ORIGINAL ARTICLE

CONTENTS

Antibacterial activity of new azole derivatives incorporating Etodolac

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ABSTRACT

Aim: This research paper investigates the synthesis and antibacterial activity of novel azole derivatives incorporating Etodolac.

Materials and Methods: The study focused on the reaction of Etodolac with three different aromatic amines: o-phenylene diamine, 2-aminophenol, and 2-aminothiophenol, resulting in three new compounds (1-3). The antibacterial activity of these compounds was assessed against *Escherichia* coli, *Klebsiella*, *Staphylococcus* aureus, and *Streptococcus* mutans.

Results: Compound 1 demonstrated the most potent antimicrobial activity against all four bacteria, exhibiting a remarkably low MIC against *Escherichia* coli.

Conclusions: The results of this research suggest that incorporating Etodolac into the synthesis of azole derivatives can lead to potent antimicrobial agents. Further exploration of these compounds is warranted to fully understand their potential therapeutic applications.

KEY WORDS: anti-bacterial agents, azoles, drug synergism, Etodolac, structure-activity relationship

Wiad Lek. 2025;78(11):2313-2319. doi: 10.36740/WLek/212545 DOI

INTRODUCTION

Azole derivatives have emerged as a significant class of compounds in medicinal chemistry due to their diverse biological activities. These compounds have demonstrated efficacy against a broad range of infections, including bacterial, fungal, malarial, and viral infections [1]. Furthermore, azole derivatives exhibit potential in the treatment of cancer and inflammation [2]. Some of azoles derivatives show antibacterial activity Research has highlighted the antibacterial activity of certain azole derivatives [3-6], Others exhibit both antibacterial and antifungal properties [7-8], while some possess antifungal activity alone [9], Additionally, azole derivatives have demonstrated cytotoxic [10], and anticancer properties, as well as antimicrobial activity [11]. Etodolac, a non-steroidal anti-inflammatory drug (NSAID), is commonly used to alleviate pain and inflammation [12]. Derivatives of Etodolac have been shown to exhibit a range of biological activities, including antimicrobial [13], anti-inflammatory [14-16], cytotoxic [17-18] and anticancer activity [19-22]. Etodolac derivatives have also been explored as enzyme inhibitors and have demonstrated a reduced ulcerogenic potential, an important factor in NSAID development [23].

AIM

This research paper investigates the synthesis and antibacterial activity of novel azole derivatives incorporating Etodolac

MATERIALS AND METHODS

All reactions were conducted in oven-dried glassware. Commercial grade solvents and reagents were purified by distillation prior to use. Thin-layer chromatography (TLC) using silica gel GF 254 on microscopic glass slides coated with silica gel was employed to monitor reaction progress. Melting points were determined using an electrothermal melting point apparatus with open capillary tubes. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature using Bruker 400 MHz spectrometers. Samples were prepared by dissolving the compounds in deuterated chloroform (CDCl) with

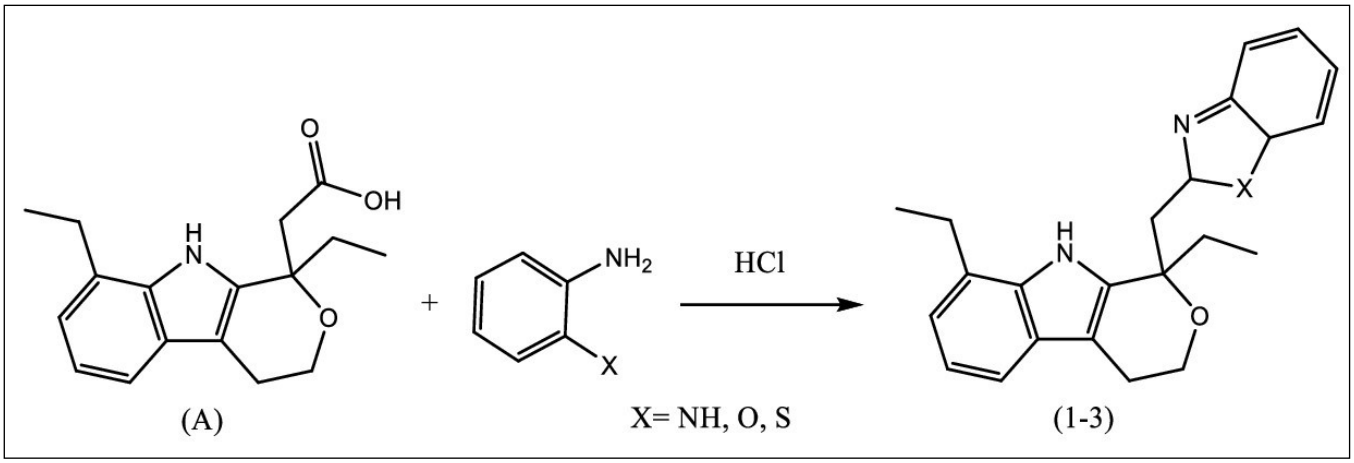

Fig. 1. Synthesis of azole derivatives
Source: Own materials

tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm).

GENERAL PROCEDURE FOR SYNTHESIS OF TITLE COMPOUND [24]

To synthesize the desired product, Etodolac (A) was reacted with three diffterent aromatic amines: *o*-phenylene diamine, 2-aminophenol, and 2-aminothiophenol. The reaction was carried out in an acidic environment using 4N hydrochloric acid and heated under reflux at 100°C for 5 hours with constant stirring. The progress of the reaction was monitored using thin-layer chromatography (TLC). Once the reaction was complete, the mixture was carefully neutralized with a 10% sodium hydroxide solution. The resulting solution was then cooled in an ice bath for 5 minutes to promote precipitation of the product. The solid product was then isolated by filtration and dried.

RESULTS

This study included the synthesis of some azole derivatives through the reaction of Etodolac (A) with different aniline derivatives (*o*-phenylene diamine, 2-aminophenol and 2-aminothiophenol) in the presence of HCl as shown in Figure 1.

SYNTHESIS OF ORGANIC COMPOUNDS (1-3)

SYNTHESIS OF 1-((2,7A-DIHYDRO-1H-BENZO[D]IMIDAZOL-2-YL) METHYL)-1,8-DIETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-B] INDOLE (1)

This compound Fig 2 was synthesized by reacting Etodolac (A) with *o*-phenylene diamine in the presence of HCl as both solvent and catalyst. The resulting product is a brown powder with a melting point of 91°C. Structure (1). The compound (1) was identified by:

FTIR (KBr) (cm $^{-1}$): ν: N-H (3518-3489), C-H aliphatic (2995-2892), C-H aromatic (3080), C = C (1584, 1482), C = N (1681), C-N (1340-1000), C-O (1301-992).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.88 (1H, s, N-H), 11.67 (1H, s, N-H of $_{indole}$), 8.32-7.07 (6H, m, C-H $_{aromatic}$ and N-H $_{of\ imidazole}$), 3.69 (2H, m, CH_2-O), 3.02(2H, s, CH_2), 2.71 (2H, q, CH_2), 2.62 (2H, t, CH_2-CH_2-O), 1.67 (2H, q, CH_2-CH_3),1.18(3H, t, CH_3-CH_2) 0.89 (3H, t, CH_3-CH_2).

SYNTHESIS OF 1-((2,7A-DIHYDROBENZO[D] OXAZOL-2-YL) METHTYL)-1,8-DIETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-B] INDOLE (2)

This compound Fig 3 was synthesized by reacting Etodolac (A) with 2-aminophenol in the presence of HCl as both solvent and catalyst. The resulting product is a brown powder with a melting point of 90°C. Structure (2). The compound (2) was identified by:

FTIR (KBr) (cm $^{-1}$): ν: N-H (3525-3492), C-H aliphatic (3000-2899), C-H aromatic (3092), C = C (1590, 1482), C = N (1677), C-N (1344-989), C-O (1310-993).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.80 (1H, s, N-H), 11.65 (1H, s, N-H of $_{indole}$), 8.30-7.06 (6H, m, C-H $_{aromatic}$), 3.70 (2H, m, CH_2-O), 3.03(2H, s, CH_2), 2.73 (2H, q, CH_2), 2.60 (2H, t, CH_2-CH_2-O), 1.66 (2H, q, CH_2-CH_3),1.19(3H, t, CH_3-CH_2) 0.89 (3H, t, CH_3-CH_2).

SYNTHESIS OF 1-((2,7A-DIHYDROBENZO[D] THIAZOL-2-YL) METHYL)-1,8-DIETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-B] INDOLE (3)

This compound Fig 4 was synthesized by reacting Etodolac (A) with 2-aminothiophenol in the presence of

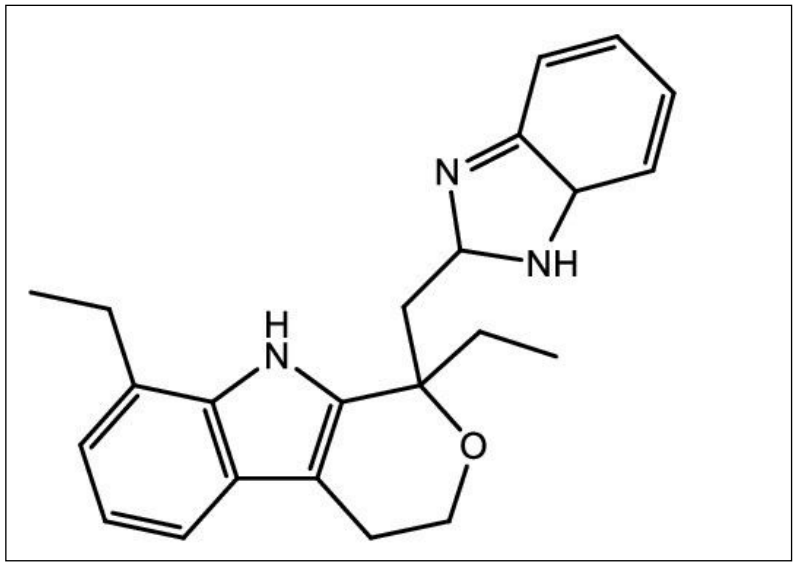

Fig. 2. Structure of compound (1)
Source: Own materials

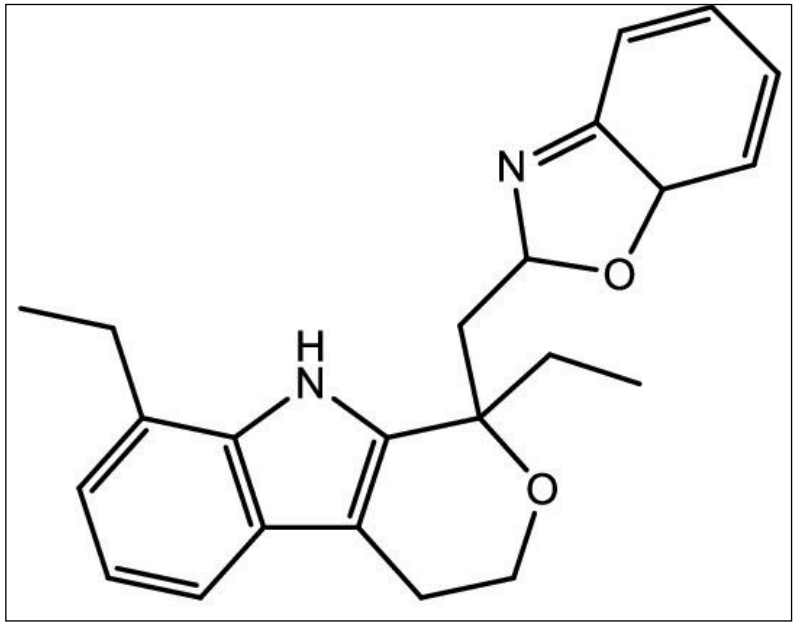

Fig 3. Structure of compound (2)
Source: Own materials

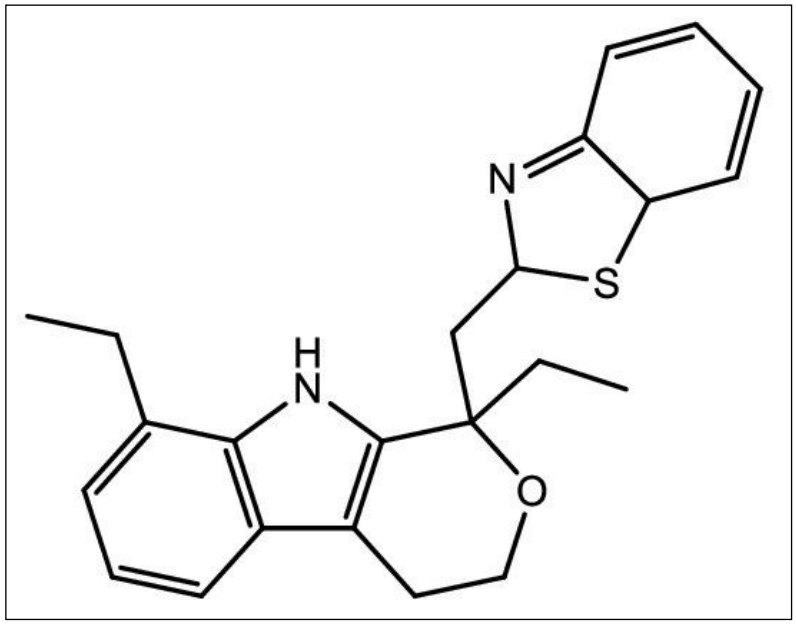

Fig. 4. Structure of compound (3)
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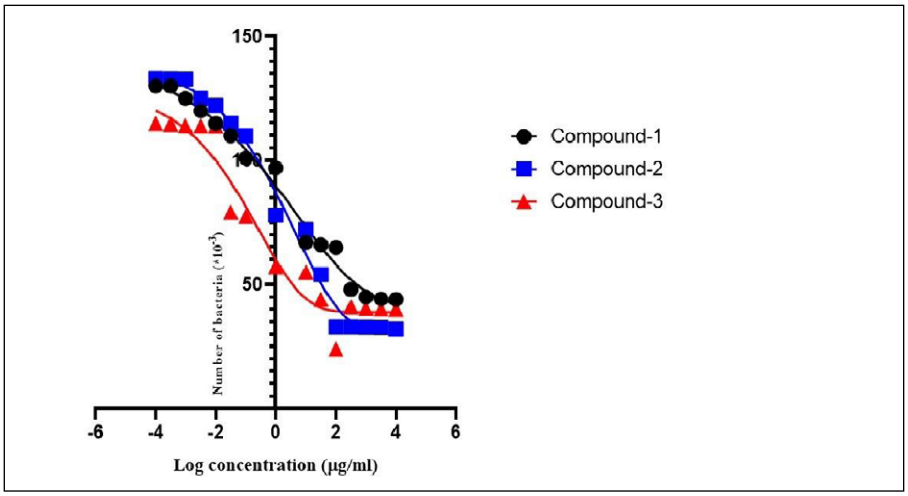

Fig. 5. Antimicrobial biological activity of Compounds 1, 2, and 3 against *E. coli*
Source: Own materials

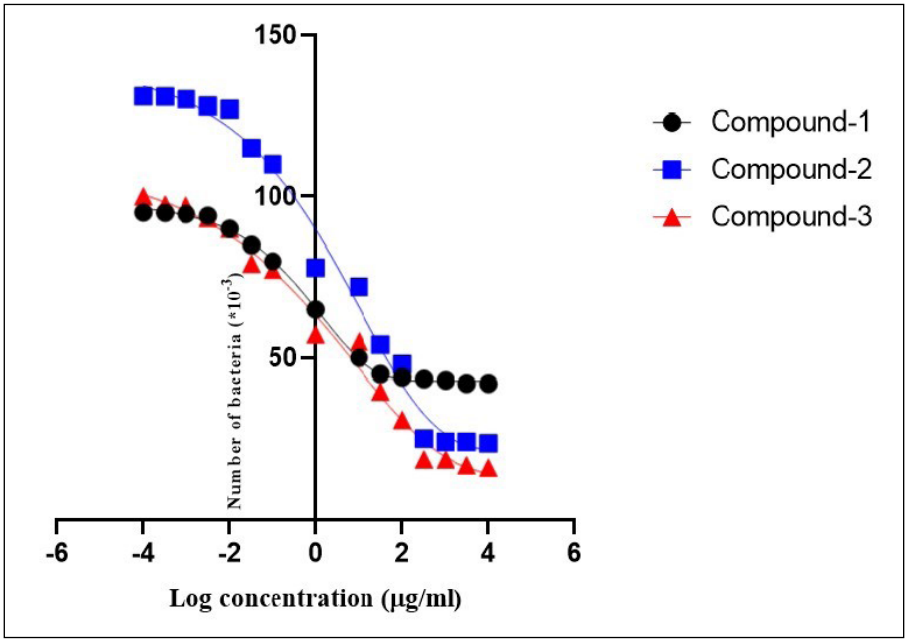

Fig. 6. Antimicrobial Biological Activity of Compounds 1, 2, and 3 against *Klebeiella*
Source: Own materials

HCl as both solvent and catalyst. The resulting product is a brown powder with a melting point of 89°C. Structure (3). The compound (3) was identified by:

FTIR (KBr) (cm $^{-1}$): ν: N-H (3525-3492), C-H aliphatic (3003-2890), C-H aromatic (3050), C = C (1580, 1482), C = N (1677), C-N (1344-989), C-O (1310-993), C-S (605-701).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.80 (1H, s, N-H), 11.65 (1H, s, N-H of $_{indole}$), 8.30-7.06 (6H, m, C-H $_{aromatic}$), 3.73 (2H, m, CH_2-O), 3.05(2H, s, CH_2), 2.73 (2H, q, CH_2), 2.63 (2H, t, CH_2-CH_2-O), 1.66 (2H, q, CH_2-CH_3),1.18(3H, t, CH_3-CH_2) 0.89 (3H, t, CH_3-CH_2).

ANTIBACTERIAL ACTIVITY

The antibacterial properties of compounds 1–3 were evaluated against both Gram-negative and Gram-positive bacteria. The results are summarized below:

Escherichia coli (Gram-negative): Compound 1 showed the strongest activity, with a very low MIC value (9.089 µg/mL). Compound 3 was moderately active (173.9 µg/mL), while compound 2 was weak (908.1 µg/mL) (Fig. 5).

Klebsiella (Gram-negative): Again, Compound 1 was the most effective (21.3 µg/mL). Compound 2 and 3 showed much weaker activity (583.6 µg/mL and 993.2 µg/mL, respectively) (Fig. 6).

Staphylococcus aureus (Gram-positive): Compound 3 showed the best activity in this case (568.4 µg/mL), followed by compound 1 (844.2 µg/mL) and compound 2 (1271 µg/mL) (Fig. 7).

Streptococcus mutans (Gram-positive): Compound 2 performed best (583.6 µg/mL), compared to compound 3 (844.2 µg/mL) and compound 1 (1220 µg/mL) (Fig. 8).

DISCUSSION

Our results demonstrate that modifying Etodolac into new azole derivatives can lead to compounds with promising antibacterial activity, but their effectiveness varies depending on the bacterial species.

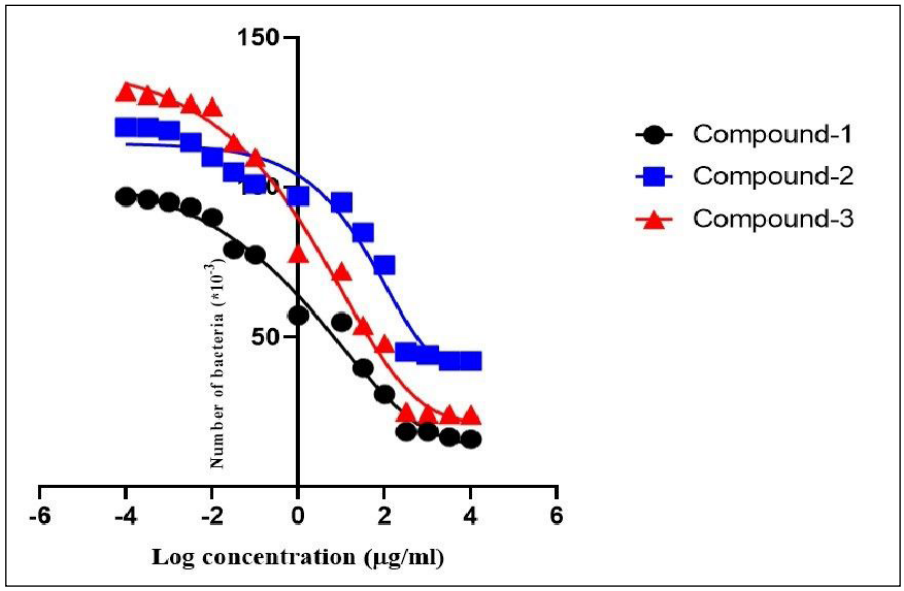

Fig. 7. Antimicrobial Biological Activity of Compounds 1, 2, and 3 against *Staphylococcus aureus*
Source: Own materials

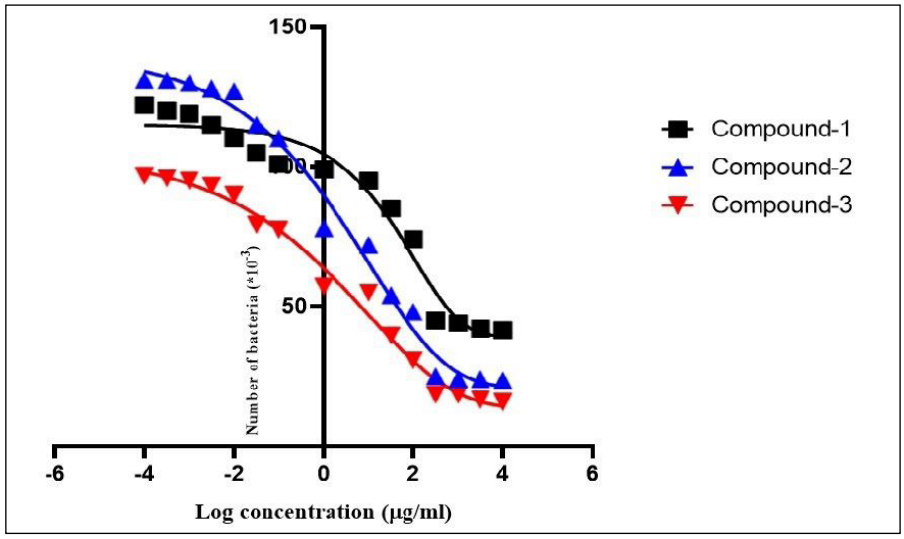

Fig. 8. Antimicrobial Biological Activity of Compounds 1, 2, and 3 against *Streptococcus mutans*
Source: Own materials

Compound 1, containing the benzimidazole ring, was the most effective overall, particularly against Gram-negative Bacteria *E. coli* and *Klebsiella*. This suggests that the benzimidazole moiety may enhance interactions with bacterial targets in Gram-negative strains. On the other hand, Compound 3, with a thiazole ring, showed stronger effects against the Gram-positive Strain *S. aureus*, possibly due to the sulfur atom increasing lipophilicity and membrane penetration. Interestingly, Compound 2, the oxazole derivative, displayed generally weaker activity but was the most active against *S. mutans*.

Compared with previously reported azole derivatives [3–6], the very low MIC value of Compound 1 against *E. coli* is particularly notable, highlighting its potential as a strong antibacterial candidate. However, the relatively high MICs observed for the Gram-positive bacteria indicate that further structural optimization is needed to achieve broader-spectrum activity.

These findings align with earlier studies showing that Etodolac derivatives can gain new biological properties beyond their original use as anti-inflammatory drugs [12–14]. Taken together, our study suggests that Etodolac-based azole derivatives are worth pursuing as potential antibacterial agents, although more detailed mechanistic studies and in vivo testing will be essential to confirm their therapeutic relevance.

CONCLUSIONS

This work demonstrates that modifying Etodolac into new azole derivatives can yield compounds with meaningful antibacterial properties. The benzimidazole derivative showed particular promise against Gram-negative strains, while the thiazole and oxazole analogues exhibited selective effects against Gram-positive bacteria. These findings suggest that Etodolac can serve as a useful scaffold for the development of novel antibacterial agents. Future efforts should aim to optimize these derivatives and evaluate their potential in preclinical studies.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 09.05.2025
ACCEPTED: 13.10.2025