IJPSR (2018), Volume 9, Issue 5 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 July, 2017; received in revised form, 12 October, 2017; accepted, 20 October, 2017; published 01 May, 2018

SYNTHESIS, EVALUATION AND POLYMORPHISM STUDIES OF NEW BENZIMIDAZOLE DERIVATIVES AS POTENT ANTIBACTERIAL AGENTS

K. L. S. Konyak, M. M. Maste, A. Saxena * and P. Inamdar

Department of Pharmaceutical Chemistry, KLE University College of Pharmacy Belagavi, KLE Academy of Higher Education and Research, Belagavi - 590010, Karnataka, India.

Keywords:

Benzimidazole, Orthophenylenediamine, Antibacterial activity DSC, Polymorphism

Correspondence to Author:
Mr. Akash Saxena.

Assistant Professor,
Department of Pharmaceutical Chemistry
KLE University College of Pharmacy
KLE Academy of Higher Education and Research KLE University Belagavi - 590010, Karnataka, India

E-mail: akashdeensaxena@gmail.com

ABSTRACT: Ten, 2-substituted benzimidazole derivatives were prepared and assessed against two Gram-positive bacteria (*Streptococcus mutans*, *Staphylococcus aureus*) and two Gram-negative bacteria (*Psuedomonas aeruginosa*, *Escherichia coli*). The derivatives were obtained by the condensation of 2-((1*H*-benzo[*d*] imidazol-2-yl) thio) acetohydrazide**(**4) with different substituted aromatic aldehydes and their structures were characterized by FTIR, ^{1}H NMR. The compound (*E*)-2-((1*H*- benzo [*d*] imidazole-2-yl) thio)- *N´*- (furan- 2- yl- methylene) acetohydrazide (6g) showed potent activity against both Gram-positive species (0.2-0.8 µg/ml of MIC) which was better than the standard drug Ciprofloxacin. The derivative (*E*)-2-((1*H*-benzo[*d*]imidazole-2-yl) thio)-*N´*-(4-methoxybenzylidene) acetohydrazide (6a) was evaluated for potential polymorphism by differential scanning calorimetry (DSC). It was then subjected to crystallization using different solvents. The crystal obtained from acetonitrile solvent displayed different thermal transition (240.82 °C) from that of the parent crystal (234.52 °C).

INTRODUCTION: Pneumonia, cystitis, urinary tract infection (UTI), meningitis, otitis, foodborne diarrhoea, gonorrhea, tuberculosis is common health-care associated and community-acquired infections caused by bacteria [1]. But in recent times, resistance of common and life threatening infections to available anti-bacterial drugs is becoming a world-wide occurrence. Antibacterial resistance (ABR) is resistance of bacterial organisms to antibiotics and other antibacterial drugs as a result of mutation. Disease like cystitis which responded well to oral drugs earlier now need injectable drugs.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(5).1929-34

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(5).1929-34

Immunocompromised patients in organ transplant, cancer treatment and patients suffering from Acquired Immuno Deficiency Syndrome (AIDS) are most susceptible to infections and treatment failure will lead to fatal results. ABR evidently exacerbates the clinical outcome of patients and affects economy due to consumption of health-care resources. ABR is a reality in case of Tuberculosis (TB) and gonorrhea. ABR has been seen in *Escherichia coli* to 3rd generation cephalosporins, fluoroquinolones and in *Klebsiella pneumonia* to carbapenems [1].

In 2013, 1.5 million died of TB and one fourth of all HIV-related deaths were caused by TB [2]. While pneumonia was responsible for 15% of all deaths of children under 5 years old worldwide [3]. The sulphonamides, quinolones, nitro heteroaromatic compounds like metronidazole, β-lactam antibiotics, carbapenems, tetracyclines, aminoglycosides and

macrolides are the antibacterial drugs in current use. The β-lactam antibiotic acts by inhibiting the bacterial cell wall biosynthesis [4].

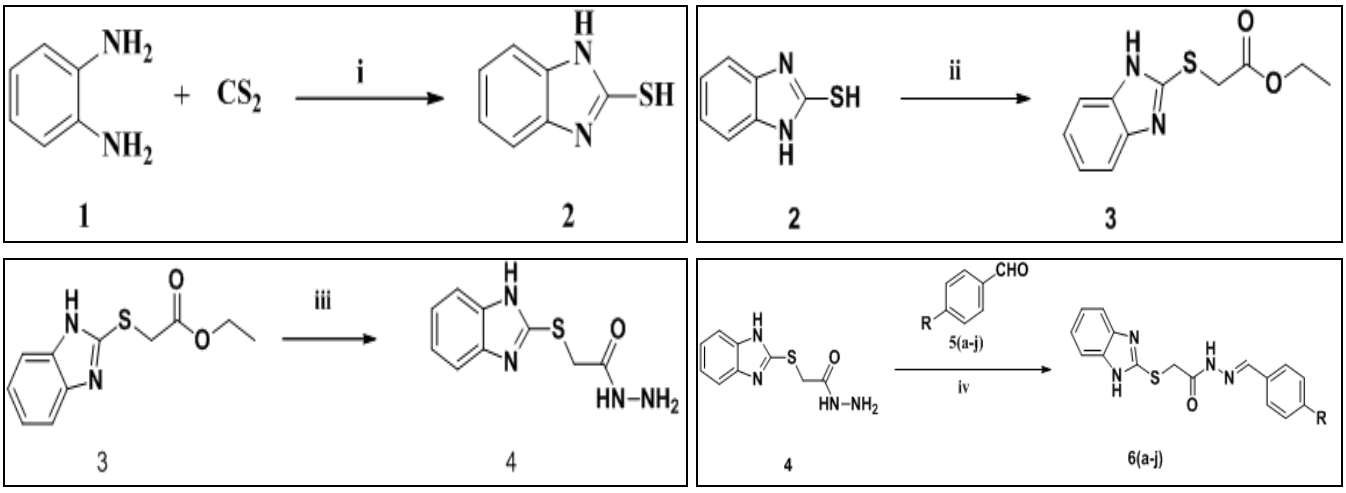
Benzimidazole is a heterocyclic compound in which a phenyl ring is fused to an imidazole ring. The first Benzimidazole was synthesized by Hoebrecker in 1872 [5]. The benzimidazole structure with its substituted derivatives have been reported to show a wide range of biological activities like anticancer, antiviral, antibacterial, anti-fungal, anthelmintic, anti-inflammatory, antihistaminic, proton pump inhibitor, antioxidant, anti-hypertensive and anticoagulant properties [6]. The effectiveness of benzimidazole nucleus is because of its inhibitory activity as well as favourable selectivity ratio [7].

Polymorphism is the ability of an organic molecule to crystallize into more than one crystal arrangement. This characteristic property profoundly affects the shelf life, solubility and different uptake rates which consequently influences the biological activity [8]. The techniques commonly used to study the polymorphic characteristics of drug substances are infrared spectroscopy (IR), solid state nuclear magnetic resonance spectroscopy (SSNMR), Raman spectroscopy, X-ray powder diffraction (XRPD) and thermal analysis techniques of which differential scanning calorimetry (DSC) is the most widely used for drug polymorphism studies, mainly as a qualitative tool [9].

MATERIALS AND METHODS: The melting points of the organic compounds were determined by open capillary tube and were uncorrected. The Thin layer chromatography (TLC) was performed on the glass slides prepared manually with silica gel G (Rankem). IR spectra were recorded in IR Affinity-1 FTIR Shimadzu using DRS 8000 spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 spectrometer at 400 MHz using tetramethylsilane as the internal standard. Thermal enthalpy, the difference in temperature was recorded on (Differential Scanning Calorimetry) DSC-60 Shimadzu and the resultant result was recorded as mW.

Preparation of 1*H*-benzo[*d*] imidazole-2-thiol (2): A mixture of o-phenylenediamine (15.2 g, 0.14 mole), ethanol (240 ml), carbon disulfide (32 ml, 0.42 mole), and KOH (15.6 g, 0.28 mole) were heated under reflux for 8 h. Then the solvent was evaporated and the residue poured into 240 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol to obtain compound (2).

General Scheme of Present Work:



SCHEME 1: GENERAL SCHEME OF PRESENT WORK

Reagents and conditions (i) KOH, C_2H_5OH, reflux 8h; (ii) $ClCH_2COOC_2H_5$, C_2H_5OH, KOH, reflux 30 min, stirring 48 h; (iii) $NH_2NH_2.H_2O$, C_2H_5OH, reflux 6 - 8 h; (iv) CH_3COOH, CH_3OH, reflux 17-24 h.

Preparation of ethyl 2-((1*H*-benzo[*d*]imidazol-2-yl)thio) acetate (3): A mixture containing 2-mercaptobenzimidazole (2) (0.03 mole, 4.5 g), 60 ml of ethanol and potassium hydroxide (0.03 mole, 1.68 g) was stirred and refluxed for 30 minutes.

Then ethyl chloroacetate (0.03 mole, 3.66 ml) was added in one portion which sets off an exothermic reaction. After stirring for 48 h, the reaction mixture was added to crushed ice (100 g) and stirred for 30 minutes while the temperature was maintained at 0 - 10 °C. The product obtained was washed with water until free of chlorides, filtered and air dried to obtain compound (3).

Preparation of 2-((1*H*-benzo[*d*]imidazol-2-yl) thio) acetohydrazide (4): Compound ethyl 2-((1H-benzo[d]imidazol-2-yl)thio) acetate (3) (0.021 mole, 5 g) and hydrazine hydrate 99 - 100% (0.105 mole, 5.1 ml) in ethanol (30 ml) was refluxed for 10 - 12 h. After cooling to room temperature the resulting reaction mixture was added to crushed ice. The solid was filtered, dried, and washed with water to obtain compound (4).

General Procedure for the Preparation of 2-substituted 1*H*-benzo[*d*] imidazole (6a- 6j): A mixture of 2- ((1H- benzo[d]imidazol- 2-yl) thio) acetohydrazide (4) (0.009 mole, 2 g) with various substituted aromatic aldehydes (0.009 mole) and 1ml of glacial acetic acid in ethanol (20 ml) was refluxed for about 17 - 72 h. The solvent was then evaporated on a steam bath and the residue was recrystallized from corresponding solvents to yield compounds (6a - 6j).

***In vitro* Antibacterial Assays:** Minimum inhibitory concentration (MIC) values for the synthesized compounds (6a - 6j) were determined using serial dilution method. The bacterial strains used were Gram negative bacterias (*Streptococcus mutans*, *Staphylococcus aurreus*), and Gram-negative bacteria (*Psuedomonas aeruginosa*, *Escherichia coli*).

The nutrient medium used for the assay was brain heart infusion (BHI) (HiMedia M210 - 500G). Ciprofloxacin was used as the control drug. The MIC values in µg/ml were summarized in **Table 1** below.

TABLE 1: ANTIBACTERIAL ACTIVITY DATA OF SYNTHESIZED COMPOUNDS (6a - 6j)

S. no.	Compounds	R	MIC (µg/ml)		MIC (µg/ml)	
			A	B	C	D
1	6a	4-OCH_3	100	6.25	-	-
2	6b	4-CH_3	0.4	-	100	50
3	6c	4-Br	0.8	-	-	50
4	6d	4-Cl	0.2	100	50	50
5	6e	4-NO_2	0.4	3.12	12.5	25
6	6f		50	0.8	50	-
7	6g		0.2	0.8	100	12.5
8	6h		6.25	0.8	50	25
9	6i	4-OH	6.25	6.25	100	50
10	6j	4-CN	-	0.4	-	25
11	Ciprofloxacin	-	2	2	4	2

A = *Streptococcus mutans*; B = *Staphylococcus aureus*; C = *Psuedomonas aeruginosa*; D = *Escherichia coli* (-) = resistant

Procedure: MIC was observed by making nine dilutions of each drug with Brain Heart Infusion (BHI) media. In the initial tube, 20 microlitres (ml) of drug was added into 380 ml of BHI broth. For dilution, 200 ml of BHI broth was added into the next 9 tubes separately. From the initial tube, 200 ml was transferred to the first tube containing 200 ml of BHI broth. It was considered as 10^{-1} dilution. From 10^{-1} diluted tube, 200 ml was transferred to second tube to make 10^{-2} dilution. The serial dilution was repeated up to 10^{-9} dilutions for each drug. From the maintained stock cultures of required organisms, 5 ml was taken and added into 2 ml of BHI (brain heart infusion) broth. In each serially diluted tube, 200 ml of above culture suspension was added. The tubes were incubated for 24 hours at 37 °C in the incubator and observed for turbidity [10].

Polymorphism Study of Synthesized Compound (*E*)-2- ((1H-benzo[*d*]imidazol-2-yl)thio)- *N*'- (4-methoxybenzylidene) acetohydrazide(6a):

Selection of Solvent System: The solvent was selected on a trial and error basis. Solubility of 6a was checked in water, methanol, ethanol, ethyl acetate, hexane, acetonitrile, n-butanol, dichloro-methane, acetone, isopropyl alcohol and dimethyl formamide at room temperature.

General Procedure for Crystallization: The polymorphs were prepared by the method of crystallization from a single solvent. The compound 6a was weighed (10 mg) and taken in a beaker and solvent (10 ml) was added so that the concentration of the mixture was 1mg/1ml. The mixture was gradually heated up to its boiling point. When most of the solute dissolved hot filtration was performed to remove any insoluble impurities.

The filtrate was allowed to cool at room temperature and crystallization was observed. Care was taken to protect the solution from airborne contaminants. The DSC thermogram data of different crystals were summarized in **Table 2** below.

TABLE 2: DSC THERMOGRAM DATA OF DIFFERENT CRYSTALS

S. no.	Code	Solvent used to obtain crystals	Thermal transition of different crystals	Peak
1	SBS-A (Std 6a)	Ethanol	234.52	Endothermic
2	SBS-B	Acetonitrile	240.82	Endothermic
3	SBS-C	Ethyl acetate	238.25	Endothermic
4	SBS-D	Methanol	235.05	Endothermic
5	SBS-F	Isopropyl alcohol	238.98	Endothermic

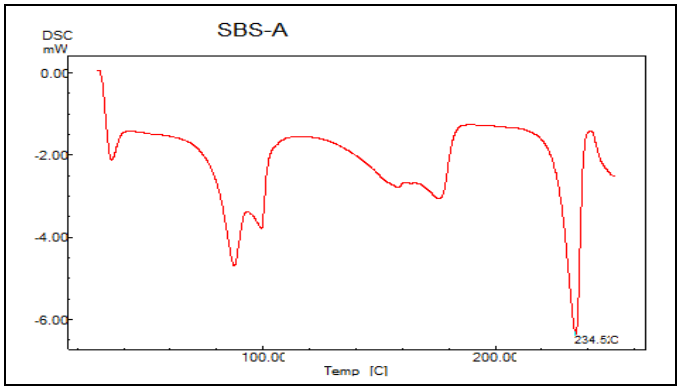


FIG. 1: DSC THERMOGRAM OF 6a (STARTING MATERIAL)

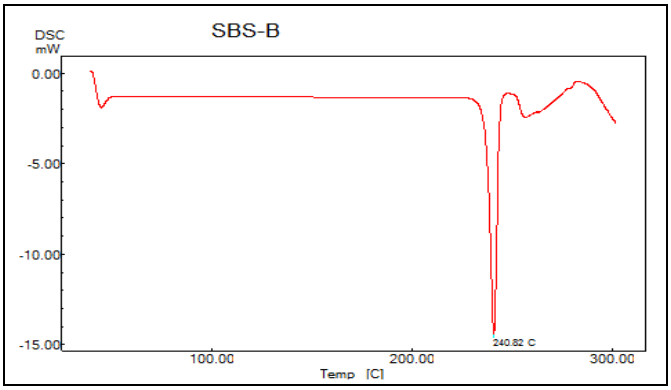


FIG. 2: DSC THERMOGRAM OF 6a ISOLATED FROM ACETONITRILE

RESULTS:

1*H*-benzo[*d*] imidazole-2-thiol (2): White solid. 83% yield, mp 300 - 304 °C, FTIR (KBr) νcm^{-1}: 3135 (N-H), 2573 (S-H), 1514 (C=N), 3045 (Ar-H); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 12.48 (s, 1H, NH), 3.31 (s, 1H, SH), 7.12-7.1 (m, 4H, *J*=15.6 Hz, Ar-H).

Ethyl 2-((1*H*-benzo[*d*]imidazol-2-yl)thio)acetate (3):White solid. 63% yield, mp 90 - 94 °C. FTIR ν (KBr) cm^{-1}: 3132 (N-H), 2972 (C-H), 1743 (C=O), 3051 (Ar-H), 1178 (-O-); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 12.37(s, 1H, NH), 1.18 - 1.14 (t, 3H, -CH_3), 4.13- 4.08 (m, 2H, *J* =21.2 Hz,-CH_2), 4.19 (s, 2H, -CH_2), 7.4- 7.39 (m, 2H, *J* = 7.6 Hz, Ar-H), 7.09 - 7.06 (m, 2H, *J* = 9.2 Hz, Ar-H).

2-((1*H*-benzo[*d*]imidazol-2-yl) thio)acetohydrazide (4): Purple solid. 45% yield, mp 200 - 204 °C. FTIR (KBr) νcm^{-1}: 3315, (-NHNH$_2$), 3064 (Ar-H), 2870 (C-H), 1699 (C=O), 1566 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 1.9 (s, 2H, -NH_2), 7.78 (s, 1H, -CONH), 10.9 (s, 1H, NH), 4.4 (s, 2H,-CH_2), 7.12 - 7.09 (d, 2H, *J* = 10 Hz, Ar-H), 6.84-6.82 (d, 2H, *J* = 9.2 Hz, Ar-H).

2-((1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*'-(4-methoxy-benzylidene)acetohydrazide(6a): Creamish solid. 67% yield, mp210-214°C; FTIR (KBr) νcm^{-1}: 3396 (N-H), 3062 (Ar-H), 2835 (C-H), 1681 (C=O), 1608 (C=N), 1247 (Ph-O-CH_3); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.45 (s, 1H, NH), 7.96 (s, 1H, -CONH), 7.2 (s, 1H, -N=CH), 2(s, 2H, -CH_2), 3.8(s, 3H, -OCH_3), 7.74 - 7.72 (d, 4H, *J* = 8.8 Hz, Ar-H), 7- 6.9 (m, 4H, *J*= 9.6 Hz, Ar-H).

2-((1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*'- (4-methyl benzylidene) acetohydrazide (6b): Orange solid.

39% yield, mp 250 - 252 °C; FTIR (KBr) νcm^{-1}: 3450 (N-H), 3061 (Ar-H), 2850 (C-H), 1651 (C=O), 1600 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 2.3 (s,3H, -CH_3), 11.48 (s, 1H, NH), 1.8 - 2 (s, 2H, -CH_2), 7.98 (s, 1H, -CONH), 11.3 (s, 1H, -N=CH), 7.24 - 7.22 (d, 4H, *J* = 8 Hz, Ar-H), 6.96 - 6.94(m, 4H, *J* = 9.2 Hz, Ar-H).

2-((1H-benzo[d]imidazol-2-yl)thio)-N'-(4 bromo-benzylidene) acetohydrazide (6c): White solid. 42% yield, mp 280 – 282 °C; FTIR (KBr) νcm^{-1}: 3450 (N-H), 3061 (Ar-H), 2833 (C-H), 1651 (C=O), 1604 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.55 (s, 1H, NH), 2.0 (s, 2H, -CH_2), 7.98 (s, 1H, -CONH), 11.45 (s, 1H, -N=CH), 7.77-7.75 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.6 - 7.59 (d, 2H, *J* = 9.2 Hz, Ar-H) 6.96 - 6.94 (m, 4H, *J* = 8 Hz, Ar-H).

2-((1*H*-benzo[*d*]imidazol-2-yl)thio)-*N*'-(4-chloro-benzylidene)acetohydrazide (6d): Reddish brown solid. 52% yield, mp 204 - 206 °C; FTIR (KBr) νcm^{-1}: 3450 (N-H), 3061 (Ar-H), 2833 (C-H), 1681 (C=O), 1604 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.65 (s, 1H, NH), 1.9 (s, 2H, -CH_2), 7.88 (s, 1H, -CONH), 11.5 (s, 1H, -N=CH), 7.73-7.71 (d, 2H, *J* = 8 Hz, Ar-H), 7.64 - 7.61 (d, 2H, *J* = 8.8 Hz, Ar-H) 6.95 - 6.92 (m, 4H, *J* = 10 Hz, Ar-H).

2- ((1*H*-benzo[*d*]imidazol-2-yl)thio) -*N*'-(4-nitro-benzylidene)acetohydrazide (6e): Red solid. 56% yield, mp 306 – 308 °C; FTIR (KBr) νcm^{-1}: 3388 (N-H), 3062 (Ar-H), 2841 (C-H), 1633 (C=O), 1587 (C=N), 1300 (N=O); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.9 (d, 1H, NH), 4 (s, 2H, -CH_2), 8.1 (s, 1H, -CONH), 11.7 (s, 1H, -N=CH), 8.25 - 8.23 (d, 2H, *J* = 9.2 Hz, Ar-H), 8.06 - 8.04 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.24 - 7.22 (m, 2H, *J* = 8.4 Hz, Ar-H), 7 - 6.98 (m, 2H, *J* = 8.4 Hz, Ar-H).

2- ((1*H*-benzo[*d*]imidazol-2-yl) thio)- *N*'- ((E)-3phenylallylidene) acetohydrazide (6f): Light green solid. 46% yield, mp 242 - 244 °C; FTIR (KBr) νcm^{-1}: 3414 (N-H), 3051 (Ar-H), 2827 (C-H), 1654 (C=O), 1577 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.47 (d, 1H, NH), 6.8 (s, 2H, -CH_2),11.33 (s, 1H, -N=CH), 7.8 (s, 1H, -CONH), 7.38 (t, 1H, -C=H), 7.28 (t, 1H, -C=H), 7.5 - 7.52 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.2 - 7.19 (d, 2H, *J* = 7.6 Hz, Ar-H), 6.98 - 6.96 (m, 5H, *J* = 8.4 Hz, Ar-H).

2-((1*H*-benzo[*d*]imidazol-2-yl) thio)-*N*'-(furan-2-ylmethylene)acetohydrazide (6g): White solid. 21% yield, mp 228 - 230 °C; FTIR (KBr) νcm^{-1}: 3269 (N-H), 3059 (Ar-H), 2868 (C-H), 1633 (C=O), 1651 (C-O), 1589 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.38 (d, 1H, NH), 6.5 (s, 2H, -CH_2), 11.31 (s, 1H, -N=CH), 7.94 (s, 1H, -CONH), 7.7 (d, 1H, Ar-H), 6.7(d, 1H, Ar-H), 6.6 (m, 1H, Ar-H), 7.2 (s, 2H, Ar-H), 6.9 (s, 2H, Ar-H).

2-((1*H*-benzo[*d*]imidazol-2-yl) thio)-*N*'-(pyridin-4-ylmethylene)acetohydrazide(6h): Green solid. 15% yield, mp 296 - 298 °C; FTIR (KBr) νcm^{-1}: 3433 (N-H), 3061 (Ar-H), 2879 (C-H), 1633 (C=O), 1566 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.7 (d, 1H, NH), 6.9 (s, 2H, -CH_2), 11.6 (s, 1H, -N=CH), 8.5 (d, 2H, Ar-H), 7.98 (s, 1H, -CONH), 7.7 (d, 2H, Ar-H), 7.2 (d, 2H,Ar-H), 6.9 (d, 2H, *J* = 8.8 Hz, Ar-H).

2- ((1*H*-benzo[*d*]imidazol- 2- yl) thio)- *N*'- (4-hydroxybenzylidene)acetohydrazide (6i): Grey solid. 57% yield, mp 154 – 156 °C; FTIR (KBr) ν cm^{-1}: 3388 (N-H), 3336 (-OH), 3045 (Ar-H), 2845 (C- H), 1681 (C=O), 1587 (C=N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.77 (s, 1H, NH), 11.6 (s, 1H, -N=CH), 6.4 (s, 2H, -CH_2), 6.3 (1s, 1H, -OH) 7.88 (s, 1H, -CONH), 11.6(s, 1H, -N=CH), 7.77 - 7.75 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.6 - 7.58 (d, 2H, *J* = 8 Hz, Ar-H) 6.97 - 6.95(m, 4H, *J* = 9.6 Hz, Ar-H).

2- ((1*H*-benzo[*d*]imidazol- 2- yl) thio)- *N*'- (4-cyanobenzylidene) acetohydrazide (6j): Green solid. 69% yield, mp 312 – 314 °C; FTIR (KBr) ν cm^{-1}: 3433 (N-H), 3061 (Ar-H), 2879 (C- H), 1643 (C=O), 1566 (C=N), 1394 (C-N); ^{1}H-NMR (400 MHz, δ, ppm, DMSO-d_6): 11.39 (s, 1H, NH), 6.9 (s, 2H, -CH_2), 8.08 (s, 1H, -CONH), 11.27 (s, 1H, -N=CH), 7.67 - 7.6 (d, 2H, *J* = 9.6 Hz, Ar-H), 7.69 - 7.67 (d, 2H, *J* = 8 Hz, Ar-H) 6.95 - 6.93 (m, 4H, *J* = 7.6 Hz, Ar-H).

DISCUSSION: The synthesis of 2-substituted benzimidazole derivatives (6a- 6j) were prepared by reacting 2-((1*H*-benzo[*d*]imidazol-2-yl) thio) acetohydrazide (4) with various substituted aromatic aldehydes. The reaction resulted in formation of Schiff's base with yields ranging from 15 - 69%. In this reaction, compound (4) (0.009

mole) and the substituted aromatic aldehydes (0.009 mole) were refluxed for 17 - 72 h in methanol with acetic acid as catalyst. The reaction was monitored by TLC. The formation of compound (2) was confirmed by the appearance of signal at δ 12.48 ppm of (N-H) and FTIR band at 2573 cm^{-1} of (S-H). The stretching band at 1743 cm^{-1} (C=O), the ^1H NMR peak at δ 11.78 ppm due to terminal oxygen (-O-) and the absence of the thiol (S-H) band confirmed the formation of compound (3). Compound (4) is an acetohydrazide and its formation was confirmed by a stretching band at 3315 cm^{-1} of hydrazine (-$NHNH_2$) and ^1H NMR peak δ 7.78 ppm of acetamide (-CONH).

The derivatives (6a - 6j) were also confirmed by FTIR, ^1H NMR. The band around 1587 - 1604 cm^{-1} confirmed the presence of (C=N) group which was not present in compound (4). All the ten derivatives has signal for eight aromatic protons at δ 8.06 - 6.6 ppm (Ar-H, *J* = 9.6-7.2 Hz) which confirmed the presence of two aromatic rings.

The antibacterial activity results revealed that the synthesized compounds 6b, 6c, 6d, 6e, 6f, 6g, 6j exhibited better activity against Gram- positive bacteria *Streptococcus mutans* and *Staphylococcus aureus* than the standard drug Ciprofloxacin with MIC as low as 0.2 µg/ml. However its activity against Gram-negative bacteria was comparatively lower than the Gram- positive bacteria.

The synthesized derivative 6a was crystallized with different solvents to check for change in crystal nature. All the crystals obtained from different solvents like acetonitrile, ethyl acetate, methanol and isopropyl alcohol were screened by differential scanning calorimetry (DSC). The themogram obtained from crystal in acetonitrile solvent (240.52 °C) showed different thermal enthalpy from that of the parent crystal (234.52 °C).

CONCLUSION: In the present study 2-substitutes benzimidazole derivatives were successfully prepared and characterized by analytical methods and was evaluated by antimicrobial activity which revealed the success of compounds 6b, 6c, 6d, 6e, 6f, 6g and 6j being potent antibacterial agents. Furthermore the polymorphism studies also shown the success of 6a to exhibit polymorphic properties. Further studies are necessary to investigate the therapeutic potential of substituted Benzimidazole moiety.

ACKNOWLEDGEMENT: This author likes to acknowledge KLEU's College of Pharmacy, Belagavi for providing all the necessary facilities to carry out the research work successfully.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

REFERENCES:

1. World Health Organization. Antimicrobial resistance global report on surveillance: World Health Organization; 2014. Available from: http://www.who.int/drugresistance/documents/surveillance report/en/
2. World Health Organization. Tuberculosis fact sheet World Health Organization; [updated 2014 Oct; cited Feb 2015]. Available from: http://www.who.int/mediacentre/fact sheets /fs104/en/
3. World Health Organization. Pneumonia Fact Sheet: World Health Organization; [updated 2014 Nov; cited Feb 2015]. Available from: http://www.who.int/mediacentre/fact sheets/fs331/en/-
4. Lemke TL, Williams DA, Roche VF and Zito SW: Foye's principles of medicinal chemistry. Lippincott Williams and Wilkins, South Asian 2013.
5. Wright JB: The chemistry of the benzimidazoles. Michigan: Research laboratories the Upjohn Company 1951.
6. Tuncbilek M, Kiper T and Altanlar N: Eur J Med Chem., 2009; 44: 1024-1033.
7. Desai NC, Shihory NR, Kotadiya GM and Desai P: Eur J Med Chem., 2014; 82: 480-489.
8. Purohit R and Venugopalan P: Resonance 2009; 882-89.
9. McGregor C and Bines E: Int J Pharm. 2008; 350: 48-52.
10. Schwalve R, Moore LS and Goodwin AC: Antimicrobial susceptibility testing protocols CRC Press 2007.

How to cite this article:
Konyak KLS, Maste MM, Saxena A and Inamdar P: Synthesis, evaluation and polymorphism studies of new benzimidazole derivatives as potent antibacterial agents. Int J Pharm Sci Res 2018; 9(5): 1929-34.doi: 10.13040/IJPSR.0975-8232. 9(5).1929-34.