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# Synthesis, characterization, and Antibacterial Study of some Imidazole and Molecular Docking of New Heterocyclic from Furan Derivatives

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## Abstract

New imidazole contents and thioxo-imidazolidin were synthesized by using simple methods. All compounds were synthesized by using the derivatives of aniline as starting materials, which were obtained from furfural and sodium nitrite. Hydrochloric acid derivatives ($S_6$, $S_7$) were obtained from the reaction of ($S_6$, $S_7$) with Thiosemicarbazide; while the reaction of ($S_{13}$, $S_{14}$) with chloroethyl acetate derivatives led to the formation of ($S_{20}$, $S_{21}$). The reaction of Benzene sulphonyl chloride with ($S_{18}$, $S_{19}$) Triethylamine led to the formation of ($S_{25}$, $S_{26}$). Finally, the reaction of acetyl chloride with ($S_{27}$, $S_{28}$) Triethylamine led to the formation of ($S_{34}$, $S_{35}$). FTIR, 1HNMR, and GC MASS spectra as well as molecular docking, were used to characterize the derivatives used as antibacterials and were tested against several bacterial species including *S.aureus, S. epidermidis, Escherichia coli,* and *Klebsiella sp*.
All the synthesized compounds having promising docking results with COX-2 active site as shown in compounds ($S_{27}$, $S_{20}$, $S_{35}$, $S_{34}$, $S_{13}$, $S_{28}$, and $S_{21}$) showed H-bond interactions with Arg121 and Tyr356 and these two amino acids exist in the binding with five approved NSAIDs. These compounds have H-bond with Arg121 and Tyr356, which exist in the binding site of diclofenac, lumiracoxib, and tolfenamic acid.

**Key words:** imidazole, Schiff base, and pharmacological

## Introduction

The nucleus of furfural (Furan) can be prepared from tetra hydro phenol (Döbereiner, 1832). It is an important structural fragment for many active pharmaceutical ingredients and pharmacologically active compounds (Meotti et al., 2003). Furan is a common structural motif available in many natural products (Keay and Dibble, 1996). Its derivatives obtained from synthetic and natural resources have a wide range of pharmaceutical interests because of biological activities. The furan derivatives showed interesting biological activities such as nematocidal (Bakker et al., 1979), insecticidal, (Iyengar et al., 1987) antibacterial, (Matsuura et al., 1996; Mohammadzadeh et al., 2018) antifungal (Chan et al., 1975), antiviral (Hudson et al., 1989), antioxidant (Malmström et al., 2001; Awad et al., 2018), anti-inflammatory (Beers et al., 1997; Zeni et al., 2001), and anti-nociceptive (Lopez et al., 2002; Meotti et al., 2003; Mazı et al., 2018) properties. They are compounds with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group (Smith, 2007; Solomon, 1999). Molecular docking is to computationally simulate the molecular identification process and accomplish an optimized conformation so that the free energy of the overall system is minimized (Pozzan, 2006).

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## Methods

*General procedure for the synthesis of 5-Aryl-furan-2-carbaldehyde ($S_6$, $S_7$)*

4-Substituted aniline (0.68 mol) was diluted in a mixture of concentrated HCl (16.85 mL) and $H_2O$ (11.25 mL). The solution was cooled to 0ºC and diazotized at 0-5 ºC with sodium nitrite (4.75 g, 0.69 mol) dissolved in $H_2O$ (25 ml). The solution was stirred for 10 min, filtered, and then 7.7 g (0.8 mol) furan-2-carboxaldehyde dissolved in 25 mL $H_2O$ was added to 2.5 g (0.02 mol) $CuCl_2.H_2O$ in $H_2O$ (12.5 mL) at 13-16 ºC. The reaction mixture was slowly warmed up to 45 ºC and stirred at this temperature for 3h (Puterová et al., 2004).

*Synthesis of (2-((5-Arylfuran-2-yl) methylene) hydrazine-1-carbo-thioamide) ($S_{13}$, $S_{14}$)*

2-3 drops of glacial acetic acid were added to the compound derivatives (5 Aryl furan-2-carbaldehyde) ($S_6$, $S_7$), (0.01 mol in 30ml ethanol) at room temperature. The mixture was stirred for 10 min and then thiosemicarbazide (0.01mol, 0.009g) was added to it. The mixture was refluxed for 12h. The reaction was allowed to cool, then the mixture was poured into the crushed ice and recrystallized from ethanol or methanol to yield the desired compound.

*Synthesis of (1-(((5-Arylfuran-2-yl) methylene) amino)-2-thioxoimidazolidin-4-one) ($S_{20}$ - $S_{21}$)*

0.02 mol $S_{13}$-$S_{14}$ was added to 30ml 1,4-dioxane at room temperature. After that, 0.02 mol (0.645g) sodium bicarbonate was added to the mixture and stirred for 30min. Then, 0.02 mol (2.46g) ethyl chloroacetate was added to it and the final mixture was refluxed for 30h. After this time, the mixture was put into the ice water. Finally, the precipitate was filtered off and the solid product was recrystallized by using dioxane to yield the desired compound.

*Synthesis of ((Z)-1-(((5-Arylfuran-2-yl) methylene) amino)-3-(phenylsulfonyl)-2-thioxoimidazolidin-4-one) $S_{27}$ - $S_{28}$*

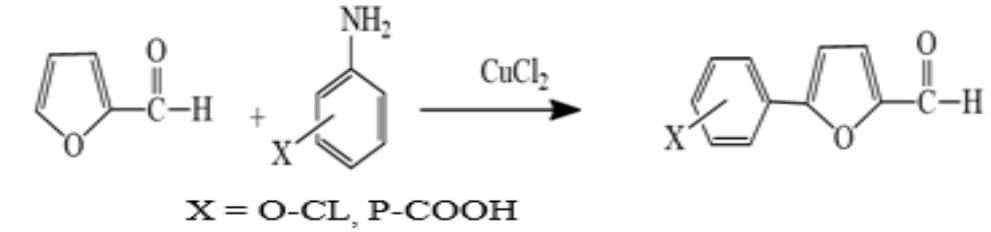
0.001mol of the compounds **$S_{20}$ – $S_{21}$** was added to 25ml of 1, 4-dioxane and stirred for 10 min. Then, triethylamine $Et_3N$ was added and the stirring was continued for 1h on the ice bath. After that, 0.001 (0.176 g) mol benzene sulphonyl chloride was added and the stirring was continued. Finally, the mixture was refluxed at 120 $^oC$ for 22h.

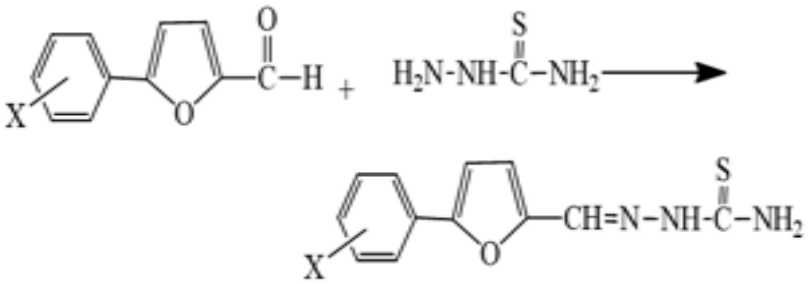
*Synthesis of ((Z)-3-acetyl-1-(((5-phenylfuran-2-yl) methylene) amino)-2-thioxoimidazolidin-4-one) compounds $S_{34}$- $S_{35}$*

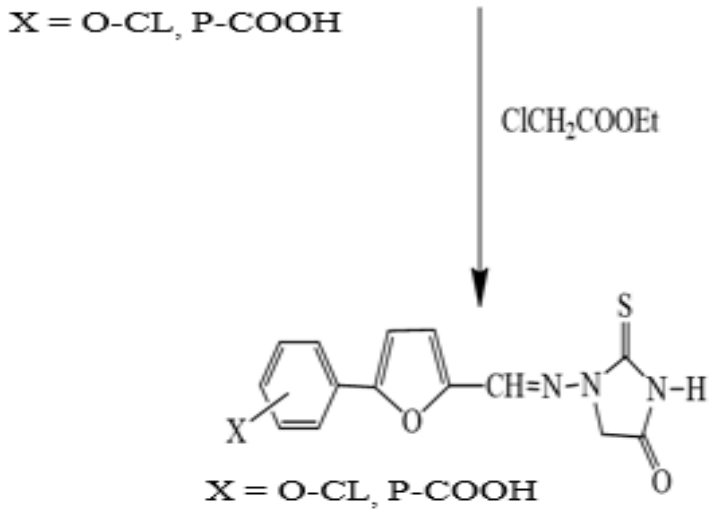
0.001 mol of the $S_{27}$-$S_{28}$ compounds was added to 25ml of 1, 4-dioxane and stirred for 10 min. Then, triethylamine $Et_3N$ was added to the mixture and stirring was continued for 1h on the ice bath. After that, 0.001 mol (0.078g) acetyl chloride was added to the stirred solution of the compound and the mixture was refluxed at 110 $^\circ C$ for 10h.

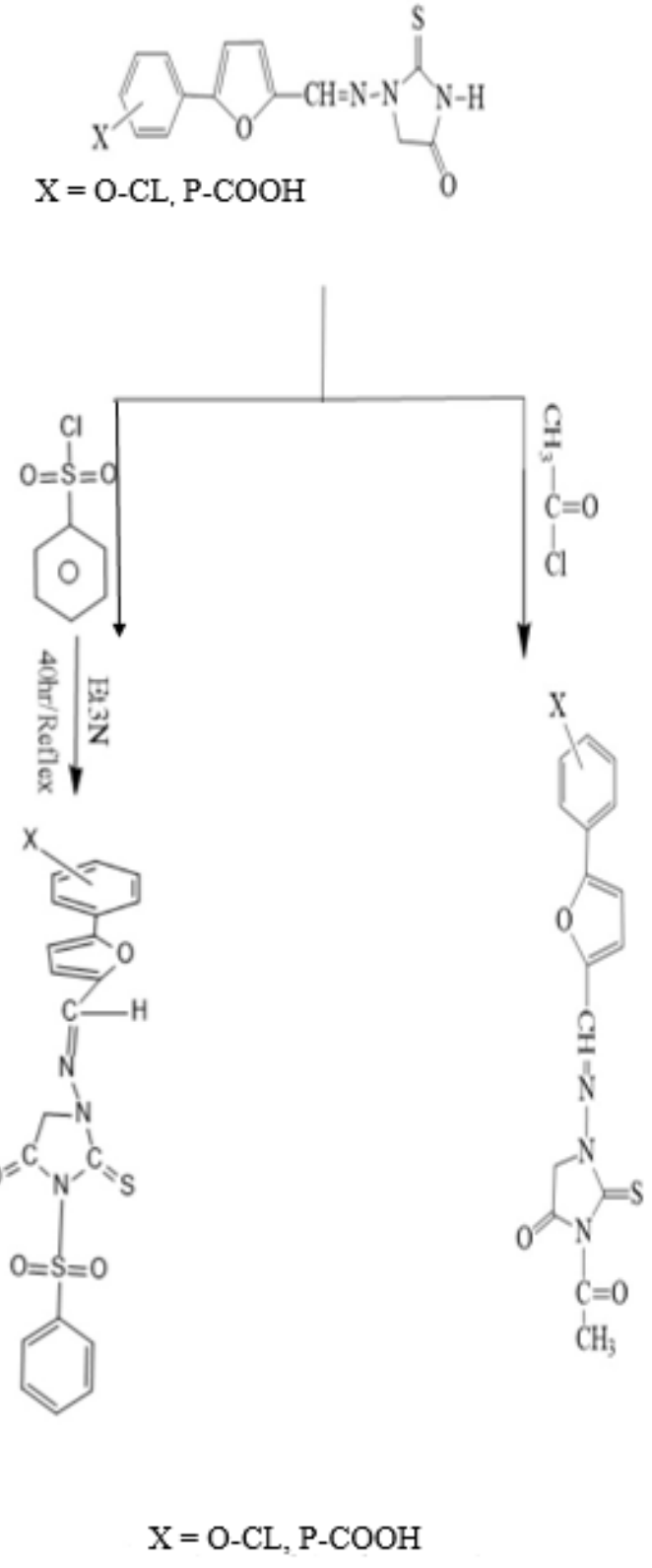
## Results and Discussion

Figure (1) shows all the synthesized compounds






The synthesis of the target **($S_6$)** was done by the reaction of 4-substituted aniline with Furan-2-carboxaldehyde through a nucleophilic mechanism. With (50%).m.p (100,103), color (White Yellow). The FT-IR spectrum of the compound ($S_6$) showed a stretching vibration of (C=C) of Aldehyde at 1516-1597 $cm^{-1}$ and the appearance of a new band at 1680 $cm^{-1}$ for

(C=O) and (C-H) at. (3070)

The compound ($S_6$) was treated with aryl and led to the formation of the compound ($S_{13}$).

**($S_7$)**: yield = 56%, FT-IR ($cm^{-1}$): C=O (1674), (C=C)ar. (1529,1610), (C-H)ar. (3064), and (OH) acid (2542, 3404)

The compound ($S_7$) was treated with aryl and led to the formation of the compound ($S_{14}$).

**($S_{13}$)**: yield = 65%, FT-IR ($cm^{-1}$): C=N (1602), (C=C) ar. (1504,1591), (C-H) ar. (3061), and CL (1026), 1H-NMR (ppm), s,(8.99) for (N=CH), S(11.54) (NH) (7.39-7.77) (m,aromatic protons).

**($S_{14}$)**: yield (60%), FT-IR $cm^{-1}$ C=N (1606), (C=C) ar. (1527,1583), (C-H) ar. (3059), (C=O) (1668). 1H-NMR (ppm), s (8.23) for (N=CH), s (11.57) for (NH) (7.34-7.98) (m, aromatic protons).

**($S_{20}$)**: yield = 69%, FT-IR $cm^{-1}$: C=N (1643), C=O (1708), (C=C) ar. (1516,1591), (C-H) ar. (3050), 1H-NMR(ppm), s, (3.86) for ($CH_2$), s,(8.29) for (N=CH), (7.36,7.99) (m, aromatic protons) $^{13}$C-NMR (ppm), (151.72) for (C=O), (149.66) for (C =S), (145.57) (C=N) the mother ion peak at (m/z=319), as a base peak, which corresponds to (M+). The other fragments and their relative abundances obtained the molecular formula of the compound $C_{14}H_{10}N_3O_2SCL$.

The treatment of (**$S_{20}$**) with benzene sulphonyl chloride gives (**$S_{27}$**).

**($S_{21}$)**: yield = 67%, FT-IR ($cm^{-1}$): C=S (1109), C=N (1681), (C=O) (1716), (C=C) ar. (1527, 1608), (C-H) ar. (3063), the mother ion peak is at (m/z=329), which is related to (M+). The other fragments and their relative abundances obtained the molecular formula of the compound $C_{14}H_{11}N_3O_4S$.

Treatment of (**$S_{21}$**) with benzene sulphonyl chloride gives (**$S_{28}$**).

**($S_{27}$)**: yield = 72%, FT-IR ($cm^{-1}$): C-CL (802), C=N(1635), C=O(1714), (C=C) ar. (1516,1602), (C-H) ar. (3080) 1H-NMR (ppm), s, (3.91) for ($CH_2$), s, (8.29) for (N=CH), (7.29.8.06) (m,aromatic protons),$^{13}$C-NMR (ppm), (150.76) for (C=O), (148.69) for (C =S), (144.57) (C=N).

**($S_{28}$)**: yield = 71%, FT-IR $cm^{-1}$ OH acid (2530,3425), C=N(1635), C=O(1712), (C=C) ar. (1512,1600), (C-H) ar. (3066) (figure 1),

Treatment of (**$S_{28}$**) with acetyl chloride gives (**$S_{34}$**).

**($S_{34}$)**: yield = 58%, FT-IR $cm^{-1}$ C-CL ortho (756), C=N (1651), C=O imidazole (1732), (C=C) ar. (1506,1600), (C-H) ar. (3086), (C=S), (1026)., (C=O) Amid (1660), the mother ion peak is at (m/z=361), which is related to (M+). The other fragments and their relative abundances the molecular formula of the compound $C_{16}H_{12}N_3O_3SCL$. (figure 2)

**($S_{35}$)**: yield = 51%, FT-IR ($cm^{-1}$), C=N (1625), C=O imidazole (1699), (C=C) ar. (1527,1606), (C-H) ar. (3043), (C=S), (1020), (C=O) Amid (1681),

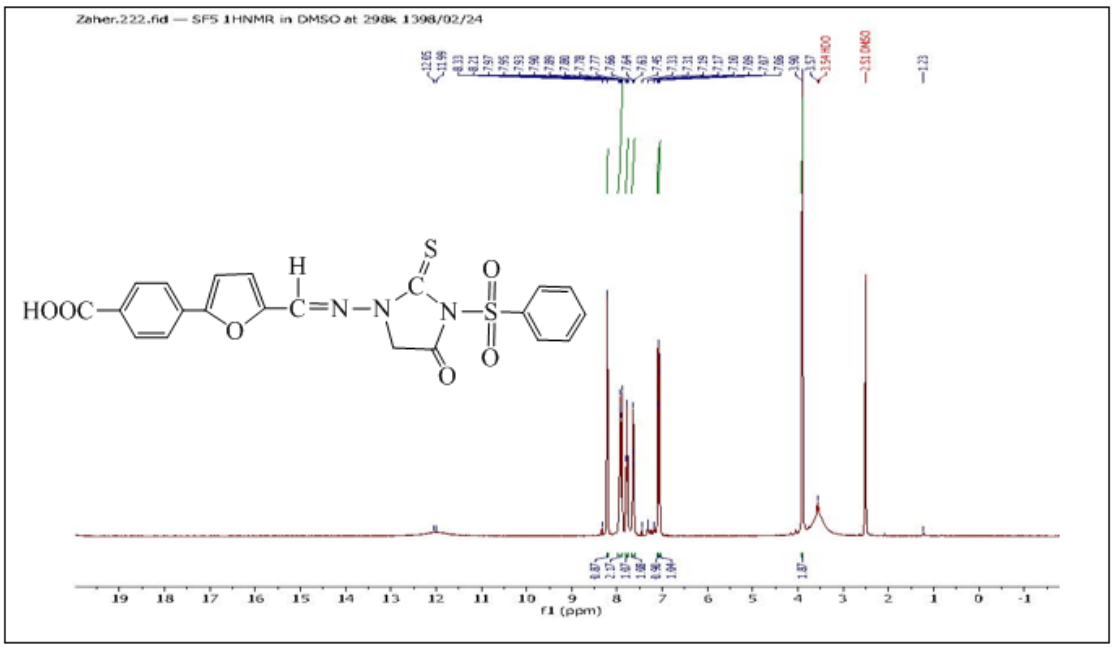



**Figure 1:** The 1 HNMR spectrum of compound S28

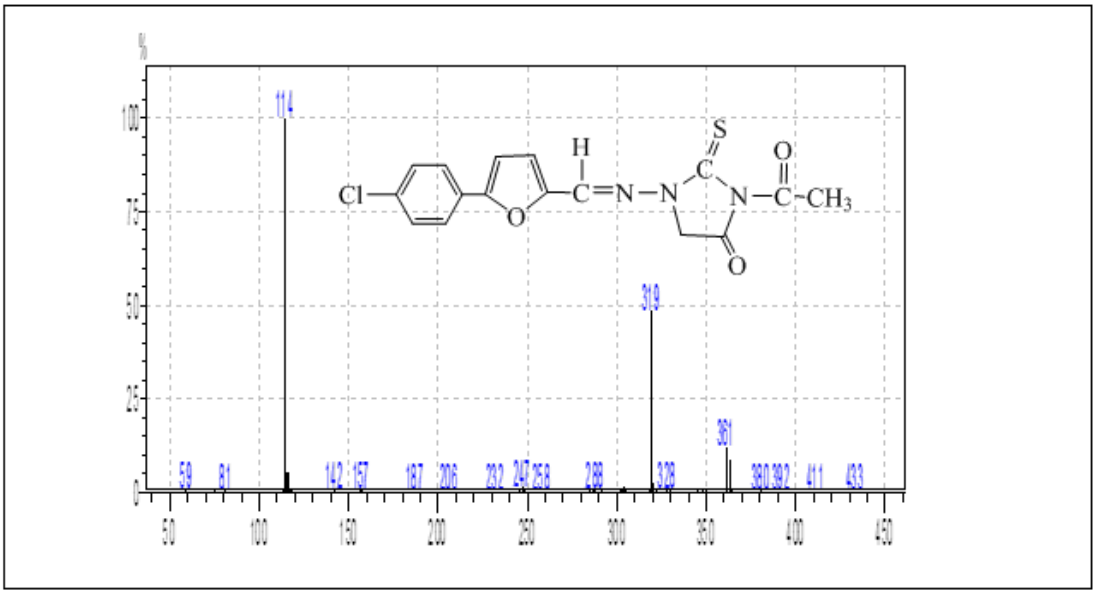



**Figure 2:** The Mass spectrum of compound $S_{34}$

*Antibacterial activity of derivatives*

The effect of compounds **($S_{13}$, $S_{14}$, $S_{20}$, $S_{21}$, $S_{27}$, $S_{28}$, $S_{34}$, $S_{35}$)** on *Staphylococcus aureus* and *Staphylococcus epidermidis* (gram-positive bacteria), *Escherichia coli* and *Klebsiella sp* (gram-negative bacteria) was evaluated. Most of the prepared compounds revealed a good activity against *S. aureus* and *S epidermidis*. It was observed that the tested derivatives were active but S13, S21, S27, S28, S34, and S35 had a high activity against *S. aureus*; S14 and S20 had a high activity against *S. epidermidis*; the compounds S13, S20, S28, and S34 had a high activity against *S. aureus*; S14, 21 S27, and S35 had a high activity against *S. epidermidis*; and weak activity toward all types of tested bacteria. The compound S28 showed a high inhibition against *S. aureus*.

Table 1. Antibacterial Activity of derivatives ($S_{13}$, $S_{14}$, $S_{20}$, $S_{21}$, $S_{27}$, $S_{28}$, $S_{34}$, $S_{35}$)

| Comp. No. | Inhibition Zone | | | |
|---|---|---|---|---|
| | ***S. aureus*** | ***E. coli*** | ***S. epidermidis*** | ***K. sp*** |
| S13 | 15 | - | 20 | - |
| S14 | 13 | - | 13 | - |
| S20 | 11 | 10 | 18 | - |
| S21 | 16 | 9 | 13 | - |
| S27 | 18 | - | 11 | - |
| S28 | 21 | 12 | 18 | - |
| S34 | 17 | - | 20 | - |
| S35 | 21 | - | 13 | 10 |

(-) No inhibition zone

*Interpretation of the results of docking study*

The COX-2 inhibitory activity of the compounds ($S_{27}$, $S_{20}$, $S_{35}$, $S_{34}$ $S_{13}$, $S_{28}$, and $S_{21}$) 6MNA, diclofenac, and naproxen were ranked based on their PLP fitness involved in the complex formation at the active sites. The PLP fitness of the docked compounds on COX-2 was found in the range of 70.36, 68.97, 68.08, 68.02, 66.26, 65.05, and 62.68, respectively Table (2)

Table 2: the binding energies for NSAIDs docked with COX-2.

| Code | Binding energy (PLP Fitness) | Amino acid included in H-bonding | No of bonding | Power of bonding |
|---|---|---|---|---|
| Ibuprofen | 65.81 | ARG121<br>TYR356 | 1<br>1 | 2.920<br>2.651 |
| S27 | 70.36 | SER120 | 1 | 3.009 |
| S20 | 68.97 | TYR356<br>SER120 | 1<br>1 | 2.996<br>2.960 |
| S35 | 68.08 | ARG121<br>SER531 | 1<br>1 | 3.036<br>2.868 |
| S34 | 68.02 | ARG121 | 1 | 2.793 |
| S13 | 66.26 | LEU353<br>SER356<br>HIS90 | 1<br>1<br>1 | 3.062<br>2.971<br>2.682 |
| S28 | 65.05 | TYR116 | 1 | 2.388 |
| S21 | 62.68 | ARG121<br>SER531 | 1<br>1 | 3.024<br>3.001 |

## Conclusions

The compounds were synthesized by using the derivatives of aniline as starting materials obtained from furfural and sodium nitrite with hydrochloric acid to give derivatives of aldehyde. The effects of compounds **($S_{13}$, $S_{14}$, $S_{20}$, $S_{21}$, $S_{27}$, $S_{28}$, $S_{34}$, and $S_{35}$)**

against different pathogenic bacteria and yeast (*Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli,* and *Klebsiella Sp.*) were evaluated using 125 µg/ml of each compound. All the synthesized compounds had promising docking results with COX-2 active site as shown in compounds ($S_{27,}$ $S_{20,}$ $S_{35,}$ $S_{34,}$ $S_{13,}$ $S_{28}$, and $S_{21}$).

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