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"Synthesis, Characterization, In Silico Studies Of Substituted Azetidinone Bearing Triazole And Thiadiazole Ring, Their Antibacterial Activity"

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Abstract:
This study explores the potential of compounds as antibacterial agent by examining its binding interactions with biotin protein ligase and DNA gyrase, essential enzymes in bacterial metabolic pathways. Molecular docking simulations reveal strong affinities between compound 6a and both target proteins. The study also a class of compounds 6(a-e) of substituted azetidinone derivatives of drug. Among of them, Synthesis of novel compound 6(a-e) were showed valuable characteristic and efficacy as antibacterial activity. 6c, 3-chloro-4-(4-chlorophenyl)-1-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)azetidin-2-one, Chloro and nitro substituted of azetidinone 6c and 6d derivatives were showed moderate to better biological activity as compare to standard drugs moxifloxacin, for regarding this observation, heterocyclic compounds of these derivative are very useful in the field of medicinal chemistry. These derivatives of azetidinone nucleus were possesses remarkable, better clinically efficacy with low toxicity. Purity of these derivatives were checked with the help of TLC.The structure of new synthesised compounds was identified and confirmed by elemental analysis, IR, NMR, and activity of new synthesised these drugs were screened for their antibacterial activity.

Keyword: Azetidinone, Triazole, Thiadiazole, Biological Activity, molecular docking.

Introduction:

Heterocyclic compounds, owing to their diverse structures and reactivity, have emerged as pivotal entities in the quest for novel therapeutic agents. Among of these, azetidenone derivatives, notably those incorporating the triazole, azetidinone moiety, have exhibited remarkable antibacterial efficacy. Azetidenone derivatives, comprising a four-membered ring, have showcased noteworthy antibacterial, antifungal, and anti-inflammatory effects. The incorporation of the triazole moiety into these structures has further enhanced their antibacterial activity, emphasizing the significance of the structural modifications in tailoring biological effects. Recent research endeavors have illuminated the antibacterial potential azetidenone derivatives., our surrounding, we see different life treating infection cause by bacterial infection. triazole are useful structural

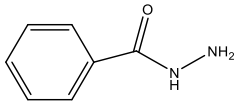
requirement in the field of medicinal chemistry. triazole derivatives exhibit different biological activity like biological active agent[1,2,3,4,5,6,10]Alzheimer[7] antimicroial agent[8]anticorona virous[9] and azetidinone ring possess various activity as anti depressant agent [11]and antimicrobial agent activity [,12,16,24,26,27]. And as a breast cancer agent [13], cholesterol absorber inhibitor agents[14], anti-bacterial and antioxidant [15,21,25,28].And moiety of azetidinone also play a vital role in the field of meditational, these also work as biological active agents [17,18,19,20,22,23,29,30].and anticancer agent[26]. antibiotic agent[31]. azetidinone derivatives which contain small ring heterocyclic nitrogen, chlorine and oxygen,attached electro negative active atom show better results due to their medicinal properties in biological system and it also affected by different rate, in compare ,older drug show high frequency of renal toxicity and several adverse effect. However this research work, synthesised some novel drug derivatives 5(a-e), and 6(a-e) which shown the better to moderate antibacterial activity with less side effects.

Material and Method:

All the chemical and reagents are purchase from sigma Aldrich, CDH, used as such without further purification. Melting point of the new derivatives which were synthesis were taken in an open capillary with the help of thermonic melting point apparatus and it may be incorrect the purity of the compound were checked by thin layer chromatography on silica gel G. Eluent was the mixture of methanol and ethyl acetate and spot were visualized by iodine .The structure of these compounds were analysis by IR,^{1}H-NMRand elemental analysis The IR (KBr)spectra were recorded on FTIR Paragon 500(Perkin -Elmer, Max in cm^{-1}

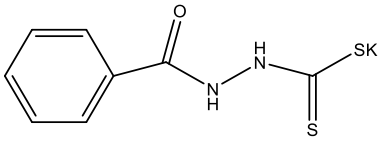
Experimental:

1: Synthesisof Benzohydrazide (1):



Organic compound Methyl benzoate (0.01mol) was transferred into 100 ml R B Flask and makes a solution in ethyl alcohol and mixed with hydrazine hydrate (0.01) with continuously shaking it for 30 min on magnetic stirrer. Then reflux on water bath for 6 hr. The reaction was monitored for desire form of molecules with help of TLC using silica gel. Pour into cool acidic water wait for some till crystal formation take place, then filtered, washed with cool H_2O. The final product was dried in vacuum desiccators to give white spiny solid crystal compound (1) IR (KBr) ν_{max} in cm^{-1},2880 C-H, 785 C-S,1775 C=O,3348 N-H, ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppm δ ,7.50-7.90 ,5×1H (m, - CHAr,) , δ 9.64 ,1×1H (t, -**NH**) , δ 4.49,1×2H (d, $-NH_2$). m/z: 136.06 (100.0%), 137.07 (7.6%).

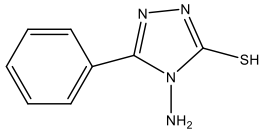
synthesis of potassium 2-benzoylhydrazine-1-carbodithioate (2) :



Take the compound (1) and transferred into RB Flask of 150 ml and added 30 ml of ethyl alcohol then catalytic amount of potassium hydroxide was added and reaction mixture was stirrer it for 15 min at room temp then add 10 ml of liquid $CS_2$with drop wise at a continues stirring for 3hours.

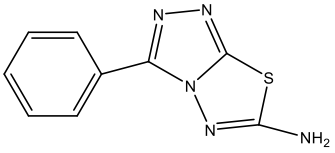
This mixture was turn colorless to yellowish solution. Progress of the reaction was recorded by (silica gel) TLC by using toluene and ethyl acetate solution as eluent in 4:1 ratio. It was visualize in iodine chamber. After completion, it put aside for some time to decrease the temperature now it cooled, filtered & washed with distilled H_2O. It is dried and obtained compound (2). IR (KBr) ν_{max} in cm^{-1} 2881C-H,783 C-S ,1762 C=O,3345 N-H, ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.52-7.90 ,5×1H (m, - CHAr,) , δ 8.35 ,1×1H (d, -**NH-CO**) , δ 11.3,1×1H (d, -NHC=S). m/z: 249.96 (100.0%), 251.96 (9.0%), 250.97 (8.7%).

Synthesis of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (3):



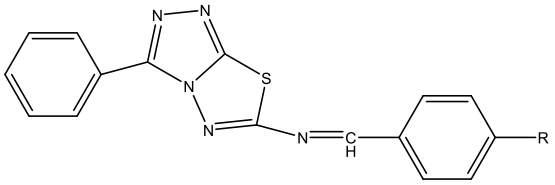
Take the compound (2) and transferred into RB Flask of 250 ml and added 22ml of ethyl alcohol then add liquid hydrazine hydrate(0.01) at continues stirring it for 2hr. Progress of reaction was recorded by (silica) TLC by using toluene and ethyl acetate solution as eluent in 4:1 ratio. It was visualize in iodine chamber. After completion, it put for some time to decrease the temperature now it cooled, filtered & washed with distilled H_2O. It is dried and obtained compound (3). IR (KBr) ν_{max} in cm^{-1} 2880 C-H, 782 C-S,1766 C=O,3350 N-H , ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.51-8.05 ,5×1H (m, - CHAr,) , δ 5.70 ,1×2H (s, -**NH_2**) , δ 13.9,1×1H (s, -SH). m/z: 192.05 (100.0%), 193.05 (8.7%).

Synthesis of3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-amine (4):



Take the compound (3) and transferred into RB Flask of X ml and cyanogen bromide in 15 ml of ethyl alcohol then stirring for 2hr mixture preparation. Then reflux for 6hr Progress of reaction was recorded by (silica) TLC by using toluene and ethyl acetate solution as eluent in 4:1 ratio. It was visualise in iodine chamber. After completion, it put aside for some time to decrease the temp now it cooled, filtered & washed with distilled H_2O. It is dried and obtained compound (4). IR (KBr) ν_{max} in cm^{-1} 2879 C-H, 784 C-S,1762 C=O,3347 N-H, ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.50-8.30 ,5×1H (m, - CHAr,) , δ 7.22 ,1×2H (s, -**NH_2**) . m/z: 217.04 (100.0%), 218.05 (9.7%),

General process for formation of N-substitutedbenzylidene-3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-amine (5):



R=H ,-CH_3 ,-C_2H_5 ,p-NO_2 ,p-OH

5(a) Take Compound (4) (0.01mol) in round bottom flask 250 and then transferred various aldehyde into it and add solvent then stirrer for 10 min then transfer into a dean stark apparatus

condensation process may performed a Schiff base 5a is prepared and purified ,dried. For conformation data analysis may be performed a IR (KBr) ν_{max} in cm^{-1}2881 C-H, 785 C-S,1563C=N,1725 C=C. ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.49-8.30 ,9×1H (m, - CHAr, both ring) , δ 8.88 ,1×1H (s, -CH=N) . m/z: 305.07 (100.0%), 306.08 (17.3%),

A similar method like (5a) are use to prepare various Schiff base 5((b-e), data of thesewere recorded as below .

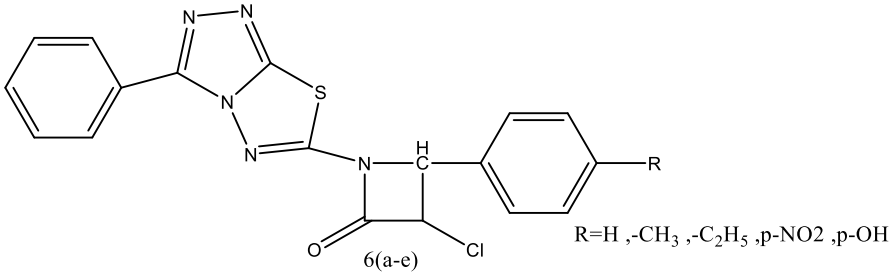
5b):IR (KBr) ν_{max} in cm^{-1}2875 C-H, 783 C-S,1566C=N,1726 C=C. δ ,7.50-8.31 ,10×1H (m, -CHAr,both ring) ,. ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ 9.0 ,1×1H (s, -CH=N) , δ 2.41 ,1×3H (s, -CH_3) m/z: 319.09 (100.0%), 320.09 (18.4%),

5(c) IR (KBr) ν_{max} in cm^{-1} 2878 C-H, 780 C-S,1565 C=N,1723 C=C,748C-Cl . , ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.52-8.29 ,9×1H (m, - CHAr,both ring) , δ 8.98 ,1×1H (s, -CH=N) , m/z: 339.03 (100.0%), 341.03 (32.0%),

5d) IR (KBr) ν_{max} in cm^{-1} 2880 C-H, 782 C-S,1562C=N,1721 C=C,1475 N-O .^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.51-8.28 ,9×1H (m, - CHAr, both ring) , δ 8.99 ,1×1H (s, -CH=N) . m/z: 350.06 (100.0%), 351.06 (17.3%),

5(e): IR (KBr) ν_{max} in cm^{-1} 2882 C-H, 781 C-S,1560C=N,1724 C=C,3405 O-H.^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.50-8.31 ,9×1H (m, - CH-Ar,both ring) , δ 9.0 ,1×1H (s, -CH=N) , δ 9.68 ,1×1H (s, -OH) . m/z: 321.07 (100.0%), 322.07 (17.3%),

General process for formation of 4-substitutedphenyl-1-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)azetidin-2-one :



6(a): Take a schiff base 5a 0.01 mol in a RB 150 ml then added 0.01 mol then stirrer of it for 15 min then add some amount of dioxin solvent then refluxed it till completion of reaction and progress of reaction may be checked through TLC(silica gel G). Data analysis of the reaction may be performed.ieIR (KBr) ν_{max} in cm^{-1}2875 C-H, 780 C-S,1766 C=O,1724 C=C. ,^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.48-8.30 ,10×1H (m, - CHAr, both ring) , δ 4.79 ,1×1H (d,N-CH-C) , δ 5.18 ,1×1H (d, -C-CHCl-C) . m/z: 381.05 (100.0%), 383.04 (32.0%).

Similar patterns of synthesis, evaluation were followed like 6a for the preparation of 6(b-e)data are observed as below.

6(B) IR (KBr) ν_{max} in cm^{-1}2875 C-H, 780 C-S,1764 C=O,1722 C=C., ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.49-8.32 ,9×1H (m, - CHAr, both ring) , δ 5.44 ,1×1H (d,N-CH-Cl four member ring) , δ 5.08 ,1×1H (d, -CH-N-CH-C) , δ ,2.19 ,1×3H (s, p- CH_3). m/z: 395.06 (100.0%), 397.06 (32.0%).

6C: IR (KBr) ν_{max} in cm^{-1}2879 C-H, 781 C-S,1765 C=O,1726 C=C.752 C-Cl. , ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.48-8.31 ,9×1H (m, - CHAr, both ring) , δ 5.45 ,1×1H (d,N-CH-Cl four member ring) , δ 5.07 ,1×1H (d, -CH-N-CH-C) . m/z: 415.01 (100.0%), 417.00 (63.9%),

6d): IR (KBr) ν_{max} in cm^{-1}2877 C-H, 777 C-S,1762 C=O,1720 C=C.1467 N-O ., ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,7.49-8.30 ,9×1H (m, - CHAr, both ring) , δ 5.44 ,1×1H (d,N-CH-Cl four member ring) , δ 5.08 ,1×1H (d, -CH-N-CH-C) . m/z: 426.03 (100.0%), 428.03 (32.0%),

6E): IR (KBr) ν_{max} in cm^{-1}2876 C-H, 783 C-S,1763 C=O,1722 C=C,3402 O-H., ^{1}HNMR($CDCl_3$ + DMSO-d_6) δ in ppmδ ,6.71-7.05 ,4×1H (m, - CHAr, ring attached subst) , δ ,7.50-8.30 ,5×1H (m, - CHAr, ring ,δ 5.43 ,1×1H (d,N-CH-Cl four member ring) , δ 5.09 ,1×1H (d, -CH-N-CH-C), δ9.06,1×1H (s, -p-OHAr) . m/z: 397.04 (100.0%), 399.04 (32.0%),

Observation Table:

Table 1 Physical & Analytical data of compounds (1-17):

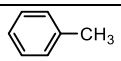
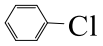
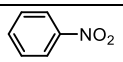
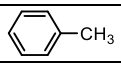
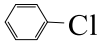
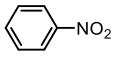
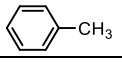
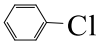
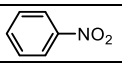
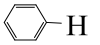
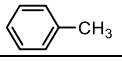
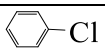
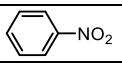
Compound No.	R Group and their Position	Molecular Formula	Yield %	Recrystalised Solvent	Elemental Analysis					
					%C		%H		%N	
					Calctd.	Found.	Calcd.	Found	Calcd.	Found
1	-	$C_7H_8N_2O$	83	Ethyl Alcohal	61.75	61.74	5.92	5.91	20.58	20.58
2	-	$C_8H_7KN_2OS_2$	72	Ethyl Alcohal	38.38	38.36	2.82	2.83	11.19	11.20
3	-	$C_8H_8N_4S$	74	Methyl Alcohal	49.98	49.97	4.19	4.18	29.14	29.15
4	-	$C_9H_7N_5S$	70	Ethyl Alcohal	49.76	49.75	3.25	3.22	32.24	32.21
5a		$C_{16}H_{11}N_5S$	65	Ether	62.93	62.92	3.63	3.61	22.94	22.95
5b		$C_{17}H_{13}N_5S$	69	Ethyl Alcohal	63.93	63.94	4.10	4.11	21.93	21.92
5c		$C_{16}H_{10}ClN_5S$	64	Ethyl Alcohal	56.56	56.55	2.97	2.96	20.61	20.62
5d		$C_{16}H_{10}N_6O_2S$	-	Ethyl Alcohal	54.85	54.84	2.88	2.87	23.99	23.98
5e	*Ph-OH*	$C_{16}H_{11}N_5OS$	60	Ethyl Alcohal	59.80	59.81	3.45	3.45	21.79	21.80
6a		$C_{18}H_{12}ClN_5OS$	67	Ether	56.47	56.48	3.42	3.41	18.29	18.27
6b		$C_{19}H_{14}ClN_5OS$	69	Ether	57.50	57.52	3.81	3.80	17.65	17.63
6c		$C_{18}H_{11}Cl_2N_5OS$	62	Ethyl Alcohal	51.81	51.53	2.90	2.91	16.78	16.78
6d		$C_{18}H_{11}ClN_6O_3S$	72	Ethyl Alcohal	50.53	50.52	2.83	2.80	19.64	19.65
6e	*Ph-OH*	$C_{18}H_{12}ClN_5O_2S$	74	Ethyl Alcohal	54.21	54.20	3.29	3.30	17.56	17.55

Table 2 Anti Bacterial activity of compounds5(a-e),6(a-e) :

Sno	Substituent R Group	Compounds	E. coli mm	S. Aureus mm
1	-	$C_7H_8N_2O$	-	-
2	-	$C_8H_7KN_2OS_2$	-	-
3	-	$C_8H_8N_4S$	-	-
4	-	$C_9H_7N_5S$	-	-
5a		$C_{16}H_{11}N_5S$	12	14

5b		$C_{17}H_{13}N_5S$	13	15
5c		$C_{16}H_{10}ClN_5S$	18	17
5d		$C_{16}H_{10}N_6O_2S$	15	14
5e	*Ph-OH*	$C_{16}H_{11}N_5OS$	14	15
6a		$C_{18}H_{12}ClN_5OS$	13	15
6b		$C_{19}H_{14}ClN_5OS$	15	16
6c		$C_{18}H_{11}Cl_2N_5OS$	19	17
6d		$C_{18}H_{11}ClN_6O_3S$	16	15
6e	*Ph-OH*	$C_{18}H_{12}ClN_5O_2S$	14	16
	Reference	Moxifloxacin	17	16

Molecular docking:

The rise of antibiotic resistance requires the creation of novel antibacterial agents. Biotin protein ligase (BPL) and DNA gyrase are essential enzymes in bacterial metabolic pathways and have been recognized as potential targets for antibacterial treatment. This work utilizes molecular docking to examine the binding interactions between a possible antibacterial ligand and the two target proteins. The 3D structures of biotin protein ligase (PDB ID: 3V7R) and DNA gyrase (PDB ID: 4URO) were obtained from the Protein Data Bank. The proteins were produced using dehydration, hydrogenation, and structural optimization using AutoDockTools.The ligand, created with the intention of having antibacterial properties, was built using Chem draw 3D and then optimized using the OpenBabel GUI. Subsequently, the ligand was transformed into the PDBQT format via AutoDockTools.The docking simulation produced several conformations of the ligand within the binding sites of the proteins. The optimal binding postures were chosen by considering both the binding affinity (measured in kcal/mol) and a thorough examination of the interactions occurring within the binding pocket.

Biotin Protein Ligase (PDB ID: 3V7R)

The docking simulation revealed that the ligand establishes a connection with the active site of biotin protein ligase, exhibiting a binding affinity of -9.1 kcal/mol. The primary interactions consist of the establishment of hydrogen bonds with Ser151 and Phe123, along with hydrophobic interactions with lle150, Ile 317 and Ala194. The ligand is securely enclosed within the binding pocket, indicating the creation of a durable complex.

Figure 1:Binding pose of the ligand within the active site of biotin protein ligase (PDB ID: 3V7R).

DNA Gyrase (PDB ID: 4URO)

The ligand exhibited a binding affinity of -8.6 kcal/mol for DNA gyrase. The study found notable hydrogen bonding interactions with residues Phe 204, Try 229 and Arg200, as well as hydrophobic contacts with Ile261 and Pro264. These data suggest a very advantageous binding orientation.

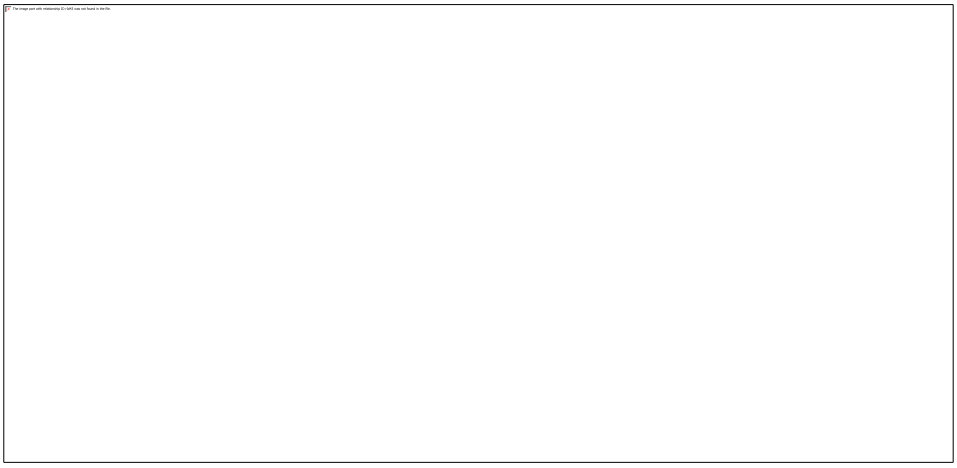


Figure 2: Binding pose of the ligand within the active site of DNA gyrase (PDB ID: 4URO).

Result and Discussion:

Docking studies: The strong affinities of -9.1 kcal/mol for biotin protein ligase and -8.6 kcal/mol for DNA gyrase indicate that the compound 6a has considerable promise as an antibacterial agent. The docking research has discovered distinctive interactions that provide vital insights into the molecular mechanisms by which the ligand disrupts the activity of these enzymes. The stability of the ligand-protein complex and the likelihood of effective inhibition are dependent on the existence of hydrogen bonds and hydrophobic interactions.

Pharmacological evaluation (antibacterial): All Synthesized derivatives were tested for their antibacterial activity. First of all, it was incubated with loopful growth culture of the organism activity and it was recorded by disc diffusion method. Take the nutrient agar- agar and it was poured onto the sterilized Petri disc. The plate was incubated at 20-25 ^{0}C at 25 hr for antibacterial. The material was allowed to set 1-1.4 h. The 5% solution of newly synthesized compound was seeded with the help of sterilize syringe. The gram +ve staphylococcus aures and E coli and data were recorded in table 2. The standard drugs moxifloxacin were also screen under similar condition and their comparative study was performed.

Antibacterial activity: All the newly derivatives are tested against the gram +ve staphylococcus aures and E coli micro-organism.

Table -2, antibacterial activity, data of (6a-6e) azetidinone, indicates that these compounds were showed antibacterial activity. Amongst azetidenones of these compounds 6b, 6c, were found to be relatively more effective against bacterial stain which were mention here. It was showing a zone of inhibition, respectively. It was noticed from the data that other substitutes of compounds, were also showed better activity against organism with low toxicity.

Conclusion:The results of the molecular docking analysis suggest that compound 6a has significant binding affinities towards biotin protein ligase and DNA gyrase, suggesting its potential as an antibacterial agent. The discovered interactions highlight the importance of hydrogen bonding and hydrophobic contacts in preserving the complexes established between the ligand and protein. Further experimental validation and refinement of the ligand might lead to the development of innovative antibacterial therapies that selectively target these essential bacterial enzymes. The recently developed medications, which are derivatives of azetidenone and comprise a triazole and thidiazole component, have demonstrated superior efficacy in protecting against many types of disorders. These medications were highly effective in protecting against living organisms compared to normal treatments, and they may exhibit efficacy against many bacterial diseases.The addition of a triazole substituent to the ring connected to the Azetidinone linkage improves the antibacterial effectiveness of new medications and reduces their toxicity. The 4-chloro azetidinone derivatives, namely 6c, demonstrated superior antibacterial efficacy against E.coli and S. Aureus, with 19 mm and 17 mm zones of inhibition, respectively. These results were compared to the conventional antibiotic moxifloxacin. The derivatives of azetidinone with aromatic substitutions at the para positions 6a, 6b, 6d, and 6e, namely H, -CH3, NO2, and OH, respectively, exhibited values of -13mm, 15mm, 16mm, and 14mm against the bacterial strain E.coli. Against the bacterial strain S. Aureus, these derivatives showed values of 15mm, 16mm, 15mm, and 16mm. These values indicate moderate to high effectiveness with low toxicity. Therefore, these novel drugs are highly beneficial for protecting the living system.

Conflict of interest : There is no conflict of interest

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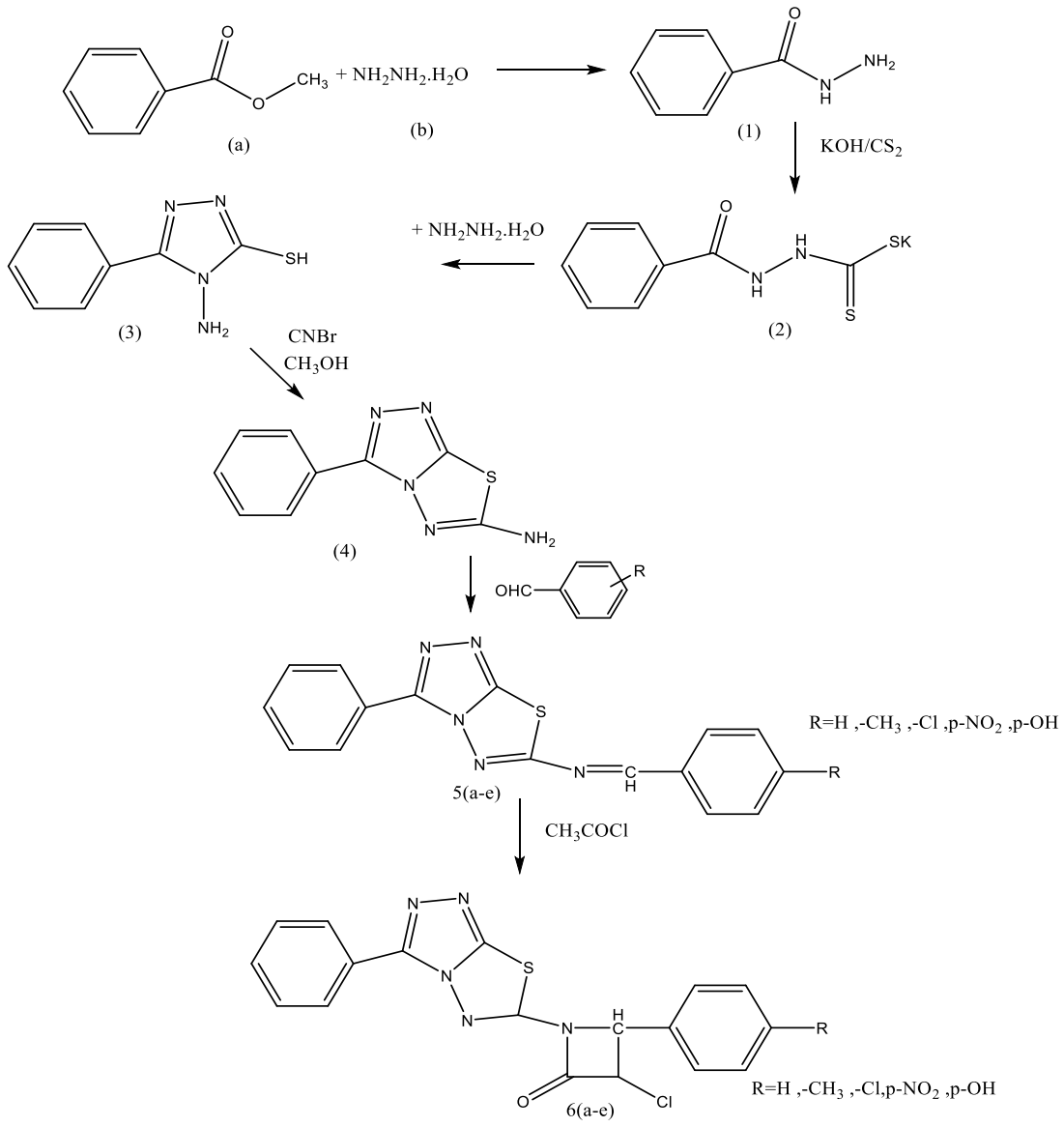

A Propose Plan of the Synthesis Novel Derivatives

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