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Synthesis, antibacterial and *in silico* study of 1, 3, 4 oxadiazole, triazole compounds derived from paracetamol

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Abstract
In the current work, a series of compounds containing of [1, 3, 4]oxadiazole-2-thione and triazole structural framework synthesized by multistep reaction, the first step synthesis of ethyl 2-(4-acetamidophenoxy)acetate (P_1) by reaction of N-(4 hydroxyphenyl) acetamide with ethylchloroacetate, This ester were converted to the corresponding N-[4-(2-hydrazineyl-2-oxoethoxy) phenyl] acetamide (P_2) by reaction with hydrazine hydrate, which reacted with carbon disulfide to afford [1, 3, 4] oxadiazole -2- thion (P_3). The compound was prepared by two methods, microwave and classic method after which derivatives of oxadiazole (P_{3a}-P_{3b}) were prepared from the reaction of S- alkylation with chloroacetic acid and methyl iodide. Then, triazole (P_4) was prepared by reacting oxadiazole with 99% hydrazine hydrate. The prepared compounds were characterized by element analysis, ^{1}H-NMR, ^{13}C-NMR, and FT-IR spectral techniques biological activity of synthesized compounds was investigated against two groups of four bacterial genera. The compounds showed inhibitory activity against *Klebsiella* pneumonia bacteria whereas effective against other species. *In silico* molecular docking study was performed for the active compound where the (P3a and P3b) compounds showed good docking scores and RMSD values with good binding mods. To anticipate the action, response, and transport of synthesized molecules in human metabolism *In silic*o sADME calculations were conducted and showed the two compounds safe and have good hydrophilicity.

Keywords: *In silico* study, 1, 3, 4 oxadiazole, Triazole, Paracetamol

1. Introduction
Heterocyclic compounds with five-membered ring systems, consisting of two carbon atoms, two nitrogen atoms, and one oxygen atom, hold significant importance in both the medical and industrial fields, known as oxadiazolesm [1] have great importance in various areas of medicinal chemistry, pesticides as well as polymer and materials science. 1, 3, 4-Oxadiazole is a heterocyclic organic compound containing two carbon atoms at 2,5 position, two nitrogen atoms at 3, 4 positions and one oxygen atom at 1 position, and two double bonds [2]. It derived from furan when the replacement of two methine (-CH=) by two nitrogen (-N=) at positions 3 and 4 [3]. 1, 3, 4-Oxadiazole ring is associated with various biological properties such as anti-inflammatory [4], antimicrobial activity against Staphylococcus aureus, Staphylococcus epidermidis, and Escherichia coli [4] antiproliferative activity of the compounds against four different types of original cancer cells (HELA, HEPG2, BGC823, and SW1116) [6], antioxidant [7], pharmacological activity [8], anti-breast cancer activity [9], anti-influenza drugs [10].
Triazole is a heterocyclic organic compound containing two carbon atoms,three nitrogen atoms and two double bonds [11]. Triazole is a significant heterocyclic moiety that holds a distinctive place in the heterocyclic chemistry and medicine fields. It is valued for its numerous biological activities and serves as a core molecule for developing and synthesizing various medicinal compounds [12], and anticancer activities against four types of human cancer cell lines including lung cancer (A549), breast cancer (MCF-7, MDA MB-231), and prostate cancer (DU-145) [13]. Antibacterial activities using the Acinetobacter baumanii ATCC 19606; Pseudomonas aeruginosa ATCC 19433; Citrobacter freundii ATCC 8090: Staphylococcus epidermidis ATCC 14990: Staphylococcus aureus ATCC 12600; [14],

antifungal [15], anti-oxidative stress and anti-inflammatory [16], antitubercular [17], antihypertensive agents [18], antimicrobial [19].

2. Experimental part

2.1 Chemistry

The melting points (MPs) of all derivatives were determined using the open capillary tube method (Staurt SMP10) melting point apparatus. The spectra of IR were obtained using a KBr disc on an FT-IR -8400s (SHIMADZU) at the chemistry lab at the College of Science, Tikrit University. ^{1}H NMR and ^{13}C NMR spectra were obtained using a deuterated solvent. i.e. the exchangeable protons were exchanged by D_2O DMSO using 400 MHz (^{1}H NMR) and 100MHz (^{13}C NMR). The chemical shift was expressed in δppm by using tetramethyl silane (TMS) as a reference.

2.1.1 Synthesis of ethyl 2-(4-acetamidophenoxy)acetate (Paracetamol Ester) (P_1) [20]

(1.15g/0.01 mol) of p-acetamido phenol(Paracetamol)was dissolved in 10ml or excess of dry acetone in a 100ml round bottom flask, then (1.38 g/0.01 mol) of anhydrous potassium carbonate and 2 ml or excess of ethyl chloro acetate was introduced to the mixture. The mixture was refluxed for 8 hrs. The solution was concentrated, then poured onto crushed ice, filtered, washed with cold distilled water several times, and dried(Color: white, percentage yield: 88.2%, MP: 122-125 ^{o}C)**.**

FT-IR (KBr,cm^{-1}): 3381 (N-H amide), 3074 (C-H Ar), 2993 (C-H alph), 1741 (C=O ester), 1678 (C=O amide), 1531 (C=C Ar), 1213 (C-O).

2.1.2: Synthesis of N-[-4-(2-hydrazinyl-2-oxoethoxy) phenyl] (Paracetamol hydrazide) (P_2)

2.1.2.1: Classic Method [21]

(1.64 g, 0.0069 mol) of ethyl 2-(4-acetamidophenoxy) acetate (P_1) was dissolved in 10ml of ethanol in a 100 ml RBF (Round Bottom Flask), Then (5 ml /0.1030 mol) of hydrazine hydrate 80% was added to the mixture. The mixture was refluxed for 6 hr. The solution was concentrated, then poured onto crushed ice, filtered, washed with cold distilled water several times, and dried (Color: white, percentage yield: 58.76%, Melting point: 207-209 ^{o}C)**.**

2.1.2.2: Microwave Method [22]

(2.210 g, 0.00932 mol) of ethyl 2-(4-acetamidophenoxy) acetate (P_1) was mixed with (7 ml) of hydrazine hydrate 80% in a 50 ml beaker. The solution was exposed to microwave irradiation (400 watt) for about 1 min. The reaction solution was cooled, filtered, washed with cold distilled water, and dried. (Color: white, percentage yield: 96.2%, Melting point: 206 ^{o}C)

FT-IR (KBr,cm^{-1}) :3277-3323 (sym-asym, NH_2), 3080 (C-H Ar), 2937(C-H alph), 1645(C=O amide), 1512 (C=C Ar), 1244 (C-O).

2.1.3 Synthesis of N-(4-((5-mercapto-1, 3, 4-Oxadiazol-2-yl) methoxy) phenyl) acetamide (Paracetamol Oxadiazole) (P_3) [22]

2.1.3.1 Classic method [23]

(3.7g, 0.01659mol) of N-[-4-(2-hydrazinyl-2-oxoethoxy) phenyl] (P_2) was dissolved in ethanol. (1.858 g, 0.03318 mol) of KOH dissolved in distilled water in a 100 ml round flask and added into the reaction mixture. Then was (1.89 g/ 0.02488 mol) of carbon disulfide (CS_2) added to the mixture, stirred at RT for half an hour, and refluxed for 24 hr, until the evolution of H_2S gas ceased the precipitate was formed concentrated acidified with diluted HCl, filtered, washed with cold distilled water and dried. (Color: white, Percentage yield: 81.11%, Melting point: 223-225 ℃).

2.1.3.2: Microwave method [24]

(0.1 g, 0.00044 mol) of N-[-4-(2-hydrazinyl-2-oxoethoxy) phenyl] (P_2) was dissolved in DMF, (0.044. g, 0.0008 mol) of KOH dissolved in distilled water, and (0.032 ml/ 0.00055 mol) of carbon disulfide in a 50 ml beaker. The solution was exposed to microwave irradiation (400 watt) for three intermittent minutes to avoid evaporation of CS_2. Acidified with diluted HCl. The reaction mixture was cooled, then filtered after that washed with cold distilled water and dried. Color: white, percentage yield: 63.64%, Melting point: (223-225℃).

FT-IR (KBr, cm^{-1}): 3298 (N-H amide), 3093 (C-H Ar), 2877 (C-H alph), 1668 (C=O amide), 1604 (C=N oxadiazole), 1510 (C=C Ar). ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 2.02 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 7.00 (d, 2H, ArH), 7.50 (d, 2H, ArH), 9.85 (s, 1H, NH amide) 14.03 (s, 1H, SH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 24.29 (CH_3), 60.34 (CH_2), 115.57, 120.91 (C Ar), 134.28 (C-NH), 153.22 (C-O), 160.18 (C=N), 168.36 (C=O).

2.1.4: Synthesis of Oxadiazole derivatives

2.1.4.1 Synthesis of N-(4-((5-(methylthio)-1, 3, 4-Oxadiazol-2-yl) methoxy) phenyl) acetamide (P_{3a}) [25]

(0.25 g, 0.000943 mol) of oxadiazole was dissolved in (15 ml) of dry acetone with (0.130 g, 0.000943 mol) of anhydrous potassium carbonate. Then (0.133 g, 0.000943 mol) of methyl iodide was added and the solution was stirred for 4 hrs. The precipitate was concentrated, filtered, washed with cold distilled water and dried. Color: white, percentage yield: 48.15%, Melting point: (121 – 123 ^{o}C).

FT-IR (KBr, cm^{-1}): 3254 (N-H amide)), 3036 (C-H Ar), 2922 (C-H alph), 1678 (C=O amide), 1593 (C=N oxadiazole), 1512 (C=C Ar). ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 2.02 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 5.33(s, 2H, CH_2),7.01(d, 2H, ArH), 7.52 (d, 2H, ArH), 9.85 (s, 1H, NH amide); ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 14.74 (S-CH_3), 24.28(CH_3), 60.21 (CH_2), 115.57,120.94 (Car), 134.20 (C-NH), 153.35 (C-O), 164.12 (C=N), 168.36 (C=O).

2.1.4.2 Synthesis of 2-((5-((4-acetamidophenoxy) methyl)-1, 3, 4-oxadiazol-2-yl) thio) acetic acid (P_{3b}) [26]

(0.5 g, 0.001886 mol) of oxadiazole was dissolved in (15 ml) of dry acetone. Then (0.5 g, 0.003772 mol) of anhydrous potassium carbonate and (0.22 g/0.00235 mol) of chlouro acetic acid were added to the mixture and then refluxed for 8 hrs. The precipitate was concentrated, acidified with concentrated HCl, then filtered, and after that washed with cold distilled water and dried. Color: white, percentage yield: 40%, Melting point: (172 – 175 ^{o}C).

FT-IR (KBr, cm^{-1}): 3225 (N-H amide), 3088 (C-H Ar), 2987 (C-H alph), 1639 (C=O amide), 1608 (C=N oxadiazole), 1510(C=C Ar) ; ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 2.01 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 5.33 (s, 2H, CH_2),7.00(d, 2H, ArH), 7.50 (d, 2H, ArH), 9.85 (s, 1H, NH amide) 13.15 (s, 1H, OH) ; ^{13}C-NMR (100 MHz, DMSO-d_6)

δ(ppm): 24.28 (CH_3), 34.37 (CH_2-C=O), 60.22(CH_2), 115.59-120.93 (C Ar), 134.22 (C-NH), 153.35 (C-O), 164.23(C=N) 168.36 C=O), 169.15 (NH-C=O).

2.1.5 Synthesis of N-(4-((4-amino-5-mercapto-4 H-1, 2, 4-triazol-3 -yl) methoxy) phenyl) acetamide (Paracetamol Trizole) (P_4) [27]

(2 g, 0.00754 mol) of N-{4-[(5-mercapot-1, 3, 4-oxadiazole-2-yl) methoxy] pheny} acetamide was mixed with (0.73 ml/0.015 mol) of hydrazine hydrate (99%) in a 100 ml round bottom flask, then was 5ml of ethanol add to the solution. the solution was refluxed for 6 hr and concentrated, filtered, washed with cold distilled water, and dried. Color: pink, percentage yield: 40%, Melting point: (250-253 ºC)

FT-IR (KBr,Cm^{-1}): (3462-3448) (sym-asym, NH_2), 3281 (N-H amide), 3059 (C-H Ar), 2924 (C-H alph), 1658 (C=O amide), 1610 (C=N oxadiazole), 1514 (C=C Ar) ; ^{1}H-NMR (400 MHz, DMSO-d_6) δ(ppm): 2.02 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 6.14 (s, 2H, NH_2), 7.04(d, 2H, ArH), 7.51 (d, 2H, ArH), 9.83 (s, 1H, NH amide) ; ^{13}C-NMR (100 MHz, DMSO-d_6) δ(ppm): 24.29 (CH_3), 59.58(CH_2), 115.40-120.88 (C Ar), 133.70 (C-NH), 152.07 (C-N), 154.12 (C=N), 168.28 (C=O).

2.2: Biological activity

Initially, the culture medium for testing biological activity was prepared according to the instructions of the preparing company. The biological activity (antimicrobial) of the compounds was studied on gram-positive bacteria *Staphylococcus aureus*, *Enterococcus faecalis*, and gram-negative bacteria *Klebsiella* and *E. coli*

Activation of bacteria: The bacteria were activated before conducting the tests using NBLNB (Nutrient Broth liquid nutrient broth), by re-seeding them in the above medium. Then it was incubated in the incubator of the laboratory for 24 hours at 37 °C to be ready to test its biological effectiveness.

Inoculation of culture media and Sensitivity assay: The bacterial inoculum was prepared. The biological effectiveness was recorded using the Agar-well diffusion method, according to what was stated in (Balouiri *et al*, 2016; Gonelimali *et al*, 2018) [27-28]. In this method, the bacterial inoculum is spread evenly across the culture medium using a glass diffuser. Subsequently, wells are created in the AM (agar medium) using a drill. A 6 mm-diameter sterilizer is used to load solutions with a volume of 100 microliters of each concentration in a way that allows three different concentrations of the same solution to be loaded onto one plate in which one bacterial model is grown. This step was repeated for all prepared solutions with their concentrations and each of the bacterial models used in this study. After loading the dishes with solutions, they were left for 15-20 minutes at RT, then they were placed in the incubator and the results were read after 18-24 hours. The effectiveness of the compounds was assessed by measuring the diameter of the inhibition zone in millimeters around each hole using an electronic ruler, Caliper, for all samples.

2.3: *In silico* studies

2.3.1: Molecular Docking (MD) study

MD study for the compounds that have high activity against of *Klebsiella* pneumonia bacteria (P3a, P3b) via employing Auto Dock 4.2.6 programs *Klebsiella* pneumoniae AcrB (PDB:ID:8FFS) were found from RCSB, PDB (Protein Data Bank) site. The minimization energy of new compounds was accomplished by using MM2 in chem 3D program. The ligand and protein preparation were achieved by Auto DockTools-1.5.6 program. Finally, Discovery Studio 2020 Client was used to visualize 2D and 3D binding modes.

2.3.1 *In silico* ADMET study

ADMET studies for P_{3a} and P_{3b} compounds were performed online by (http://www.swissadme.ch/)

3: Results and Discussions

3.1: Chemistry

This work includes reaction of paracetamol with chloro ethyl acetate to produce paracetamol ester (P1) through nucleophilic substitution mechanism.

Paracetamol ester was converted into corresponding hydrazide (P2) through tetrahydric mechanism. Paracetamol 1, 3, 4 oxadiazole -2-thiol (P3) was synthesized by nucleophilic cyclization mechanism of (P2) compound with carbon disulfide. P_{3a} and P_{3b} were prepared by S-alkylation nucleophilic reaction of (P_3) with methyl iodide and chloroacetic acid respectively. Finally, triazole derivatives (P_4) compound was prepared by reaction of P_3 compound with pure hydrazine, as depicted in following synthetic path scheme:

FT-IR Spectral data for (P_3, P3a, P3b, P4) compounds revealed disappearance peak of (C=O) in (P_2) compound at 1645 cm^{-1}, in presence peak of (C=N) group at (1593 – 1610) cm^{-1}.

Spectral data measurements of ^{1}H-NMR showed matches the number of protons with proposed structures. ^{13}C-NMR spectral data revealed: appearance of (C=N) cabons of oxadiazoles and triazoles at **δ**= 154 – 164 ppm.

3.2: Biological part

The results of testing the effectiveness of various solutions against different bacterial species are shown in Table (1). The results in the tables and figure showed that these solutions have differentiated biological effectiveness against *Klebsiella* pneumonia bacteria according to their concentrations and as shown in the Tables listed below, Where the diameter of the inhibition of the microphone Zone of Inhibition (ZoI) (mm) is between 12 to 24 mm.

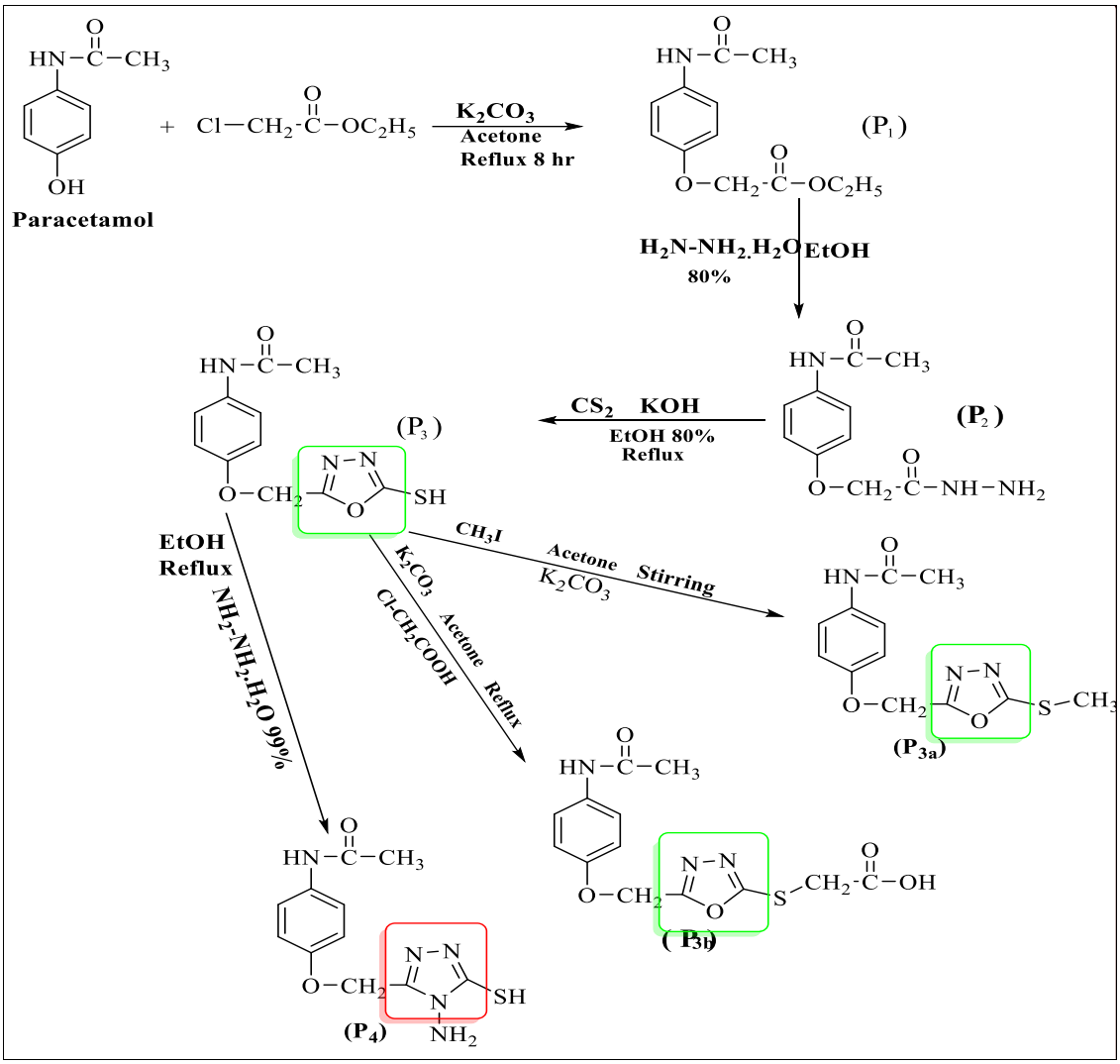

Table 1: Biological activity against bacteria.

Compound	ZoI (mm) of *Klebsiella* pneumonia			ZoI (mm) of *E. coli*			ZoI (mm) S. aureus		
	$2x10^{-1}$	$2x10^{-2}$	$2x10^{-3}$	$2x10^{-1}$	$2x10^{-2}$	$2x10^{-3}$	$2x10^{-3}$	$2x10^{-3}$	$2x10^{-3}$
P_3	13	13	-	-	-	-	-	-	-
P_{3a}	22	0	-	-	-	-	-	-	-
P_{3b}	24	12	-	-	-	-	-	-	-
P_4	12	0	-	-	-	-	-	-	-
Amoxicillin	22	19							

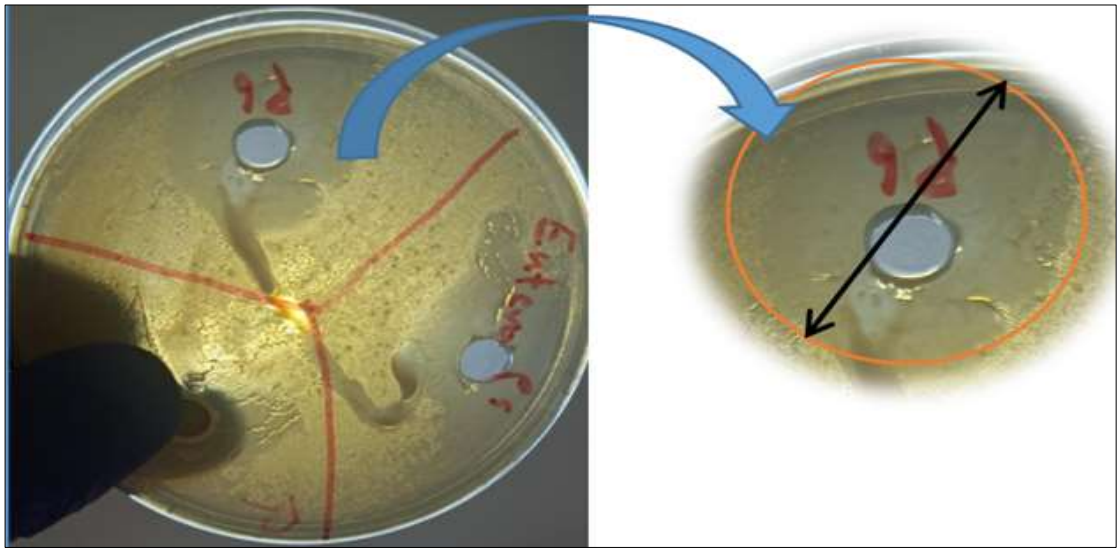

Fig 2: Showing the result of the transplantation of bacteria and their scattering with the additive.

3.3 *In silico* studies

3.3. Molecular docking study of (P3a and P3b) compounds

Molecular docking modeling process was performed for compounds (P3a and P3b) against the binding site *Klebsiella* pneumoniae AcrB (PDB:ID:8FFS) to interpretation of inhibitor effect of these compounds, the obtained results were showed: the compound (P3a) overlaps with the amino acid residues at docking score =-7.1 kcal/mol by four hydrogen bonds: between GLU:A:672, SER:A:135 with the carbonyl group of acetamide(-NH-CO-CH_3) and SER:A:389 with O and S atoms in oxadiazole part, RMSD value =2.65 as depicted in figure (2). The compound (P3b) overlap with the amino acid residues of binding site of enzyme at docking score = -7.6 kcal/mol by three hydrogen bond: two H-bond between the amino acid residue PRO:A:40 with two nitrogen atoms in oxadiazole ring, in addition to one H-bond of ASP:A:680 with OH group as depicted in figure (3), table (11) showed the docking score and RMSD values:

Table 1: The docking results of (P3a and P3b) compounds with the binding site of H-Donor *Klebsiella* pneumoniae AcrB (PDB:ID:8FFS)

Comp. No.	Docking Score(kcal/mol)	RMSD	Residue involve H-bond
P3a	-7.1	2.65	A:SER135: H-Donor, A:SER389: H-Donor, A:SER389: H-Donor, A:GLU672: H-Donor
P3b	-7.6	0.00	A:TYR77: H-Donor, A:GLN864: H-Donor, A:ASP680: H-Acceptor

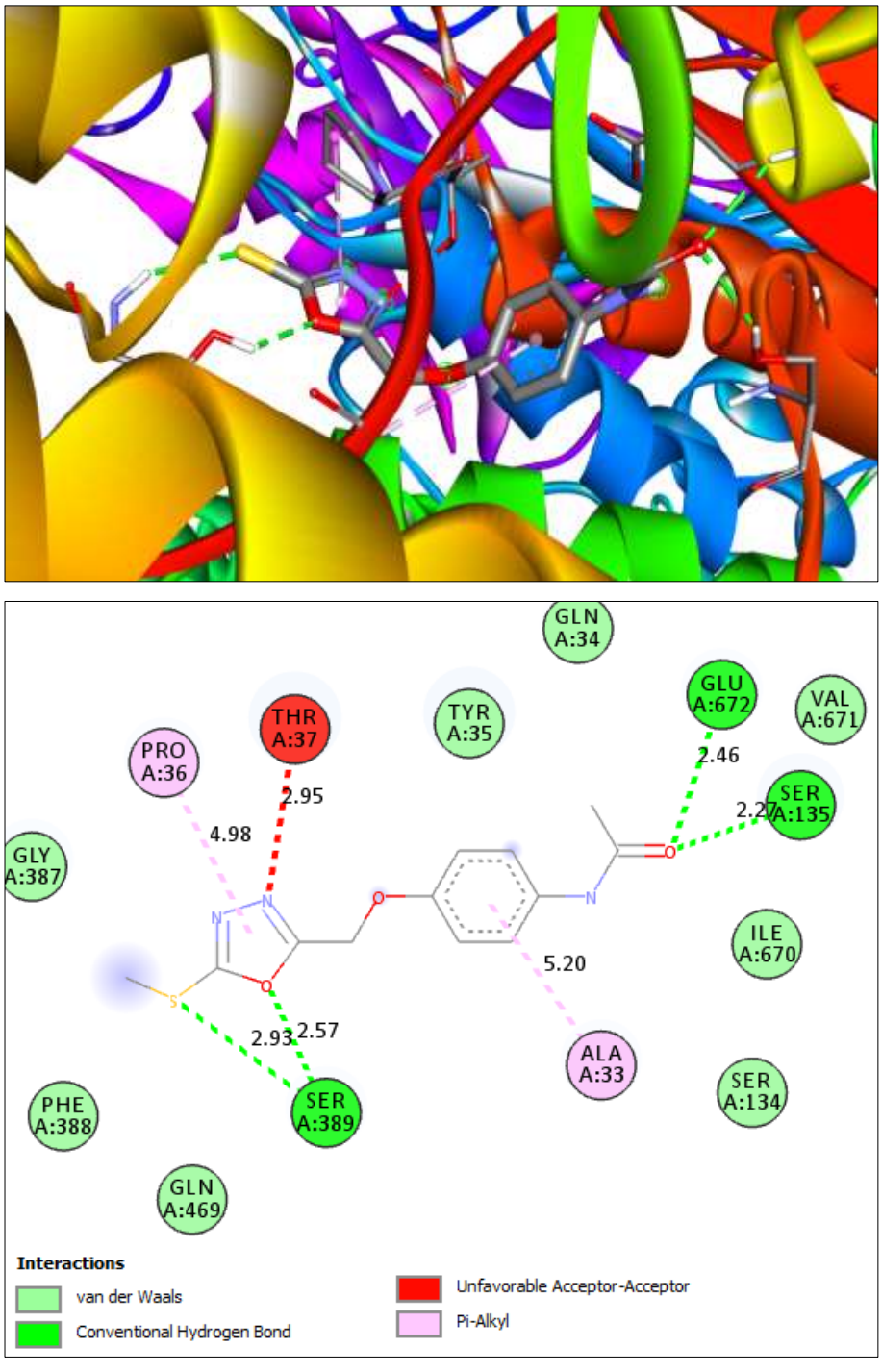

Fig 2: The interaction between compound (P3a) with *Klebsiella* pneumoniae AcrB(PDB:ID:8FFS) in 3D and 2D dimensions.

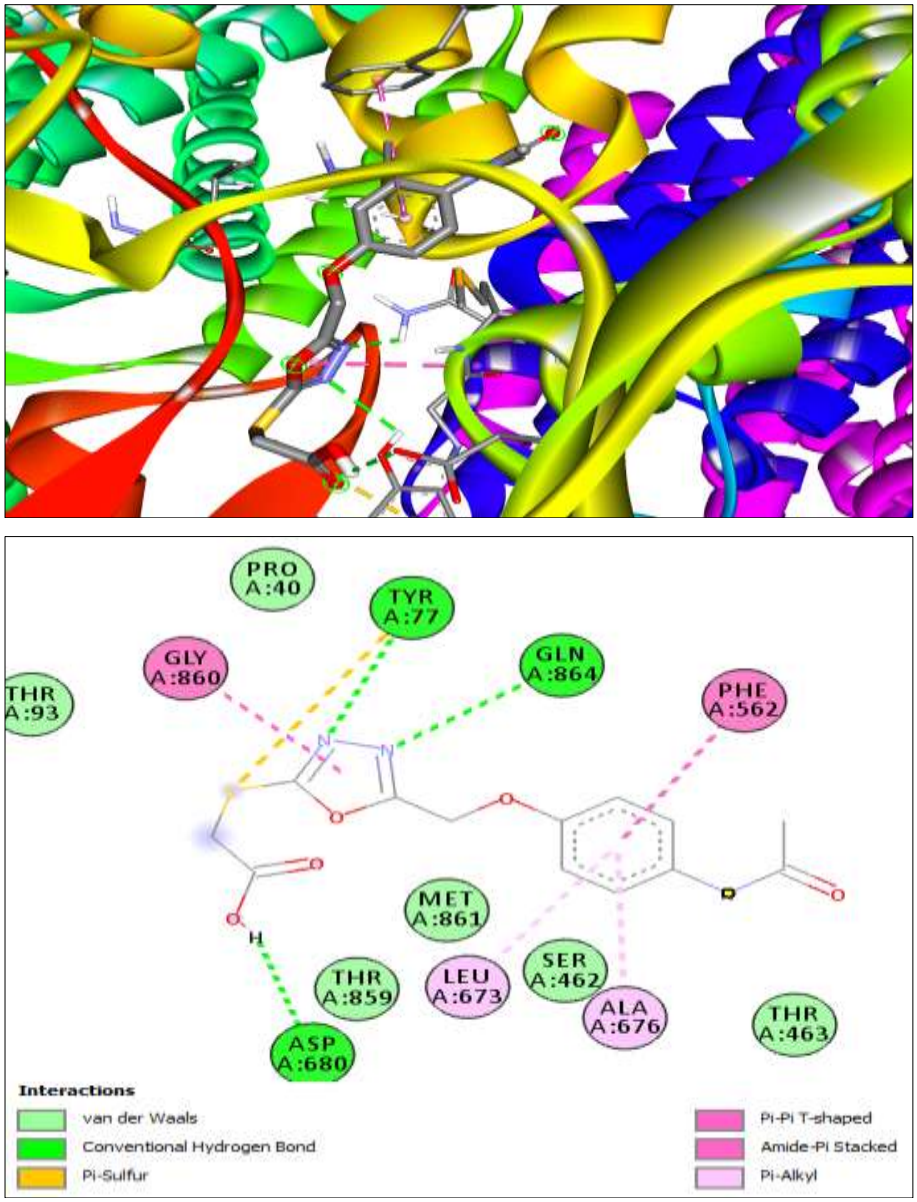

Fig 3: Molecular docking between compound (P3b) with *Klebsiella* pneumoniae AcrB (PDB:ID:8FFS) in 3D and 2D dimensions.

3.3.2 *In silico* ADME

Insilico ADME studies exhibited the P3a and P3b compounds accordance completely with lipinisky limitations. Water solubility: P3a soluble moderately in water while P3b compound good soluble in water. Both componds have high GI absorbitions, no Blood Brain Barrier (BBB) penetration level, anticipated to be safe to CNS.

The cytochrome p450 2D(CYP2D6) showed: two compounds non-inhibitors of CYP2D6 therefor the hepatic dysfunction side effect unexpected.

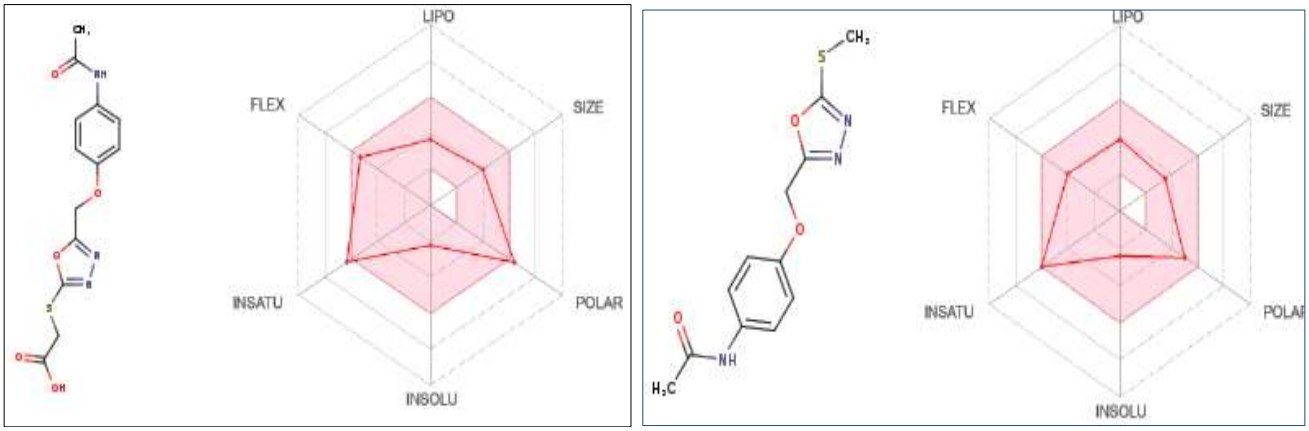

Fig 4: ADME results of (P3a) (rieght) and (P3b) (left)

4. Conclusions

Finally, we developed and synthesized new chemical derivatives of paracetamol that includes oxadiazole and triazole moieties with reasonable yields, oxadiazole derivatives showed antibacterial activity against of *Klebsiella* pneumonia bacteria docking studies suggested the new compounds acts as a good inhibitory agent against *Klebsiella* pneumoniae AcrB enzyme. ADME studies showed: Two compounds (P3a and P3b) non-inhibitors of CYP2D6 therefor the hepatic dysfunction side effect unexpected and accordance completely with Lipinski limitations.

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