

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

Safaa Abdulhameed Dadoosh\*, Monther Faisal Mahdi and Abdul Jabar Kh. Atia

Received: 02 August 2019 / Received in revised form: 20 November 2019, Accepted: 02 December 2019, Published online: 27 December 2019  
© Biochemical Technology Society 2014-2019  
© Sevas Educational Society 2008

## 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,  $^1\text{H}$ NMR, 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

**Safaa Abdulhameed Dadoosh\***

Department of Chemistry, College of Science, Diyala University, Diyala, Iraq.

**Monther Faisal Mahdi**

Department of Pharmacy, of Ashur University College, Baghdad, Iraq

**Abdul Jabar Kh. Atia**

Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, Iraq.

\*Email: safaa.abd1999@gmail.com

(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 antinociceptive (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).

## 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  $\text{H}_2\text{O}$  (11.25 mL). The solution was cooled to  $0^\circ\text{C}$  and diazotized at  $0-5^\circ\text{C}$  with sodium nitrite (4.75 g, 0.69 mol) dissolved in  $\text{H}_2\text{O}$  (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  $\text{H}_2\text{O}$  was added to 2.5 g (0.02 mol)  $\text{CuCl}_2 \cdot \text{H}_2\text{O}$  in  $\text{H}_2\text{O}$  (12.5 mL) at  $13-16^\circ\text{C}$ . The reaction mixture was slowly warmed up to  $45^\circ\text{C}$  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<sub>20</sub> - S<sub>21</sub>)*

0.02 mol S<sub>13</sub>-S<sub>14</sub> 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<sub>27</sub> - S<sub>28</sub>*

0.001mol of the compounds S<sub>20</sub> - S<sub>21</sub> was added to 25ml of 1, 4-dioxane and stirred for 10 min. Then, triethylamine Et<sub>3</sub>N was added and the stirring was continued for 1h on the ice bath. After

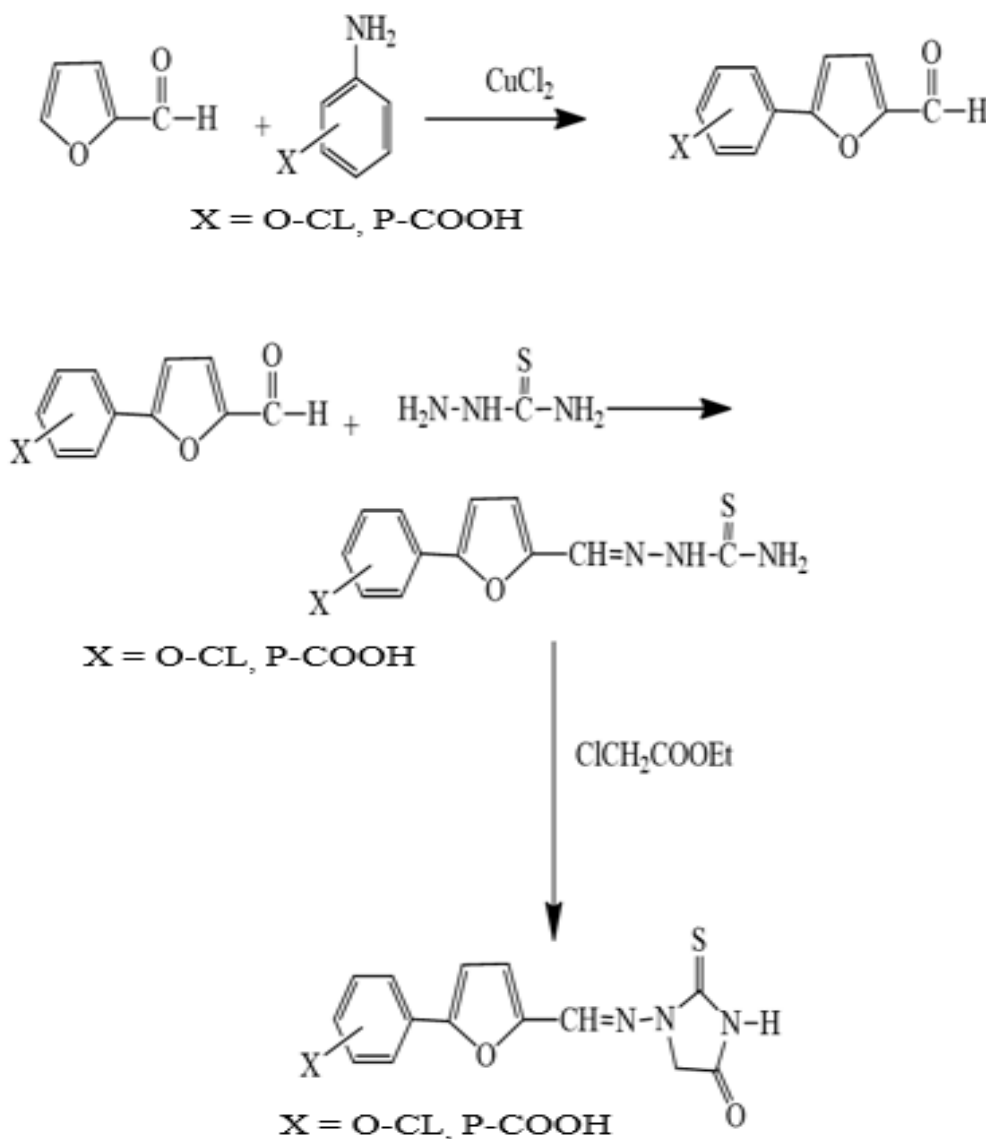
that, 0.001 (0.176 g) mol benzene sulphonyl chloride was added and the stirring was continued. Finally, the mixture was refluxed at 120 °C for 22h.

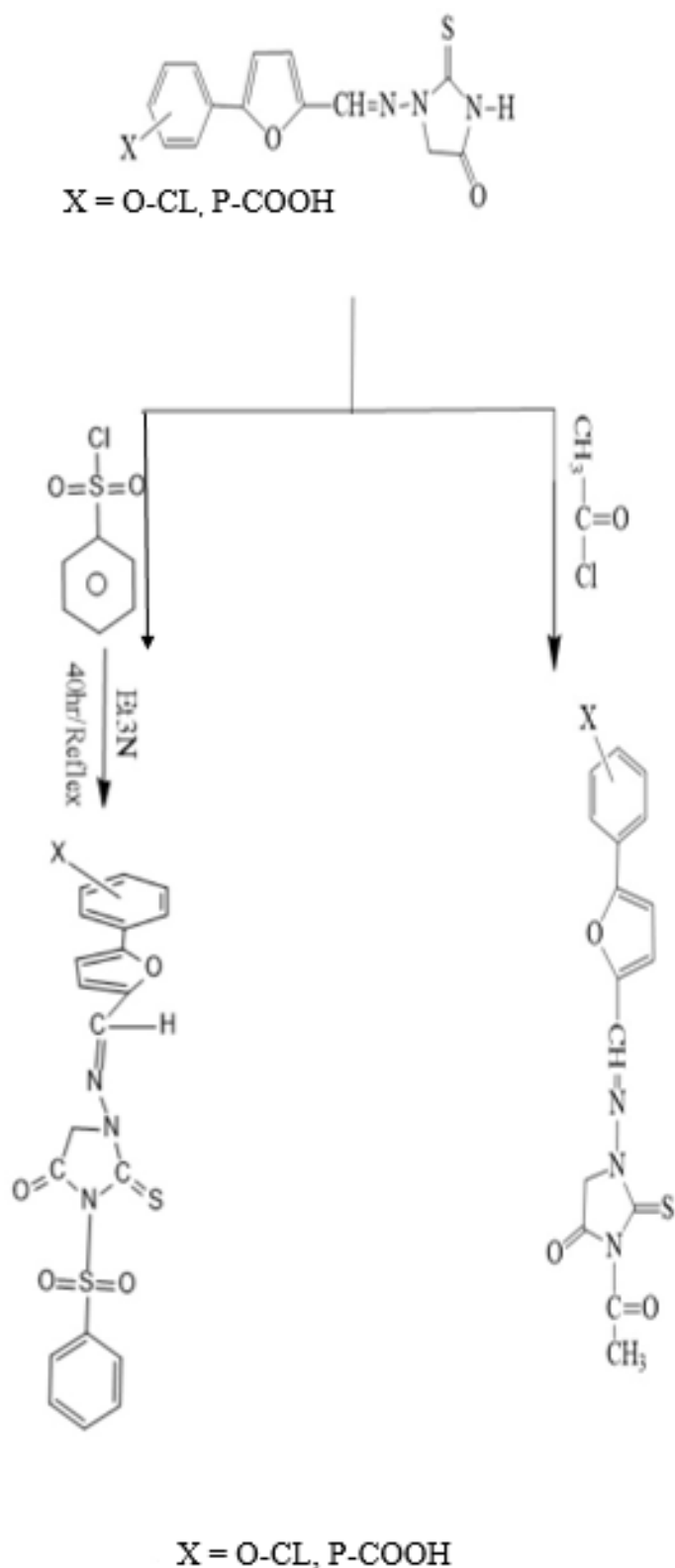
*Synthesis of ((Z)-3-acetyl-1-(((5-phenylfuran-2-yl) methylene) amino)-2-thioxoimidazolidin-4-one) compounds S<sub>34</sub>- S<sub>35</sub>*

0.001 mol of the S<sub>27</sub>-S<sub>28</sub> compounds was added to 25ml of 1, 4-dioxane and stirred for 10 min. Then, triethylamine Et<sub>3</sub>N 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 °C for 10h.

## Results and Discussion

Figure (1) shows all the synthesized compounds





The synthesis of the target (**S<sub>6</sub>**) 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<sub>6</sub>**) showed a stretching vibration of (C=C) of Aldehyde at 1516-1597  $\text{cm}^{-1}$  and the appearance of a new band at 1680  $\text{cm}^{-1}$  for

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

The compound (**S<sub>6</sub>**) was treated with aryl and led to the formation of the compound (**S<sub>13</sub>**).

(**S<sub>7</sub>**): yield = 56%, FT-IR (cm<sup>-1</sup>): C=O (1674), (C=C)ar. (1529,1610), (C-H)ar. (3064), and (OH) acid (2542, 3404)

The compound (**S<sub>7</sub>**) was treated with aryl and led to the formation of the compound (**S<sub>14</sub>**).

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

(**S<sub>14</sub>**): yield (60%), FT-IR cm<sup>-1</sup> C=N (1606), (C=C) ar. (1527,1583), (C-H) ar. (3059), (C=O) (1668). <sup>1</sup>H-NMR (ppm), s (8.23) for (N=CH), s (11.57) for (NH) (7.34-7.98) (m, aromatic protons).

(**S<sub>20</sub>**): yield = 69%, FT-IR cm<sup>-1</sup>: C=N (1643), C=O (1708), (C=C) ar. (1516,1591), (C-H) ar. (3050), <sup>1</sup>H-NMR(ppm), s, (3.86) for (CH<sub>2</sub>), s,(8.29) for (N=CH), (7.36,7.99) (m, aromatic protons) <sup>13</sup>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<sup>+</sup>). The other fragments and their relative abundances obtained the molecular formula of the compound C<sub>14</sub>H<sub>10</sub> N<sub>3</sub>O<sub>2</sub>SCL.

The treatment of (**S<sub>20</sub>**) with benzene sulphonyl chloride gives

(**S<sub>27</sub>**).

(**S<sub>21</sub>**): yield = 67%, FT-IR (cm<sup>-1</sup>): 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<sup>+</sup>). The other fragments and their relative abundances obtained the molecular formula of the compound C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>S.

Treatment of (**S<sub>21</sub>**) with benzene sulphonyl chloride gives (**S<sub>28</sub>**).

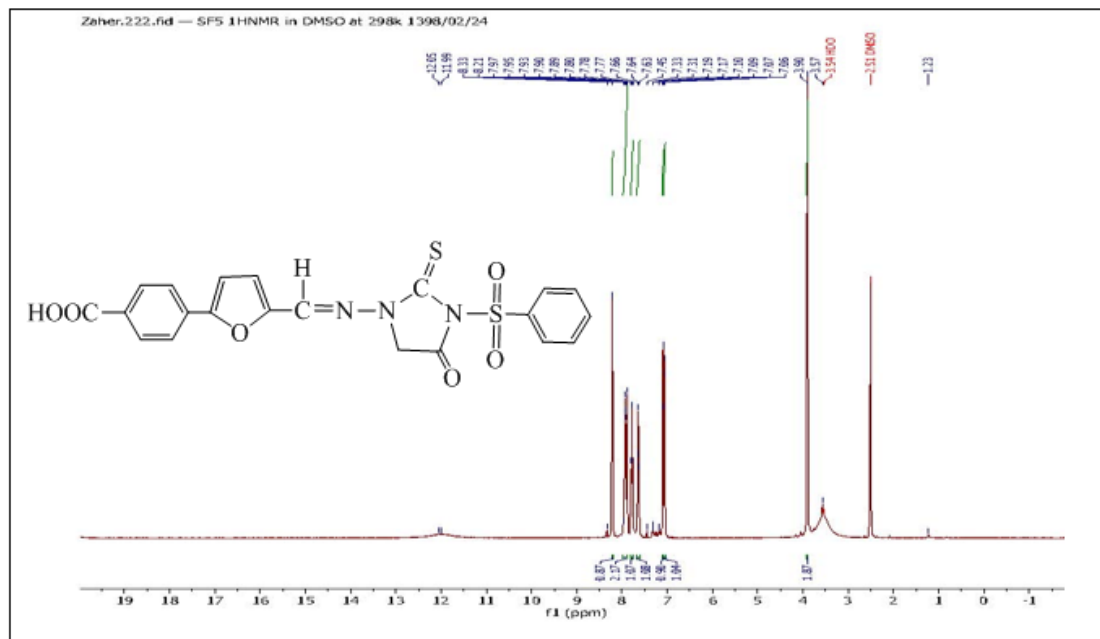
(**S<sub>27</sub>**): yield = 72%, FT-IR (cm<sup>-1</sup>): C-CL (802), C=N(1635), C=O(1714), (C=C) ar. (1516,1602), (C-H) ar. (3080) <sup>1</sup>H-NMR (ppm), s, (3.91) for (CH<sub>2</sub>), s, (8.29) for (N=CH), (7.29.8.06) (m,aromatic protons), <sup>13</sup>C-NMR (ppm), (150.76) for (C=O), (148.69) for (C =S), (144.57) (C=N).

(**S<sub>28</sub>**): yield = 71%, FT-IR cm<sup>-1</sup> OH acid (2530,3425), C=N(1635), C=O(1712), (C=C) ar. (1512,1600), (C-H) ar. (3066) (figure 1),

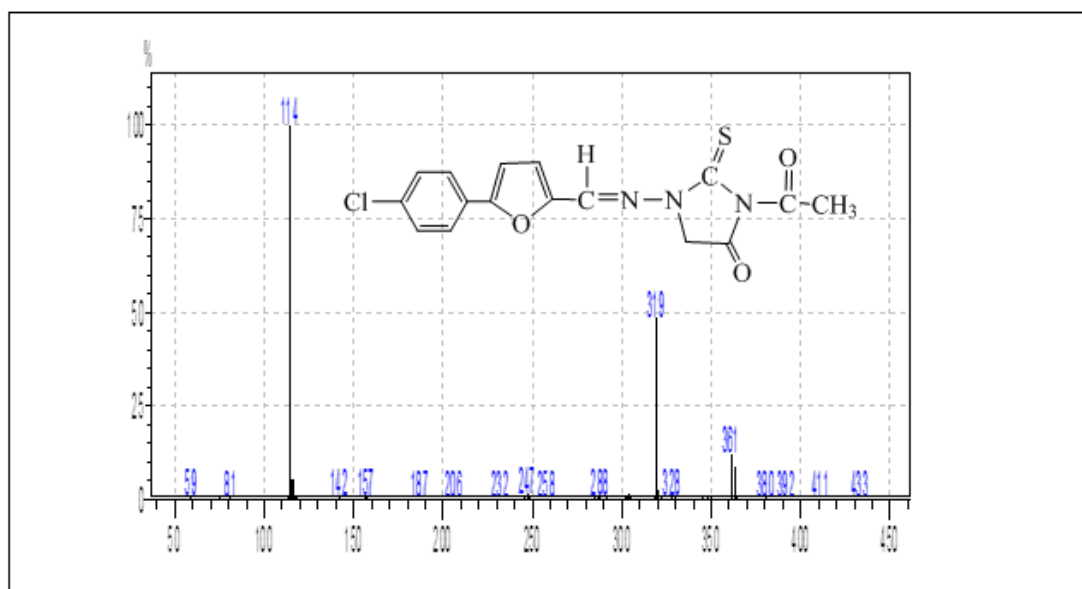
Treatment of (**S<sub>28</sub>**) with acetyl chloride gives (**S<sub>34</sub>**).

(**S<sub>34</sub>**): yield = 58%, FT-IR cm<sup>-1</sup> 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<sup>+</sup>). The other fragments and their relative abundances the molecular formula of the compound C<sub>16</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub>SCL. (figure 2)

(**S<sub>35</sub>**): yield = 51%, FT-IR (cm<sup>-1</sup>), 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 <sup>1</sup>HNMR spectrum of compound S28



**Figure 2:** The Mass spectrum of compound S<sub>34</sub>

#### Antibacterial activity of derivatives

The effect of compounds (S<sub>13</sub>, S<sub>14</sub>, S<sub>20</sub>, S<sub>21</sub>, S<sub>27</sub>, S<sub>28</sub>, S<sub>34</sub>, S<sub>35</sub>) 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 S<sub>13</sub>, S<sub>21</sub>, S<sub>27</sub>, S<sub>28</sub>, S<sub>34</sub>, and S<sub>35</sub> had a high activity against *S. aureus*; S<sub>14</sub> and S<sub>20</sub> had a high activity against *S. epidermidis*; the compounds S<sub>13</sub>, S<sub>20</sub>, S<sub>28</sub>, and S<sub>34</sub> had a high activity against *S. aureus*; S<sub>14</sub>, S<sub>21</sub>, S<sub>27</sub>, and S<sub>35</sub> had a high activity against *S. epidermidis*; and weak activity toward all types of tested bacteria. The compound S<sub>28</sub> showed a high inhibition against *S. aureus*.

**Table 1.** Antibacterial Activity of derivatives (S<sub>13</sub>, S<sub>14</sub>, S<sub>20</sub>, S<sub>21</sub>, S<sub>27</sub>, S<sub>28</sub>, S<sub>34</sub>, S<sub>35</sub>)

Comp. No.	Inhibition Zone			
	<i>S. aureus</i>	<i>E. coli</i>	<i>S. epidermidis</i>	<i>K. sp</i>
S <sub>13</sub>	15	-	20	-
S <sub>14</sub>	13	-	13	-
S <sub>20</sub>	11	10	18	-
S <sub>21</sub>	16	9	13	-
S <sub>27</sub>	18	-	11	-
S <sub>28</sub>	21	12	18	-
S <sub>34</sub>	17	-	20	-
S <sub>35</sub>	21	-	13	10

(-) No inhibition zone

#### Interpretation of the results of docking study

The COX-2 inhibitory activity of the compounds (S<sub>27</sub>, S<sub>20</sub>, S<sub>35</sub>, S<sub>34</sub>, S<sub>13</sub>, S<sub>28</sub>, and S<sub>21</sub>) 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 TYR356	1 1	2.920 2.651
S <sub>27</sub>	70.36	SER120	1	3.009
S <sub>20</sub>	68.97	TYR356 SER120	1 1	2.996 2.960
S <sub>35</sub>	68.08	ARG121 SER531	1 1	3.036 2.868
S <sub>34</sub>	68.02	ARG121	1	2.793
S <sub>13</sub>	66.26	LEU353 SER356 HIS90	1 1 1	3.062 2.971 2.682
S <sub>28</sub>	65.05	TYR116	1	2.388
S <sub>21</sub>	62.68	ARG121 SER531	1 1	3.024 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<sub>13</sub>, S<sub>14</sub>, S<sub>20</sub>, S<sub>21</sub>, S<sub>27</sub>, S<sub>28</sub>, S<sub>34</sub>, and S<sub>35</sub>)

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<sub>27</sub>, S<sub>20</sub>, S<sub>35</sub>, S<sub>34</sub>, S<sub>13</sub>, S<sub>28</sub>, and S<sub>21</sub>).

## References

- Awad, S. M., Youns, M. M., & Ahmed, N. M. (2018). Design, Synthesis and Biological Evaluation of Novel 2-Thiouracil-5-Sulfonamide Isosteres As Anticancer Agents. *Pharmacophore*, 9(3), 13-24.
- Bakker, J., Gommers, F. J., Nieuwenhuis, I., & Wynberg, H. (1979). Photoactivation of the nematocidal compound alpha-terthienyl from roots of marigolds (*Tagetes* species). A possible singlet oxygen role. *Journal of Biological Chemistry*, 254(6), 1841-1844.
- Beers, S. A., Malloy, E. A., Wu, W., Wachter, M., Ansell, J., Singer, M., ... & Argentieri, D. (1997). N-(5-substituted) thiophene-2-alkylsulfonamides as potent inhibitors of 5-lipoxygenase. *Bioorganic & medicinal chemistry*, 5(4), 779-786.
- Chan, G. F. Q., Towers, G. N., & Mitchell, J. C. (1975). Ultraviolet-mediated antibiotic activity of thiophene compounds of *Tagetes*. *Phytochemistry*, 14(10), 2295-2296.
- Döbereiner, J. W. (1832). Ueber die medicinische und chemische Anwendung und die vortheilhafte Darstellung der Ameisensäure. *Annalen der Pharmacie*, 3(2), 141-146.
- Hudson, J. B., Graham, E. A., Miki, N., Towers, G. H. N., Hudson, L. L., Rossi, R., ... & Neri, D. (1989). Photoactive antiviral and cytotoxic activities of synthetic thiophenes and their acetylenic derivatives. *Chemosphere*, 19(8-9), 1329-1343.
- Iyengar, S., Arnason, J. T., Philogene, B. J. R., Morand, P., Werstiuk, N. H., & Timmins, G. (1987). Toxicokinetics of the phototoxic allelochemical  $\alpha$ -terthienyl in three herbivorous Lepidoptera. *Pesticide biochemistry and physiology*, 29(1), 1-9.
- Keay B.A., & Dibble P.W., (1996). In *Comprehensive Heterocyclic Chemistry*. Pergamon Oxford, 2, 395-436.
- Lopez, F. J., Jett, M. F., & Muchowski, J. M. (2002). Synthesis and biological evaluation of ketorolac analogs. *Heterocycles*, 56(1), 91-95.
- Malmström, J., Jonsson, M., Cotgreave, I. A., Hammarström, L., Sjödin, M., & Engman, L. (2001). The antioxidant profile of 2, 3-dihydrobenzo [b] furan-5-ol and its 1-thio, 1-seleno, and 1-telluro analogues. *Journal of the American Chemical Society*, 123(15), 3434-3440.
- Matsuura, H., Saxena, G., Farmer, S. W., Hancock, R. E. W., & Towers, G. H. N. (1996). Antibacterial and antifungal polyine compounds from *Glehnia littoralis* ssp. *leiocarpa*. *Planta medica*, 62(03), 256-259.
- Mazi, C., Karaderi, S., & Ariöz, F. (2018). Determination of UV-Vis Spectrophotometric Method of Metal Complexes Stoichiometry between Cu (II) and Zn (II) with Vilazodone Hydrochloride. *International Journal of Pharmaceutical Research and Allied Sciences*, 7(3), 146-152.
- Meotti, F. C., Silva, D. O., dos Santos, A. R., Zeni, G., Rocha, J. B. T., & Nogueira, C. W. (2003). Thiophenes and furans derivatives: a new class of potential pharmacological agents. *Environmental toxicology and pharmacology*, 15(1), 37-44.
- Meotti, F. C., Silva, D. O., dos Santos, A. R., Zeni, G., Rocha, J. B. T., & Nogueira, C. W. (2003). Thiophenes and furans derivatives: a new class of potential pharmacological agents. *Environmental toxicology and pharmacology*, 15(1), 37-44.
- Mohammadzadeh I, Khabazzadeh H, Eskandarizadeh A, Bavafa M, Shahravan A, Saidi A. (2018). Synthesis of 3-(2, 5-Dimethylfuran-3-Yl)-1h-Pyrazole-5(4h)-One, A New Antibacterial Compound and Use It for Creating Excellent Anti-Bacterial Properties in Flowable Composites. 6(4).
- Pozzan, A. (2006). Molecular descriptors and methods for ligand based virtual high throughput screening in drug discovery. *Current pharmaceutical design*, 12(17), 2099-2110.
- Puterová, Z., Sterk, H., & Krutošiková, A. (2004). Reaction of substituted furan-2-carboxaldehydes and furo [b] pyrrole type aldehydes with hippuric acid. *Molecules*, 9(1), 11-21.
- Smith MB. (2007). *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, A John Wiley & Sons. Inc., Hoboken, New Jersey.
- Solomon, P. H. (1999). *Writing reaction mechanisms in organic chemistry*. Elsevier.
- Zeni, G., Lüdtke, D. S., Nogueira, C. W., Panatieri, R. B., Braga, A. L., Silveira, C. C., ... & Rocha, J. B. (2001). New acetylenic furan derivatives: synthesis and anti-inflammatory activity. *Tetrahedron Letters*, 42(51), 8927-8930.