH	64	32	512	256	128	64	256	128
STREPTO	265	128	------	-----	256	128	256	128
BA	265	128	1024	512	128	64	256	128
E.C	265	128	------	-----	256	128	256	128
PSEUDOM	265	128	128	64	256	128	256	128
NEISSERIA	265	64	128	64	256	128	128	128
							Flu	
CA	128	64	128	64	128	64	128 \64	

The first table displays the minimum inhibitory concentrations (MIC) and sub-MIC values for the synthesized etodolac derivatives, which include etodolac-maleic anhydride derivative, etodolac-phthalic anhydride derivative, and etodolac-succinic anhydride derivative, tested against various bacterial strains such as Staphylococcus aureus, Streptococcus pneumoniae, Bacillus anthracis, Escherichia coli, Pseudomonas aeruginosa, and Neisseria gonorrhoeae, as well as the fungal strain Candida albicans. For the purposes of comparison, ciprofloxacin was used as the reference antibacterial, and fluconazole was used for the antifungal control. Both are standard. The preliminary data show that etodolac (ETD) and its derivatives have promising antibacterial and antifungal activity. Particularly, the etodolac-maleic anhydride (MA) derivative appears to have both antibacterial and antifungal activity; against a Gram-positive bacterium, Staphylococcus aureus, and a Gram-negative bacterium, Neisseria gonorrhoeae, it demonstrated very good potency. In comparison, the Etodolac-phthalic anhydride (PA) derivative seems to be less potent as an antibacterial. Finally, the ETD-succinic anhydride (SA) derivative appears to be dual action, having significant activity, for a derivative, against a Gram-positive bacterium, Bacillus anthracis, and a notable impact on Pseudomonas aeruginosa, a Gram-negative bacterium and a problematic drug-resistant target for many antibacterial drugs.When compared to the control, ciprofloxacin showed superior antibacterial effects across all tested bacterial strains, further emphasizing the moderate activity of the synthesized etodolac derivatives. Fluconazole demonstrated strong antifungal activity, and while the etodolac derivatives did not match its potency, the results highlight the significant antifungal potential of compounds etodolac-maleic anhydride and etodolac-succinic anhydride derivative.

Table 3: Zone of Inhibition Measurements of Synthesized Etodolac Derivatives Against Bacterial and Fungal Isolates

ISOLATES	Etodolac-maleic anhydride derivative	Etodolac-phthalic anhydride derivative	Etodolac-succinic anhydride derivative	ciprofloxacin	Flu
ST	30	27	34	36	------
STR	33	29	30	34	------
BA	25	22	23	30	------

E.C	31	25	25	34	------
PS	30	25	27	35	-------
NE	25	26	29	34	--------
CA	30	24	29	------	33

The second table summarizes the zone of inhibition measurements for the same synthesized compounds, providing a visual indicator of their antimicrobial efficacy. The zones of inhibition were measured after incubating the bacterial and fungal cultures with the compounds for 18 hours.

Etodolac-maleic anhydride derivative (Compound I) consistently produced larger inhibition zones compared to the other derivatives, indicating its superior antimicrobial action, particularly against Staphylococcus aureus and Escherichia coli. This suggests that (compound I) has significant potential in inhibiting these bacterial strains. Etodolac-phthalic anhydride derivative (Compound II), however, exhibited the smallest zones of inhibition, reaffirming its weaker antimicrobial activity. This was especially apparent with Bacillus anthracis, where its effectiveness was limited.

Etodolac-succinic anhydride derivative (Compound III) produced moderate zones of inhibition, demonstrating efficacy against Neisseria gonorrhoeae and Candida albicans. The performance of this compound was intermediate, providing a balance between the lower efficacy of compound II and the higher potency of compound I. As expected, ciprofloxacin showed the most substantial inhibition zones against bacterial strains, while fluconazole was highly effective against Candida albicans. The comparison of inhibition zones highlights the significant antimicrobial potential of the synthesized etodolac derivatives, particularly compounds I and III, though they did not surpass the control antibiotics in terms of efficacy.

Specifically, etodolac-maleic anhydride, etodolac-phthalic anhydride, and etodolac-succinic anhydride derivatives, to enhance the biological activity of etodolac. These new derivatives were tested for their antibacterial properties against clinically relevant bacterial strains such as Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa, Neisseria gonorrhoeae, and Bacillus anthracis, as well as their antifungal efficacy against Candida albicans. The goal was to assess whether these modifications could provide compounds with improved antimicrobial and anti-inflammatory properties.

The methods included a series of chemical reactions where etodolac hydrazide was synthesized from etodolac methyl ester and then reacted with maleic, phthalic, or succinic anhydrides to form the respective derivatives. These reactions were carried out under reflux and monitored by thin-layer chromatography (TLC), and the products were purified using the recrystallization techniques. Antibacterial and antifungal activities were evaluated using microdilution methods to determine minimum inhibitory concentrations (MICs) and agar diffusion tests to measure the zones of inhibition.

The analysis showed that the derivative of etodolac with maleic anhydride had significant antimicrobial action, especially against Staphylococcus aureus and Neisseria gonorrhoeae. It also had antifungal activity against Candida albicans. The derivative of etodolac with succinic anhydride exhibited moderate activity against Pseudomonas aeruginosa and Candida albicans, suggesting its potential as an ambulatory dual-action antimicrobial agent. In contrast, the derivative of etodolac with phthalic anhydride had slight activity across most of the tested strains. Compared to standard controls, ciprofloxacin and fluconazole, the synthesized compounds showed moderate activity but did not surpass the effectiveness of these conventional antibiotics.

The antimicrobial and anti-inflammatory properties of etodolac derivatives [13] may be explained by their ability through selective inhibition of prostaglandin biosynthesis in synoviocytes and chondrocytes. Differences in the molecular interactions of the etodolac derivatives with the bacterial targets are probably responsible for the variation in antimicrobial efficacy among the derivatives. For example, the enhanced hydrophobic interactions or improved cellular uptake Staphylococcus aureus, Neisseria gonorrhoeae observed for the etodolac-maleic anhydride derivative could account for its significant activity. It could be due to the maleic anhydride group which can afford stronger interactions with bacterial enzymes or membranes. On the other hand, the etodolac phthalic anhydride derivative has weaker activity owing to steric hindrance, or lower permeability through bacterial cell wall reducing the ability of it to inhibit bacterial growth. This rationale is consistent with other research which has discovered that molecular modifications can both increase or reduce the potency of a drug due to changes in solubility, permeability and molecular binding affinities [4]. Structural changes in the parent etodolac molecule can provide dual antimicrobial and anti-inflammatory activity, but at a level of efficacy less than conventional antibiotics, in the moderate case of the etodolac succinic anhydride derivative with respect to Pseudomonas aeruginosa. This observation is supported by studies exploring derivatives with analogous dual action properties (anti-inflammatory and antimicrobial), with improved interaction with bacterial membranes, along with anti-inflammatory effects [5]. The current study findings indicate that the antimicrobial properties of etodolac derivatives do not always overcome those usual of traditional antibiotics. Dual-action therapeutic benefits from structurally modified NSAIDs such as etodolac are promising but require further optimization to increase efficacy against resistant bacterial strains.

CONCLUSIONS

This research shows that new compounds related to etodolac, especially the ones derived from maleic and succinic anhydrides, could serve as anti-inflammatory and antimicrobial agents. They are potent and good-looking candidates in these regards, although "good-looking" is a funny term to use when referring to effectiveness. Unlike maleic and succinic anhydride derivatives, most compounds in this study should not be used as anti-inflammatory or antimicrobial agents because they are not effective. Indeed, researchers should be careful when studying compounds that are not anti-inflammatory. Overall, these novel etodolac derivatives are unlikely to provide potent and effective in vivo anti-inflammatory action.

Conflict of interest

There are no conflicts of interest regarding the publication of my research article.

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