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# Synthesis, Characterization, Biological Assay of New 5-(pyridine-2-yl)-1,3,4-oxadiazol-2-amine Derivatives and their Molecular docking Studies

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**ABSTRACT**

This study introduces a novel class of titled compounds, that are produced through a reaction of picolinohydrazide with various unsymmetrical anhydrides. The confirmation of the successful syntheses is affirmed through a detailed characterization protocol including Proton-NMR, $^{13}$C-NMR, FTIR, and Mass spectral studies. The resulting products, 2 as well as 3(a-e), underwent successive evaluations to determine their antibacterial capabilities on *S. aureus* and *E. coli*, and antifungal evaluation in relation to *Candida albicans*. Assessment of antimicrobial activity using the disc diffusion method and reference compounds revealed good efficacy in most of these synthesized compounds, revealing some that had very approving results. Computational docking showed that all new compounds exhibit good interactions. This study highlights the power of 5-(pyridine-2-yl)-1,3,4-oxadiazolo alkanamides against both anti-microbial strains.

**Keywords:** 1,3,4-oxadiazol-2-amine derivatives, Docking study, biological activity.

## INTRODUCTION

Since from the human evolution, microbial infections have become a challenging one in the medical treatment[1], within the last few years, in addition to other complications faced during the treatment of infectious diseases today is antimicrobial resistance that has increased its prevalence almost exponentially. Abusing and overuse of antibiotics have sped up the creation of resistant bacteria strains by becoming ineffective treatments that were previously effective. The phenomenon has highlighted the need to develop innovative approaches for combating microbial diseases[2]. The important classes refer to heterocyclic compounds, which have very diverse ring structures containing at least one atom such as nitrogen, sulphur or oxygen and show variety of biological activities[3]. However, in the process of antimicrobial drug formulation such substances present a promising potential to retard growth and increase the proliferation of various microbes. Scientists are currently investigating heterocyclic structure synthesis and modification in an attempt

to improve their antimicrobial properties without adverse side effects.

Pyridine has a hetero aromatic ring with one nitrogen atom[4]. The analogues of pyridine have shown antimicrobial[5-8], anticancer[9-11], antiviral[12], antidiabetic[13], anti-inflammatory properties[14-15]. Derivatives of oxadiazole are significant organic substances with a variety of uses. In the last ten years, 1,3,4 oxadiazoles, heterocycles with one oxygen and two nitrogens[16], have clearly shown promising activity as potential antibacterial[17-22], antifungal[23-25], antiviral[26], anticancer[27-30], antidiabetic[31-32] drugs. As to combat the challenges, in the present work we extended a new class of analogues using oxadiazoles and pyridine. The microbial assay and molecular binding studies of the prepared analogues were also presented.

## MATERILAS AND METHODS

Each chemical reagent used in the current synthesis is bought from a commercial source and utilized as envisioned. Newly synthesized amide analogues and their chemical structures were confirmed using spectral techniques such as NMR, IR, and Mass interpretation. The NMR spectra of new samples were obtained under $CDCl_3$ or DMSO-$d_6$ solvent using a Bruker 300 Mz. The chemical shifts are presented in ppm with signals from TFA-d: δ. 11.50 ppm for $^1H$ and δ 164.2 ppm for $^{13}C$ NMR were driven further by the coupling constant (J). The infrared spectrum between 4000-500 $cm^{-1}$ was recorded using the nicolate 380 FTIR spectrophotometer. Mass spectra obtained with a spectrophotometer Shimadzu LCMS 2010. In MEL-TEMP II, the melting points of prepared compounds were assessed. In addition, the obtained values are uncorrected.

### General Procedure for 5-(Pyridine-2-yl)-1,3,4-oxadiazol-2-amine (2)

Picoline hydrazide (10 m.mol) (2), Cyanogen bromide (15 mmol) and ethanol were taken in RB flask. Refluxing the contents for a duration of 12 hours. After the stipulated time, the solution is cooled, and it is neutralized using an excess of $NaHCO_3$ solution. Further purification was done by recrystallization with ethanol, resulting in pure compound (2) in good yields.

### Synthesis of Acylated N-(5-(Pyridine-2-yl)-1,3,4-Oxadiazol-2-yl) amines-(3a-e)

This produced compound 2 (1 g) was taken in 5 mL of symmetrical anhydride and refluxed gently in a short-air condenser for about 12 hours. Then the compound was cooled using little amount of water. Finally, purified by recrystallization from ethanol, resulting in the corresponding pure form of titled compounds in quantitative yield. Similarly, the remaining derivatives were prepared.

**Table 1: The synthetic compounds Physical data**

| S. No | Compounds | Molecular Formula | Molecular Weight | m.p.($^0$C) | Yield(%) |
|---|---|---|---|---|---|
| 1 | 2 | $C_7H_6N_4O$ | 162.15 | 197-199 | 71% |
| 2 | 3a | $C_{13}H_{16}N_4O_2$ | 260.29 | 235-237 | 69% |
| 3 | 3b | $C_{14}H_{18}N_4O$ | 274.32 | 247-249 | 76% |
| 4 | 3c | $C_{15}H_{20}N_4O_2$ | 288.34 | 143-145 | 81% |
| 5 | 3d | $C_{16}H_{22}N_4O_2$ | 302.37 | 176-178 | 73% |
| 6 | 3e | $C_{17}H_{24}N_4O_2$ | 316.4 | 210-212 | 75% |

### Characterization data

### Compound 2

IR (KBr, v $cm^{-1}$): 3270.11, 3098.95 (-$NH_2$-stretching), 1646.07 (C=N) 1045.62 (C-O-C, stretching, Oxadiazol ring); $^1H$-NMR (400M. Hz, δ ppm, dimethyl sulfoxide-$d_6$) : 7.42-7.50 (br, 2H, -$NH_2$, $D_2O$ Exchangeable), 7.51-7.52 (dd, 1H, C-H-stretching), 7.94-7.99 (m, 2H), 8.67 (dd, Ar-H); $^{13}C$-NMR (400 M. Hz, dimethyl sulfoxide-$d_6$) 121.54, 125.37, 137.90, 143.62, 150.12, 157.62, 164.70; M.S: (m/z) 163.2 $[M+1]^+$; Elemental Analysis: Found % (Calculated %): C, 51.85(51.89); H, 3.73 (3.79); N, 34.55 (34.59); O, 9.87 (9.92).

### Compound 3a

IR (KBr, v $cm^{-1}$): 3131.64 (-NH-stretch), $^1H$-NMR (400M. Hz, dimethyl sulfoxide-$d_6$) : δ 0.82 (t, methyl-H), 1.32 (m, 6H), 1.61 (t, Methylene-H), 2.42

(br, 1H,-NH-), 7.60 (dd, 1H, Aromatic-H), 8.02 (m, 1H), 8.08 (m), 8.66(dd); M.S: m/z 261.4 $[M+1]^+$; Elemental Analysis: Found % (Calculated %): C, 59.99 (60.03); H, 6.20 (6.24); N, 21.52 (21.54); O, 12.29 (12.33).

**Compound 3b**

IR (KBr, v $cm^{-1}$): 3329.43 (-NH-stretch), 1H-NMR (400M. Hz, dimethyl sulfoxide-d6) : δ 00.85-.87 (t, 3H), 1.27 (m, 6H), 01.56 -01.59 (m, 2H), 2.30-2.34 (t, 2H-), 3.5 (br, 1H, -NH-), 7.53 (dd, 1H), 8.01 (m, 1H), 08.04-8.05 (m,1H), 8.71 (dd, 1H, -CH-); M.S: m/z 275.5 $[M+1]^+$; Elemental Analysis: Found % (Calculated %): C, 61.30 (61.35); H, 6.61 (6.67); N, 20.42 (20.44); O, 11.66 (11.69).

**Compound 3c**

IR (KBr, v $cm^{-1}$): 3039.40 (-NH-stretch), $^1$H-NMR (400M. Hz, dimethyl sulfoxide-$d_6$) : δ 00.85 (t, Methyl-H), 1.26 (m, 8H), 1.60 (m, 2H), 2.40 ( t, 2H, -$CH_2$), 07.60 (m, 1H), 8.01 (m, 1H), 8.10 (m, 1H), 8.74 (m, 1H, -CH-), 9.60 (1H, -NH-). M.S: m/z 289.5 $[M+1]^+$; Elemental Analysis: Found % (Calculated %): C, 62.48 (62.52); H, 6.99 (7.04); N, 19.43 (19.47); O, 11.10 (11.14).

**Compound 3d**

IR (KBr, v $cm^{-1}$): 3059.24 (-NH-stretch), 1727.57 (-C=O); 1642.89 (C=N) 1047.67 (C-O-C, stretching, Oxadiazol ring); $^1$H-NMR (400M.Hz,dimethyl sulfoxide-$d_6$) : δ 0.84 - 0.86 (t, Methyl-H), 1.25-1.28 (m, 10H) 01.58-01.61 (t,2H), 2.43-2.51 (m,2H), 07.60-07.62 (dd, 1H), 08.02 - 8.05 (m, 1H), 08.05-8.12 (m,1H), 8.7-8.76 (dd, 1H) 11.80 (br, 1H, -NH ), $^{13}$C-NMR (400 M. Hz, dimethyl sulfoxide-$d_6$): δ 14.11, 22.27, 24.57, 24.65, 28.65, 28.74, 28.89, 31.42, 122.47, 126.23, 138.00, 142.90, 150.32, 158.23, 160,03, 171.03; M.S: (m/z) 303.5, $[M+1]^+$; Elemental Analysis: Found % (Calculated %) : C, 63.55 (63.59); H, 7.33 (7.36); N, 18.53 (18.57); O, 10.58 (10.63).

**Compound 3e**

IR (KBr, v $cm^{-1}$): 3129.56 (-NH-stretch), $^1$H-NMR (400 M. Hz, ppm, dimethyl sulfoxide-$d_6$) :δ 0.86 (t, Methyl-H), 1.26 (m, 12H), 1.50 (m, methylene-H), 2.28 (t, 2H), 3.40 (br, 1H, -NH-). 7.52 (m, 1H), 08.01-8.6 (m, 2H), 8.70 (m, Ar-H); M.S: m/z 317.6 $[M+1]^+$; Elemental Analysis: Found % (Calculated %): C, 64.53 (64.59); H, 7.65 (7.68); N, 17.71 (17.75); O, 10.11 (10.15).

**Biological activity**

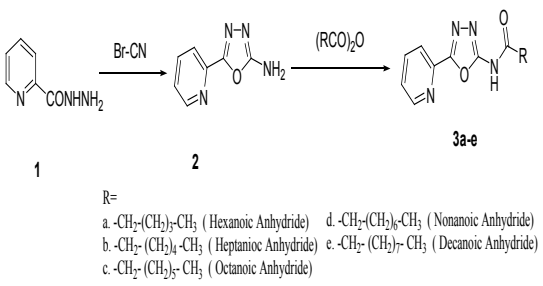
The potential antimicrobial activities of compound 2 and their novel various analogues 3 (a-e) were investigated. Four concentrations (25, 50, 75, and 100 µL) of the Agar well-diffusion method were used to assess the antibacterial activity. The activity index is calculated, and the zone of inhibition is calculated after 18 to 24 h of incubation at 37°C. Using the well diffusion method, antifungal activity was investigated on Candida albicans at four concentrations (25-100 µL). Fungus spread on the prepared SDA culture plates, and after 48 h of incubation, The activity index was computed.

**Molecular Docking Study**

The protein-ligand interactions of the prepared compounds 2, 3(a-e) were studied using Auto Dock Vina 4.2[33]. The calculation of the gradient effectively gives the optimization algorithm a "sense of direction" from a single evaluation. By using multithreading, The evaluation of the speed and accuracy of Vina during flexible redocking of the 190 receptor-ligand complexes making up the AutoDock 4 training set showed approximately two orders of magnitude improvement in speed and a simultaneous significantly better accuracy of the binding mode prediction. Targeted proteins' structures were obtained from the RCSB Protein Data Bank[34]. Utilizing BIOVIA-2020[35] and Auto Dock tools[36], structural preparation and cleaning were completed. Improvement of ligand structure is made using Gaussian09 software package[37].

## RESULTS AND DISCUSSION

Aiming at developing new drugs with promising antimicrobial activity, we synthesised a new amide derivatives of N-(5-(Pyridine-2-yl)-1,3,4-Oxadiazol-2-yl)amine with good pharmaceutical applications. The synthesized compounds label as 2 and 3(a-e). Different analytical methods such as $^1$H NMR, $^{13}$CNMR, mass spectrometry and FTIR were employed to structurally validate the synthesized compounds.




R=
a. -$CH_2$-($CH_2$)$_3$-$CH_3$ ( Hexanoic Anhydride)
b. -$CH_2$-($CH_2$)$_4$-$CH_3$ ( Heptanioc Anhydride)
c. -$CH_2$-($CH_2$)$_5$-$CH_3$ ( Octanoic Anhydride)
d. -$CH_2$-($CH_2$)$_6$-$CH_3$ ( Nonanoic Anhydride)
e. -$CH_2$-($CH_2$)$_7$-$CH_3$ ( Decanoic Anhydride)

**Scheme 1. Synthesis of compound 2 and 3 (a-e)**

The IR absorption values of the compound **(2)** structure analysis based on IR absorptions of the $NH_2$ primary amine group have a stretching vibration at 3270.11 and 3098.95 $cm^{-1}$. IR absorptions of the -C=N- (oxadiazol ring) and C-O-C functional groups vibration at 1646.07 and 1045.62 $cm^{-1}$ respectively. The IR absorption values of the compound **(3d)** structure analysis based on IR absorptions of the NH-secondary amine group have a stretching vibration at 3059.24 $cm^{-1}$. IR absorptions for -C=N (oxadiazol ring) and C-O-C functional groups vibration at 1642.89 and 1047.67 $cm^{-1}$ respectively. $^1H$ NMR Spectroscopy chemical shift values of compound **(2)** structure values are the aromatic protons were detected between 7.51 to 8.67 ppm, the -$NH_2$ broad peak singlet located at 7.42–7.50 ppm ($D_2O$ exchangeable). $^1H$ NMR Spectroscopy chemical shift values of the compound **(3d)** structure values are the aromatic protons were seen between 7.60 to 8.76 ppm, the -NH- broad peak singlet peak located at 11.80 ppm ($D_2O$ exchangeable), the methyl group of the side chain at 0.84-0.87 ppm, the -$CH_2$- group attached to carbonyl at 2.43-2.51 ppm and the remaining twelve protons of methylene protons were observed at 1.26-1.61 ppm. $^{13}C$ NMR spectroscopy of the compound **(2)** signals C-2 and C-5 carbons observed at 157.62 (C2-oxadiazol ring), 164.70 (C5- oxadiazol ring) ppm. Compound **(3d)** signals C-2 and C-5 carbons observed at 158.23 ($C_2$-oxadiazol ring), 160.03 ($C_5$-oxadiazol ring) ppm and signal of carbonyl carbon is seen at 171.03 ppm.

**Anti-microbial activity report of synthesized compounds**

The anti-bacterial assay of new compounds noted as **3(a-e)** was investigated with reference to ampicillin against bacterial stains such as *S. aureus* and *E. coli*. All the products have established promising results as mentioned in Table 2. The effectiveness of recently synthesized compounds was evaluated against *Staphylococcus aureus* and *E. coli* bacteria with standard reference (ampicillin) (Fig. 1, Table 2). The compounds **3d**, **3c** and **3b** showed better antibacterial strength at a 100 µg/mL concentration on *S. aureus*, with 17, 14 and 11 mm zones of inhibition. Compounds **3d** and **3a** showed good antibacterial strength at 100 µg/mL zones of inhibition 10 and 8 mm respectively on *E. coli*.

The antifungal activity of new compounds studied with *Candida albicans* using spread plate technique. The analysis of antifungal data (Fig. 2, Table 2) revealed that all the synthesized compounds **2,3 (a-e)** exhibited the most promising results against the tested fungus *Candida albicans*. The compound **3c** has a zone of inhibition of 13mm, 15mm at 75 and 100 µg concentrations. Whereas compound **3d** has a zone of inhibition of 12mm and 17mm. compound **3e** exhibits a zone of inhibition of 9mm and 17mm, compound **3b** has a 12mm and 14mm zone of inhibition at concentrations of 75, 100 µg, which is more effective than the standard compound Fluconazole.

**Table 2: Anti-Microbial activity against new compounds 2 & 3 (a-e)**

| Compounds | Concentration (µg)/Zone of Inhibition (mm) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Anti Bactrial Activity | | | | | | | | Anti Fungal Activty | | | | | | | |
| | *Staphylococcus aureus* | | | | | *E. Coli* | | | | | *Candida albicans* | | | | | |
| | 25 | 50 | 75 | 100 | 25 | 50 | 75 | 100 | 25 µg | 50 µg | 75 µg | 100 µg | 25 µg | 50 µg | 75 µg | 100 µg |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 9 | 18 | 0 | 0 | 0 | 0 |
| 3a | 0 | 0 | 5 | 8 | 0 | 0 | 5 | 8 | 0 | 0 | 10 | 14 | 0 | 0 | 0 | 0 |
| 3b | 0 | 0 | 5 | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 14 | 0 | 0 | 0 | 0 |
| 3c | 0 | 6 | 9 | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 13 | 15 | 0 | 0 | 0 | 0 |
| 3d | 9 | 11 | 16 | 17 | 0 | 6 | 8 | 10 | 0 | 0 | 12 | 17 | 0 | 0 | 0 | 0 |
| 3e | 0 | 0 | 6 | 6 | 0 | 0 | 5 | 5 | 0 | 0 | 9 | 17 | 0 | 0 | 0 | 0 |
| Ampicillin | 17 | 19 | 23 | 20 | 16 | 18 | 20 | 26 | - | - | - | - | - | - | - | - |
| Fluconazole | - | - | - | - | - | - | - | - | 0 | 0 | 8 | 15 | 0 | 0 | 0 | 0 |

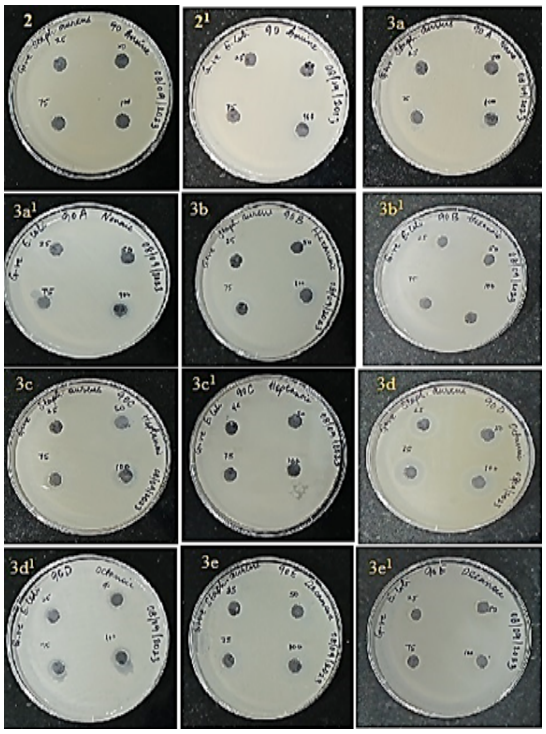


**Fig. 1. Anti-bacterial activity of compounds 2 & 3 (a-e)**

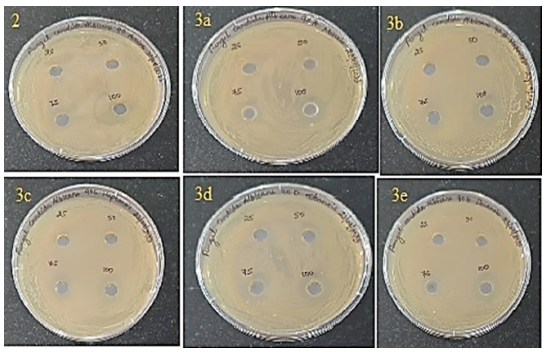


**Fig. 2. Compound 2 and 3(a-e) anti-fungal efficacy against *Candida albicans***

## Docking study

The interaction behaviour and the binding energies of the **2** and **3(a-e)** derivatives were examined using PDB ID: 5JZX, the family of Mur proteins catalyzes biosynthetic conversions of more than ten formation of the peptidoglycan layer on bacterial cell walls. UDP-N-acetylglucosamine-nolpyruvate reductase (MurB) further has a significant role to bind NADPH in protein. Fungal protein PDB ID: 4M8B Crystal structure of an isatin hydrolase bound to product analogue thioisatinate. The protein-ligand least energy docked poses show the hydrogen bonds that develop between the ligands and the designated proteins. (Shown in Fig. 3 & 4 and Table 3 & 4). All compounds showed favourable docking energy within the limit of -6.0 to -8.73 kcal/mol, as denoted as Table 3 and Table 4. Among all the synthesized compounds **3e, 3d** and **3c** showed good binding energy against (PDB ID: 5JZX, 4M8D). Compounds **3e** (-8.73 kcal/mol), **3d** (-8.38 kcal/mol), **3c** (-8.17 kcal/mol) were demonstrated better binding score.

**Table 3: Compounds of 2 and 3 (a–e) binding energies using the PDB ID: 5JZX**

| S. No | Compounds | Binding Strength (K. Cal mol$^{-1}$) PDB ID: 5JZX | | |
|---|---|---|---|---|
| | | Binding energy | Hydrogen-Bonds | Bonding-Proteins |
| 1 | 2 | -6.31 | 5 | SER130(2), SER70(2), ASN71 |
| 2 | 3a | -7.86 | 6 | SER130, SER70(2), ALA67, GLY69(2) |
| 3 | 3b | -7.87 | 5 | SER70(2), GLY68, GLY69(2) |
| 4 | 3c | -8.17 | 4 | GLY69(2), SER70, ALA67 |
| 5 | 3d | -8.38 | 3 | SER130, SER70, GLY68 |
| 6 | 3e | -8.73 | 4 | SER130, PRO128, GLY68, ALA67 |
| 7 | Amplcillin | -8.79 | 6 | GLY69, PRO128, SER130(3), ALA67 |
| 8 | Fluconazole | -5.48 | 3 | VAL192, GLY69, ASN71 |

**Table 4: Compounds of 2 and 3 (a–e) binding energies using the PDB ID: 4M8B**

| S. No | Compounds | Binding Strength (K. Cal mol$^{-1}$) PDB ID: 4M8B | | |
|---|---|---|---|---|
| | | Binding energy | Hydrogen -Bonds | Bonding -Proteins |
| 1 | 2 | -6.0 | 2 | SER122, VALR178, |
| 2 | 3a | -6.7 | 5 | TYR144(3), LYS119, SER75, |
| 3 | 3b | -7.0 | 2 | ARG30(2) |
| 4 | 3c | -7.2 | 3 | ARG30(2), THR6 |
| 5 | 3d | -7.1 | 3 | ARG30(2), THR6 |
| 6 | 3e | -7.2 | 3 | ARG30(2), THR6 |

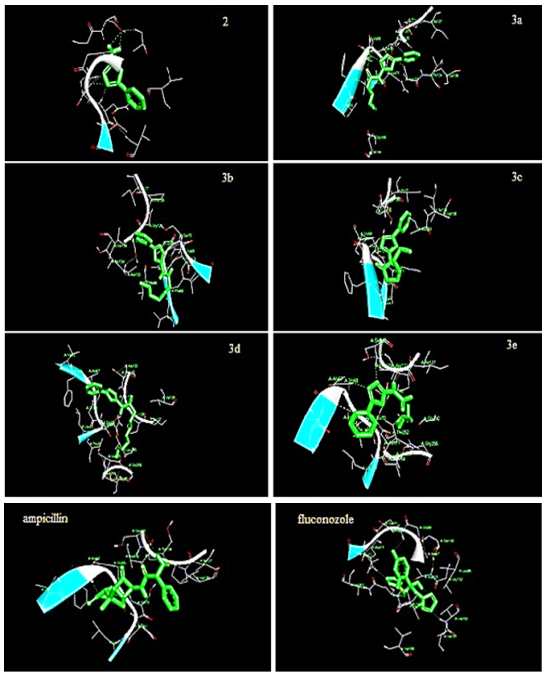



**Fig. 3. Indicating the binding poses and interactions of compound 2 and 3(a-e), internal standard to binding sites of target proteins**

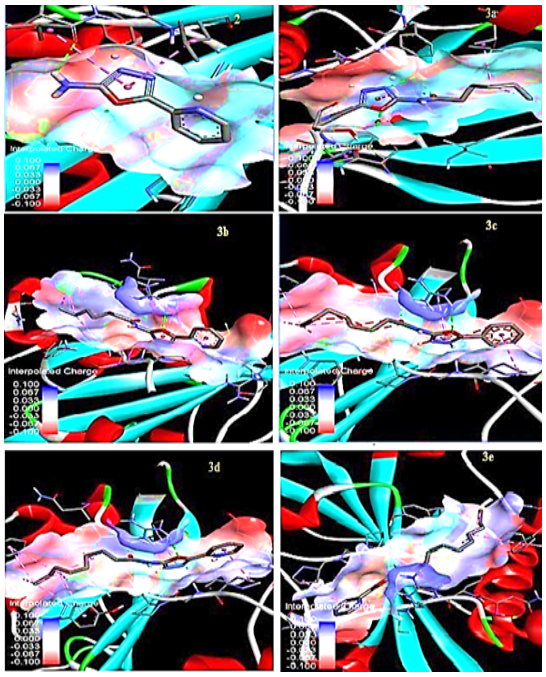



**Fig. 4. Indicating the binding poses and interactions of compound 2 and 3(a-e), to binding sites of target proteins**

## CONCLUSION

In conclusion, our successful and effective method has resulted in design of new analogues ranging from **3a–e**, which were established by various spectroscopic analyses. The synthesized compounds were then subjected to assessment of their antimicrobial properties including antibacterial and anti-fungal activities. The results of newly synthesised derivatives were found promising. Notably, compounds **3d, 3c**, and **3e** were found with good antibacterial activity against *S. auras* and *E. coli*. All the new derivatives have shown excellent anti-fungal properties among which compound **3d**, **3c** and **3e** have a zone greater than the reference compound against the *Candida albicans* fungal strain. Finally, this research highlights the antimicrobial potential of newly synthesized compounds, which may act as an option to fight with anti-microbial resistant. Among all the synthesized compounds **3e, 3d** and **3c** showed good binding energy against PDB ID 5JZX. As well as PDB ID 4M8B. Compounds **3c, 3d,** and **3e** demonstrated better binding score.

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### Conflict of interest

The author declare that we have no conflict of interest.

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