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Novel Benzofused five membered nitrogen containing heterocyclic compound N-substituted-2-substituted Benzimidazole: Synthesis and Molecular Docking

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ABSTRACT: Background: The major cause of sickness and death is infectious diseases worldwide. As bacteria develop resistance at a quicker pace, novel antimicrobial compounds with various sites of action and sensitivity to resistant bacteria, as well as safety, are needed as a superior alternative to currently existing treatments. Heterocyclic compounds have long caught the interest of researchers due to their broad spectrum of applications and convenience of modification, dating back to the early days of chemical study. In medicinal chemistry, the benzimidazole molecule is a prominent pharmacophore and preferred structure.

Method: The method described in the literature was used to synthesize benzimidazole and mercapto-benzimidazole utilising microwave irradiation. In the presence of K2CO3, benzimidazole/mercapto-benzimidazole was reacted with 2-chloro-N-substituted acetamide to produce desirable N-substituted-2-substituted benzimidazole derivatives (5a-l). Microwave irradiation speeds up the process and reduces impurities. IR, 1HNMR, 13CNMR and MS is used to confirm the structure of synthesised derivatives.A molecular docking investigation was done on two protein targets, DNA gyrase subunit B (5L3J) and Staphylococcus aureus tyrosyl-tRNA synthetase (1JIJ), using a typical docking technique.

Result: The desired compounds were synthesised with excellent purity and yield by Microwave aided synthesis. 5d, 5e, and 5k have a high yield.The biological activity of derivatives on a given target side can be predicted via a molecular docking research. The docking score indicates that they have a stronger binding contact than the reference ligand. The maximum binding affinity is found in 5c, 5e, and 5k.

Conclusion: According to the findings, compounds 5c, 5d, 5e and 5k show a strong potential for antibacterial action. The potency of benzimidazole derivatives might be improved with more SAR studies.

Keywords—N-substituted benzimidazole, Molecular docking, DNA gyrase, auotodock viva, microwave assisted synthesis

1. INTRODUCTION

Infectious agents of over 1400 different species have been found to cause infections in humans. Pathogens for 347 illnesses of long-term clinical relevance were amongst them.[1] According to WHO study, microbial illness could become one of the leading reasons for human death in the near future.[2]Because of the production, transmission, and survival of multidrug-resistant microorganisms, which cause diseases that do not respond to normal therapies, antibiotic resistance is one of the most important public health challenges of the twenty-first century.[3] Furthermore, infection produced by a variety of bacteria is a severe problem for the medical community, and the create necessity for the discovery for new antimicrobial medicines as an efficient treatment.[4] One of the most efficient antibacterial medications are heterocyclic molecules containing nitrogen atoms.[5] A phenyl ring is fused to an imidazole ring in benzimidazoles.[6] Benzimidazole derivatives have been linked to a variety of pharmacological actions, including antibacterial, anticancer, and anti-inflammatory properties, according to the literature. [7–9]This broad spectrum of activity is attributed to the unusual chemical characteristics of azole rings, which are able to interact noncovalently with

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a variety of targets due to the presence of an electron-rich aromatic structure and heteroatoms.[10] The goal of this study is to synthesise some new N-substituted-2-substituted benzimidazoles and anticipate their bacterial activity using molecular docking against two targets: E. Coli DNA gyrase subunit B (5L3J) and tyrosyl t-RNA synthetase (1JIJ).

2. EXPERIMENTAL METHODS OR METHODOLOGY

2.1. Chemistry:

All chemicals were procured by commercial supplier and utilized without additional purification. reaction was monitored by TLC, and the melting point was measured and corrected using the open capillary method.

Vertex 80 FTIR was used to record Infrared (IR) spectra and ECZR Series 600 MHz was used to obtain ^{1}H-NMR and ^{13}C-NMR. AccuTOF GCV mass spectrometer and FLASH EA 1112 series analyser was used to record mass spectra and CHNS analysis respectively.

2.1.a. General Procedure for the Synthesis of 2-chloro-*N*- substituted acetamide (2a-g): [11,12]

With continuous shaking, 0.01 M of substituted aromatic amine (**1**) was introduced to a conical flask containing a 10% NaOH solution. In a fuming hood, the conical flask was cooled on an ice bath, and (0.015 M) chloro acetyl chloride was added drop by drop using a dropping funnel. The solution was stirred on magnetic stirrer until complete addition of chloro acetyl chloride and fumes from the reaction mixture ceased completely. The solution was then stirred overnight. The target product (2a-g) was isolated as a precipitate after dumping the reaction mixture into ice-cold water. The filtered precipitate was rinsedwith cold water and dried. 95% ethanol was used to re-crystallize it.

2.1.b. General Procedure for the Synthesis of 2-(1H-benzimidazol-1-yl)-N-substituted-2-substituted acetamide (5a-l)[13]

Microwave irradiation was used to synthesise benzimidazole**(3)**[14], as described in the literature using o-phenylene diamine (0.025 mol) and 90% formic acid (0.034 mol). The general procedure given by wang and liu was used for preparing 2- mercapto benzimidazole **(4)**.[15–17]

The final desired product was prepared by refluxing 2-chloro-N-Aryl acetamide derivative **(2a-g)** (0.02mole) and Benzimidazole/ mercaptobenzimidazole (0.02mole) in DMF in the presence of potassium carbonate and potassium iodide using microwave irradiation at 245W. TLC was used to monitor the reaction's progress. After the reaction was completed, the solution was poured into ice-cold water, and the precipitate was filtered, dried, and recrystallized using ethanol.[13,18]

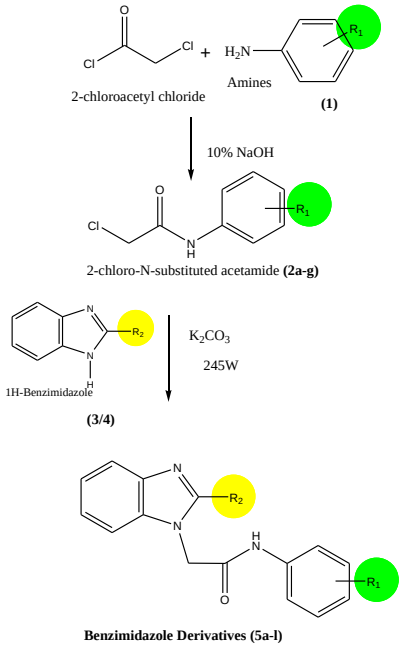

Fig.1. Scheme for synthesis of benzimidazole derivatives

2-(1-H-Benzimidazol-1-yl)-N-phenylacetamide (5a)

IR (KBr)γ_{max} (cm^{-}): 3337.23 (N-H str.**),** 2918.51 (=C-H str.), 1688.41 (C=O str.), 1513.03 (N-H bend) ,1460.10 (C-N str.), 819.19-738.00(Aromatic ring); ^{1}H NMR (600 MHz, δ ppm):3.84 (s, CH_2), 4.98 (s, =CH-N), 8.14(s, NH), 7.55(d,=CH benzimidazole), 7.44(d,=CH benzimidazole), 7.29-6.97(m, CH Ar);^{13}C NMR(600 MHz, δ ppm): 39.84 (CH_2), 165.73(C=O), 119.73-110.91(CH Ar.),146.53 (CH-Imidazole), 136-125.49(CH- Benzimidazole) ; Anal. Cal. (Found) for $C_{15}H_{13}N_3O$: C 66.52 (62.54), H 5.21(4.83), N 16.26 (14.13), O 5.65 (5.92); m/z: 254.02(M^{+}).

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2-(1-H-Benzimidazol-1-yl)-N-(p-tolyl) acetamide (5b)

IR (KBr)γ_{max} (cm^{-}): 3259.81 (N-H str.), 3043.77 (=C-H str.), 1658.84 (C=O str.), 1543.10 (N-H bend) ,1435.09 (C-N str.), 785-652(Aromatic ring).^{1}H NMR (600 MHz, δ ppm): 2.14 (s, CH_3), 3.89 (s, CH_2), 8.31(s, CH-imidazole), 7.35(NH amide), 7.25 (d,=CH benzimidazole), 7.36(d,=CH benzimidazole), 6.72-6.46(d, CH Ar), ^{13}C NMR(600 MHz, δ ppm): 25.02 (CH_3), 39.63 (CH_2), 166.04(C=O), 117.94-115.22 (CH Ar.),149.98 (CH-Imidazole), 136.94-123.72(CH-Benzimidazole), m/z: 264.99(M^{+})

2-(1-H-Benzimidazol-1-yl)-N-(p-chlorophenyl) acetamide (5c)

IR (KBr)γ_{max} (cm^{-}): 3267.52 (N-H str.**),** 3128.64 (=C-H str.), 1670.71 (C=O str.), 1537.32 (N-H bend) ,1491.02 (C-N str.), 831.36(Aromatic ring), 668.30 (C-Cl).

2-(1-H-Benzimidazol-1-yl)-N-(p-nitrophenyl) acetamide (5d)

IR (KBr)γ_{max} (cm^{-}): 3263.66 (N-H str.), 3068.85 (=C-H str.), 1687.77 (C=O str.), 1591.33 (N-H bend) ,1464.66 (C-N str.), 1591.30 and 1446.66 (NO_2 str.), 758-642(Aromatic ring);^{1}H NMR (600 MHz, δ ppm): 3.98 (s, CH_2), 7.91(s, CH-imidazole), 7.48 (NH amide),7.29 (d,=CH benzimidazole), 7.59(d,=CH benzimidazole), 6.95-6.93(d, CH Ar). ^{13}C NMR(600 MHz, δ ppm):39.52 (CH_2), 168.25 (C=O), 109.81-107.05 (CH Ar.),148.76 (CH-Imidazole), 129.96-120.00(CH- Benzimidazole), Anal. Cal. (Found) for $C_{15}H_{12}N_4O_3$:C 60.81 (61.68), H 4.08(3.63), N 19.91 (20.45), O 16.20 (16.92), m/z: 296.46(M^{+}).

2-(1-H-Benzimidazol-1-yl)-N-(o-nitrophenyl) acetamide (5e)

IR (KBr)γ_{max} (cm^{-}): 3213.77 (N-H str.), 3062.24 (=C-H str.), 1679.89 (C=O str.), 1587.34 (N-H bend) ,1458.85 (C-N str.),1619.04 and 1458.85 (NO_2 str.), 768-634(Aromatic ring).

2-(1-H-Benzimidazol-1-yl)-N-(p-fluorophenyl) acetamide (5f)

IR (KBr)γ_{max} (cm^{-}): 3271.38 (N-H str.), 3053.42 (=C-H str.), 1668.48 (C=O str.), 1543.10 (N-H bend) ,1475.59 (C-N str.), 785-540(Aromatic ring), 1062.52 (C- F)

2-(1-H-Benzimidazol-1-yl)-N-(p-methoxyphenyl) acetamide (5g)

IR (KBr)γ_{max} (cm^{-}): 3279.10 (N-H str.), 3107.43 (=C-H str.), 1670.41 (C=O str.), 1591.33 (N-H bend) ,1475.59 (C-N str.), 785-652(Aromatic ring), 1070.53(O-C str.)

2-(2-mercapto-1H-benzo[d]imidazole- 1-yl)-N-phenylacetamide (5h)

IR (KBr)γ_{max} (cm^{-}): 3211.7 (N-H str.), 2977.6 (=C-H str.), 2929.2(-SH str.), 1671.6 (C=O str.), 1594.0 (N-H bend) ,1251.3 (C-N str.), 798.6-698.0(Aromatic ring); ^{1}H NMR (600 MHz, δ ppm):4.36 (s, CH_2), 8.38(s, NH), 7.90(d,=CH), 7.87 (d,=CH), 7.74-7.05(m, CH_2 Ar), 12.4(s,SH); ^{13}C NMR(600 MHz, δ ppm): 39.63 (CH_2), 164.47(C=O), 168.11(C-SH), 119.85-109.54(CH Ar.),133.90-122.37(CH- Benzimidazole) ; m/z: 283(M^{+}), Anal. Cal. (Found) for $C_{15}H_{13}N_3OS$: C 63.58 (62.91), H 4.62(4.81), N 14.84 (14.93), O 5.65 (5.92), S 11.32 (10.65).

2-(2-mercapto-1H-benzo[d]imidazole- 1-yl)-N-(p-tolyl) acetamide (5i)

IR (KBr)γ_{max} (cm^{-}): 3335.17 (N-H str.), 3113.80(=C-H str.), 2985.92(-SH str.),1652.91 (C=O str.), 1514.15 (N-H bend), 1260.78 (C-N str.), 789.72-718.17 (Aromatic ring).

2-(2-mercapto-1H-benzo[d]imidazole- 1-yl)-N-(4-chlorophenyl) acetamide (5j)

IR (KBr)γ_{max} (cm^{-}): 3211.4 (N-H str.), 2976.3(=C-H str.), 2928.3(-SH str.),1673.2 (C=O str.), 1533.9(N-H bend), 1251.7 (C-N str.), 798.8-717.8 (Aromatic ring), 698.2 (C-Cl), ^{1}H NMR (600 MHz, δ ppm): 4.75 (s, CH_2), 7.25(s, NH), 7.87(d,=CH), 7.73 (d,=CH), 7..71-7.09(m, CH_2 Ar), 12.54(s, SH); ^{13}C NMR(600 MHz, δ ppm): 39.63 (CH_2), 164.47(C=O),168.07(C-SH), 113.38-109.54(CH Ar.), 122.36-119.70 (=CH Benzoimidazole), 134.46(C-Cl); m/z: 317(M^{+}), Anal. Cal. (Found) for $C_{15}H_{12}ClN_3OS$: C 56.69 (55.94), H 3.81(3.62), N 13.22 (12.53), O 5.03 (5.20) S 10.09(9.63)

2-(2-mercapto-1H-benzo[d]imidazole- 1-yl)-N-(4-nitrophenyl) acetamide (5k)

IR (KBr)γ_{max} (cm^{-}): 3258.94(N-H str.), 3093.39(=C-H str.), 2951.71(-SH str.),1666.08 (C=O str.), 1593.47 (N-H bend),1626.01 and 1405.52 (NO_2 str.), 1291.57 (C-N str.).

2-(2-mercapto-1H-benzo[d]imidazole- 1-yl)-N-(4-fluorophenyl) acetamide (5l)

IR (KBr)γ_{max} (cm^{-}): 3369.4 (N-H str.), 2918.7 (=C-H str.), 2850.2(-SH str.), 1675.7 (C=O str.), 1553.3 (N-H bend), 1269.3 (C-N stre), 793.9-705.6 (Aromatic ring), 1069.4 (C- F)

2.2. Molecular Docking Study:

2.2.a. Target selection:

The 3D structure of E. Coli DNA gyrase subunit B (5L3J) and tyrosyl t-RNA synthetase (1JIJ) was acquired from the RCSB Protein Data Bank (https://www.rcsb.org).

2.2.b. Target protein Preparation:

Pymol software [19] was used to invent the active site of the target protein and Discovery studio visualizer[20]was used find the active site amino acid that were used for creating the grid box. The proteins were prepared for docking and saved in proper format (PDBQT) after removal of the bonded ligand, water molecule and hetero atom.

2.2.c. Ligand preparation:

2D structures of derivatives were drawn using Chemdraw Ultra program V.12.0.2 [21] and then converted to the docking-compatible formats PDB and PDBQT using Open Babel (version 3.0.0).[22]

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2.2.d. Molecular docking protocol:

A ligand molecule library was screened against E. coli DNA gyrase subunit B (5L3J) and tyrosyl t-RNA synthetase using Autodock Vina (1JIJ). [23,24] For identifying the interaction of ligand molecules with targeted proteins, the searching grid for the active site was built according to the visualisation in Discovery studio. The grid box was centred at the binding site and was 60 X 60 X 60 $Å^3$. Then Kollman charges, Gasteiger-type polar hydrogen charges, and polar hydrogen were allocated along with internal degrees of freedom and torsions[25]. The results were evaluated by ranking the different complexes according to their predicted binding energy. A more in-depth study of the protein-ligand interaction was performed using the Discovery Studio Visualizer tool [26].

3. RESULTS AND DISCUSSION

3.1. Chemistry:

The intended product was produced by condensing benzimidazole/mercaptobenzimidale with chloro-N- substituted acetamide in the presence of potassium carbonate as a base catalyst in a microwave synthesiser.(Figure 1). Table 1 summarizes the physical properties of benzimidazole derivatives. All of the synthesised compounds were obtained in high purity and yield.

Table 1: Physical properties of synthesised N-substituted-2-substituted benzimidazole derivatives

Compound	R_1	R_2	mp (℃)	Yield (%)	Rf value
5a	H	H	224-228	65.35	0.59
5b	CH_3	H	218-220	59.62	0.68
5c	4-Cl	H	198-202	63.25	0.56
5d	4- NO_2	H	266-268	72.50	0.52
5e	2- NO_2	H	242-246	70.65	0.51
5f	4- F	H	248-252	62.35	0.57
5g	4-OCH_3	H	184-186	71.46	0.72
5h	H	SH	242-246	65.42	0.58
5i	CH_3	SH	248-252	61.30	0.60
5j	4-Cl	SH	262-264	64.20	0.59
5k	4- NO_2	SH	196-198	75.25	0.62
5l	4- F	SH	232-238	56.40	0.56

The structure of solid substances was validated using elemental analysis. The derivatives were characterised using MS, ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy.N-H stretching band for secondary amide was obtained at 3337- 3211 cm^{-1}while stretching of the C = O group of amides was observed at1688 to 1652 cm^{-1}in the FTIR spectrum.A distinct peak for the aromatic proton of the benzoimidazole ring was found higher δ value than the phenyl ring was noted with the secondary amide peak at δ, 8.14-7.35 in ^{1}H spectra. In the ^{13}C spectra amide carbon peak obtained at δ, 164-166 and benzimidazole carbon at δ, 125-136. These spectral results confirm the structure of the synthesised molecule.

3.2. Docking study:

Two targets were chosen for study: Staphylococcus aureus tyrosyl-tRNA synthetase (PDB: 1jij) and DNA gyrase subunit B (PDB: 5l3j).

The enzyme DNA gyrase is essential for DNA synthesis. DNA gyrase creates negative supercoils in the DNA next to the replication fork.[27,28]Tyrosyl-tRNA synthetase, on the other hand, mediates the covalent attachment of amino acids to their corresponding tRNA, resulting in charged tRNA, which is essential for protein synthesis.[3]As a result, these are a promising target enzyme for antibacterial drug development. [29,30]

The binding affinities of newly synthesized molecules and target proteins 1jij and 5l3j) were investigated using molecular docking. All of the synthesized derivatives and amino acid in the binding pocket displayed significant bonding interactions, according to the docking results. Table 2 shows the amino acid interaction binding affinity of the N-substituted-2-substituted benzimidazole derivative to the target protein.

N-substituted-2-substituted benzimidazole had a binding affinity of -7.3 to -8.8 kcal/mol against Staphylococcus aureus tyrosyl-tRNA synthetase, whereas a binding affinity of -7.1 to -8.8 kcal/mol against DNA gyrase subunit B, compared to reference ligand with binding affinity of -7.9 kcal/mol and -7.8 kcal/mol respectively.The benzimidazole derivatives interacts with amino acid in binding pocket through carbon hydrogen bonding, Pi-cation, Pi-anion, alkyl Pi-alkyl, van der waals, and traditional hydrogen bonding. Because of the amide in the structure, all of the derivatives exhibit a high affinity for t-RNA synthetase.

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5e has the lowest docking score of –8.8 kcal/mol against to t-RNA synthetase and DNA gyrase subunit B. The bond length analysis shows that the 5e has a shorter bonding length than the typical ligand, implying that it binds better. The electron-withdrawing Nitro-group could be the cause of the strong binding.The docking energy of 5d,5c, and 5k is the second lowest. Derivatives having electron withdrawing groups, such as chloro, fluro, and nitro, have a lower docking score, indicating substantial enzyme inhibition.

Fig. 2–9 show the 2D interaction of derivatives with the type of interaction and the 3D interaction of derivatives with the amino acid in the protein's binding pocket with the lowest docking score.

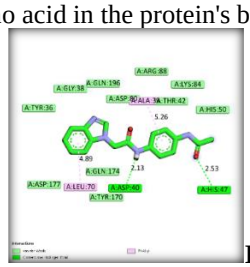
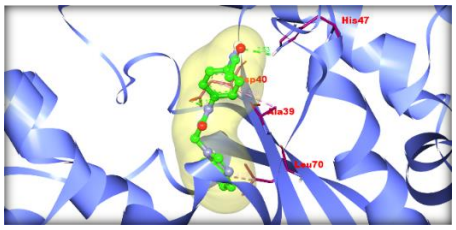
A.  B. 

Fig.2. A- 2D interaction of 5e with tyrosyl t- RNA synthetase (1JIJ), B-3D interaction of 5e with tyrosyl t- RNA synthetase (1JIJ)

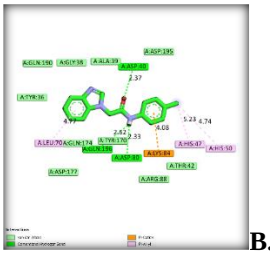
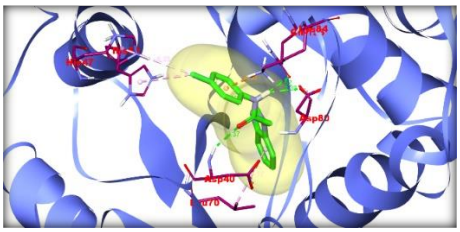
A.  B. 

Fig.3. A- 2D interaction of 5c with tyrosyl t- RNA synthetase (1JIJ), B-3D interaction of 5c with tyrosyl t- RNA synthetase (1JIJ)

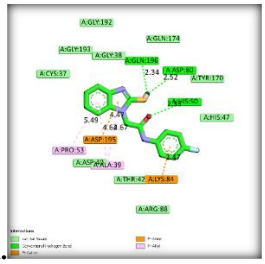
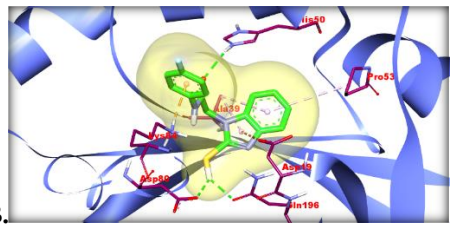
A.  B. 

Fig.4. A: 2D interaction of 5k with tyrosyl t- RNA synthetase (1JIJ) B: 3D interaction of 5k with tyrosyl t- RNA synthetase (1JIJ)

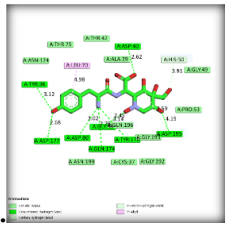
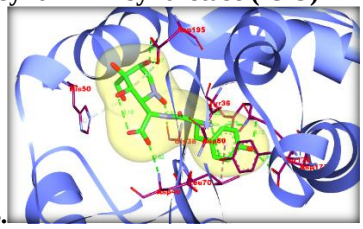
A.  B. 

Fig.5. A: 2D interaction of Ligand with tyrosyl t- RNA synthetase (1JIJ) B: 3D interaction of Ligand with tyrosyl t- RNA synthetase (1JIJ)

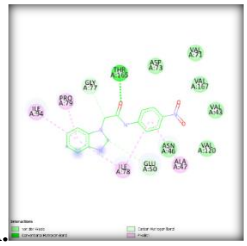
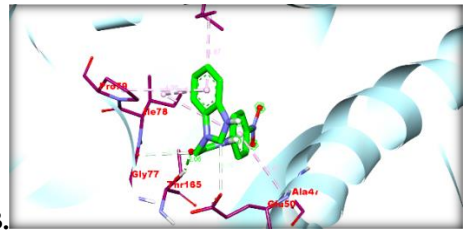
A.  B. 

Fig.6. A: 2D interaction of 5d with DNA gyrase subunit B (5l3j) B: 3D interaction of 5d with DNA gyrase subunit B (5l3j)

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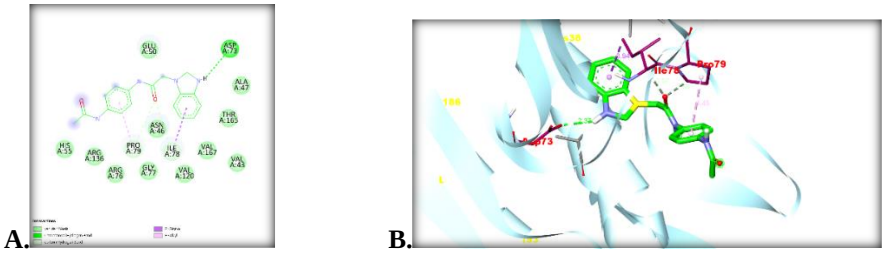

Fig.7. A: 2D interaction of 5e with DNA gyrase subunit B (5l3j)
B: 3D interaction of 5e with DNA gyrase subunit B (5l3j)

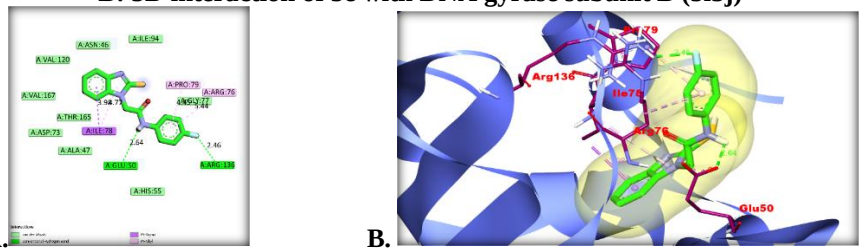

Fig.8. A: 2D interaction of MB5 with DNA gyrase subunit B (5l3j)
B: 3D interaction of MB5 with DNA gyrase subunit B (5l3j)

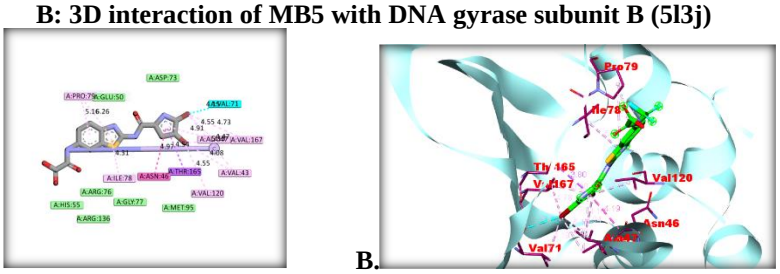

Fig.9. A: 2D interaction of Ligand with DNA gyrase subunit B (5l3j)
B: 3D interaction of Ligand with DNA gyrase subunit B (5l3j)

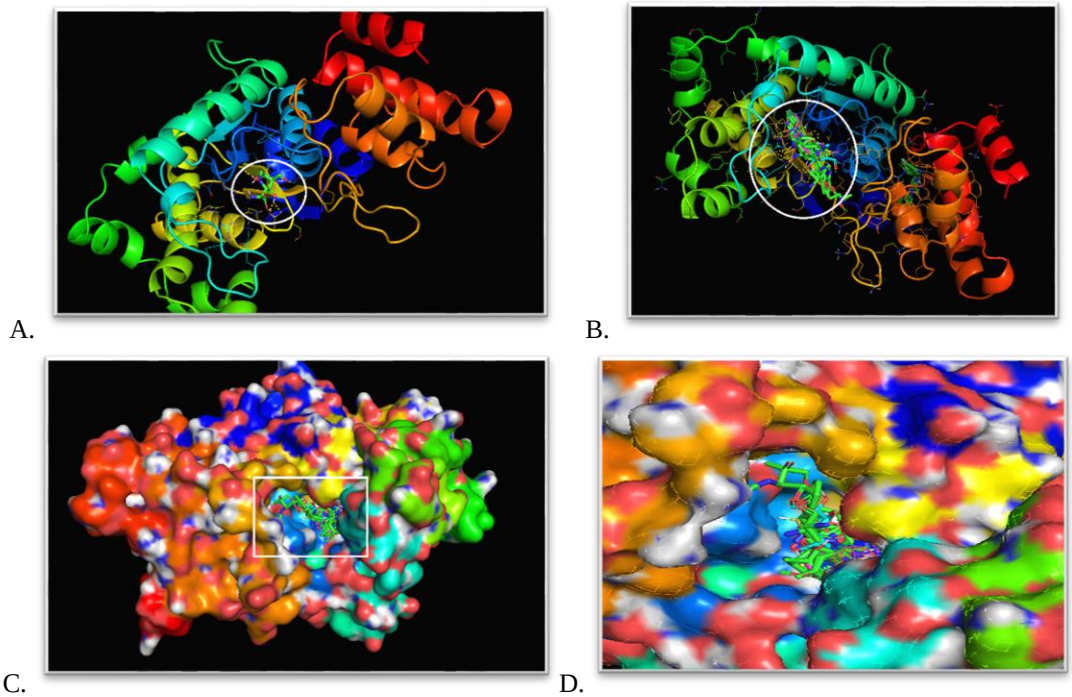

Fig.10. A: Interaction of Ligand in active site of Receptor
B: Interaction of All derivative in active site of Receptor
C: Surface display of receptor active site
D. Interaction of derivatives in surface display

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Table 1: Binding score and interaction of benzimidazole derivatives with proteins

Comp Code	Protein 1jij			Protein 5l3j		
	Binding affinity (kcal/ mol)	Type of interaction	Interacting Amino acid	Binding affinity (kcal/ mol)	Type of interaction	Interacting Amino acid
5a	-8.2	Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl,Van der Waals,	Tyr36, Gly38, Ala39, Asp40, Thr42, His50, Leu70, Asp80, Ser82, Lys84, Arg88, Tyr170, Gln174, Asp177, Gln190, Asp195, Gln196	-7.2	Conventional hydrogen bond, Pi-alkyl, Van der waals	Val43, Asp73, Glu50, Asp49, Asn46, Ala47, Ile78, Pro79, Ile94, Val120, Thr165, Val167,
5b	-8.3	Conventional Hydrogen bond, Carbon hydrogen Bond, Pi-Cation, Pi-Alkyl,Van der Waals,	Tyr36, Gly38, Ala39, Asp40, Thr42, His50, Leu70, Asp80, Thr75, Lys84, Arg88, Tyr170, Gln174, Asp177, Gln190, Asp195, Gln196	-7.3	Conventional hydrogen bond, Pi- anion, Pi-alkyl, Van der waals	Val43, Asn46, Ala47, Asp49, Asp73, Val120, Val167, Glu50, Ile78, Ile94, Thr165
5c	-8.4	Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl,Van der Waals,	Tyr36, Gly38, Ala39, Asp40, Thr42, His47, His50, Leu70, Asp80, Lys84, Arg88, Tyr170, Gln174, Asp177, Gln190, Asp195, Gln196	-7.3	Conventional hydrogen bond, Pi- sigma, Alkyl, Pi-alkyl, Van der waals	Val43, Asn46, Ala47, Asp73, Arg76, Gly77, Ile94, Arg136, Thr165, Val167, Glu50, Ile78, Pro79, Val120
5d	-8.7	Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl,Van der Waals,	Gly38, Ala39, Asp40, His47, Gly49, His50, Pro53,Asp80, Lys84, Arg88, Tyr170, Gln174, Gly193, Asp195, Gln196, Leu223	-7.5	Conventional hydrogen bond, Pi-alkyl, Van der waals	Ala47, Glu50, Gly77, Ile78, Pro79, Ile94, Thr165, Val43, Asn46, Val71, Asp73, Val120, Val167
5e	-8.8	Conventional Hydrogen bond, Pi-Cation, Pi-Alkyl, Van der Waals,	Tyr36, Gly38, Ala39, Asp40, Thr42, His50, Leu70, Thr75, Asp80, Ser82, Lys84, Arg88, Asn124, Tyr170, Gln174, Asp177, Gln190, Asp195, Gln196	-8.8	Conventional hydrogen bond, Carbon Hydrogen Bond, Pi-sigma, Pi-alkyl, Van der waals	Val43, Ala47, Asn46, Glu50, His55, Arg76, Gly77, Arg136, Val120, Thr165, Val167, Asp73, Ile78, Pro79
5f	-8.4	Conventional Hydrogen bond, Halogren(Fluorine) ,Pi- Anion, Pi-Donor Hydrogen Bond, Pi-Alkyl, Van der Waals,	Tyr36, Gly38, Ala39, Asp40, His50, Leu70, Asp80, Thr75, Asn124, Tyr170, Gln174, Asp177, Gly193, Asp195, Gln196, Asn199	-7.1	Conventional hydrogen bond, Pi-anion, Pi-sigma, Pi-alkyl, Van der waals	Val43, Ala47, Asn46, Glu50, Ala53, His55, Arg76, Gly77, Pro79, Ile94, Arg136, Val120, Thr165, Val167.
5g	-8.1	Conventional Hydrogen bond, Carbon hydrogen Bond, Pi-Cation, Pi-Alkyl, Van der Waals,	Tyr36, Gly38, Ala39, Asp40, Thr42, His50, Leu70, Thr75, Asp80, Lys84, Arg88, Asn124, Tyr170, Gln174, Asp177, Gln190, Asp195, Gln196	-7.1	Conventional hydrogen bond, Carbon-hydrogen bond, Pi-sigma, Alkyl, Pi-alkyl, Van der waals	Ala47, Asn46, Glu50, His55, Arg76, Asp73, Gly77, Ile78, Pro79, Ile94, Val120, Arg136, Thr165, Val167

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5h	-7.3	Van der Waals, Carbon hydrogen Bond, Pi-Donar hydrogen bond, Pi-Alkyl	Tyr36, Cys37, Gly38, Ala39, Asp40, Thr42, Phe54, Pro53, His50, Asp80, Thr75, Lys84, Arg88,Tyr170, Gln174, Asp177, Gln190, Val 191, Gly192, Gly193, Asp195,Gln196, Ile200	-6.6	van der waals, Amide-pi-stackedPi-sigma Pi-alkyl,	Val43, Ala47,Asn46, Glu50, Ala53, Asp73, Gly77, Ile78, Pro79, Ile 94, Arg136, Val120, Thr165, Val167
5i	-7.4	Van der Waals, Pi-Cation, Pi-anion, Pi- sigma, Pi-Pi -T-Shaped, Amide- Pi-Stacked, Alkyl	Val 4, Glu7, Trp11, Asp8, Arg12, His6., Phe273, Agr59, Glu62, Leu274, Gly275, Lys276.	-8.1	van der waals, Carbon Hydrogen Bond, Alkyl, Pi-alkyl,	Val43, Ala47,Asn46, Asp49, Glu50, Ala53, Asp73, Ile78, Pro79, Ile 94, Met95, Val120, Thr165, Val167
5j	-7.4	Van der Waals, Pi-Cation, Pi-anion, Pi- sigma, Pi-Pi -T-Shaped, Amide- Pi-Stacked, Alkyl	Tyr36, Gly38, Ala39, Asp40, Thr42, Pro53, His50, Asp80, Leu70, Lys84, Tyr170, Gln174, Asp177, Gln190, Gly192,Gly193, Asp195, Gln196,	-7.5	van der waals, Conventional Hydrogen Bond, Pi-sigma, Alkyl, Pi-alkyl,	Ala47,Asn46, Glu50, His55, Asp73,Arg76, Gly77, Ile78, Pro79, Ile 94, Arg136, Val120, Thr165, Val167
5k	-8.3	Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-anion, Pi-Pi -T- Shaped, Alkyl, Pi- Alkyl	Gly38, Ala39, Asp40, His47, Gly49, Pro53, His50, Asp80, Lys84, Tyr170, Gln174, Gly192,Gly193, Asp195, Gln196,	-7.1	van der waals, Conventional Hydrogen Bond, Pi-sigma, Amide-pi-stacked, Pi-alkyl,	Val43, Ala47,Asn46,Asp49, Glu50, Ala53, Asp73,Gly75, Arg76, Gly77, Ile78, Ile 94, Val120, Thr165, Val167
5l	-8.1	Van der Waals, Conventional Hydrogen Bond,Pi-cation,Pi-anion, Pi- Alkyl	Cys37, Gly38, Ala39, Asp40, Thr42, His47, Gly49, Pro53, His50, Asp80, Lys84, Arg88, Tyr170, Gln174, Gly192,Gly193, Asp195, Gln196,	-7.8	van der waals, Conventional Hydrogen Bond, Pi-sigma, Pi-alkyl,	Ala47,Asn46,Glu50, His55, Asp73,Gly75, Arg76, Gly77, Ile78, Ile 94, Val120, Arg136, Thr165, Val167
Ligand	-7.9	Van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Donar Hydrogen Bond, Pi- Alkyl	Tyr36, Cys37, Ala39, Asp40, Thr42, Pro53, Gly49, His50, Gly58 Asp80, Leu70, Thr75, Lys84, Asn124, Tyr170, Gln174, Asp177, Gln190, Gly192,Gly193, Asp195, Gln196,	-7.8	Conventional hydroge Bond, Pi- sigma Pi-alkyl, van der waals	Ala47, Asn46, Asp49, Glu50, His55, Asp73, Gly77, Arg76, Ile78, Ile 94, Val120, Arg136, Thr165, Val167

CONCLUSION

Microwave aided synthesis was used to produce new N-substituted-2-substituted benzimidazole derivatives. Compounds 5c, 5d, 5e, and 5k exhibit considerable enzyme inhibitory activity, implying that they may have significant antibacterial potential. Further insights of SAR study can alter the activity of derivatives and can lead to the development of alternative antibacterial agent.

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