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Synthesis, characterization and Theoretical study of some 2-Oxopyridine Carbonitrile derivatives that contain tetrazole ring and evaluation of their Biological activity

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***Abstract*— A series of 2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl-1,2-dihydropyridine-3-carbonitrile 3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl) phenyl]-1,2-dihydropyridine-3-carbonitrile and 2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile), were prepared from the reaction of 4-aminoacetophenone, sodium azide in the presence of glacial acetic acid via cyclization reaction to produce (1-(4-(1H- 1,2,3,4tetrazole-1-yl) phenyl) ethan-1-one). Followed by condensation of (1-(4-(1H- 1,2,3,4tetrazole-1-yl) phenyl) ethan-1-one) with ethyl cyanoacetate, aromatic aldehydes, and ammonium acetate at 110℃ to give(3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile and 2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl-1,2-dihydropyridine-3-carbonitrile 3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl) phenyl]-1,2-dihydropyridine-3-carbonitrile and 2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile. The synthesized compounds were characterized by spectral methods (FT-IR and ^{1}H-NMR & ^{13}C-NMR). The synthesized compounds have been estimated in lab. for biological efficiency. Preliminary biological testing reveals that the compounds have exhibited activity against the two types of bacteria (staphylococcus aureus, and Klebsiella pneumonia). Both Compounds had high activities. Docking experiments for the compounds were undertaken in order to better understand the ligand-protein interactions in terms were done using py-px and BIOVIA/ Discovery studio of binding affinity. The computed binding affinities were consistent with the MIC values**

***Keywords*— Antibacterial activity, (Molecular docking,), pyridine derivatives, Tetrazole.**

I. INTRODUCTION

Tetrazole moiety has a significant group of nitrogen-rich heterocyclic compounds with numerous practical uses in a variety of industries, including high-energy materials, agriculture, medicine, and photography.[3-5]. It has a wide use in medicinal chemistry as anti-hyperglycemic[4], anti-inflammatory [5-6], antiviral [7-8], anticancer [9], antioxidants [10]. In this study, tetrazole was produced from cyclization of primary amine, sodium azide and triethyl orthoformate [11-12]. Then, the reaction of tetrazole derivative with ethyl cyanoacetate, ammonium acetate and aromatic aldehydes via multicomponent reaction (MCR) for synthesis of pyridine derivatives [13-14] as in the scheme The growth and development of organic synthesis and medicinal chemistry both depend significantly on multicomponent reactions [15-17]. The fundamental benefit of these reactions is that no separation or purification techniques are required, which saves time, money, and avoids the production of waste products[18-19] cross inhibition of PDE3 together with other PDEs [20]. Sulfonyl bis compounds carrying 2-pyridone moiety exhibited a good anticancer activity against human breast cell line (MCF7) The creation of novel 2-pyridone compounds with minimal toxicity can be used as antibacterial [20-21] and anti-inflammatory medicines

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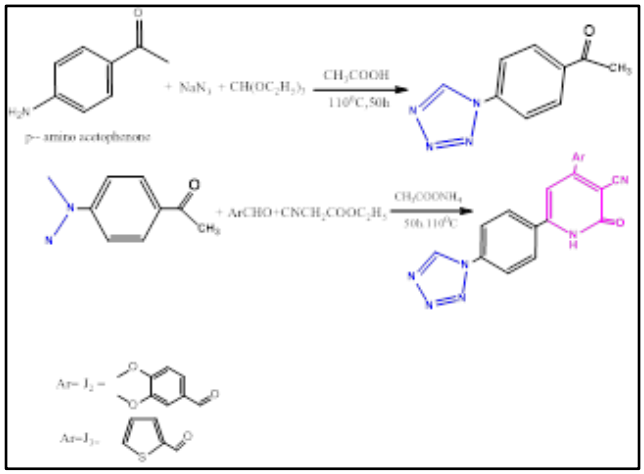


Scheme1. synthesis of 2-Ox opyridine Carbonitrile derivatives (J2 & J3).

II. MATERIALS AND METHODS

All Melting points are measured and were inaccurate using SMP3 apparatus. Thin layer chromatography was performed on Merck TLC Silica gel 60 F254 with detection by iodine vapor. Characterization with Infra-red spectra (KBr disc) were recorded on ―Perkin Elmer, tensor 27 (Bruker). 1H- NMR spectrum were registered on ―a Bruker-DRX - 500 MHz spectrophotometer. ‖ (Solvent d6-DMSO) with internal standard TMS.

A. Synthesis & characterization of 1-(4-(1H-1,2,3,4tetrazole-1-yl) phenyl) ethan-1-one (J_1).

p-amino acetophenone (1.35gm, 0.01mole) was dissolved in glacial acetic acid 25ml with NaN_3 (0.65gm,0.01mole) and triethyl orthoformate (2ml, 0.01 mole) were added. The resulting mixture was heated under reflux for 50 hr. The progress of reaction was monitored by TLC. After completion of the reaction.The mixture was poured into crushed ice and the solid was filtered, washed with water and recrystallized by ethanol[22]. Some of the physical properties are summarized in table 1. Yield (70%) , Rf =0.2 (Ethanol 50% v/v); faint yellow; m.p.166-168℃ ; IR(KBr) Umax(cm-1): 3113(C-H of Tetrazole ring) ,3048 (C-H Ar.),1675 (C=O, Ketone),1589 (C=N),1H-NMR(d6-DMSO) :10.25(s,1H, HC=N tetrazole (, 7.68-7.90 (dd, 4H, Aromatic proton) , 2.07 (s, 3H, CH3).

B. General proce dure for preparation ($J_2$and J_3)

A mixture of 1-(4-(1H-1,2,3,4 tetrazole-1-yl) phenyl) ethan-1-one (0.5gm,0.0026mole), ethylcynoacetate (0.3ml,0.0026mole), ammonium acetate (1.6gm,0.0208 mole) with appropriate aldehyde (3,4dimethoxy benzaldehyde,2-thiophenecarboxaldehyde (0.432gm,0.33319 0.0026mole) respectively in (30ml) of ethanol. The reaction was heated under reflux for 50h . The reaction was monitored by using TLC precipitate was formed, then filtrate, dried and recrystallized from methanol get the desired compounds [23-24].

C. (3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile (J2)

Yield (50%) ; Rf =0.5(ETOH:DMF 4:1 v/v) ; light yellow; m.p 283-285℃ ; IR (KBr)U max (cm^{-1}): 3342 (NH), 3137(C-H of tetrazole) ,3081, 3056, 3032 (C-H of Ar.), 2215(CN), 1703 (C=O) amide),1621 (C=N), 1H- NMR(500 MHz,DMSO-d6:δ ppm): 12.58(s, 1H, OH tautomeric), 10.25(s,1H, CH=N tetrazole) , 7.72-7.86(d,4H, aromatic proton) ,7.12-7.33(s,3H, aromatic proton), 6.80(s,1H, pyridone (C-H), 3.84(s,6H,OCH3) .13 C- NMR(101MHz, DMSO-d6: δ ppm), 169.33 (C=O), 162.69,150.86,105,97 (Pyridone ring) , 142.46 (C of tetrazole), 117.60(CN) , 129.57,128.97,126.73,121.88(Carbon of Phenyl ring), 151.14,149.02,119.12,137.48,112.28,111.98(dimethoxyphen yl ring),56.12 (carbon of methoxy).

D. (2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)- 1,2-dihydropyridine-3-carbonitrile (J3)

Yield (61): Rf=0.62(ETOH:DMF) 4:1 v/v ; Yellow powder, m.p.180-182 ℃; IR (KBr) Umax(Cm^{-1});3366(NH. Of pyridone ring),3098,3068 (C-H of Aromatic),2205(CN of Pyridone 1685(C=Oof amide , 1654 , 1601 of (C=N) ,^{1}HNMR (500MHz , d_6-DMSO- δ ppm): 12.61(s,1H,OH), 10.26(s ,CH=N) of tetrazole ring, , ^{13}C-NMR(101MHz, DMSO-d6: δ ppm):169.35 (C=O) of amide , 162.65,151.40,145.42,119.14 (carbon of pyridone ring , 142.8(Carbon of terazole ring) , 37.32,133.08,132.27,131.78 ,129.09,129, 126.36 (carbon of phenyl and thiophene ring),117.64 (CN).

III. RESULTS AND DISCUSSION

In this study, 4-amino acetophenone was used as a precursor for synthesis - 1 (4-(1H-tetrazole-1-yl) phenyl) ethenone (J1) via cyclization of primary amine and azide salt and triethyl orthoformate with good yield. The compounds (J2 and J3) were obtained by cyclization reaction of acetophenone derivative, ammonium acetate, ethyl cyanoacetate, and aromatic aldehyde as in the scheme 2 and 3hich illustrated the mechanism of the reaction. The prepared compounds have been identified by IR and 1HNMR. 1H-NMR of compound (J1) has been shown singlet signal at 10.25 ppm which belongs to azomethine (CH=N) of tetrazole ring and two doublets single at (7.68-7.90) belonging to the aromatic proton as in figure 1

Table(1): show the physical properties for the prepared compounds(J2& J3)

Compound	Molecular formula	M.wt. g/mole	yield%	m. p.
J_1	$C_9H_8N_4O$	188.2	70	166-168
J_2	$C_{21}H_{16}N_6O_3$	400.39	50	283-285
J_3	$C_{17}H_{10}N_6OS$	346.37	61	180-182

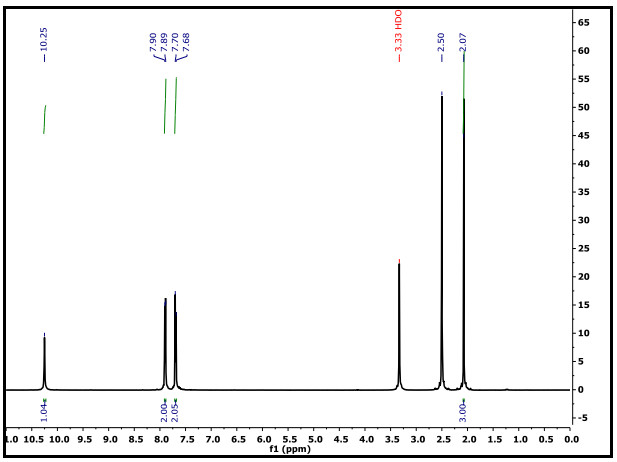
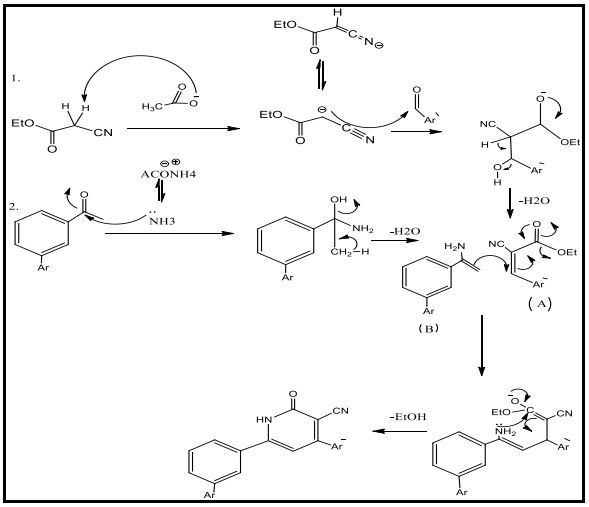


Fig1:[1]H-NMR-(4-(1H-1,2,3,4tetrazole-1-yl)phenyl) ethan-1-one(J_1)



Scheme 3: proposed mechanism for Synthesis (J2&J3)

IR-spectra of compound (4-(1H-1,2,3,4tetrazole-1-yl)phenyl) ethan-1-one) revealed the presence of medium to weak bands at 3342 and 3366 cm-1, respectively which belong to the stretching vibration of NH. Medium bands at 2215 and 2205, cm-1, respectively attributed to the nitrile CN group. The appearance of sharp strong band at 1703 and 1685cm-1 respectively belong to the carbonyl group C=O of amide as in Fig. . 2 and 3

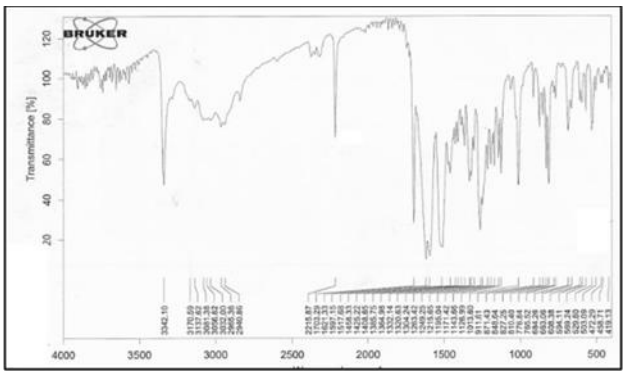


Fig2 : FTIR spectrum of (3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile (J2)

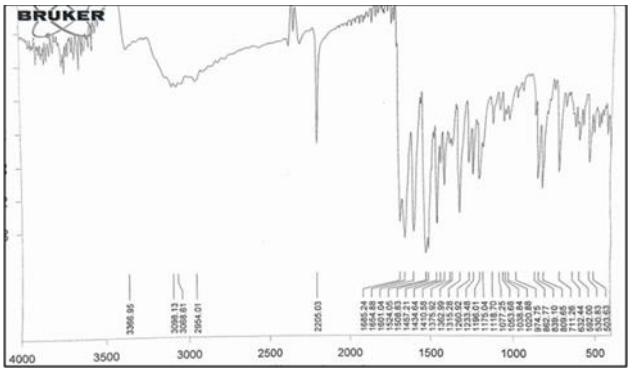


Fig 3.:FTIR spectrum of (2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)- 1,2-dihydropyridine-3-carbonitrile (J3)

[1]HNMR spectrum of3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile(J_2)and (2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)- 1,2-dihydropyridine-3-carbonitrile(J_3) have been showed singlet signal at chemical shift (12.58-12.61) due to tautomeric of OH also singlet signal at (10.25-10.26) attributed to azomethane of tetrazole ring. Moreover, appearance singlet signal at (6.80-6.89) corresponding to (C-H) of pyrdione ring.

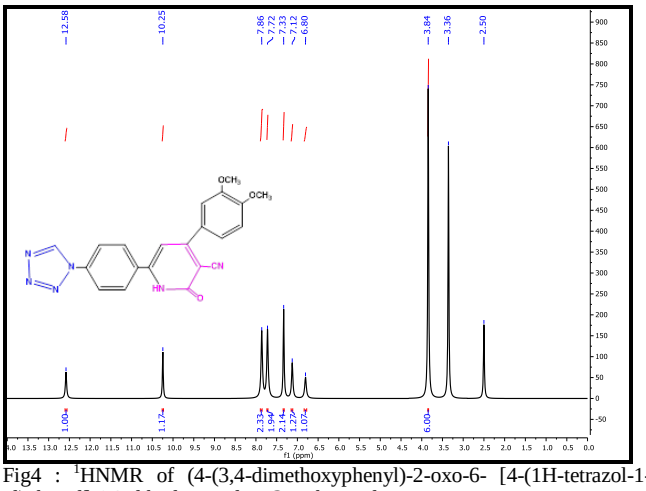


Fig4 : [1]HNMR of (4-(3,4-dimethoxyphenyl)-2-oxo-6- [4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile

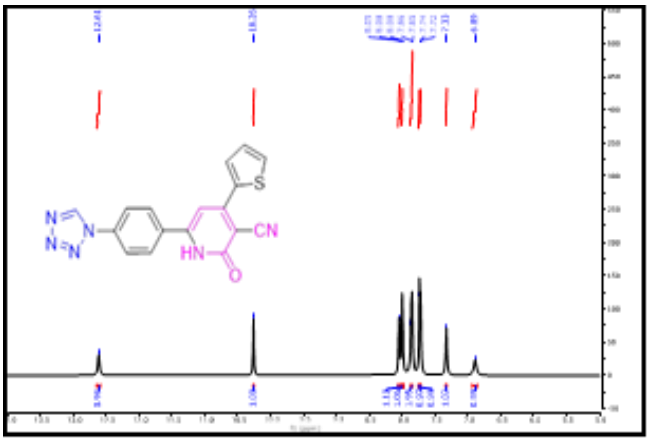


Fig 5: [1]HNMR of (2-oxo-6-[4-(1H-tetrazol-1-yl)phenyl]-4-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile.

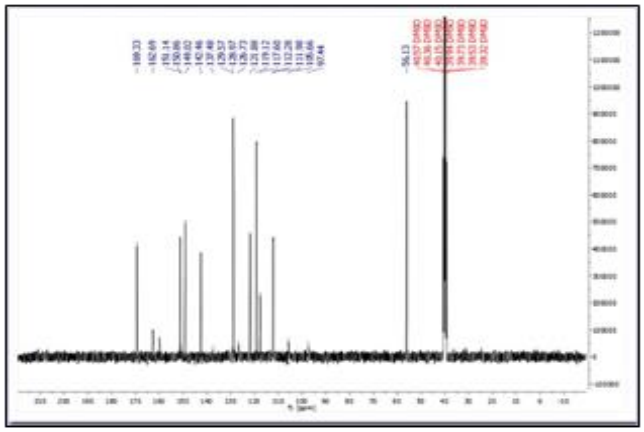


Fig.6:[13]C-NMRof(3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile (J_2)

The [13]C-NMR of (3,4-dimethoxyphenyl)-2-oxo-6-4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile (J2) showed the following data in ppm:169.33 refer to carbonyl of amide (C=O), 162.69,150.86,105,97 attributed to pyridone ring, 142.46 refers to carbon of tetrazole ring , 117.60 belong to nitrile (CN),129.57,128.97,126.73,121.88due to phenyl ring,151.14,149.02,119.12,137.48,112.28,111.98 belong to dimethoxy phenyl ring, 56`.12 attributed to carbon of methoxy (OCH3). The[13]C-NMR of(2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)- 1,2-dihydropyridine-3-carbonitrile (J3) showed the following data in ppm:169.35 refers to carbonyl group of amide 162.65,151.40,145.42,119.14 attributed to pyridine ring ,142.58 refers to carbon of tetrazole ring 37.32,133.08,132.27,131.78,129.09,129,126.36 attributed to phenyl ring and thiophene ring , 117.64 belong to nitrile CN

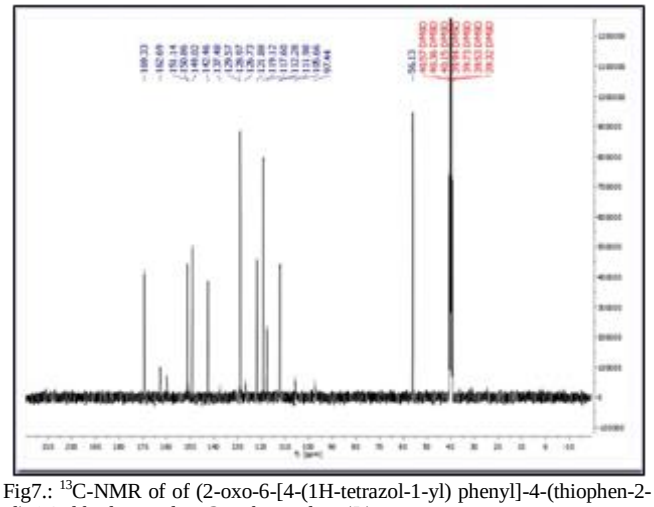


Fig7.: [13]C-NMR of of (2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (J_3)

A. Biological activity:

The compounds J2 and J3 have been tested for their biological activity against two kinds of bacteria Staphylococcus aureus and Klebsiella pneumonia as described in Table 3. The compounds showed moderate activity against negative and positive bacteria

Table (2): illustrates the antibacterial activity of compounds J_2 and J3

Bacteria	conc.(Mg/ml)	*Staphylococcus aureus* (Gram positive)	*Klebsiella pneumoniae (Gram negative)*
Name	Diameter of inhibition Zone in mm		
J_3	1000	4	9
	500	4	6
	250	3	6
	100	4	5
J_2	1000	3	3
	500	3	4
	250	4	4
	100	4	35
Ciprofloxacin		8	32
Azithromycin		11	15
Amoxicillin clavulanate		Nill	Nill
Gentamicin		Nill	Nill
Doxycycline		22	14
Ampicillin		Nill	Nill

B. Molecular docking

For docking investigations, the suggested ligands (J_2 and J_3) and standards were checked against bacterial protein 3FYV from S. aureus and 7BYE of Klebsiella pneumonia in PyRx software. The docking results of the ligands with the middle score when compared with the standard were selected and given in Tables 4 and 5. The interaction energy comprises bonds van der Waals energy, electrostatic energy, as well as intermolecular hydrogen bonding (H-bond) was calculated for all complexes of compounds J2-J3. The docking score was against protein 3FYV (-7.5 Kcal/mol and -7.8 Kcal/mol) in compounds J2 and respectively. While, the docking score was being against protein 7BYE in compounds J2, J3(-7. 5 Kcal/mol and -7.8 Kcal/mol). The compound's derivatives,4- amino acetophenone, could be used to make antibacterial medications. The standard Ciprofloxacin is linked mainly with protein 3FYV by the three H-bonds displayed with residues: TRP; X:22, HIS;X:23, and LEU:X:24. The inhibitor is perceptible through hydrophobic interactions such as carbon . Furthermore, Ciprofloxacin is bonded mainly with protein 7BYE by four H-bonds via ASP B:35, ASP;E:35, and LYS: F:108. which is an inhibitor through hydrophobic interactions such as Fluorine. while all compounds J2 and J3 bonded with proteins appeared lower bonded by amino acid by H- bond. that was referred to in Table 3. This is consistent with the results of biological activity in Table 2. The compounds are possible projects to develop drugs by adding active groups to the structure as florin.

Table .3. Various interactions are involved between receptors and compounds (J2 and J3)

Code.	Bond length(A°)	Type of bond
J_2 3FYV(S.aureus)	2.59 2.44 2.69 4.13 1.79	Conventional hydrogen bond Conventional hydrogen bond Conventional hydrogen bond Pi-Alkyl Doner-doner
J_2 7BYE (Klebsiella pneumonia)	2.47 2.92 3.4 5.2 4.15	Conventional hydrogen bond Conventional hydrogen bond Pi-Sigma Pi-Alkyl Pi-anion
J_3 3FYV(S.aureus)	2.55 4.13 5.48 4.65 5.94 4.81 5.38 4.28	Conventional hydrogen bond Pi-Alkyl Pi-Alkyl Pi -Pi stacked Pi -Pi stacked Pi -sulfur Pi –sulfur Pi -cation
J_3 7BYE (Klebsiella pneumonia)	3.95 3.93 4.64 3.34 5. 42 3.84	Conventional hydrogen bond Pi-Sigma Pi-alkyl Pi- Donor Pi-Alkyl Pi-anion
Ciprofloxacin 3FYV (S. aureus)	2.34 1.87 2.15 3.43	Conventional hydrogen bond Conventional hydrogen bond Conventional hydrogen bond carbon
Ciprofloxacin 7BYE(Klebsiella pneumonia)	2.58 2.59 2.25 5.23, 4.19 4.03 2.93, 3.43	Conventional hydrogen bond Conventional hydrogen bond Conventional hydrogen bond Pi-Alkyl Pi-Cation Fluorine

Table 4. Binding affinity(kcal/mol) with bacteria protein and hydrophobicontacts (from molecular docking) in ligands J_2 and J_3.

Code	B.P.	Binding affinity (kcal/mol)	H- bond contacts
J_2	3FYV (S. aureus)	-7.5	ARG;X:12, GLU;X:114
J_2	7BYE (Klebsiella pneumonia)	-7.8	ASP;E:35, LYS:F:108
J_3	3FYV (S. aureus)	-7.8	SER;X:135.
J_3	7BYE (Klebsiella pneumonia)	-7.5	ASP B:35
Ciprofloxacin	3FYV (S. aureus)	-5.7	TRP;X:22, HIS;X:23, LEU:X:24
Ciprofloxacin	7BYE(Klebsiella pneumonia)	-6.3	ASP B:35, ASP;E:35 LYS:F:108

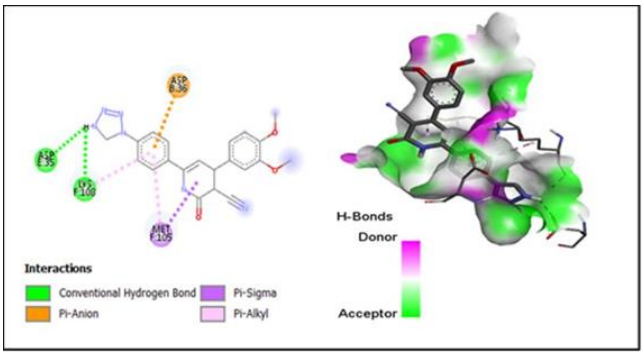


Fig 6.: 3D and 2D Binding site Interaction of compound J_2

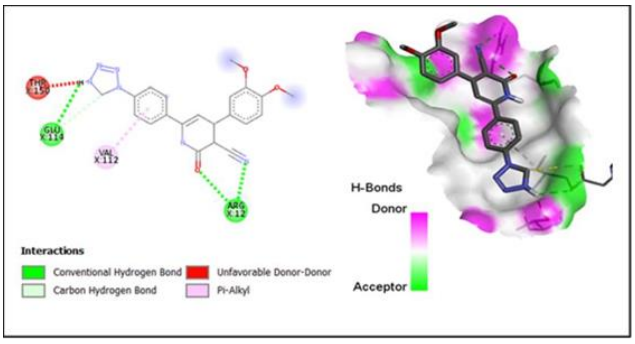


Fig 7. 3D and 2D Binding site Interaction of compound J2 with Klebsiella pneumonia PDB ID. 7BYE).

IV. Coclusion

In this study two derivatives of (4-(3,4-dimethoxyphenyl)-2-oxo-6- [4-(1H-tetrazol-1-yl)phenyl]-1,2-dihydropyridine-3-carbonitrile and 2-oxo-6-[4-(1H-tetrazol-1-yl) phenyl]-4-(thiophen-2-yl)- 1,2-dihydropyridine-3-carbonitrile(J2 and J3) were synthesized from reaction of tetrazole derivative with aromatic

aldehydes (3,4 -dimethoxy benzaldehyde , 2- thiophene carboxaldehyde) respectively, ethyl cyanoacetate and ammonium acetate via cyclization reaction . The synthesized compounds were confirmed by some of spectral methods such as FTIR,^{1}H-NMR and ^{13}C-NMR .The prepared compounds were evaluated in vitro for their biological activity against two types of bacteria (*staphylococcus aureus, and Klebsiella pneumonia*) which showed moderate inhibition . In an attempt to understand the ligand–protein interactions in terms of the binding affinity, docking studies were performed using Py-Rx and BIOVIA\Discovery Studio 2021 for the compounds. the binding affinities calculated were in agreement with the MIC values.

AUTHOR'S CONTRIBUTION

This work was carried out in participation of A.H.M, M.J.D and A.G.S. A.H.M. contributed to the design and M.J.D Performed the experiments, to the analysis of the results and to the writing of the manuscript and A.G.S implemented the molecular Duking studies and writing the manuscript.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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