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Synthesis, in silico studies and antibacterial activity of some novel 2-substituted benzimidazole derivatives

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Abstract

Background: The o-phenylenediamine is a versatile starting material for several compounds. Synthesized o-phenylenediamine and amino acids (glycine, alanine, aspartic acid, and L-proline) undergo condensation via Phillips reaction. The synthesized compound showed the promising antibacterial activity of *Bacillus subtilis* and *Pseudomonas aeruginosa* at the concentration of 100, 50, 25, 12.5, 6.25, 3.12, 1.6, 0.8, 0.4, and 0.2 μg/ml. Ciprofloxacin was used as standard drug. Synthesis of benzimidazole derivatives was carried out and purified by recrystallization process using ethanol. Substituted derivatives were characterized by melting point, TLC and spectroscopic methods include FT-IR and ^{1}H-NMR.

Results: In silico studies were adopted for synthetic derivatives by Molinspiration, ChemDraw, and online software tool. Minimum inhibitory concentration (MIC) values of *B. subtilis* and *P. aeruginosa* were reported, and benzimidazole ligands and Molinspiration scores were generated and listed.

Conclusion: The more negative values indicate a higher binding affinity. The generated ligand observations can be visualized. Physical constants of synthesized derivates such as solubility and melting point were determined. Bioactivity scores were noted for different derivatives and predicted percentage absorption in the gut. The antibacterial activity was performed using the MIC method (aerobic).

Keywords: Analytical methods, Antibacterial activity, Benzimidazole derivatives, MIC method, Molinspiration tool

Background

Benzimidazole consists of a benzene ring fused with imidazole. It is a cyclic ring that has two nitrogens as heteroatoms and is called heterocyclic aromatic compounds. It has a fine structure and medicinal properties useful worldwide. The simple example of benzimidazole is cyanocobalamin vitamin [1]. Recently, infections are causing microbial diseases to many people globally; they are showing resistance to several antimicrobial agents such as β-lactam antibiotics like penicillins, cephalosporins, macrolides, fluoroquinolones, vancomycin, and erythromycin. One goal is the proper usage of the present available marketed antibiotics, and the other goal is the development and synthesis of new antimicrobial agents. So, there is always a need and the necessity to find novel chemotherapeutic agents to overcome the resistance and shorten the duration of therapy [2].

The benzimidazole structure is important in the drug discovery process. Many important drugs used therapeutically in research area contain benzimidazole ring. Example: proton pump inhibitors (lansoprazole, omeprazole), antihistamines (astemizole), antihypertensives (telmisartan, candesartan), anthelmintics (albendazole, flubendazole, mebendazole) etc. Benzimidazole and its analogues have received much consideration due to their medicinal values. Benzimidazole analogues have found the gratefulness in diverse healing areas including antimicrobial, antioxidant, anthelmintic, antihypertensive, anti-inflammatory, antiprotozoal, anti-hepatitis B virus,

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antiviral, antifungal and anticonvulsant activity, analgesic, antiulcer, and anticancer [3]. Amoxicillin, norfloxacin, and ciprofloxacin are the most commonly used drugs for this bacterial contamination but are related to severe side effects [4]. A continuous increase in the number of infections produced by bacteria resistant to one or multiple antibiotic classes has a significant threat and may lead to treatment failures and complications. Therefore, significant hard work has been made by many research groups to find out new antibacterial agents [5–7].

Methods

All the compounds or derivatives were determined by the melting point apparatus. IR spectra of derivatives have been recorded on FT-IR Spectrophotometer (BRUKER) and TLC using Merck 0.25 mm silica gel plates. the progress of each reaction was observed in the present examination. The chemicals used are obtained from SD Fine Chemicals Limited, Mumbai, and are of AR grade. Compounds were synthesized, identified, and characterized by following methods such as melting point determination, thin layer chromatography, and infrared spectroscopy [8–10].

In silico studies

Bioinformatics is a combination of biology, computer science, and information science merged into a single discipline. It manages and analyses biological data using advanced computing techniques. In silico means "performed on the computer or through computer simulation". The term "in silico" was first used by Pedro Miramontes. He carried biological experimentations carried out mainly on a computer. As structural analogues of more protein targets become presented through bioinformatics, NMR, and crystallography methods, so there is a rising demand for computational tools that can identify and analyse the active sites and give potential drug molecules that can bind to these sites specifically. To fight life-threatening illnesses such as malaria, tuberculosis, and HIV, everybody's efforts are essential. The time and cost required for designing a new drug are immense at an unacceptable level. In silico modelling is a computer-based modelling whose technologies are useful in drug target identification or drug finding processes [11, 12].

Phillips reaction

The Phillips reaction involves the condensation of o-phenylenediamines with organic acids in the presence of dilute mineral acids to furnish 2-benzimidazoles [13, 14].

Procedure

0.05 mole of o-phenylenediamine compound and 0.05 mole of amino acids (glycine, alanine, Laspartic acid, L-proline) were transferred to a round bottom flask and add 10 ml of 4N HCl and then heated in a water bath for 1 h. After heating, the reaction was cooled by using ice cubes and it is alkalized by adding 10% sodium hydroxide until the litmus converts to blue colour. The solid separated was collected by filtration, dried, and recrystallized with ethanol [15–17].

Calculation of molecular physicochemical properties

Log *p* in Molinspiration measures the totality of fragment-based aids and correction factors. This method processes all organic and organometallic molecules. TPSA is sum of fragment contributions, polar fragments like centred O and N are considered. It is a good descriptor containing drug absorption plus intestinal absorption, bioavailability, and blood-brain barrier penetration. Molecular volume is based on contributions (group). These were obtained by fitting nearly of the fragment aids to real 3D volume for a training set of about 12,000, mostly drug-like molecules. Several rotatable bonds are a measure of molecular flexibility. It is a good descriptor of oral bioavailability of drugs. Rotatable bond is distinct as any single non-ring bond, confined to a non-terminal heavy atom.

Rule of 5 properties

It is a simple molecular descriptor used by Lipinski. The rule states that most drug-like molecules have log *p* less than or equal to 5, molecular weight less than or equal to 500, number of hydrogen bond acceptors less than or equal to 10, and number of hydrogen bond donors less than or equal to 5. Molecules crossing more than one of these rules may have problems of bioavailability. The rule is called Rule of 5.

Molinspiration batch property calculation tool kit

Molinspiration is a molecular processing and property calculation tool kit. It is written in Java. Molinspiration may be used in a batch mode to process a large number of molecules. This can process data speed of about 10, 000 molecules per minute. It can access through web interface directly on your internet. Molecular descriptors were calculated and used for property-based virtual screening of large collection of molecules.

Results (Tables 1 and 2)

The results describe that compound C4 shows the log *p* value 1.68, and all compounds show TPSA less than 150 A^0 indicating a good permeability of drug in the cellular plasma membrane. %ABS means percentage absorption

Table 1 Results of prediction of molecular descriptors

Compound codes	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)
C1	$C_8H_9N_3$	147.18	102–105 °C	78
C2	$C_9H_{11}N_3$	161.21	98–102 °C	75
C3	$C_{10}H_{11}N_3O_2$	205.22	95–100 °C	70.25
C4	$C_{11}H_{13}N_3$	187.25	110–115 °C	3.32

which should be in the range of 77.26–94.96% signifying good absorption in the intestine.

Formula for calculation of percentage absorption

$$\%ABS = 109 - 0.345 \times TPSA$$

Calculation of bioactivity score towards these compounds revealed that C1 is active as an ion channel modulator. C3 is active as a GPCR ligand, ion channel modulator, and enzyme inhibitor. C4 is active as an ion channel modulator and enzyme inhibitor. For organic molecules, the probability is that if the bioactivity score is greater than 0, then it is active. If the score is in between − 5 and 0, then it is moderately active. If the score is less than − 5, then it is inactive (Tables 3 and 4).

Spectral data of compounds

1-(1H-Benzo[d]imidazol-2-yl) methenamine: C1

Dark brown; yield 78%; mp 102–105 °C; TLC Rf value = 0.74 (4:1:5 n-butanol:water:glacial acetic acid). IR = 1460 cm^{-1} (C-H) Aliphatic, 1267 cm^{-1} (1^0Amine) (C-N), 1496 cm^{-1} (C=C), 1629 cm^{-1} (C=N), 3033 cm^{-1} (C-H) Aromatic; $C_8H_9N_3$ (147.18). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.61–7.58 (dd, *J* = 9.4 and 3.2 Hz, 2H), 7.26–7.22 (dd, *J* = 9.3 and 3.1 Hz 2H), 5.02 (dd, *J* = 8.1 and 2.9 Hz, 1H), 3.81 (s, 2H), 2.0 (s, 2H).

1-(1H-Benzimidazol-2-yl)ethanamine: C2

Light brown; yield 75%; mp 98–102 °C; TLC Rf value = 0.75 (4:1:5 n-butanol:water:glacial acetic acid). IR = 1460 cm^{-1} (C-H) Aliphatic, 1270 cm^{-1} (1^0Amine) (C-N), 1498 cm^{-1} (C=C), 1631 cm^{-1} (C=N), 3031 cm^{-1} (C-H) Aromatic; $C_9H_{11}N_3$ (161.21). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.61–7.58 (dd, *J* = 9.4 and 3.2 Hz, 2H), 7.26–7.22 (dd, *J* = 9.3 and 3.1 Hz 2H), 5.02 (dd, *J* = 8.1 and 2.9 Hz, 1H), 4.08 (q, 1H), 2.0 (s, 2H), 1.40 (d, 3H).

3-(1H-Benzimidazole-2-yl)-3-aminopropanoic acid: C3

Cream; yield 70.25%; mp 95–100 °C; TLC Rf value = 0.76 (4:1:5 n-butanol:water:glacial acetic acid). IR = 1779 cm^{-1} (C=O), 3032 cm^{-1} (OH), 1496 cm^{-1} (C-H) Aliphatic, 1267 cm^{-1} (1^0Amine) (C-N), 1631 cm^{-1} (C=C), 1588 cm^{-1} (C=N), 3189 cm^{-1} (C-H) Aromatic; $C_{10}H_{11}N_3O_2$ (205.22). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 11.0 (S, 1H), 7.61–7.58 (dd, *J* = 9.4 and 3.2 Hz, 2H), 7.26–7.22 (dd, *J* = 9.3 and 3.1 Hz 2H), 5.02 (dd, *J* = 8.1 and 2.9 Hz, 1H), 4.23 (t, 1H), 2.85–2.80 (d, 2H), 2.0 (s, 2H).

2-Pyrrolidin-2-yl-1H-benzoimidazole: C4

Red; yield 3.32%; mp 110–115 °C; TLC Rf value = 0.70 (4:1:5 n-butanol:water:glacial acetic acid). IR = 1330 cm^{-1} (C-H) Aliphatic, 1267 cm^{-1} (1^0Amine) (C-N) Proline, 1496 cm^{-1} (C=C), 1634 cm^{-1} (C=N), 3034 cm^{-1} (C-H) Aromatic; $C_{11}H_{13}N_3$ (187.25). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.61–7.58 (dd, *J* = 9.4 and 3.2 Hz, 2H), 7.26–7.22 (dd, *J* = 9.3 and 3.1 Hz 2H), 5.02 (dd, *J* = 8.1 and 2.9 Hz, 1H), 4.03 (t, 1H), 2.80–2.70 (t, 2H), 2.0 (s, 1H), 1.9–1.54 (m, 4H) (Fig. 1).

Antibacterial activity

The synthesized compounds or derivatives were exposed to antibacterial activity on *Bacillus subtilis* and *Pseudomonas aeruginosa* [18]. The standard drug used in this MIC test is ciprofloxacin 2 μg/ml. This activity was performed at Maratha Mandal's Central Research Laboratory, Belgaum. The material used in the antibacterial activity is Himedia M210 and brain heart infusion broth. The ingredients in BHI broth are calf brain infusion 200 g/l, beef heart infusion 250 g/l, protease peptone 10 g/l, dextrose 2 g/l, sodium chloride 5 g/l, and disodium phosphate 2.5 g/l. The final pH (at 25 °C) is 7.4 ± 0.2 [19].

Procedure for aerobic MIC test

We have taken each drug of 9 dilutions with BHI for MIC. In the initial tube, 20 μl of the drug was added into

Table 2 Bioactivity scores

Compound codes	Mi log *p*	TPSA	*n* atoms	MW	*N* ON	*n* OHNH	*n* viol	*n* rotb	Volume	%ABS
C1	0.72	54.71	11	147.18	3	3	0	1	136.96	90.13
C2	− 0.60	54.71	12	161.21	3	3	0	1	153.54	90.13
C3	− 1.46	92.00	15	205.22	5	4	0	3	180.78	77.26
C4	1.68	40.71	14	187.25	3	2	0	1	177.66	94.96

Table 3 Physical characterization of compounds

Compound codes	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
C1	− 0.61	0.13	− 0.59	− 1.79	− 0.75	− 0.20
C2	− 0.47	− 0.14	− 0.72	− 1.44	− 0.82	− 0.28
C3	0.12	0.12	− 0.53	− 0.79	− 0.22	0.10
C4	− 0.22	0.20	− 0.51	− 1.50	− 0.63	0.01

the 380 μl of BHI broth [20]. Take 9 tubes to prepare dilutions of BHI broth of 200 μl added separately. Then, from the initial tube, 200 μl was transferred to the first tube containing 200 μl of BHI broth. This was measured as 10–1 dilution, and from 10–1 diluted tube, 200 μl was shifted to the second tube to make 10–2 dilution. This serial dilution was repetitive up to 10–9 dilution for each drug [21]. From the stock cultures of essential organisms, 5 μl was taken and added into 2 ml of brain heart infusion broth. Each tube serially diluted 200 μl of above culture suspension was added. The glass tubes were incubated for 24 h, then observe its turbidity [22, 23].

In silico study revealed many interesting observations. Based on these theoretical predictions, the percentage absorption value for C4 is 94.96% [24, 25]. The more negative values indicate higher binding affinity. The generated ligand values can be visualized. The compounds showed better scores [26, 27] (Table 5).

Discussion

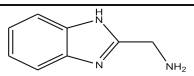
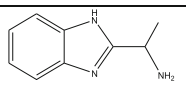
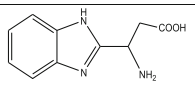
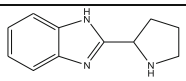
Results are summarized in tables and schemes and showed the details of the synthetic strategy adopted for these compounds [28]. The o-phenylenediamine is a starting material for preparing number of compounds. o-Phenylenediamine and amino acids (alanine, glycine, aspartic acid, L-proline) had undergone condensation via Phillips reaction. The different compounds were recrystallized by suitable solvents like ethanol. IR, TLC, and melting point are confirmed for different compounds and also determined physicochemical parameters. In silico studies were done by using ChemDraw and Molinspiration software tool. MIC values of *B. subtilis* and *P. aeruginosa* with benzimidazole derivatives were determined [29]. Ligands and Molinspiration scores were generated and listed [30]. Bioactivity scores were noted for different derivatives, predicted percentage absorption values in the gut, and found good absorption values. The results showed very good ligand observations. The calculated binding energy values should be minimum for benzimidazole ligands.the calculated binding energy values should be minimum for benzimidazole ligands. The more negative values indicate higher binding affinity [31, 32]. The generated ligand values and the compounds showed better scores [33].

In silico study revealed many interesting observations. Based on theoretical predictions, the percentage absorption value for C4 is 94.96%. We say benzimidazole is a very good moiety for further investigation [34, 35]. The produced compounds were evaluated for antibacterial activity by using the MIC test [36]. The compound C3 showed very good antibacterial activity at very low concentration, and other synthesized compound showed the promising antibacterial activity of *B. subtilis* and *P. aeruginosa* at the concentration of 100, 50, 25, 12.5, 6.25, 3.12, 1.6, 0.8, 0.4, and 0.2 μg/ml.

Conclusion

In the present study, benzimidazole analogues were synthesized and investigated for their antibacterial action by

Table 4 Solubilities and appearance of synthesized compounds

code	Compound structure	appearance	Water	Spirit	Acetone	DMF
C1		Dark Brown	soluble	Insoluble	Insoluble	Insoluble
C2		Light Brown	Soluble	soluble	Soluble	Soluble
C3		Cream	Soluble	soluble	Soluble	soluble
C4		Red	Soluble	soluble	Soluble	soluble

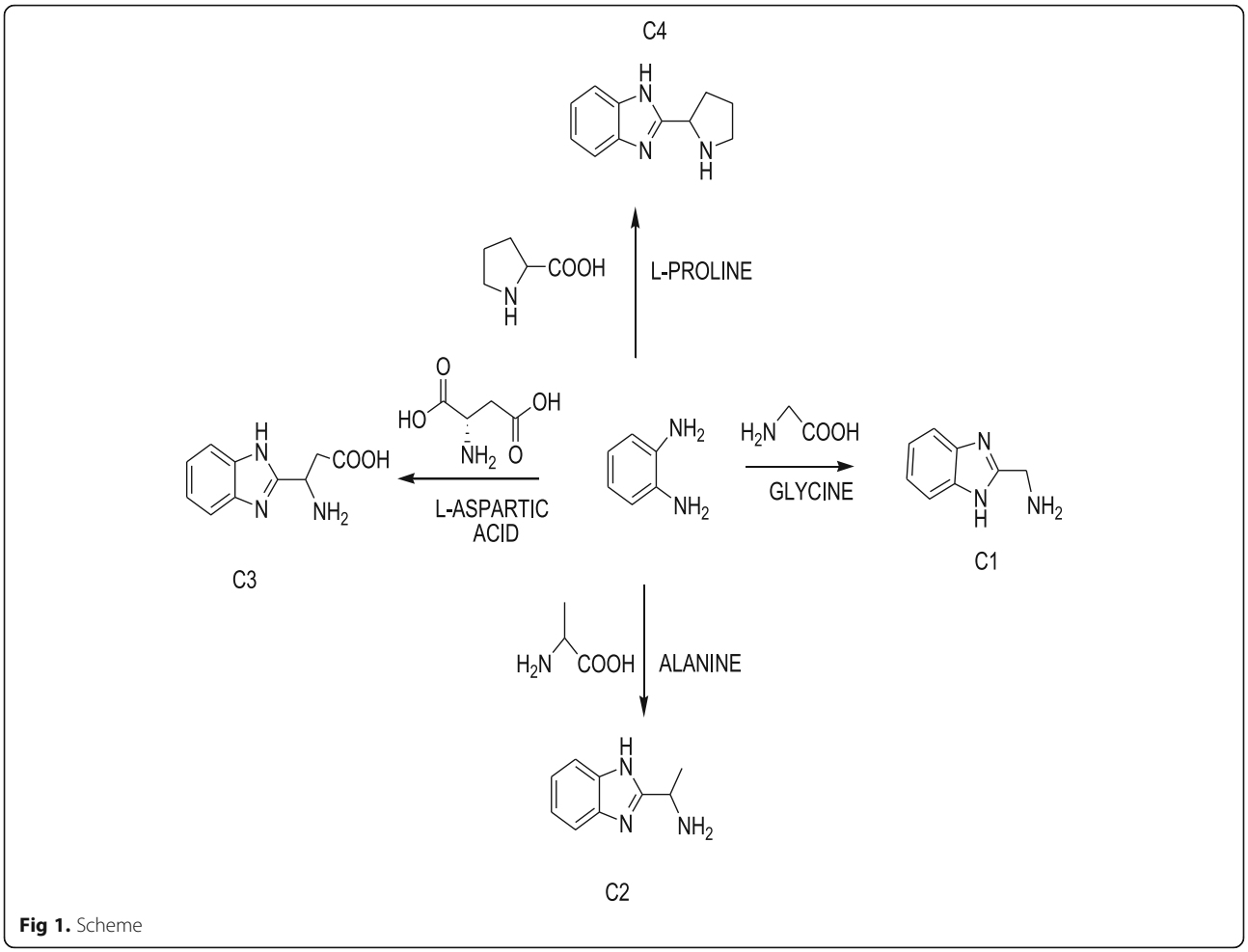


Fig 1. Scheme

the MIC method. Further synthesis work can be extended to derivatives of benzimidazole. After comparing the antibacterial activity of benzimidazole derivatives, C3 is highly sensitive to *B. subtilis* at concentration 100, 50, 25, 12.5, 6.25, 3.12, 1.6, 0.8, and 0.4 μg /ml. C1 is sensitive to *P. aeruginosa* at concentration 100, 50, 25, and 12.5 μg/ml. The useful effects of these drugs reveal that the results thus hold a great promise for the use of benzimidazole derivatives as potential future antibacterial drugs.

In silico study revealed many interesting observations. Based upon these theoretical predictions, the

Table 5 MIC results

Sample code	100 μg/ml	50 μg/ml	25 μg/ml	12.5 μg/ml	6.25 μg/ml	3.12 μg/ml	1.6 μg/ml	0.8 μg/ml	0.4 μg/ml	0.2 μg/ml
Bacillus subtilis										
C1	**S**	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
C2	**S**	**S**	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**
C3	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**R**
C4	**S**	**S**	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**
Pseudomonas aeruginosa										
C1	**S**	**S**	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**
C2	**S**	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
C3	**S**	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**	**R**
C4	**S**	**S**	**R**	**R**	**R**	**R**	**R**	**R**	**R**	**R**

S sensitive, *R* resistant

percentage absorption value for C4 is 94.96% and it can be decided that benzimidazole moiety is a beneficial pharmacophore present in a variety of pharmacologically active agents and chemical modifications of this moiety are possible with oral bioavailability and permeability.

Abbreviations

MIC: Minimum inhibitory concentration; TLC: Thin layer chromatography; FT-IR: Fourier transform infrared; PDB: Protein data bank

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Authors' contributions

RC analysed the data and synthesis, characterization, and in silico studies. GM analysed the antitubercular activity and had given her ideas in writing the manuscript. All authors have read and approved the manuscript.

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Consent for publication

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Competing interests

The authors declare that there are no competing interests.

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