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Synthesis,Antimicrobialand Molecular docking studies of novel Benzimidazole derivatives

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Abstract:*2-(2-Chlorophenyl)-1H-benzo[d]imidazolederivatives were prepared by condensing2-(2-Chlorophenyl)-1H-benzo[d]imidazole with different heterocycles.The synthesized derivatives were characterized by IR,[1]H NMR,[13]C NMR,massand elemental analysis. The compounds were screened for in vitro and microbial activity against panel of selected gram positive and gram negative bacterial strains using Ciprofloxacin as standard and molecular docking done with a Biotin carboxylase from E. Coli PDB CODE(3JZI).*

Keywords:*2-(2-Chlorophenyl)-1H-benzo[d]imidazole; Antimicrobial agents;ciprofloxacin:Molecular docking:*

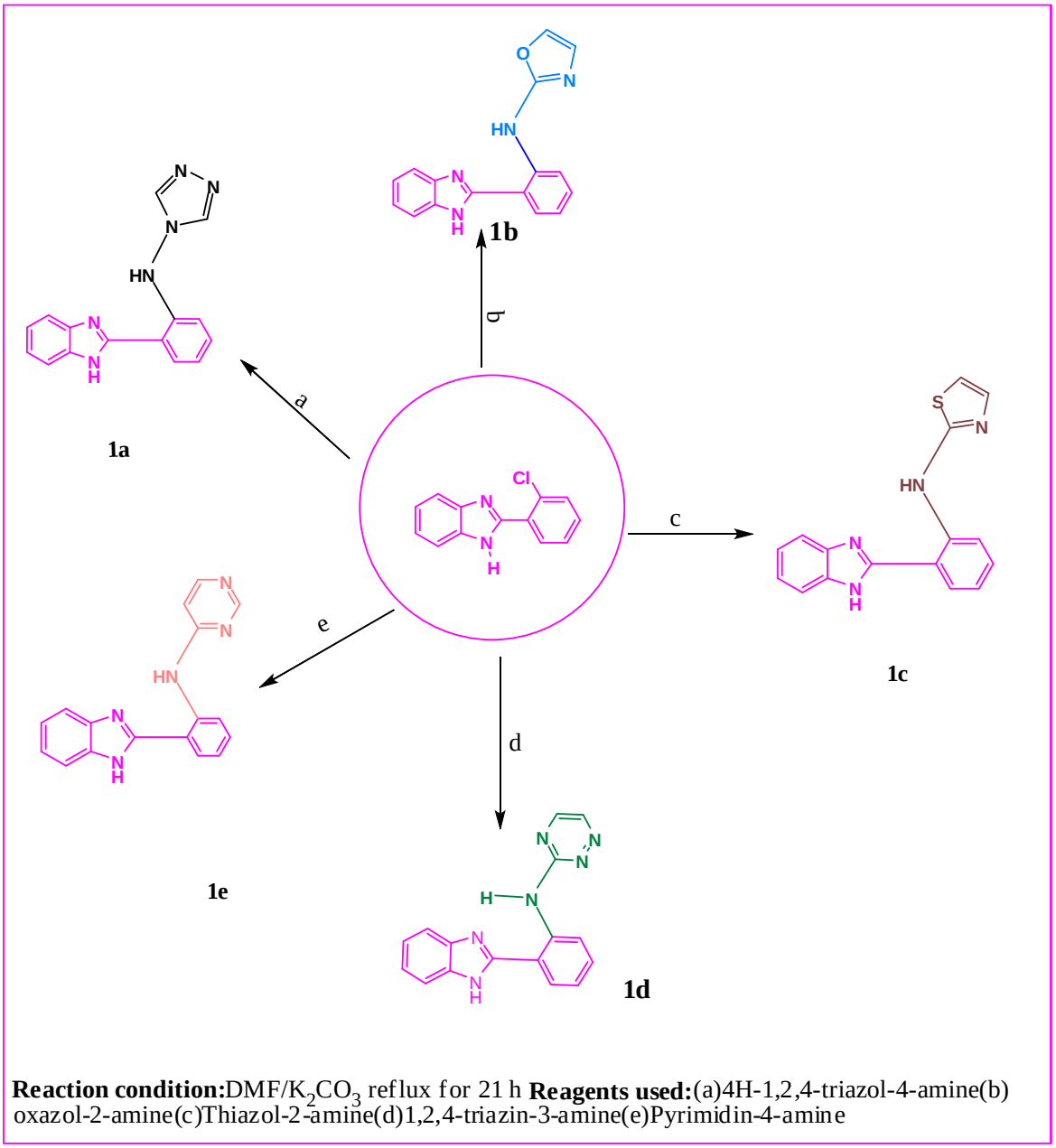
I. Introduction

Benzimidazole derivatives have found applications in diverse therapeutic areas includingantitumor [1,2], antiulcer [3], anti- inflammatory [4], antiviral [5,6], antihelmintics [7,8], antibacterial [9,10] and antifungal[11,12] properties. Optimization of substituent around the benzimidazole nucleus has resulted in many drugs like albendazole, mebendazole, thiabendazole as antihelmintics; omeprazole, lansoprazole, pantoprazole as proton pump inhibitors and many lead compounds in a wide range of other therapeutic areas [13].The widespread interest in benzimidazole containing structures has prompted extensive studies for their synthesis. Recently the interest in benzimidazole chemistry has been revived by the discovery that the 5,6,-dimethyl benzimidazole moiety is part of the chemical structure of vitamin B12[14].

Though all seven position in the benzimidazole nucleus can be substituted with variety of chemical entities, but most of the biologically active benzimidazole based compounds bear functional groups at 1,2 and/or 5(or 6).Based on the above observations, we have planned to synthesize a novel series of benzimidazole derivatives derived from**:** 2-(2-Chlorophenyl)-1H-benzo[d]imidazole followed by their In-Vitro antibacterial activities.As an inception, various2-(2-Chlorophenyl)-1H-benzo[d]imidazole derivatives were synthesized and characterized by FT-IR, NMR (^{1}H,^{13}C), mass, CHN analysis and the antimicrobial activities were screened. We used newly synthesized active inhibitors to exposé the binding cavity of Biotincarboxylase from E.Coliby using Schrodinger suite program.

II. Results and Discussion

The synthesis of various benzimidazole derivatives were carried out as depicted in scheme-1. A broad band at 3413-3435 cm^{-1} is ascribed to N-H stretching frequency of the imidazole moiety. A strong band at 3057 cm^{-1} is due to the Aromatic(C-H) stretching frequencies. Hence the IR data illustratethe formation of the 2-(2-Chlorophenyl)-1H-benzo[d]imidazole derivatives.A sharp singlet at 12-13ppm is assignable to –NH proton of benzimidazole and also peak at 4.7ppm show the presence of CH_2. . On focusing the ^{13}CNMR spectral assignments, the signals at 164ppm is due to C-N of heterocyclic compounds (1b-1e).



Reaction condition:DMF/K_2CO_3 reflux for 21 h **Reagents used:**(a)4H-1,2,4-triazol-4-amine(b) oxazol-2-amine(c)Thiazol-2-amine(d)1,2,4-triazin-3-amine(e)Pyrimidin-4-amine

scheme-1

2.1. Antimicrobial studies

The antimicrobial activities of the synthesized compounds against different pathogens were determined by Agar Well diffusion method. Using sterile inoculation loop, 20 pure colonies of the test organism are transferred to 5ml of sterile nutrient broth and incubated at 37^{o}C overnight for 18hrs. The modified agar well diffusion method of Perez et al. [15] was employed. Each selective medium was inoculated with the microorganism suspended in sterile water. Once the agar was solidified, it was punched with a six millimeters diameter wells and filled with 50µg/mlof the sample and blanks (ethanol and antibiotic). The test was carried out by triplicate. The plates were incubated at 35 ± 2°C for 24 h. The antimicrobial activity was calculated by applying the expression in µg/ml.. The antibacterial activities in terms of minimum inhibitory concentration (MIC) of compounds (1a-1e) are depicted in Table-1.

Table – 1: Antibacterial activities of compounds 1a –1e, for bacterial strains in MIC (µg/ml)

Bacterial strains (MIC)	Compounds					
	Ciprofloxacin	1a	1b	1c	1d	1e
K. pneumoniae	15	15	50	50	20	12
S. Typhic	10	15	50	50	20	12
S. Aureus	5	15	50	-	25	10
B.Subtilis	5	10	50	45	-	10
P. auruginosa	5	15	50	45	20	10
E.coli	5	8	35	50	15	4

And their MIC's were compared with ciprofloxacin standard drug. MIC values in Table-1 revealed that compound 1e exhibited excellent activity against E.Coli at MIC 4µg/ml than standard drug ciprofloxacin.

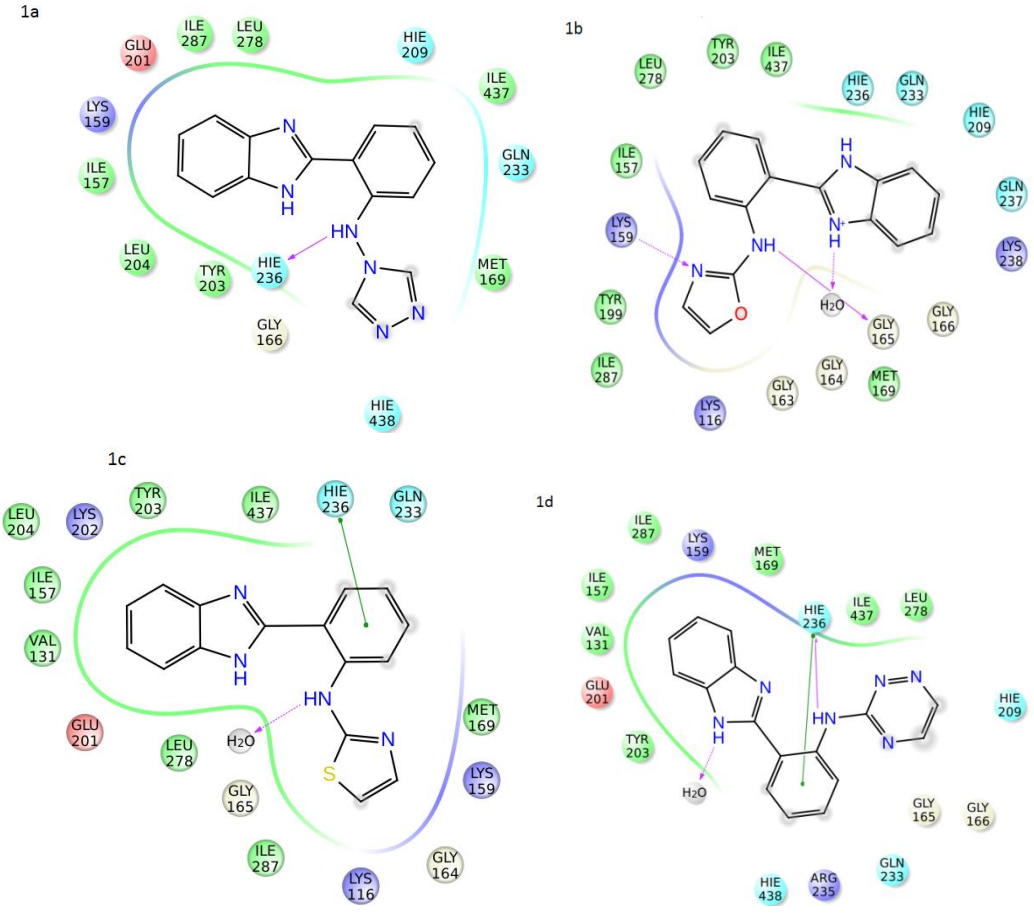
2.1.1. Molecular docking studies.

Crystal structure of BIOTIN CARBOXYLASE from E.Coli complexed with benzimidazole series with resolution of 2.31A^{0}and corresponding entry code 3JZI was recovered from the PDB data base(www.pdb.org). The antimicrobial potency of all newly synthesized compounds(1a-1e) were subjected to explore the binding pattern against Biotin carboxylase from E.Coli by using Schrodinger suite.Docking of all newly synthesized inhitors showed hydrogen bond interactions with HIE 236,GLY 165,HIE209,TYR203 mentioned in Figure 1.Docking results were summarized in Table-2.

Table2.Explains about protein 3JZI and the hydrogen bond interaction between ligands (1a-1e)

PDB code	Compounds	Glide score	H-bond energy	Interacting Residues
3JZI	1a	-6.4	-2.33	HIE 236
3JZI	1b	-2.2	-0.72	GLY165,LYS159
3JZI	1c	-2.7	-0.81	HIE236
3JZI	1d	-5.7	-1.51	HIE236
3JZI	1e	-7.2	-2.55	HIE209,HIE 236,TYR203

Figure 1. Ligand –Protein 2D interaction



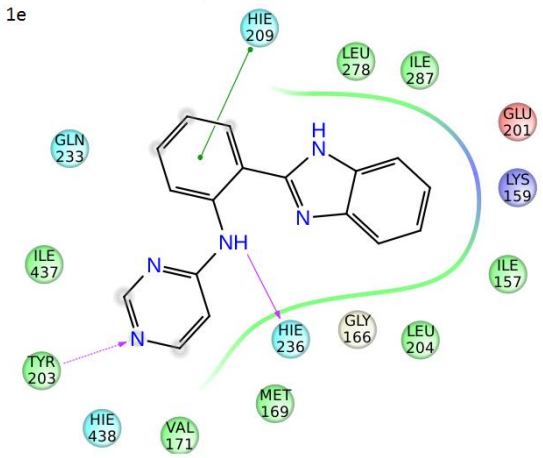
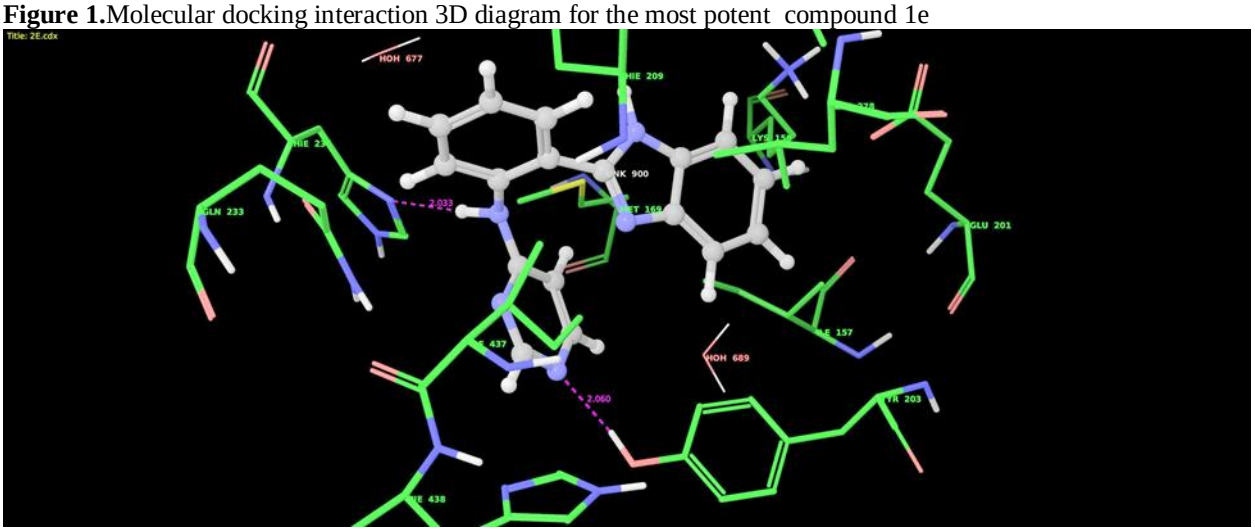


Figure 1. Molecular docking interaction 3D diagram for the most potent compound 1e



III. Experimental Section

Melting point (mps) were determined by open capillary method and are uncorrected. IR spectra were recorded by Jasco FTS 3000 HX(KBr pellets). 1HNMR spectra were recorded on Bruker ADVANCE III NMR spectrometer (500 MHZ) using TMS as internal standard (Chemical shifts in ppm). ^{13}CNMR spectra were recorded on the same instrument at 125.76 MHZ and are referenced using the central line of the solvent signal (DMSO –d6 septet at S =39.5 ppm). Mass spectra were recorded with JOEL ac MATE II instrument. Elemental anaylsis (C,H and N) were performed with a Perkin Elmer 2400 series II CHN Analyzer.**General procedure for synthesis of compounds (1a-1e)[14]:**

N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)-4H-1,2,4-triazol-4-amine(1a);2-(2-Chlorophenyl)-1H-benzo[d] imidazole (2.2867g, 0.01mol) and K_2CO_3 (0.02mol,2.76g) were stirred at room temperaturein dimethyl formamide (25 ml) for half an hour and pinch of KI was added.After that 4H-1,2,4-triazole-4-amine (0.840g,0.01mol) was added to reaction mixture which was refluxed for 21 hours until TLC showed completion of of reaction.The reaction mixture was poured into water (20ml) and the mixture was extracted with ethylacetate.The organic extracts was washed with water,dried over anhydrous sodium sulphate and concentrated to obtain crude product. The residue was crystallised from diethyl ether to give pure compound. at room temperature. Physical data of compounds(1a-1e) are presented in **Table-3.**Begie yellow solid, Yield (35%); mp 350^0C (dec); IR (KBr) 3339(NH Str)**,** 3057 (-CH Str), 1613(aromatic,C=C str) ,1184(C-N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6) δ: 12.272(s,1H),,8.219 (s,2H), 7.56-7.23(m,6H),7.09 (s,1H) 6.94-6.79(m,2H),^{13} CNMR (125.76 MHz, DMSO-d6) δ:154.29, 146.9,144.2,128.6,125.2,123.1,119.8, 116.5, 115.8,115.6,107.64;Mass(m/z):276.11

N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)oxazol-2-amine(1b);2-(2-Chlorophenyl)-1H-benzo[d] imidazole (2.2867g, 0.01mol) and K_2CO_3 (0.02mol,2.76g) were stirred at room temperature in dimethyl formamide (25 ml) for half an hour and pinch of KI was added. After that oxazol-2-amine (0.840g,0.01mol) was added to reaction mixture which was refluxed for 36 hours until TLC showed completion of reaction. The reaction mixture was poured into water (20ml) and the mixture was extracted with ethylacetate. The organic extracts was washed with water, dried over anhydrous sodium sulphate and concentrated to obtain crude

product. The residue was crystallized from diethyl ether to give pure compound. at room temperature. yellow solid, Yield (45%); mp 432^{0}C (dec); IR (KBr) 3358 (N-H Str)**,** 3013 (-CH Str), 1608 (aromatic,C=C str) ,1180 (C-N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6) δ: 12.23(s,1H),10.6 (s,1H),7.6(d,1H),7.56-7.23(m,5H),7.169(d,1H),7.160(m,1H)6.94-6.76 (m,2H),^{13} CNMR (125.76 MHz, DMSO-d6) δ:164.8,154.2,146.9,144.2,128.6,125.2,123.0,119.8, 116.5, 115.8,115.6,107.64;Mass(m/z):276.29

N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)thiazol-2-amine(1c):2-(2-Chlorophenyl)-1H-benzo[d]imidazole (2.2867g, 0.01mol) and K2CO3 (0.02mol,2.76g) were stirred at room temperature in dimethyl formamide (25 ml) for half an hour and pinch of KI was added. After that thiazole-2-amine (1.001g, 0.01mol) was added to reaction mixture which was refluxed for 35 hours until TLC showed completion of reaction. The reaction mixture was poured into water (20ml) and the mixture was extracted with ethyl acetate. The organic extracts was washed with water, dried over anhydrous sodium sulphate and concentrated to obtain crude product. The residue was crystallized from diethyl ether to give pure compound. at room temperature. yellow solid, Yield (50%); mp498^{0}C dec); IR (KBr) 3334 (N-H Str), 3050(-CHStr),1608(aromatic,C=Cstr),1186(C-N)cm-1;1HNMR(500MHz,DMSO-d6)δ: 12.23(s,1H),10.5(s,1H), ,7.7(d,1H),7.56-7.09(m,6H),)6.94-6.76 (m,2H),6.72(dm1H);13CNMR(125.76MHz,DMSO-d6)δ: 160.1,153.4,,148.9,142.4,137.8,129.8,121,119,115..5,115.3,113.6,108:Mass(m/z):292.36.**N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)-1,2,4-triazin-3-amine(1d):**2-(2-Chlorophenyl)-1H-benzo[d] imidazole (2.2867g, 0.01mol) and K_2CO_3 (0.02mol,2.76g) were stirred at room temperature in dimethyl formamide (25 ml) for half an hour and pinch of KI was added. After that 1,2,4-triazin-3 – amine (0.960g,0.01mol) was added to reaction mixture which was refluxed for 45 hours until TLC showed completion of reaction. The reaction mixture was poured into water (20ml) and the mixture was extracted with ethyl acetate. The organic extracts was washed with water, dried over anhydrous sodium sulphate and concentrated to obtain crude product. The residue was crystallized from diethyl ether to give pure compound. at room temperature. yellow solid, Yield (68%); mp 555^{0}C (dec); IR (KBr) 3413 (-NH Str), 3041 (-CH Str), 1609(aromatic ,C=C str) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6) δ: 12.8 (s, 1H) ,9.7 (s,1H),8.2 (d,2H),7.56-7.09 (m,6H),6.94-6.79 (m,2H);^{13} CNMR (125.76 MHz, DMSO-d6)δ:160.41, 153.4,149.89,146.6,141.45,138.53, 129.8,125.4,122.5,121.0,119.0,115.5,115.3,113.6,108.0;Mass(m/z):288.11

N-(2-(1H-benzo[d]imidazol-2-yl)phenyl)pyrimidin-4-amine(1e):2-(2-Chlorophenyl)-1H-benzo[d] imidazole (2.2867g, 0.01mol) and K_2CO_3 (0.02mol,2.76g) were stirred at room temperature in dimethyl formamide (25 ml) for half an hour and pinch of KI was added.After that pyrimidin-4-amine(0.950g,0.01mol) was added to reaction mixture which was refluxed for 45 hours until TLC showed completion of reaction. The reaction mixture was poured into water (20ml) and the mixture was extracted with ethyl acetate. The organic extracts was washed with water, dried over anhydrous sodium sulphate and concentrated to obtain crude product. The residue was crystallized from diethyl ether to give pure compound. at room temperature. yellow solid, Yield (68%); mp 495^{0}C (dec); IR (KBr) 3323 (-NH Str), 3049 (-CH Str), 1608(aromatic ,C=C str) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6) δ: 12.35 (s, 1H)9.54 (s,1H), 8.82 (s,1H), 8.50(d,2H), 8.26(d,2H), 7.56-7.04(m,6H) 6.94-6.76(m,2H);^{13} CNMR (125.76 MHz, DMSO-d6)δ:168.7, 159.6, 158.6,154.3, 148.9,146.6, 142.4,137.8,129.8, 125.4,122.5,121.0, 119.0, 115.5,113.6,108.0, 107.1:Mass (m/z): 287.12

IV. Conclusions

Fivenew 2-Chloromethyl-1H-benzimidazole derivatives weresynthesized in reasonably good yields. They were characterized by IR, ^{1}H,^{13}C NMR(1D,2DNMR), mass and elemental analysis. All the newly synthesized compounds were tested for antimicrobial activity by agar well diffusion method. Among the screened samplescompound 1a exhibited as most active against E.Coli compared to other synthesized compounds.

Conflicts of Interest

"The authors declare no conflict of interest".

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