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Synthesis, Characterisation and Biological Evaluation of Substituted 4-((1H-Benzo[d]Imidazol-2-YL) Methoxy) Coumarin Derivatives as Antimicrobial Agents

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ABSTRACT

A series of coumarin-benzimidazole derivatives i.e. 4-((1*H*-Benzo[d]imidazol-2-yl)methoxy)coumarin derivatives (7a-j) was synthesized by reacting appropriate starting materials and evaluated for its in vitro antimicrobial activity. The newly synthesized compounds have been characterized on the basis of elemental analyses, spectroscopic techniques (FT-IR). Antimicrobial studies of these compounds were performed against the both the Gram positive, MRSA (*Staphylococcus aureus, Bacillus subtilis*) as well as Gram negative (*Escherichia coli*) bacteria. The activity was investigated by using both Agar well diffusion as well as MIC assay. All the compounds were show significant bactericidal activity against all the pathogenic strains in comparison to Ciprofloxacin, a broad spectrum antibiotic against Gram positive and Gram negative bacteria. Most of the synthesized derivatives appeared as excellent antimicrobial agents as compared to standard drug Ciprofloxacin. Compound 7b was found to be the most active antibacterial agent against Gram positive as well as Gram negative bacteria.

INTRODUCTION

Benzimidazole rings are the most important heterocyclic nitrogen-containing compounds, which are widely utilized by the pharmaceutical industry for drug discovery [1]. Due to their special structural features and electron-rich environment, Benzimidazole containing drugs bind to a variety of therapeutic targets [2], thereby exhibiting a broad spectrum of biological activities. Compounds containing benzimidazole have been widely used in medicinal chemistry and drug research development. Benzimidazole is a valuable compound for the synthesis of a wide range of biologically active compounds such as anticancer, antihelmintic, antimicrobial, antidiabetic, antiviral, antipsychotic, antioxidant, analgesic and anti-inflammatory, anticonvulsant, antifungal, antitubercular, antiallergic, antioxidant, antimycobacterial, antiprotozoal, antiurease and lipase inhibition [3-14]. Numerous benzimidazole based drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potential [15].Benzimidazole-based chromophores

have received increasing attention due to their different linear and non-linear optical properties and ability of benzimidazole derivatives to form stable complexes with metal ions [16].The optimization of benzimidazole derivatives based on their structures has resulted in various potent drugs that are now being currently practiced in the market, like albendazole, omeprazole, mebendazole etc. [17].

Benzimidazole derivatives play important role in medical field with different Pharmacological activities such as antimicrobial, antiviral, antioxidents, antidiabetic and anticancer activity [18]. Benzimidazoles are structural isosteres to purines that are essential substrates for the biosynthesis of nucleic acids and proteins inside the bacterial

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cell wall. The purine-like structure enables benzimidazole derivatives to obstruct the biosynthesis of nucleic acids and proteins by competing with the purines, eventually leading to the death of the bacterial cell [19]. Rendering to literature survey that, the synthesis and characterisation of a series of new aminoquinoline-benzimidazole hybrids and their ferrocenyl analogues in vitro antiplasmodial activity against sensitive and resistant strains of *P. falciparum*, and explored their possible mechanism of action with respect to the haemoglobin degradation pathway [20].

Coumarin (2H-1-benzopyran-2-one; 2H-chromen-2-one) derivatives are a large class of important naturally occurring and synthetic oxygen containing that found widely in nature, and they shows the broad spectrum of activities including anticancer, antioxidant, antiinflammatory and antiviral [21]. The photophysical properties of the coumarin derivatives are strongly related to the electron-donating or electron- withdrawing capability of the substituents attached to their core and the conjugation degree of molecules. The longer p- conjugation dye molecules generally achieve a longer absorption maximum and extend the absorption region [22]. The explored antibiotics like Novobiocin, Coumaromycin and Chartesium are coumarin derivatives [23]. Introduction of fluoro and sulfonamide groups into coumarin side chain may for an improvement of biological activity because incorporation of fluorine to various heterocycles is known to influence the biological activity [24]

Materials and Methods

The synthesis was carried out using chemicals of LR grade and obtained from Spectrochem, Loba Chem. All the solvents used for the reaction were of LR grade and purified before use in different reactions. Thin layer chromatography was carried on pre coated (Merck 60F254) for monitoring the reaction. The solvent system used for developing the chromatogram was Chloroform: Methanol in variable ratios. UV and iodine chambers were used for visualization of TLC spots.

Chemicals Required

Chloroacetic acid, o-Phenylenediamine, 4-Chloro-o-phenylenediamine, 4-Nitro-o-phenylenediamine, 4-Methyl-o- phenylene diamine, Hydrochloric acid, Ammonium Hydroxide solution, Methanol, Phenol,4-Bromophenol, 4-Chloro-2- nitrophenol, p-Nitrophenol, 4-Amino-2-chlorophenol, 4- Aminophenol, Malonic acid, Phosphorus oxychloride, Anhydrous Zinc Chloride, Sodium Carbonate solution, Glacial Acetic acid, Dimethylformamide (DMF), Potassium Carbonate, Sodium Bicarbonate (Sodium Hydrogen Carbonate), Ethanol.

Equipment used

The identification and characterization of the compound were carried out determining the melting point on a melting point apparatus by capillary method and were uncorrected. All the IR spectra of the synthesized compounds were recorded on Bruker alpha-E FTIR-ATR.

1HNMR spectra were recorded on Bruker Avance II (400MHz) spectrometer using DMSO as solvent at SAIF, Punjab University; Chandigarh. TMS was taken as standard and chemical shift data were reported in parts per million (ppm) where s, d, t and m are designated as singlet, doublet, triplet and multiplet respectively. TLC development was conducted on 0.25 mm silica gel plates (Merck silica gel 60 F254 in aluminium foil).

Methods and techniques

The coumarin-benzimidazole derivative (compound 7a-j) was prepared in three steps as presented in Scheme 1 and as described below.

Synthesis

General procedure for the synthesis of 2-(chloromethyl)-1H-benzo[d]imidazole derivatives (3a-d)

A mixture of o-phenylenediamine derivatives (1a-d) (0.1mol) and chloroacetic acid (0.1mol) was refluxed for 3hr in 4N hydrochloric acid (50 ml) on water bath. Reaction mixture was cooled and basified with ammonium hydroxide solution. The precipitates thus obtained were dried and recrystallized from methanol, to give 2-(chloromethyl)-1*H*-benzo[d]imidazole derivatives (3a-b) [25].

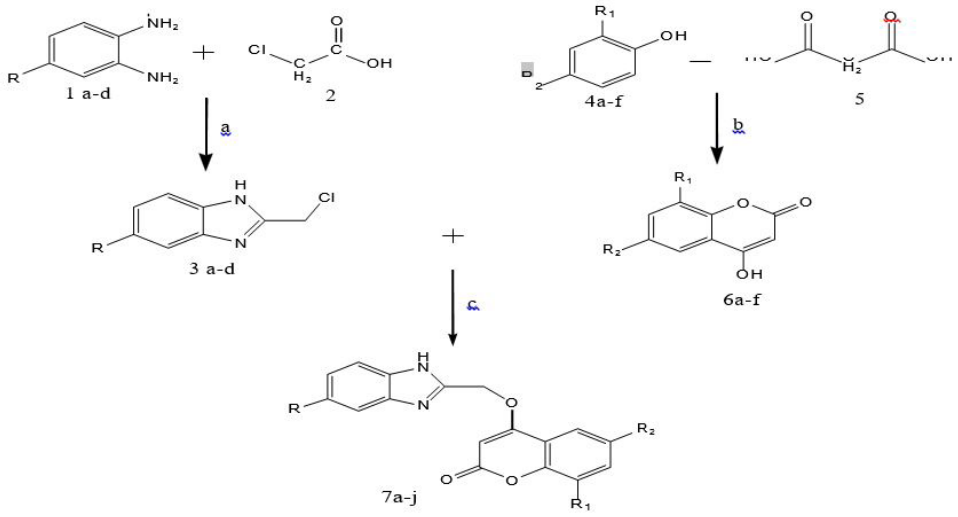
General procedure for synthesis of4-hydroxy coumarin derivatives (6a-f)

Add Phenol derivatives (4a-f) (0.1mol) and Malonic acid (0.1mol) to a mixture of Phosphorus oxychloride (40 ml), Anhydrous Zinc Chloride (30 gm) which was preheated to 60- 70 °C. The reaction mixture was then heated on water bath at 70 °C for 20-24 hr. It was then cooled after completion of reaction which was monitor by TLC and poured in ice cold water. The precipitates were formed, which were filtered and washed with water.

The crude compound was then treated with 10% Sodium Carbonate solution and filtered. The filtrate was slowly acidified with 20% Hydrochloric acid. The product was then filtered and washed with water and dried. The dried product was then recrystallized from Glacial acetic acid [26].

General procedure for synthesis of coumarin-Benzimidazole derivatives (7a-j)

In a round bottom flask containing benzimidazole derivatives (3a-d) (0.01 mol) and 4-Hydroxycoumarin



Scheme 1: 4-((1*H*-Benzo[d]imidazol-2-yl)methoxy)coumarin derivatives

Reagents and Reaction Condition: (a) 4N HCl, reflux for 3 hr.; (b) Anhydrous $ZnCl_2$, $POCl_3$, 65-70 ºC, reflux for 20 hr.; (c) K_2CO_3, DMF, reflux for 12-13 hr.

Compounds	*R*	*R1*	*R2*
7a	H	H	H
7b	Cl	H	H
7c	NO_2	H	H
7d	CH_3	H	H
7e	H	H	NO_2
7f	H	H	Br
7g	H	NO_2	Cl
7h	NO_2	Cl	NH_2
7i	NO_2	H	NH_2
7j	NO_2	H	NO_2

derivatives (6a-f) (0.01 mol), DMF and K_2CO_3 were added and reaction mixture was refluxed for 12-13 hrs The completion of the reaction was monitored by TLC on silica gel using chloroform: methanol (9:1). After the completion of the reaction, mixture was poured on crushed ice, and then solids are separated out. The solids were filtered, washed with saturated solution of $NaHCO_3$ and then recrystallized from hot ethanol and dried.

In vitro antimicrobial evaluation

All the synthesized compounds were subjected to antibacterial activity against Gram negative *E. coli* (MTCC 40) and Gram positive *S. aureus* (MTCC 87), *B. subtilis* (MTCC 121).

Agar Diffusion Studies

All the substituted 4-((1*H*-Benzo[d]imidazol-2-yl)methoxy) coumarin compounds were evaluated for their *in vitro* antimicrobial activity by agar diffusion method. The culture medium (nutrient agar) was sterilized and poured in 90mm sterile petri plate in sterile conditions. The lawn of tested bacterial strains *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC 121) and *Escherichia coli* (MTCC 40) was made by spreading 100µl of log phase bacterial strains on different nutrient agar plates.

The substituted 4-((1*H*-Benzo[d]imidazol-2-yl) methoxy) coumarin compound and standard drug (Ciprofloxacin) were suspended in DMSO at the concentration of 1mg/ml. Wells in nutrient agar (0.7cm diameter) was made and 50µl of compound suspension was added to the wells. These compounds were allowed to diffuse for at least 2 hours and were incubated at 37°C for 18-24hrs The zone of inhibition for substituted 4-((1*H*-Benzo[d]imidazol-2-yl)methoxy) coumarin compounds were recorded on next day. The zone of inhibition was observed in cm.

Minimum inhibitory concentration (MIC)

The 4-((1*H*-Benzo[d] imidazol-2-yl) methoxy) coumarin compounds were determined by micro broth dilution method. A 1mg/mL stock solution of compounds was prepared in DMSO. The MIC was determined using standard protocol in 96-well microtitre plates. The test concentration was kept in the range of 0.0078-1mg/mL for each of the three pathogenic strains.

One hundred microliters of compounds of varying concentrations was added to each well and another well was loaded with the same volume of sterile DMSO. 100µl of nutrient broth was added to each well containing 0.5 O.D. cells of each organism (at 600nm) i.e. *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC 121) and *Escherichia coli* (MTCC 40) in spate rows and was incubated at 37°C.

After the time period of 18-24hrs of incubation, turbidity was observed in the wells as MIC [27-28].

Result and Discussion

Synthesis of coumarin-benzimidazole derivative 4-((1*H*-Benzo[d]imidazol-2-yl) methoxy) coumarin compounds (7a-j)

Synthesis of coumarin-benzimidazole derivative 4-((1*H*-Benzo[d]imidazol-2-yl)methoxy) coumarin compounds (7a-j) was prepared in three steps and the anticipation was that these compounds might revealed improved antimicrobial activity properties. The chemical structure of the prepared compound (7a-j) is represented in Scheme 1. All the compounds in this series were prepared and purified as explained in the synthesis section.

Spectral data of coumarin- Benzimidazole derivatives (7a- j)

The reaction yield and physical properties, such as melting point and product colour, elemental analysis were discussed as follow:

4-((1*H*-Benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7a). Light green colored Powder; m. pt. 216-220 ºC; yield 67.60%; 0.62 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3376.48 cm^{-1} (N-H stretch), 3104.35 cm^{-1} (Ar.-C-H stretch), 2882.40 cm^{-1} (Al.-C-H stretch), 1780.61 cm^{-1} (C=O stretch), 1653.43 cm^{-1} (C=N stretch), 1602.84 cm^{-1} (Ar.-C=C stretch), 1021.92 cm^{-1} (C-N stretch), 1104.19 cm^{-1} (C-O stretch).

4-((5-Chloro-1*H*-benzo[d]imidazol-2-yl)methoxy)-2H- chromen-2-one (7b). Light purple colored Powder; m. pt. 226- 229 ºC; yield 77.78%; 0.56 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3342.80 cm^{-1} (N-H stretch), 3101.83 cm^{-1} (Ar.-C-H stretch), 2905.73 cm^{-1} (Al.-C-H stretch), 1773.24 cm^{-1} (C=O stretch), 1659.37 cm^{-1} (C=N stretch), 1603.69 cm^{-1} (Ar.-C=C stretch), 1059.68 cm^{-1} (C-N stretch), 1102.43 cm^{-1} (C-O stretch), 804.44 cm^{-1}(C-Cl stretch).

4-((5-Nitro-1*H*-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7c). Black colored Powder; m. pt. 268-270 ºC; yield 69.53%; 0.75 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3338.03 cm^{-1} (N-H stretch), 3141.81 cm^{-1} (Ar.-C-H stretch), 2949.27 cm^{-1} (Al.-C-H stretch), 1745.67 cm^{-1} (C=O stretch), 1648.76 cm^{-1} (C=N stretch), 1597.12 cm^{-1} (Ar.-C=C stretch), 1102.80 cm^{-1} (C-N stretch), 1328.54 cm^{-1}(N=O stretch),1059.60 cm^{-1} (C-O stretch).

4-((5-Methyl-1*H*-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7d). Light yellow colored Powder; m. pt. 248-250 ºC; yield 69.92%; 0.67 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3314.42 cm^{-1} (N-H stretch), 3131.47 cm^{-1} (Ar.-C-H stretch), 2999.79 cm^{-1} (Al.-C-H stretch), 1769.98 cm^{-1} (C=O stretch), 1658.14 cm^{-1} (C=N stretch), 1603.99 cm^{-1} (Ar.-C=Cstretch), 1141.13 cm^{-1} (C-N stretch), 1101.96 cm^{-1} (C-O stretch).

4-((1*H*-Benzo[d]imidazol-2-yl)methoxy)-6-nitro-2H-chromen- 2-one (7e). Brown colored Powder; m. pt. 258-262 ºC; yield 63.53%; 0.71 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3304.15 cm^{-1} (N-H stretch), 3050.99 cm^{-1} (Ar.-C-H stretch), 2920.80 cm^{-1} (Al.-C-H stretch), 1763.32 cm^{-1} (C=O stretch), 1655.21 cm^{-1} (C=N stretch), 1429.65 cm^{-1} (Ar.-C=C stretch), 1193.50 cm^{-1} (C-N stretch), 1325.40 cm^{-1}(N=O stretch),1093.47 cm^{-1} (C-O stretch).

4-((1*H*-Benzo[d]imidazol-2-yl)methoxy)-6-bromo-2H- chromen-2-one (7f). Light brown colored Powder; m. pt. 246- 248 ºC; yield 68.57%; 0.64 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3444.01 cm^{-1} (N-H stretch), 3057.19 cm^{-1} (Ar.-C-H stretch), 2921.96 cm^{-1} (Al.-C-H stretch), 1813.66 cm^{-1} (C=O stretch), 1657.06 cm^{-1} (C=N stretch), 1620.42 cm^{-1} (Ar.-C=C stretch), 1264.64 cm^{-1} (C-N stretch), 1094.21 cm^{-1} (C-O stretch), 739.29 cm^{-1}(C-Br stretch).

4-((1*H*-Benzo[d]imidazol-2-yl)methoxy)-6-chloro-8-nitro-2H- chromen-2-one (7g). Dark brown colored Powder; m. pt. 272- 276 ºC; yield 62.22%; 0.61 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3387.71 cm^{-1} (N-H stretch), 3045.45 cm^{-1} (Ar.-C-H stretch), 2930.35 cm^{-1} (Al.-C-H stretch), 1708.87cm^{-1} (C=O stretch), 1658.37 cm^{-1} (C=N stretch), 1601.58 cm^{-1} (Ar.-C=C stretch), 1136.68 cm^{-1} (C-N stretch), 1320.80 cm^{-1}(N=O stretch),1092.81 cm^{-1} (C-O stretch), 737.55 cm^{-1} (C-Cl stretch).

6-Amino-8-chloro-4-((5-nitro-1*H*-benzo[d] imidazol-2- yl)methoxy)-2H-chromen-2-one (7h). Black colored Powder; m. pt. 285-288 ºC; yield 85.6%; 0.74 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3343.10 cm^{-1} (N-H stretch), 3093.62 cm^{-1} (Ar.-C-H stretch), 2924.72 cm^{-1} (Al.-C-H stretch), 1778.41cm^{-1} (C=O stretch), 1654.23 cm^{-1} (C=N stretch), 1499.77 cm^{-1} (Ar.-C=C stretch), 1091.77 cm^{-1} (C-N stretch), 1326.94 cm^{-1}(N=O stretch),1055.53 cm^{-1} (C-O stretch),733.32 cm^{-1} (C-Cl stretch).

6-Amino-4-((5-nitro-1*H*-benzo[d]imidazol-2-yl) methoxy)-2H- chromen-2-one (7i). Black colored Powder; m. pt. 264-267 ºC; yield 64.46%; 0.69 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3343.10 cm^{-1} (N-H stretch), 3093.62 cm^{-1} (Ar.-C-H stretch), 2924.72 cm^{-1} (Al.-C-H stretch), 1778.41cm^{-1} (C=O stretch), 1654.23 cm^{-1} (C=N stretch), 1499.77 cm^{-1} (Ar.-C=C stretch), 1091.77 cm^{-1} (C-N stretch), 1326.94 cm^{-1}(N=O tretch), 1055.53 cm^{-1} (C-O stretch), 733.32 cm^{-1} (C-Cl stretch).

6-Nitro-4-((5-nitro-1*H*-benzo[d]imidazol-2-yl) methoxy)-2H- chromen-2-one (7j). Dark Brown colored

Evaluation of Zone of Inhibition of synthesized compounds

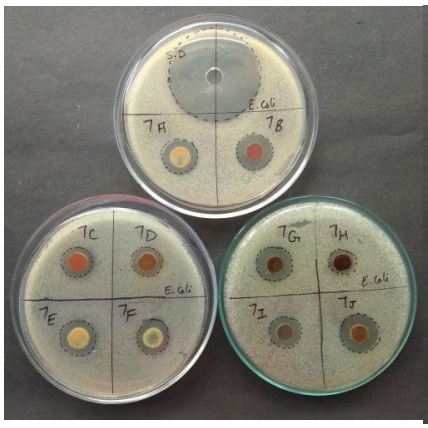


Fig. 3.3.1: Zone of Inhibition of *Escherichia coli*

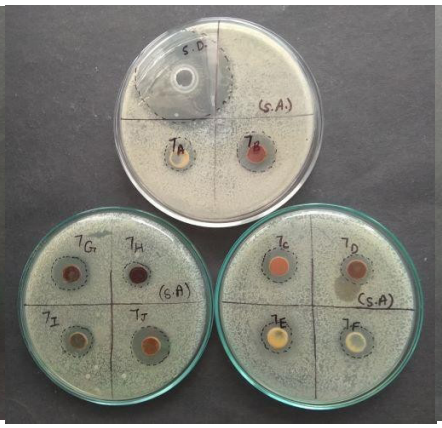


Fig. 3.3.2: Zone of Inhibition of *Staphylococcus aureus*

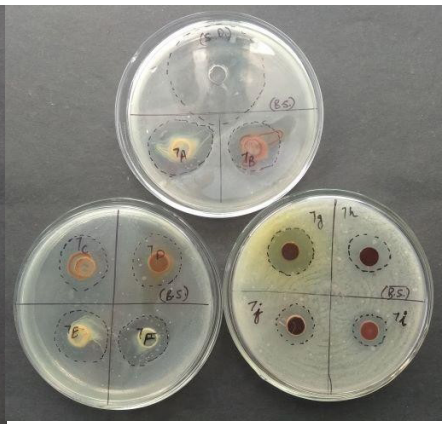


Fig. 3.3.3: Zone of Inhibition of *Bacillus subtilis*

Table No. 3.3.1: *In vitro* antibacterial activity of synthesized compounds

	Bacterial Strains					
Compounds (1mg/ mL or 1µg/ml)	*E. coli (MTCC 40)*		*S. aureus (MTCC87)*		*B. subtilis (MTCC121)*	
	Inferences	*Diameter*	*Inferences*	*Diameter*	*Inferences*	*Diameter*
7a	+	1.0 cm	+	0.7 cm	+	1.9 cm
7b	+	1.1 cm	+	1.0 cm	+	1.5 cm
7c	+	0.8 cm	+	0.8 cm	+	1.4 cm
7d	+	0.7 cm	+	0.8 cm	+	1.5 cm
7e	+	1.0 cm	+	0.7 cm	+	1.9 cm
7f	+	0.9 cm	+	0.9 cm	+	1.3 cm
7g	+	1.1 cm	+	1.1 cm	+	1.5 cm
7h	+	0.5 cm	+	0.6 cm	+	1.2 cm
7i	+	0.8 cm	+	0.9 cm	+	0.8 cm
7j	+	1.1 cm	+	1.2 cm	+	1.1 cm
DMSO	-	-	-	-	-	-
Ciprofloxacin	+	3.8 cm	+	3.9 cm	+	4.1 cm

Evaluation of Minimum Inhibitory concentration of synthesized

Table No. 3.3.2: Observation for Minimum Inhibitory Concentration (mg/ml)

	Minimum Inhibitory Concentration		
Compounds	*E. coli (MTCC 40)*	*S. aureus (MTCC87)*	*B. subtilis (MTCC121)*
7a	0.125	0.250	0.016
7b	0.016	0.125	0.125
7c	0.008	0.063	0.250
7d	0.063	0.250	0.063
7e	0.250	0.125	0.250
7f	0.063	0.500	0.125
7g	0.063	0.125	0.250
7h	0.250	0.500	0.500
7i	0.016	0.250	0.250
7j	0.125	0.500	0.500
DMSO*	0	0	0
Ciprofloxacin#	0.008	0.008	0.008

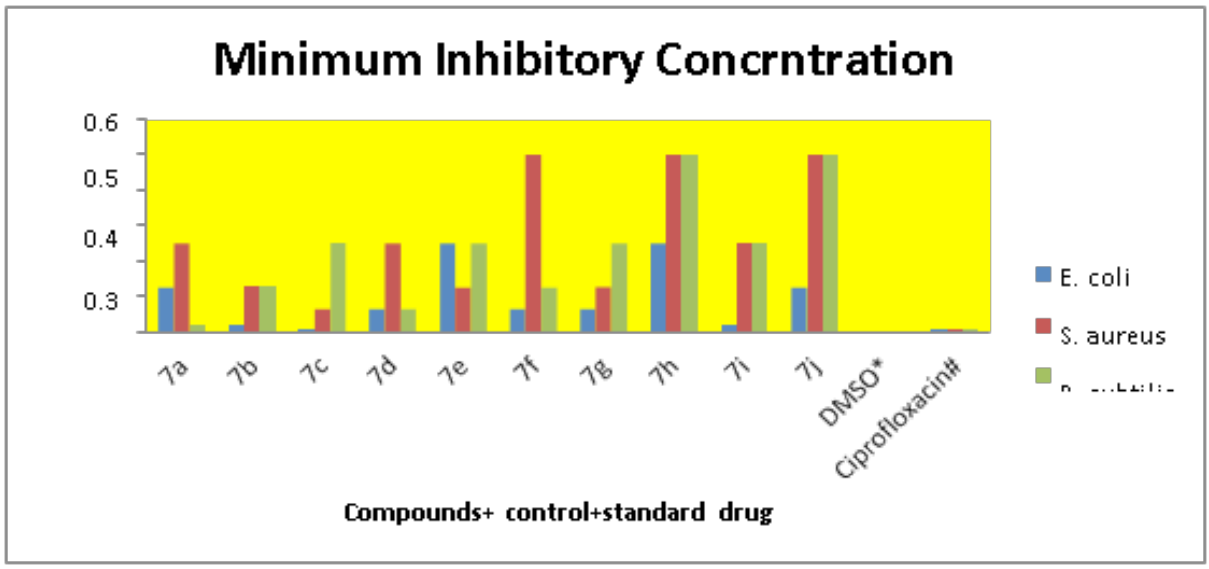


Fig. 3.3.1: MIC of all the compounds on 3 different strains

Powder; m. pt. 276- 280 ºC; yield 79.88%; 0.58 (Chloroform: Methanol 9:1); IR (cm^{-1}): 3446.31 cm^{-1} (N-H stretch), 3092.68 cm^{-1} (Ar.-C-H stretch), 2915.73 cm^{-1} (Al.-C-H stretch), 1734.51cm^{-1} (C=O stretch), 1657.75 cm^{-1} (C=N stretch), 1593.37 cm^{-1} (Ar.-C=C stretch), 1096.26 cm^{-1} (C-N stretch), 1328.90 cm^{-1}(N=O stretch),1057.37 cm^{-1} (C-O stretch).

Evaluation of anti-microbial activity of coumarin-benzimidazole derivative 4-((1*H*-Benzo[d]imidazol-2-yl)methoxy) coumarin compounds (7a-j)

All the synthesized compounds were found to be active against both the bacterial strain that is Gram negative bacteria

E. coli (MTCC 40) and Gram positive bacteria *S. aureus* (MTCC 87), *B. subtilis* (MTCC121). These active compounds are further subjected to antibacterial activity in comparison with standard drug. The primary screening was carried out by taking concentration (1mg/ml) for test and standard and then dilution's of the all the compounds and standard drug i.e. 0.500mg/ml, 0.250mg/ml, 0.125mg/ml, 0.0625mg/ml, 0.03125mg/ml, 0.0156mg/ml and 0.0078mg/ml) are used for the antimicrobial evaluation. Ciprofloxacin was used as standard drug for antibacterial and DMSO was used as control.

As compare to standard ciprofloxacin, compounds exhibited good activity against all the tested strains.

Conclusion

A series of coumarin-benzimidazole derivatives was synthesized and evaluated for its in vitro antimicrobial activity. Most of the synthesized derivatives appeared out as excellent antimicrobial agents as compared to standard drug. Compound 7b was found to be the most active antibacterial agent against Gram positive as well as Gram negative bacteria.

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