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

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 December, 2017; received in revised form, 16 February, 2018; accepted, 04 March, 2018; published 01 September, 2018

IN-SILICO DESIGN, SYNTHESIS AND *IN-VITRO* ANTI-TUBERCULAR AND ANTI-MICROBIAL SCREENING OF NOVEL BENZIMIDAZOLE DERIVATIVES

P. T. Manju [*1], A. Anton Smith [2] and V. Padmaja [1]

College of Pharmaceutical Sciences [1], Government Medical College, Trivandrum - 695011, Kerala, India.
Department of Pharmacy [2], Annamalai University, Annamalainagar, Chidambaram - 608002, Tamil Nadu, India.

Keywords:

Benzimidazole derivatives, Conventional synthesis, Docking, *In- vitro* antimicrobial activity

Correspondence to Author:
P. T. Manju

Assistant Professor,
College of Pharmaceutical Sciences, Government Medical College, Trivandrum - 695011, Kerala, India.

E-mail: manjupt80@gmail.com

ABSTRACT: The present work aims to design, synthesize some novel benzimidazole derivatives and to perform *in-vitro* evaluation of their antitubercular and antimicrobial activity. *In-silico* modelling of benzimidazole derivatives was carried out using various softwares such as, ACD Labs Chemsketch, Molinspiration, PASS (Prediction of activity spectra for substances) and Schrodinger Glide XP (Grid based ligand docking with energetics). Nine derivatives (BI 1a, 1b, 1c, BI 2a, 2b, 2c and BI 3a, 3b, 3c) were designed. The designed molecules with required physicochemical properties, drug likeness and obeying Lipinski's rule of five were selected for the synthesis. The synthesized compounds were subjected to TLC, melting point determination, FTIR and mass spectral studies. All the synthesized compounds showed characteristic peak in FTIR and Mass spectroscopic studies. As per the PASS score and GLIDE score the compounds were selected for biological studies like antitubercular, antibacterial, and antifungal activity. These results are useful for further investigation in the future. All the selected derivatives showed better activity, when compared with standard drugs.

INTRODUCTION: The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds [1]. Development of organic compounds has grown beyond traditional synthetic methods. Heterocycles be present in the core of many biologically or pharmaceutically interesting compounds. Heterocyclic compounds have been shown to have deep impact on biological activities like anti-tumor, anti-oxidant, anti-inflammatory, antimicrobial, antiviral, *etc* [2]. A number of nitrogen containing heterocyclic groups are present in many of the biologically active compounds.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(9).3705-11

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

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(9).3705-11

Hence, they were subject of interest to synthesize and study some new heterocyclic derivatives. This along with tremendous success of synthetic hetero-cyclic drugs has attracted medicinal chemist's attention to this field.

Designing of new hetero compounds are done by incorporating heterocyclic moiety into lead molecule. The nucleus selected for the present work is a combination of two hetero aromatic molecules benzimidazole and imidazole. There are numerous reports in the literature about the wide spectrum of biological activities possessed by these lead molecules.

The benzimidazole moiety is a versatile lead molecule in pharmaceutical development. It has a wide range of biological activities such as antiinflammatory, antioxidant, antimicrobial [2, 3], anthelmintic, antitubercular [4, 5], antiviral [6, 7] *etc*. The synthetic versatility of benzimidazole has lead to the extensive use of this compound in organic synthesis.

In-silico molecular modeling studies are the most important step in drug design. The *in-silico* modeling of all the proposed derivatives were carried out by using different computational software in order to predict the physiological and biological parameters. The softwares used for *in-silico* studies includes Molinspiration, ACD lab Chemsketch and Marvin sketch, PASS and Schrodinger.

MATERIALS AND METHODS:

Molecular Docking:[8] Molecular docking is usually performed between a small molecule and a target macromolecule. This is often referred to as ligand-protein docking. Docking is the computational simulation of a candidate ligand binding to a receptor. During docking a pose is generated, scored and compared with a previous pose.

Methodology of Docking:

Target Identification and Retrieval: Crystallographic structures of the targets of interests were obtained from PDB (Protein Data Bank) and saved in standard 3D coordinate format. The targets used for the present study are membrane protein of Mycobacterium tuberculosis (2OAR) and Dihydrofolate reductase (3I8A).

Protein Preparation: The procedure started with a protein and a co-crystallized ligand. It was finished with a partially optimized protein-ligand complex, to which hydrogens were added subjected to protonation states for ionizable residues, modification of tautomeric forms and the repositioning of the reorientable hydrogens.

The first step was to prepare the co-crystallized ligands by correctly defining multiple bonds and adding hydrogens. Normally, proteins are provided without attached hydrogens. When hydrogens are present, all are deleted except those in peptide bond.

The second step was to neutralize residues that did not participate in the salt bridges and that were more than a specified distance from nearest ligand atom. The script also set the tautomeric state which was assumed to be neutral, by considering potential metal ligation and the hydrogen interactions.

The third step was to preprocess the receptor before grid preparation. This is necessary as the judgment made by the preparation procedure need not to be correct always.

In the fourth step the optimization of the protein was carried out by adding hydrogens to the protein, to any cofactors and to any added structural waters and the final step carried out series of restrained minimizations on the protein-ligand complex.

Ligprep: Ligprep generates energy minimized 3D molecular structures. It is used for the versatile generation of accurate 3D molecular models. Ligprep went far beyond simple 2D to 3D structure conversions by including tautomeric, stereo chemical and ionization variations as well as energy minimization and flexible filters to generate fully customized ligand libraries that were optimized for further computational analyses.

Docking: The generated structures of various conformations of drug like molecules using Ligprep was then docked in to the binding site of receptor after generating a receptor grid around the site using glide. The docking was conducted using XP GLIDE (Extra Precision).

Procedure for Synthesis:

Synthesis of Benzimidazoles: [9, 10] Monochloroacetic acid/Lactic acid/*p*- Chlorobenzoic acid and *o*-phenylene diamine were dissolved in 50 ml of 5N HCl and refluxed for seven hours with stirring. It was then cooled to 0 - 5 °C, and was neutralised with aqueous ammonium hydroxide. The precipitated product was collected by vacuum filtration, washed with water and dried in air.

Synthesis of Thioimidazole: [11] A mixture of benzoin and thiourea was dissolved in a mixture of chloroform and ethanol (3:1). The reaction mixture was stirred thoroughly, and refluxed for 12 h. The product obtained was recrystallised from methanol.

Condensation of Thioimidazole and various Benzimidazoles to yield Thioethers: [9] The thioimidazole (0.01mol) was dissolved in 25 ml of aqueous sodium hydroxide solution by stirring at room temperature. To this clear solution it was added a pinch of cetrimide and stirring was further continued for 10 min. To this a solution of various benzimidazoles (2 - chloromethylbenzimidazole/ 2-(1-chloroethyl)-1H-benzimidazole / 2-(4-chlorophenyl)-1H-benzimidazole) (0.01mol) in 25 ml ethanol

was added over a period of 15 - 20 min. The reaction mixture was further stirred for 2 h. It was then cooled to 5- 10 °C for 1/2 h and the separated solid was filtered, washed with cold water and dried. The crude product on recrystallization from chloroform and ethanol yielded a yellowish crystalline solid. Products obtained were named BI 1a, BI 2a and BI 3a.

Mild Oxidation of Various Thioethers to Yield Various Sulfinyl Benzimidazoles: Various thio ethers(2-{[(4,5-diphenyl-2H-imidazol-2yl) sulfanyl]methyl}-1H-benzimidazole/2-{1-[(4,5-diphenyl- 2 H-imidazol-2-yl)sulfanyl]ethyl}- 1H-benzimidazol e/2-{1-[(4,5diphenyl-2H-imidazol-2-yl)sulfanyl] be nzyl}-1H-benzimidazole) were dissolved in 20 ml iso-propanol by stirring at room temperature. The reaction mixture was chilled thereafter in an ice salt bath maintaining its temperature between 0 - 2 °C, to this a solution of meta-chloroperbenzoic acid (m-CPBA) (0.02 mol) was added with stirring.

The stirring was continued for 2-3 h. After completion of the reaction the mixture was washed with 10% sodium bicarbonate and extracted with chloroform (30 ml). The organic layer was dried with anhydrous sodium sulphate and solvent was distilled off under reduced pressure at room temperature. The crude product was purified by column chromatography using toluene: methanol (4.5:0.5) as the mobile phase. Products obtained were named BI 1b, BI 2b and BI 3b.

Oxidation of Sulfinyl Benzimidazoles to Yield Various Sulfonyl Benzimidazoles: [9] Various sulfinylbenzimidazoles were treated with 15 ml of 30% aqueous Hydrogen peroxide in 20 ml acetic acid and stirred at ambient temperature for 20 h. The reaction mixture was poured over 200 ml of ether containing 10 ml of hydrogen chloride - saturated alcohol and the mixture was stirred vigorously.

The supernatant solvent was decanted and a moderate amount of ethanol was added. The mixture was stirred until a crystalline solid was formed. The product was collected, washed with ether and recrystallised. The product was again purified by column chromatography using toluene: methanol (4.5:0.5) as the mobile phase. Products obtained were named BI 1c, BI 2c and BI 3c.

Characterization: The synthesized 2-substituted benzimidazole analogues were characterized by various analytical techniques like,

a. Melting point determination,
b. Thin Layer Chromatography (TLC),
c. Vibrational Spectroscopy (IR) and
d. MASS spectroscopy (MS).

As per the PASS score and GLIDE score the analogues designed were selected for biological studies like antitubercular, antibacterial, antifungal *etc*. The designed benzimidazole analogues which were selected for various studies were compared with standard drugs for any violation of Lipinski rule of five and drug likeness score.

Antitubercular Screening (Resazurinmicrotitre Assay): [12, 13] Antitubercular screening was done on novel benzimidazole analogues (BI 1c, BI 2c, BI 3c). Mycobacterium tuberculosis H37Rv maintained in Lowenstein Jensen medium was used as the test organism for antimycobacterial screening studies. The bacterial cultures were grown till mid-log phase in the Middle brook 7H9 broth. 50 µL of the mid-log phase culture was added to 150 µL of the media taken in microtitre plates. Stock solutions of the test compounds were prepared at a concentration of 2 mg/ml.

From the stock solution the compounds were added to the wells to final concentration of 100, 200, 300, 400 µg/mL. The control wells contained culture without any compound. All the tests were done in duplicates. The plates were then incubated at 37 °C for 7 days. After incubation 20 µL of resazurin dye was added and change of colour was noted. The control wells showed no change of colour from pink. Those compounds which prevented the change of colour of the dye from blue to pink were considered to be inhibitory.

Antibacterial Screening: [14] Antibacterial screening was done on novel benzimidazole analogues (BI 1a, BI 2a, BI 3a). The organisms used were *Staphylococcus aureus* ATCC 25923 (Gram +ve) and *Escherichia coli* ATCC 25922 (Gram –ve). The test solutions were prepared in chloroform. The concentrations used for antibacterial screening were 100, 200 µg/mL. Standard drug solution of Amikacin (100 µg/mL) was prepared in distilled water.

Using a sterile cork borer of about 5 mm diameters, 4 wells were made in each petri dish. Numbers were marked on the bottom of petri dish to identify each cup. The test solutions (single and double strength), standard solution and the vehicle control (chloroform) were placed in each cup of each petri dish and incubated at 37 ± 0.5 ºC for 24 h. The presence of a definite zone of inhibition of any size was observed and compared with that of standard drug solution.

Antifungal Screening: [14] Antifungal screening was done on randomly selected novel benzimidazole analogues (BI 1a, BI 2a, BI 3a). Clotrimazole was used as standard. The organisms used were *Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404. Sabouraud dextrose agar was suspended in 1000 mL of distilled water and boiled to dissolve the medium completely. pH was adjusted using 0.1 N sodium hydroxide and sterilization was done by autoclaving at 15 psi at 121^{o}C for 15 min. 20 ml each of sterile Sabouraud dextrose broth was inoculated with organism. 5 ml of each broth was added to 100 ml of sterilized Sabouraud dextrose agar medium separately. This inoculated medium was then poured into previously sterilized, appropriately marked petri dishes and allowed to settle. All these procedures were done under aseptic conditions. The petri dishes were incubated at 25 ºC for 24 h. The zone of inhibition was observed and compared with the standard drug clotrimazole.

RESULTS: In the present study, *in-silico* design of the proposed derivatives was carried out by using different software. 3D drawing, optimizing and calculating various molecular descriptors of the proposed an derivatives were done using ACD labs chemsketch. The results are shown in **Table 1**. With the help of Molinspiration software the log P values, any violation of Lipinski rule of five and drug likeness were studied by comparing with the existing standard drugs. The results are shown in **Tables 2** and **3**.

TABLE 1: VARIOUS DERIVATIVES DESIGNED AND DRAWN USING ACD LABS CHEM SKETCH

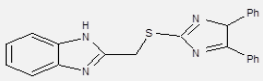
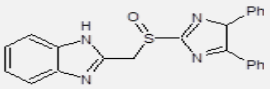
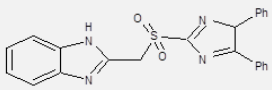
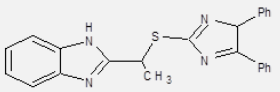
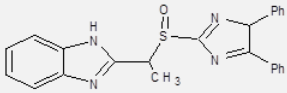
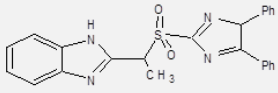
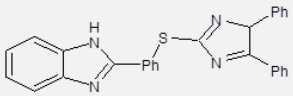
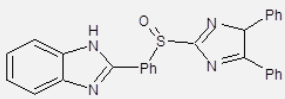
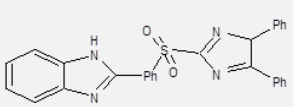
Compound	Analogues	Molecular formula	Smiles Notation
BI 1a		$C_{23}H_{18}N_4S$	c5ccc(C3=NC(SCC2Nc1ccccc1N2)N=C3 c4ccccc4)cc5
BI 1b		$C_{23}H_{18}N_4OS$	O=S(Cc2nc1ccccc1[nH]2)C5N=C(c3ccccc3)C (c4ccccc4)=N5
BI 1c		$C_{23}H_{18}N_4O_2S$	O=S(=O)(Cc2nc1ccccc1[nH]2)C5N=C(c3ccccc3) C(c4ccccc4)=N5
BI 2a		$C_{24}H_{20}N_4S$	CC(SC3N=C(c1ccccc1)C(c2ccccc2)=N3) c5nc4ccccc4[nH]5
BI 2b		$C_{24}H_{20}N_4OS$	CC(c2nc1ccccc1[nH]2)S(=O)C5N=C(c3ccccc3)C (c4ccccc4)=N5
BI 2c		$C_{24}H_{20}N_4O_2S$	CC(c2nc1ccccc1[nH]2)S(=O)(=O)C5N=C (c3ccccc3)C(c4ccccc4)=N5
BI 3a		$C_{28}H_{20}N_4S$	c6ccc(C4=NC(Sc3ccc(c2nc1ccccc1[nH]2)cc3) N=C4c5ccccc5)cc6
BI 3b		$C_{28}H_{20}N_4OS$	O=S(c3ccc(c2nc1ccccc1[nH]2)cc3)C6N=C (c4ccccc4)C(c5ccccc5)=N6
BI 3c		$C_{28}H_{20}N_4O_2S$	O=S(=O)(c3ccc(c2nc1ccccc1[nH]2)cc3)C6N=C (c4ccccc4)C(c5ccccc5)=N6

TABLE 2: ANALYSIS OF LIPINSKI RULE OF FIVE OF STANDARD DRUGS AND THE PROPOSED DERIVATIVES

Compound	LOG P	Mol. wt.	nHDon	nHAcc	nrotb	Lipinski rule alert index
Isoniazid	-0.969	137.14	3	4	1	0
Amoxicillin	-1.352	365.4	5	8	4	0
Clotrimazole	5.1	348.87	2	1	4	1
BI 1a	4.851	382.48	2	4	5	0
BI 1b	3.387	398.48	1	5	5	0
BI 1c	3.79	414.48	1	6	5	0
BI 2a	5.278	396.51	1	4	5	1
BI 2b	3.75	412.52	1	5	5	0
BI 2c	4.153	428.51	1	6	5	0
BI 3a	6.864	444.55	1	4	5	1
BI 3b	5.27	460.55	1	5	5	1
BI 3c	5.3	476.55	1	6	5	1

TABLE 3: ANALYSIS OF DRUG LIKENESS SCORE OF STANDARD DRUGS AND THE PROPOSED DERIVATIVES

Compound	GPCR ligand	Ion Channel modulator	Kinase inhibitor	Nuclear receptor ligand
Isoniazid	-1.37	-1.53	-0.67	-2.56
Amoxicillin	0.7	-0.42	-0.65	-0.47
Clotrimazole	-0.04	-0.15	-0.25	-0.5
BI 1a	-0.14	-0.17	-0.35	-0.31
BI 1b	0.01	-0.14	-0.53	-0.81
BI 1c	-0.01	-0.19	-0.34	-0.63
BI 2a	-0.05	-0.12	-0.45	-0.56
BI 2b	-0.04	-0.07	-0.58	-0.73
BI 2c	-0.06	-0.13	-0.39	-0.56
BI 3a	0.01	-0.31	-0.12	-0.78
BI 3b	0.01	-0.31	-0.12	-0.78
BI 3c	0.08	-0.41	-0.1	-0.75

Nine benzimidazole derivatives were prepared through a series of five steps. The synthesized compounds were named BI 1a, 1b, 1c, BI 2a, 2b, 2c and BI 3a, 3b, 3c. Purity of the compounds was ascertained by TLC and melting point determination. The results are shown in **Table 4**.

TABLE 4: MELTING POINT AND R_f VALUE OF THE SYNTHESIZED DERIVATIVES

Compound	Molecular formula	Yield (%)	Melting point (ºC)	R_f
BI 1a	$C_{23}H_{18}N_4S$	92	180	0.44
BI 1b	$C_{23}H_{18}N_4OS$	86	160	0.66
BI 1c	$C_{23}H_{18}N_4O_2S$	70	294	0.83
BI 2a	$C_{24}H_{20}N_4S$	94	184	0.3
BI 2b	$C_{24}H_{20}N_4OS$	88	168	0.53
BI 2c	$C_{24}H_{20}N_4O_2S$	74	296	0.76
BI 3a	$C_{28}H_{20}N_4S$	90	294	0.23
BI 3b	$C_{28}H_{20}N_4OS$	82	226	0.4
BI 3c	$C_{28}H_{20}N_4O_2S$	70	280	0.81

The results of characterization by IR and MASS are shown in **Table 5**.

Docking studies were performed using Schrodinger Glide XP software. Compounds having high (-) value is considered as the best one. Dock scores of proposed benzimidazole derivatives with membrane protein of *Mycobacterium tuberculosis* (2OAR) and Dihydrofolate reductase (3I8A) are given in **Table 6** and **7** and the images of docked complex are shown in **Fig. 1** and **2** respectively.

TABLE 5: SPECTRAL RESULTS OF SYNTHESIZED BENZIMIDAZOLE DERIVATIVES

Compound	IR spectral analysis	Mass M+ peak
BI 1a	3378 (NH str), 1594(C=N str), 746 (C-S str), 3191 (Ar-CH str)	382
BI 1b	2990(NH str), 750 (C-S str), 3194 (Ar-H str)	398
BI 1c	3402 (NH str), 1588(C=N str), 756(C-S str), 865 (S-Ostr)	414
BI 2a	3385 (NH str), 1591(C=N str), 746 (C-S str), 3191 (Ar-CH str)	396
BI 2b	3416 (NH str), 1594 (C=N str), 754 (C-S str), 1678 (Ar-C=C str)	412
BI 2c	3414 (NH str), 1595 (C=N str), 754 (C-S str, 1344 (Asymmetric SO_2 str), 977(S-O str), 1679 (Ar C=C str)	428
BI 3a	3450 (NH str), 1596 (C=N str), 1650 (Ar C=C str), 727 (C-S str)	444
BI 3b	3383 (NH str), 1618 (Ar C=C str), 1594 (C=n str) 870 (S-O), 1109 (SO2, symstr), 740 (Ar C-C v)	460
BI 3c	3399 (NH str), 1598 (C=N str), 758 (C-S str) 870 (S-O), 1109 (SO2, symstr), 740 (Ar C-C v)	476

TABLE 6: GLIDE SCORE WITH 2OAR (MEMBRANE PROTEIN OF *MYCOBACTERIUM TUBERCULOSIS*)

Compound	Glide score	glide energy (Kcal/mol)
Isoniazid	-8.50	-52.60
BI 2c	-9.16	-52.60
BI 1c	-9.08	-55.26
BI 3c	-9.01	-53.99
BI 2b	-8.98	-58.23
BI 1b	-8.88	-55.97
BI 3b	-8.85	-53.48
BI 1a	-8.76	-52.82
BI 2a	-8.23	-57.91
BI 3b	-7.91	-58.88

TABLE 7: GLIDE SCORE WITH 3I8A (DIHYDROFOLATE REDUCTASE)

Compound	Glide score	Glide energy (Kcal/mol)
Amoxicillin	-5.91	-42.60
BI 2a	-6.58	-42.67
BI 1a	-5.98	-41.05
BI 3a	-5.75	-42.58
BI 1b	-5.77	-43.88
BI 2c	-5.83	-29.73
BI 3b	-5.19	-44.73
BI 2b	-5.02	-38.93
BI 3c	-4.79	-41.96
BI 1c	-2.89	-33.75

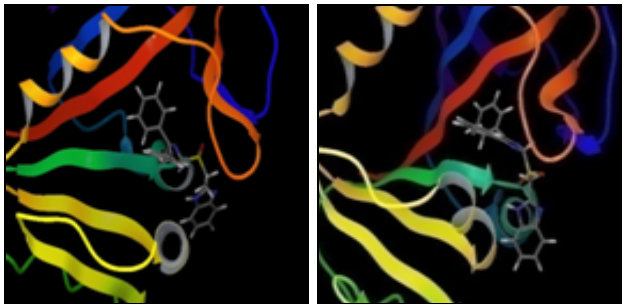


FIG. 1: DOCKING IMAGE OF BI 2c AND BI 1c TO 2OAR

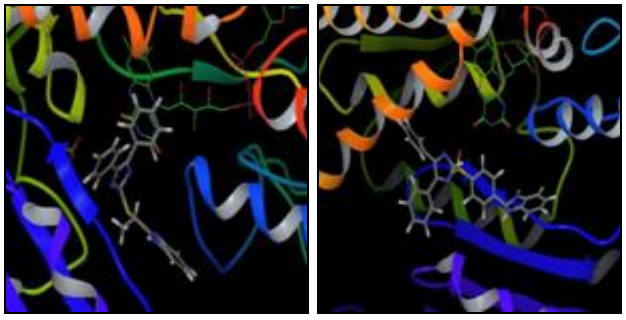


FIG. 2: DOCKING IMAGE OF BI 2a AND BI 1a TO 3I8A

Based on the Schrodinger Glide XP score, BI 1c, BI 2c, BI 3c were selected for *in-vitro* anti-tubercular evaluation and BI 1a, BI 2a, BI 3a were selected for antibacterial screening. The results of anti-tubercular, antibacterial, anti-fungal activities are shown in **Table 8**, **9**, and **10** respectively.

TABLE 8: *IN-VITRO* ANTITUBERCULAR ACTIVITY OF SELECTED BENZIMIDAZOLE DERIVATIVES

Concentration (µg/ml)	% Inhibition			
	BI 2c	BI 1c	BI 3c	Standard
0	0	0	0	0
50	46.47 ± 1.16	44.2 ± 2.54	37.5 ± 1.37	50 ± 1.12
100	51.47 ± 1.37	54.46 ± 2.98	46.42 ± 2.06	62.88 ± 1.12
150	63.52 ± 1.98	74.11 ± 2.63	57.59 ± 3.93	70 ± 1.12
200	80.88 ± 1.26	80.36 ± 2.98	72.32 ± 3.04	75.45 ± 1.12
250	88.23 ± 1.98	88.23 ± 2.54	78.57 ± 1.26	100 ± 1.12

All values are expressed as mean ± SEM. Each concentration was evaluated in triplicate

TABLE 9: ANTIBACTERIAL ACTIVITY OF SELECTED BENZIMIDZOLE DERIVATIVES

S. no	Sample	Zone of Inhibition(mm)			
		E. coli		*S. aureus*	
		100 µg	200 µg	100 µg	200 µg
1	Control	12	-	10	-
2	Standard	19	-	18	-
3	BI 2a	16 ± 0.33	19 ± 0.33	16 ± 0.33	19 ± 0.33
4	BI 1a	14 ± 0.88	16 ± 0.88	16 ± 0.66	16 ± 0.33
5	BI 3a	14 ± 0.88	17 ± 0.66	13 ± 0.66	14 ± 0.66

All values are expressed as mean ± SEM. Each concentration was evaluated in triplicate.

TABLE 10: ANTIFUNGAL ACTIVITY OF SELECTED BENZIMIDAZOLE DERIVATIVES

S. no.	Sample	Zone of Inhibition(mm)			
		Candida albicans		*Aspergillus niger*	
		100 µg	200 µg	100 µg	200 µg
1	Control	6	1	Control	6
2	Standard	14	2	Standard	14
3	BI 2a	12 ± 0.33	3	BI 2a	12 ± 0.33
4	BI 1a	10 ± 0.66	4	BI 1a	10 ± 0.66
5	BI 3a	8 ± 0.66	5	BI 3a	8 ± 0.66

All values are expressed as mean ± SEM. Each concentration was evaluated in triplicate.

DISCUSSION: *In-silico* design of all the proposed derivatives were carried out using ACD Labs Chemsketch, Molinspiration, PASS and Schrodinger Glide XP. The compounds were synthesized by conventional method and were characterized by TLC, melting point determination, FTIR and MASS. The synthesized derivatives were screened for the biological activities on the basis of Pass and Glide score.

The *in-vitro* antitubercular, antibacterial and antifungal screening of all the selected derivatives exhibited better activity. Compound BI 2c showed significant antitubercular activity and the compound BI 2a showed significant antibacterial and antifungal activity when compared with the standard. These compounds BI 2c and BI 2a needs further studies, so that these compounds give better results. So it is evident that further work on these derivatives has to be done in future for the development of clinically useful antimicrobial agents.

CONCLUSION: In summary, the main objective of the present work was to design, synthesize and biologically screen some novel benzimidazole derivatives. Various benzimidazole derivatives were synthesized and characterized by spectral studies. In the *in-vitro* antitubercular, antibacterial and antifungal screening, compound BI 2c showed significant antitubercular activity and the

compound BI 2a showed significant antibacterial and antifungal activity. Substitution of the benzimidazole moiety with hetero aromatic, sulfonyl group and sulphur atom might be responsible for the enhancement of activity. So these derivatives (BI 2c and BI 2a) can be subjected to further studies for consideration as a drug candidate.

ACKNOWLEDGEMENT: Authors are thankful to everyone who assisted in this work.

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Patrick GL: An Introduction to Medicinal Chemistry. Oxford University Press, 1995; 319-343.
2. Ramanpreet W, Hedaitullah M and Naaz SF: Benzimidazole derivatives - an overview. International Journal of Research in Pharmacy and Chemistry 2011; 1(3): 565-574.
3. Alasmary AS, Snelling AM and Zain ME: Synthesis and evaluation of selected benzimidazole derivatives as potential antimicrobial agents. Molecules 2015; 20: 15206-15223.
4. Prasad KPM and Sundararajan R: Design, synthesis, anti-tubercular and antimicrobial activities of novel thiazole substituted benzimidazole derivatives. Der Pharmacia Lettre 2017; 9(6): 270-284.
5. Gong J, He Y and Cui ZL: Synthesis, spectral characterization, and antituberculosis activity of thiazino[3,2-*A*]benzimidazole derivatives. Phosphorus, Sulfur and Silicon and the Related Elements 2016; 191(7): 1036-1041.
6. Nomi S, Janmajoy B and Sujiti S: A review on chemistry and biological significance of benzimidaole nucleus. IOSR Journal of Pharmacy 2014; 4(12): 28-41.
7. Singh G, Kaur M and Chander M: Benzimidazoles: The latest information on biological activities. International Research Journal of Pharmacy 2013; 4(1): 82- 87.
8. Manju PT, Smith AA and Padmaja V: *In-silico* design of an SGLT2 inhibitor in diabetes mellitus. Middle-East Journal of Scientific Research 2016; 24(10): 3108-3112.
9. Bariwal JB, Shan AK, Kathiravan MK, Somani RS and Jain KS: Synthesis and antiulcer activity of novel pyrimidylthiomethyl- and pyrimidylsulfinylmethyl- benzimidazoles as potential reversible proton pump inhibitors. Indian Journal of Pharmaceutical Education and Research 2008; 42: 225-229.
10. Shobhit S, Pandeya SN and Meena K: Synthesis and analgesic activity of novel derivatives of 1, 2-Substituted Benzimidazoles. Journal of Chemistry 2012; 2013: 1- 6.
11. Anshul C, Ashu S and Kumar AS: Review: A convenient approach for the synthesis of imidazole derivatives using microwaves. Der Pharma Chemica 2012; 4(1): 116-140.
12. Arul K and Smith AA: *In-silico* synthesis and *in-vitro* antitubercular activity of novel 1,2,4-triazole derivatives. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6: 213-218.
13. Arul K and Sunisha KS: *In-silico* design and anti tubercular activity of novel azetidinone containing isatin derivatives. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(9): 506-513.
14. Indian Pharmacopoeia. Indian Pharmacopoeia Commission, Ghaziabad, Vol. I, 2007; 45-52.

How to cite this article:
Manju PT, Smith AA and Padmaja V: *In-silico* design, synthesis and *in-vitro* anti-tubercular and anti-microbial screening of novel benzimidazole derivatives. Int J Pharm Sci & Res 2018; 9(9): 3705-11. doi: 10.13040/IJPSR.0975-8232.9(9).3705-11.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)