



Research Article

DOI: <https://doi.org/10.30750/ijpbr.7.2.1>

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

Harpreet Kaur¹, Baljeet Singh^{2*}¹Department of Pharmaceutical Chemistry, ASBASJSM College of Pharmacy, Bela, Ropar-140111, Punjab, India²Punjab Technical University, Jalandhar, Punjab, India²Assistant Professor, ASBASJSM College of Pharmacy, Bela, Ropar, India

ARTICLE INFO:

Article history:

Received: 10 March 2019

Received in revised form:

19 May 2019

Accepted: 30 May 2019

Available online: 30 June 2019

Keywords:

Antimicrobial activity,
Benzimidazole, Coumarin,
Coumarin-benzimidazole derivatives,
Coumarin-benzimidazole hybrids.

ABSTRACT

A series of coumarin-benzimidazole derivatives, i.e., 4-((1H-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 Minimum Inhibitory Concentration (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, antioxidants, 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

*Corresponding Author: Baljeet Singh, Assistant Professor, ASBASJSM College of Pharmacy, Bela, Ropar, Punjab, India. E-Mail: singhbaljeet8688@gmail.com

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), and 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 (400 MHz) 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 (0.1 mol) was refluxed for 3 hours 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)-1H-benzo[d]imidazole derivatives (3a-b).[25]

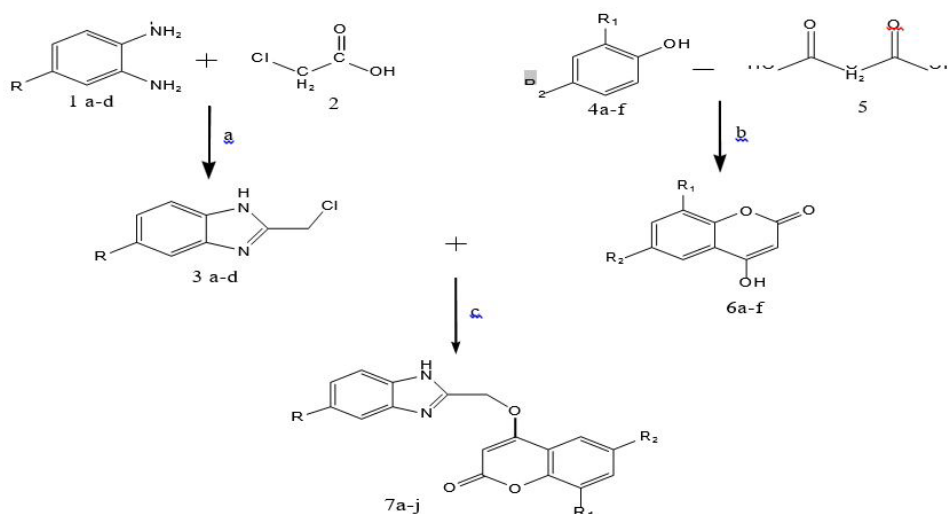
General procedure for Synthesis of 4-hydroxy Coumarin Derivatives (6a-f)

Add phenol derivatives (4a-f) (0.1 mol) and malonic acid (0.1 mol) 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 hours. 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-((1H-Benzo[d]imidazol-2-yl)methoxy)coumarin derivatives

Table 1: Reagents and Reaction Condition: (a) 4N HCl, reflux for 3 hours; (b) Anhydrous ZnCl₂, POCl₃, 65-70°C, reflux for 20 hours; (c) K₂CO₃, DMF, reflux for 12-13 hours

Compounds	R	R ₁	R ₂
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 K₂CO₃ were added and reaction mixture was refluxed for 12-13 hours. 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 NaHCO₃ 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-((1H-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 90 mm sterile petri plate in sterile conditions. The lawn of tested bacterial strains *S. aureus* (MTCC 87), *Bacillus subtilis* (MTCC 121) and *E. coli* (MTCC 40) was made by spreading 100 µL of log phase bacterial strains on different nutrient agar plates.

The substituted 4-((1H-Benzo[d]imidazol-2-yl)methoxy) coumarin compound and standard drug (Ciprofloxacin) were suspended in DMSO at the concentration of 1 mg/mL. Wells in nutrient agar (0.7 cm diameter) was made and 50 µL 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 18-24 hours. The zone of inhibition for substituted 4-((1H-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-((1H-Benzo[d]imidazol-2-yl)methoxy) coumarin compounds were determined by micro broth dilution method. A 1 mg/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 0.0078-1 mg/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. 100 µL of nutrient broth was added to each well containing 0.5 O.D. cells of each organism (at 600 nm), i.e., *S. aureus* (MTCC 87), *B. subtilis* (MTCC 121) and *E. coli* (MTCC 40) in spate rows and was incubated at 37°C. After the time period of

18-24 hours of incubation, turbidity was observed in the wells as MIC (Figure 1-4).[27-28]

RESULT AND DISCUSSION

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

Synthesis of coumarin-benzimidazole derivative 4-((1H-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-((1H-Benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7a). Light green colored powder; m. pt. 216-220°C; 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-1H-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7b). Light purple colored Powder; m. pt. 226- 229°C; 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-1H-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7c). Black colored powder; m. pt. 268-270°C; 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-1H-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7d). Light yellow colored powder; m. pt. 248-250°C; 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=C stretch), 1141.13 cm⁻¹ (C-N stretch), 1101.96 cm⁻¹ (C-O stretch).

4-((1H-Benzo[d]imidazol-2-yl)methoxy)-6-nitro-2H-chromen-2-one (7e). Brown colored Powder; m. pt. 258-262°C; 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-((1H-Benzo[d]imidazol-2-yl)methoxy)-6-bromo-2H-chromen-2-one (7f). Light brown colored Powder; m. pt. 246- 248°C; 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).

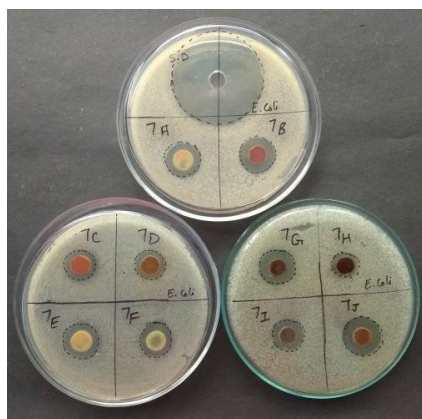
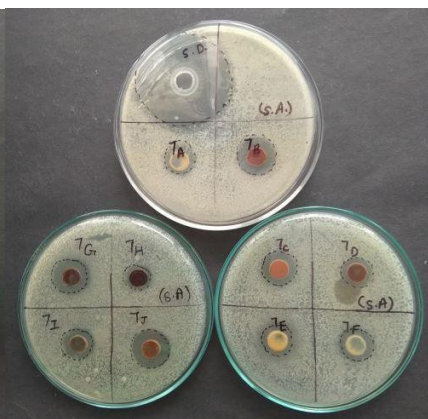
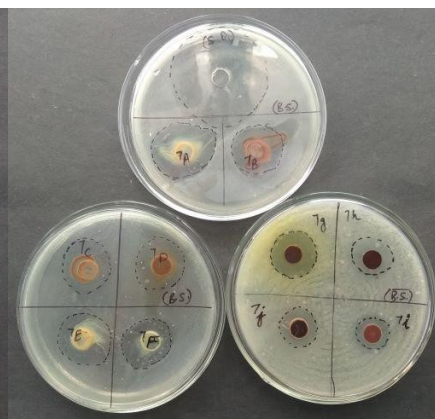
4-((1H-Benzo[d]imidazol-2-yl)methoxy)-6-chloro-8-nitro-2H-chromen-2-one (7g). Dark brown colored Powder; m. pt. 272- 276°C; yield 62.22%; 0.61 (chloroform: methanol 9:1); IR (cm⁻¹): 3387.71 cm⁻¹ (N-H stretch), 3045.45 cm⁻¹ (Ar.-C-H stretch), 2930.35 cm⁻¹ (Al.-C-H stretch), 1708.87 cm⁻¹ (C=O stretch), 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-1H-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7h). Black colored Powder; m. pt. 285-288 °C; 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), 1778.41 cm⁻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-1H-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7i). Black colored powder; m. pt. 264-267°C; 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), 1778.41 cm⁻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-Nitro-4-((5-nitro-1H-benzo[d]imidazol-2-yl)methoxy)-2H-chromen-2-one (7j). Dark brown colored

Evaluation of Zone of Inhibition of Synthesized Compounds

Figure 1: Zone of Inhibition of *Escherichia coli*Figure 2: Zone of Inhibition of *Staphylococcus aureus*Figure 3: Zone of Inhibition of *Bacillus subtilis*Table 2: *In vitro* antibacterial activity of synthesized compounds

Compounds (1 mg/mL or 1 µg/ml)	Bacterial Strains					
	<i>E. coli</i> (MTCC 40)		<i>S. aureus</i> (MTCC87)		<i>B. subtilis</i> (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 Compounds

Table 3: Observation for minimum inhibitory concentration (mg/mL)

Compounds	Minimum inhibitory concentration		
	<i>E. coli</i> (MTCC 40)	<i>S. aureus</i> (MTCC87)	<i>B. subtilis</i> (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

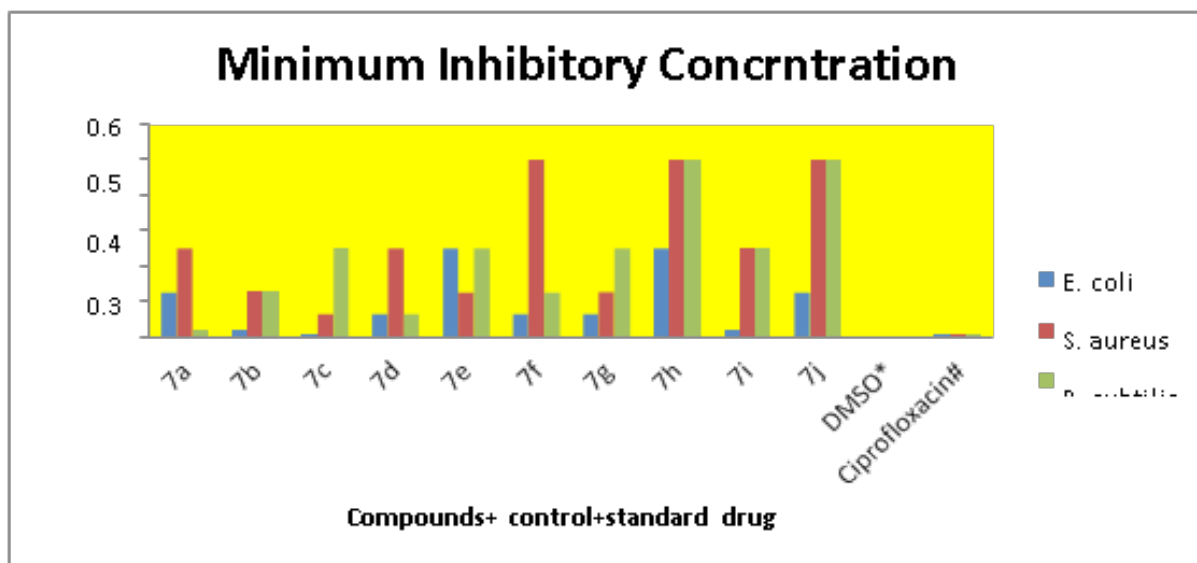


Figure 4: MIC of all the compounds on 3 different strains

powder; m. pt. 276-280 °C; 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), 1734.51 cm^{-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) (Table 1-3).

Evaluation of Anti-Microbial Activity of Coumarin-Benzimidazole Derivative 4-((1H-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 (1 mg/mL) for test and standard and then dilution's of the all the compounds and standard drug i.e. 0.500 mg/mL, 0.250 mg/mL, 0.125 mg/mL, 0.0625 mg/mL, 0.03125 mg/mL, 0.0156 mg/mL and 0.0078 mg/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.

ACKNOWLEDGEMENT

The authors thank the Institute ASBASJSM College of Pharmacy, Bela which served as temple of knowledge and provided quality education.

REFERENCES

1. Abraham D, Burger A: Burger's medicinal chemistry and drug discovery. Hoboken NJ: Wiley, 6th edition 2003.
2. Patrick L: An Introduction to Medicinal Chemistry. Oxford, 4th edition 2009.
3. Omar MA, Shaker YM, Galal SA, Ali MM, Kerwin SM, Li J, Tokuda H, Ramadan RA, El Diwani HI. Synthesis and docking studies of novel antitumor benzimidazoles. *Bioorganic & medicinal chemistry*. 2012 Dec 15;20(24):6989-7001.
4. Wubulikasimu R, Yang Y, Xue F, Luo X, Shao D, Li Y, Gao R, Ye W. Synthesis and biological evaluation of novel benzimidazole derivatives bearing a heterocyclic ring at 4/5 position. *Bulletin of the Korean Chemical Society*. 2013;34(8):2297-2304.
5. Sawant R, Kawade D. Synthesis and biological evaluation of some novel 2-phenyl benzimidazole-1-acetamide derivatives as potential anthelmintic agents. *Acta Pharmaceutica*. 2011 Sep 1;61(3):353-361.
6. Gobis K, Foks H, Bojanowski K, Augustynowicz-Kopeć E, Napiórkowska A. Synthesis of novel 3-cyclohexylpropanoic acid-derived nitrogen heterocyclic compounds and their

- evaluation for tuberculostatic activity. *Bioorganic & medicinal chemistry*. 2012 Jan 1;20(1):137-144.
7. Ranjith PK, Rajeesh P, Haridas KR, Susanta NK, Row TN, Rishikesan R, Kumari NS. Design and synthesis of positional isomers of 5 and 6-bromo-1-[(phenyl) sulfonyl]-2-[(4-nitrophenoxy) methyl]-1H-benzimidazoles as possible antimicrobial and antitubercular agents. *Bioorganic & medicinal chemistry letters*. 2013 Sep 15;23(18):5228-5234.
8. Shingalapur RV, Hosamani KM, Keri RS, Hugar MH. Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. *European journal of medicinal chemistry*. 2010 May 1;45(5):1753-1759.
9. Yadav G, Ganguly S, Murugesan S, Dev A. Synthesis, anti-HIV, antimicrobial evaluation and structure activity relationship studies of some novel benzimidazole derivatives. *Anti-infective agents*. 2015 Apr 1;13(1):65-77.
10. El-Nezhawy AO, Buiomy AR, Hassan FS, Ismaiel AK, Omar HA. Design, synthesis and pharmacological evaluation of omeprazole-like agents with anti-inflammatory activity. *Bioorganic & medicinal chemistry*. 2013 Apr 1;21(7):1661-1670.
11. Ishikawa M, Nonoshita K, Ogino Y, Nagae Y, Tsukahara D, Hosaka H, Maruki H, Ohyama S, Yoshimoto R, Sasaki K, Nagata Y. Discovery of novel 2-(pyridine-2-yl)-1H-benzimidazole derivatives as potent glucokinase activators. *Bioorganic & medicinal chemistry letters*. 2009 Aug 1;19(15):4450-4454.
12. Saify ZS, Azim MK, Ahmad W, Nisa M, Goldberg DE, Hussain SA, Akhtar S, Akram A, Arayne A, Oksman A, Khan IA. New benzimidazole derivatives as antiplasmodial agents and plasmepsin inhibitors: synthesis and analysis of structure–activity relationships. *Bioorganic & medicinal chemistry letters*. 2012 Jan 15;22(2):1282-1286.
13. Tamura Y, Omori N, Kouyama N, Nishiura Y, Hayashi K, Watanabe K, Tanaka Y, Chiba T, Yukioka H, Sato H, Okuno T. Design, synthesis and identification of novel benzimidazole derivatives as highly potent NPY Y5 receptor antagonists with attractive in vitro ADME profiles. *Bioorganic & medicinal chemistry letters*. 2012 Sep 1;22(17):5498-5502.
14. Padmavathi V, Venkatesh BC, Muralikrishna A, Padmaja A. The reactivity of gem cyanoester ketene dithiolates towards the development of potent antioxidant heterocycles. *Chemical and Pharmaceutical Bulletin*. 2012 Apr 1;60(4):449-458.
15. Lemke T, Williams D, Roche V and Zito S: *Foye's Principles of Medicinal Chemistry*. Lippincott Williams and Wilkins, 7th edition 2008.
16. Bouchouit M, Said ME, Ali MK, Bouacida S, Merazig H, Chaouche NK, Chibani A, Zouchoune B, Belfaitah A, Bouraiou A. Synthesis, X-ray structure, theoretical investigation, corrosion inhibition and antimicrobial activity of benzimidazole thioether and their metal complexes. *Polyhedron*. 2016 Nov 24;119:248-259.
17. Mariappan G, Hazarika R, Alam F, Karki R, Patangia U, Nath S. Synthesis and biological evaluation of 2-substituted benzimidazole derivatives, *Arabian Journal of Chemistry*. 2011;1-5.
18. Rang H and Dale M: *Rang and Dale's pharmacology*, Edinburgh: Elsevier / Churchill Livingstone, 7th edition 2012.
19. (a) Zhang SL, Damu GLV, Zhang L, Geng RX, Zhou CH. Synthesis and biological evaluation of novel benzimidazole derivatives and their binding behavior with bovine serum albumin, *European Journal of Medicinal Chemistry*. 2012;55:164-175; (b) Zhang HZ, Damu GLV, Cai GX, Zhou CH. Design, synthesis and antimicrobial evaluation of novel benzimidazole type of fluconazole analogues and their synergistic effects with chloramphenicol, norfloxacin and fluconazole, *European Journal of Medicinal Chemistry*. 2013;64:329–344.
20. Baartzes N, Stringer T, Seldon R, Warner DF, Taylor D, Wittlin S, Chibale K, Smith GS. Bioisosteric ferrocenyl aminoquinoline-benzimidazole hybrids: Antimicrobial evaluation and mechanistic insights, *European Journal of Medicinal Chemistry*. 2019;180:121-133.
21. Lv N, Sun M, Liu C, Li J. Design and synthesis of 2-phenylpyrimidine coumarin derivatives as anticancer agents. *Bioorganic & Medicinal Chemistry Letters*. 2017 Oct 1;27(19):4578-4581.
22. Xie Y, Han L, Ge CS, Cui YH, Gao JR. Novel organic dye sensitizers containing fluorenyl and biphenyl moieties for solar cells. *Chinese Chemical Letters*. 2017 Feb 1;28(2):285-292.
23. Murrey RDH, Medez D, Brown SA. *The natural coumarins occurrences, chemistry and biochemistry*, John Wiley Interscience, New York 1982.
24. Valgas C, De Souza SM, Smania EF A, Smania A. Screening methods to determine antibacterial activity of natural products, *Brazilian Journal of Microbiology*. 2007;38:369–380.
25. Mariappan G, Hazarika R, Alam F, Karki R, Patangia U, Nath S. Synthesis and biological evaluation of 2-substituted Benzimidazole derivatives, *Arabian Journal of Chemistry* (2011), doi:10.1016/j.arabjc.2011.008.
26. Trivedi JC, Bariwal JB, Upadhyay KD, Naliapara YT, Joshi SK, Pannecouque CC, De Clercq E, Shah AK. Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity. *Tetrahedron Letters*. 2007 Nov 26;48(48):8472-8474.
27. Abd El-Wahab H, Abd El-Fattah M, Abd El-Khalik N, Nassar HS, Abdelall MM. Synthesis and characterization of coumarin thiazole derivative 2-(2-amino-1, 3-thiazol-4-yl)-3H-benzo [f]

chromen-3-one with anti-microbial activity and its potential application in antimicrobial polyurethane coating. Progress in Organic Coatings. 2014 Sep 1;77(9):1506-11.

28. Yadav S, Narasimhan B, Lim SM, Ramasamy K, Vasudevan

M, Shah SA, Mathur A. Synthesis and evaluation of antimicrobial, antitubercular and anticancer activities of benzimidazole derivatives. Egyptian Journal of Basic and Applied Sciences. 2018 Mar 1;5(1):100-109..

Cite this article: **Harpreet Kaur, Baljeet Singh.** Synthesis, characterisation and biological evaluation of substituted 4-((1h-benzo[d]imidazol-2-yl) methoxy) coumarin derivatives as antimicrobial agents. **Indian J. Pharm. Biol. Res. 2019;7(2): 1-8.**