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Molecular Properties Prediction and Synthesis of Novel Benzimidazole Analogues as Potent Antimicrobial agents

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ABSTRACT

In the present investigation, a series of benzimidazole derivative were subjected to molecular properties prediction, druglikeness by Molinspiration (Molinspiration, 2008) and MolSoft (MolSoft, 2007) software, lipophilicity and solubility parameters using ALOGPS 2.1 program. The compounds followed the Lipinski 'Rule of five' were synthesized for antimicrobial screening as oral bioavailable drugs/leads. Maximum drug-likeness model score (0.71) was found for compound, 2b. All the synthesized compounds were characterized by IR, NMR and mass spectral analysis followed by antimicrobial screening. Among all the title compound, 2b showed maximum activity against all bacterial strains comparable to standard drug ciprofloxacin, while the compounds, 2b and 2d showed maximum antifungal activity than standard drug fluconazole.

Keywords: Benzimidazole, Antimicrobial agents, Molecular properties prediction, Lipinski 'Rule of five'

I. INTRODUCTION

In the 20th century, chemotherapy has revolutionized the treatment of infective diseases since the innovation of antibacterial dyes by Paul Ehrlich and covered the way to a great victory for human health and long life[1]. The development of resistance against currently used antimicrobial drugs led to an invigorated curiosity of the researchers in infective diseases to develop new chemical entities to battle them[2-3]. Patient morbidity, costs of treatment, rates of hospitalization, and use of broadspectrum agents are remarkably increased by antimicrobial resistance. Pathogenic microorganisms are causative agents for different types of serious and even lethal infectious diseases. Despite advancements in medication, bacterial and fungal infections continue to be a growing problem in health care[4]. As more and more bacteria become resistant to antibiotics used in therapy and an increasing number of invasive fungal species become resistant to current antifungal medications, there is considerable interest in the development of new compounds with antimicrobial activity. The compounds containing a heterocyclic ring play an important role among organic compounds with biological activity used as drugs in human and veterinary medicine or as insecticides and pesticides in agriculture. Benzimidazole is a lead molecule for most of the biological agents used in the pharmaceutical industry. It consists of a fused benzene ring with heterocyclic aromatic imidazole[5]. The existence of imidazole creates it resourceful heterocycles with an extensive range of biological activities such as antiulcer (Gastric H+/K+-ATPase inhibitors), antihypertensive, anti-inflammatory, anticonvulsant, analgesic, antiprotozoal, antitrichinellosis, antidiabetic, anti-HIV, antimicrobial, antitubercular, anticancer, antihistaminic, antioxidant, antiviral, antiparasitic agents, diuretic, and DNA binding activities[6].

Microwave assisted reactions in organic chemistry achieve the same by ensuring facilitation of faster reactions under bulk conditions as well as promoting reduction of reaction time. Reactions play the most fundamental role in synthesis[7-10]. The ideology of Green chemistry calls for the development of new chemical reactivities and reaction conditions that can potentially provide benefits for chemical syntheses in terms of resource and energy efficiency, product selectivity, operational simplicity, and health and environmental safety[11-18]. It can affect physical and chemical stability, apparent solubility, dissolution, bioavailability and bioequivalence and drug product manufacturability, which require special attention during product development as it affects drug product quality, protection and effectiveness. Recrystallization can affect physical and chemical stability, apparent solubility, dissolution, bioavailability and bioequivalence and drug product manufacturability, which require special attention during product development as it affects drug product quality, protection and effectiveness. It Isolation of impurities by recrystallization traditional techniques i.e crystallization of drug substance is used. It is one of the effective element in drug development. Microwave irradiation provides an alternative to the conventional methods, for heating or introducing energy into the system[19-31]. It utilizes the ability of mobile electric charges present in liquid or conducting ions in solid to transform electromagnetic energy into heat. Microwave radiations are electromagnetic waves. In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. The need for different organic compound libraries for drug discovery, biomaterial development, automated library screening, proteomics etc has supported the emergence of innovative technologies for rapid combinatorial organic synthesis using MAOS synthesis. Due to failure of ADME so it necessary to perform docking studies before pharmacological activity. An outbreak of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) raises an unparalleled challenge in the discovery of appropriate drugs for prevention and treatment. Given the rapid pace of scientific research and clinical data produced by the large number of people quickly infected with SARS-CoV-2, clinicians need reliable proof of successful medical care for this infection as in intial stage with help of molecular docking software it is easy to do in-silico study[32-44]. The chemical modification of drug delivery system for protein and peptide drugs is important in improving both enzymatic stability and membrane permeations can help to have good biological activity from any heterocyclic compound modification. Someday soon, you might be making your own medicines at home[45-56]. That's because researchers have tailored a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series. Encouraged by the upstairs findings and in the persistence of our work on benzimidazole derivatives, we herein report the synthesis and in vitro evaluation of benzimidazole derivatives as a potent biological agent[57-69].

II. MATERIAL AND METHODS

Molecular Properties Prediction

All the title compound (2a-f) were subjected to molecular properties prediction by Molinspiration and MolSoft (MolSoft, 2007) software in order to filter the drugs for synthesis and biological screening and to reduce enormous wastage of expensive chemicals and precious time.

Chemistry

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. Reaction Progress was observed by TLC plates, Bruker 300 MHz instrument was used to record 1H NMR spectra in DMSO/$CDCl_3$ using TMS as internal standard. Chemical shifts (d) are expressed in ppm and with ATR JASCO FTIR-4600, IR spectra

were recorded and Mass spectra were recorded on Pesciex (model no. API 2000).

General Procedure for Synthesis of 2-methylbenzimidazole derivatives

Mixture of o-phenylenediaminediamine (0.03 mole) and 20 ml of water, acetic acid (0.09 mole) was irradiated for15min at 340watt under microwave. By gradually adding the concentrated ammonia solution, the cooled reaction mixture was made distinctly basic and the precipitated product was collected and recrystallized from 10% ethanol. (scheme is shown in Fig 1.).

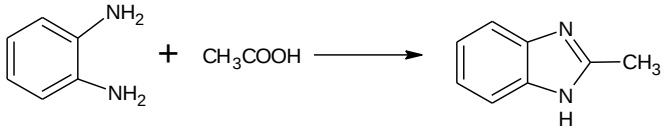


Fig 1. Synthesis of 2-methylbenzimidazole

General Procedure for Synthesis of 3-benzoylbenzimidazole derivatives

Dissolved 0.5g of the above product in 10mL of 10% sodium hydrogen carbonate solution and added 1g of benzoyl chloride. In a stoppered test tube, the reaction mixture was shaken vigorously. Since carbon dioxide evolved the stopper has been removed from time to time. After the benzoyl chloride odour had disappeared, it acidified to Congo red and washed with dilute hydrochloric acid. Extracted the solid with a bit of cold ether to remove any benzoic acid that may be present. Dilute ethanol recrystallized the benzoyl derivative. (scheme is shown in Fig 2.).

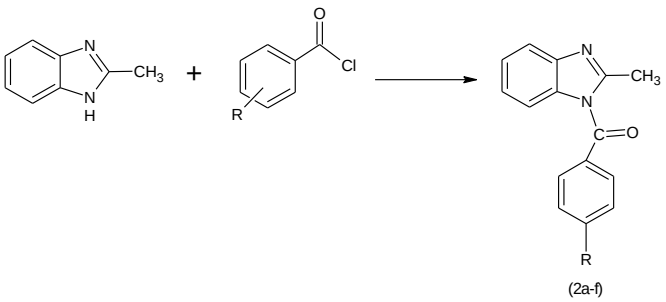


Fig 2. Synthesis of 3-benzoylbenzimidazole

Analytical Data for Novel 3-benzoylbenzimidazole derivatives

2a. (2-methyl-1H-benzimidazol-1-yl)(4-nitrophenyl)methanone

IR (KBr, cm-1) 1740.35 (C=0), 1332.51 (Ar-NO_2), 1237.40 (C-N str), 3782.82 (C-H), ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.41-7.78(q, 2H, Ar-H), 1.56-1.92 (t, 3H), 7.88-8.06 (q, 4H); mass m/z (M^+) 282.

2b. (4-methoxyphenyl)(2-methyl-1H-benzimidazol-1-yl)methanone

IR (KBr, cm-1) 1755.12 (C=0), 2819.44 (O-CH_3), 1232.58 (C-N str), 3770.39 (C-H), ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.53-7.84 (q, 2H, Ar-H), 1.31-1.58 (t, 3H), 8.05-8.37 (q, 4H); mass m/z (M^+) 265.

2c. (4-chlorophenyl)(2-methyl-1H-benzimidazol-1-yl)methanone

IR (KBr, cm-1) 1734.20 (C=0), 759.41 (C-Cl), 1239.73 (C-N str), 378.19 (C-H), ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.78-7.92 (q, 2H, Ar-H), 1.24-1.65 (t, 3H), 8.52-8.67 (q, 4H); mass m/z (M^+) 269.

2d. (4-fluorophenyl)(2-methyl-1H-benzimidazol-1-yl)methanone

IR (KBr, cm-1) 1750.23 (C=0), 254.48(Ar-F), 1231.61 (C-N str), 3712.18 (C-H), ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.32-7.64 (q, 2H, Ar-H), 1.50-1.88 (t, 3H), 7.78-8.12 (q, 4H); mass m/z (M^+) 253.

2e. (2-chlorophenyl)(2-methyl-1H-benzimidazol-1-yl)methanone

IR (KBr, cm-1) 1765.52 (C=0), 750.12 (C-Cl), 1240.11 (C-N str), 352.19 (C-H), ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 7.55-7.68 (q, 2H, Ar-H), 1.34-1.48 (t, 3H), 8.41-8.55 (q, 4H); mass m/z (M^+) 271.

2f. (2,4-dichlorophenyl)(2-methyl-1H-benzimidazol-1-yl)methanone

IR (KBr, cm-1) 1742.89 (C=0), 757.09 (C-Cl), 1238.12 (C-N str), 345.10 (C-H), ^{1}HNMR ($CDCl_3$, 300 MHz,

ppm): δ 7.88-7.94 (q, 2H, Ar-H), 1.41-1.55 (d, 2H), 8.04-8.23 (q, 4H); mass m/z (M^+) 304.

Antimicrobial Activity:

Preparation of Inoculum

The gram positive (*Bacillus subtilis and Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli*) were pre-cultured in nutrient broth overnight in a rotary shaker at 37°C, centrifuged at 10,000 rpm for 6 min, pellet was suspended in double distilled water and the cell density was standardized spectrophotometrically (A nm). The fungal inoculums (*Candida albicans, Aspergillus niger, and Dreschlera turcica*) were prepared from 6 to 10 day old culture grown on Potato dextrose agar medium. The Petri dishes were flooded with 9 to 11 ml of distilled water and the conidia were scraped using sterile spatula. The spore density of each fungus was adjusted with spectrophotometer (A595 nm) to obtain a final concentration of approximately 105 spores/ml.

Antibacterial testing

Antibacterial activity was measured using agar dilution technique. Briefly, the methanol extracts were dissolved in dimethyl sulfoxide (DMSO, Merck) and serially diluted in molten Mueller Hinton Agar (MHA, Sigma) in petri dishes (100 mm×15 mm) to obtain final concentrations: 100, 50, 25 and 12.5 µg/ml. The solvent did not exceed 1% concentration and did not affect the growth of the organisms. All bacterial strains were grown in Mueller Hinton Broth (MHB, Sigma) for 4 h at 37°C. Bacterial suspensions with 0.5 McFarland standard turbidity, which is equivalent to 108 cfu/ml were prepared by dilution with Mueller Hinton broth. The diluted inoculum was added to a Steer's replicator calibrated and incubated for 24 hr at 37 °C. After incubation, all dishes were observed for microbial inhibition by the disc diffusion method Streptomycin sulphate (10 µg/mlG) used as positive control and methanol solvent (100 µg/mlG) used as negative control. The antibacterial assay plates were incubated at 37°C for 24 hr. The diameters of the inhibition zones were measured in mm.

Antifungal Activity

The antifungal activity was tested by disc diffusion method. The potato dextrose agar plates were inoculated with each fungal culture (10 days old) by point inoculation. The filter paper discs (5 mm in diameter) impregnated with 100 µg mlG concentrations of the extracts were placed on test organism-seeded plates. Methanol was used to dissolve the extract and was completely evaporated before application on test organism-seeded plates. Blank disc impregnated with solvent methanol followed by drying off was used as negative control and Nystatin (10 µg discG) used as positive control. The activity was determined after 72 hr of incubation at 28°C. The diameters of the inhibition zones were measured in mm.

Preparation of test samples

For the antimicrobial tests, ethanolic extracts were diluted in dimethylsulfoxide (DMSO): methanol (1/1: v/v) solvent to a concentration of 20 mg/ml.

Antimicrobial bioassay

For bioassays, suspension of approximately 1.5 × 108 bacterial cells/ml in sterile normal saline were prepared and about 1.5 ml of it was uniformly seeded on Mueller-Hinton-Agar medium with 3–4 mm thickness in 12 cm × 1.2 cm glass petridishes, left aside for 15 min and excess of suspension was then drained and discarded properly. Wells of 6 mm in diameter and about 2 cm apart were punctured in the culture media using sterile cork borers. Wells were filled with 0.1 ml of 20 mg/ml concentration of each sample (2 mg/well) and incubated at 37 °C for 48 hr. Bioactivity was determined by measuring Diameter of Inhibition Zones (DIZ) in mm. Each experiment was repeated three times and the mean of the diameter of

the inhibition zones was calculated. Pure solvent was used as negative control[70-71].

III. RESULT AND DISCUSSION

Molecular Properties Prediction

A good bioavailability can be achieved with an appropriate balance between solubility and partitioning properties. The computed logP values (P is the partition coefficient of the molecule in the water/octanol system) are shown in Table 2. The ALOGPS method is part of the ALOGPS 2.1 program used to predict lipophilicity and aqueous solubility of compounds. The lipophilicity calculations within this program are based on the associative neural network approach and the efficient partition algorithm. The Log Kow (Kow-WIN) program estimates the log octanol/water partition coefficient (logP) of organic chemicals and drugs using an atom/ fragment contribution method developed at Syracuse Research Corporation. The XLOGP2 is an atom additive method applying corrections. Computed partition coefficients for drugs studied varied between 3.11 and 4.95 (XLOGP2 method) and between -0.23 and 1.05 (KoW-WIN method) is presented in Table 2. Both the XLOGP2 method and KoW-WIN best supported for most of the compounds on the basis of lipophilicity to consider an oral drug/lead. Also the absorption of a drug is usually very low if the calculated solubility is <0.0001 mg/L.18 As per the criterion compounds of the series (2a-f) almost fulfil the requirement of solubility (ALOGPS). Good intestinal absorption, reduced molecular flexibility (measured by the number of rotatable bonds), low polar surface area or total hydrogen bond count (sum of donors and acceptors), are important predictors of good oral bioavailability. Membrane permeability and bioavailability is always associated with some basic molecular descriptors such as logP (partition coefficient), molecular weight (MW), or hydrogen bond acceptors and donors counts in a molecule. Number of rotatable bonds is important for conformational changes of molecules under study and ultimately for the binding with receptors or channels. It is revealed that for passing oral bioavailability criteria, number of rotatable bond should be 610.19 The compounds in this series (2a-f) in general possess high number of rotatable bonds (5–7) and therefore, exhibit large conformational flexibility. Drug-likeness model score (a combined effect of physico-chemical properties, pharmacokinetics and pharmacodynamics of a compound and is represented by a numerical value) was computed by MolSoft (MolSoft, 2007) software for the entire compounds under study. Maximum drug-likeness score was found out to be 0.82 for compound, 2f. Molecular polar surface area (TPSA) is a very useful parameter for the prediction of drug transport properties. TPSA is a sum of surfaces of polar atoms (usually oxygen, nitrogen and attached hydrogen) in a molecule. TPSA and volume is inversely proportional to %ABS. Topological polar surface area (TPSA), that is, surface belonging to polar atoms, is a descriptor that was shown to correlate well with passive molecular transport through membranes and, therefore, allows prediction of transport properties of drugs in the intestines and blood–brain barrier crossing. TPSA was used to calculate the percentage of absorption (%ABS) according to the equation: %ABS = 109 ± 0.345 _ TPSA, as reported. From all these parameters, it can be observed that all the title compounds exhibited a great %ABS ranging from 81.23 to 88.12% and that of standard drug ciprofloxacin has %ABS of 88.78 calculated by MolSoft software. Computational study for prediction of ADME properties of all molecules performed is presented in Table 2. The number of rotatable bonds (NROTB) and Lipinski's rule of five were also calculated. The rule states that most molecules with good membrane permeability have logP, molecular weight 6500, number of hydrogen bond acceptors 610, and number of hydrogen bond donors 65. This rule is widely used as a filter for drug-like properties. Furthermore, none of the compounds violated

Lipinski's parameters, making them potentially promising agents for antimicrobial therapy.

Table 1. Physical constants and calculated partition coefficients, solubilities and drug likeness model score of the synthesized compounds

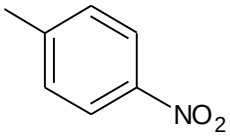
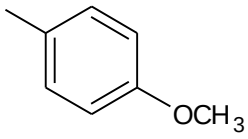
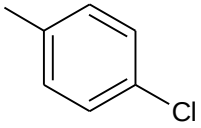
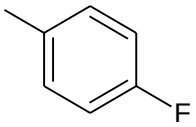
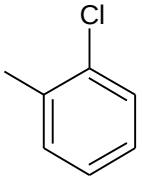
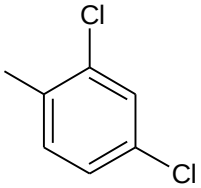
Compound	R	ALOGPS	KoW-WIN	XLOP2	Drug-likeness model score
2a		-4.42 (12.90 mg/L)	1.05	4.95	0.67
2b		-3.26 (52.40 mg/L)	1.03	3.12	0.71
2c		-3.08 (0.42 g/L)	-0.32	4.55	0.56
2d		-4.01 (80.12 mg/L)	-0.51	4.29	0.68
2e		-3.44 (0.17 g/L)	-0.48	3.62	0.32
2f		-3.55 (78.29 mg/L)	-0.23	3.11	0.49

Table 2. Pharmacokinetic parameters important for good oral bioavailability of title compounds (2a–f)

Compound	%ABS	Volume (A3)	TPSA (A2)	NROTB	HBA	HBD	LogP	MW	Lipinski's violations
Rule	-	-	-	-	<10	<5	<5	<500	<1
2a	88.12	381.96	68.02	5	4	1	2.56	374.56	0
2b	81.23	362.52	70.23	5	5	1	1.34	365.09	0
2c	84.52	391.04	66.41	6	5	2	2.48	318.23	0
2d	87.02	385.94	62.35	7	4	3	2.10	345.67	0
2e	85.14	376.91	68.16	5	4	1	2.03	375.61	0
2f	87.48	359.19	84.29	5	5	1	1.49	356.10	0

Chemistry

For preparation of Synthesis of 2-methylbenzimidazole mixture of o-phenylenediaminediamine and water, acetic acid was irradiated for 15min at 340 watt under microwave. By gradually adding the concentrated ammonia solution, the cooled reaction mixture was made distinctly basic and the precipitated product was collected and recrystallized from ethanol. In next step, for *Synthesis of 3-benzoylbenzimidazole derivative* Dissolved above product in sodium hydrogen carbonate solution and add benzoyl chloride. In a stoppered test tube, the reaction mixture was shaken vigorously. Since carbon dioxide evolved the stopper has been removed from time to time. After the benzoyl chloride odour had disappeared, it acidified to Congo red and washed with dilute hydrochloric acid. Extracted the solid with a bit of cold ether to remove any benzoic acid that may be present. Dilute ethanol recrystallized the benzoyl derivative. All structure are consistent with IR, NMR and Mass spectra.

Antimicrobial Activity

The antimicrobial activity of synthesized compounds has been evaluated *in vitro* against pathogens including three bacterial species (*Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus)* and three fungus species *(Candida albicans, Aspergillus niger, and Dreschlera turcica).* Table 3 illustrated that synthesized compounds showed antimicrobial activity against all test microorganisms. It was observed that compound 2b exhibited the highest significant antibacterial activity against *E. coli* with mean inhibition zone equal to 25±0.12 exhibited the highest significant activity against *C. albicans* with mean inhibition zone equal to 22±0.18 mm, respectively.

Table 3. Antibacterial activity of synthesized compounds (100 µg mlG1) and antibiotic (10 µg mlG1) against bacterial species tested by disc diffusion assay Zone of inhibition (mm)

Sr. no	Compound	Diameter of zone of inhibition (mm)		
		E. coli	***B. subtilis***	***S.aureus***
1	2a	14±0.38	16±0.01	18±0.21
2	2b	25±0.12	19±1.35	20±0.52
3	2c	12±0.01	13 ±0.81	16±0.23
4	2d	16±0.71	17±0.01	19±1.42
5	2e	14±0.22	17±0.06	19±0.28
6	2f	17±0.29	14±0.02	18±0.62

Table 4. Antifungal activity of synthesized compounds (100 µg mlG1) and fungicide (10 µg mlG1) against fungal species tested by disc diffusion Zone of inhibition (mm)

Sr. no	compounds	Diameter of zone of inhibition (mm)		
		C. albicans	***A. niger***	***D. turcica***
1	2a	12±0.82	15±0.01	17±0.29
2	2b	22±0.18	20±1.44	25±0.59

3	2c	16±0.04	12 ±0.73	15±0.21
4	2d	21±0.10	18±0.09	22±1.10
5	2e	11±0.52	15±0.01	16±0.02
6	2f	16±0.81	12±0.04	14±0.22

IV. CONCLUSION

All the title compound (2a-f) were subjected to molecular properties prediction by Molinspiration and MolSoft (MolSoft, 2007) software in order to filter the drugs for synthesis and biological screening and to reduce enormous wastage of expensive chemicals and precious time. We have described an efficient and benign synthesis of benzimidazole gives more yields and requires less time by microwave method. The current study was initiated because of the increasing resistance to antibiotics including bacteria and fungi. Compounds are of new interest as antiseptics and antimicrobial agents. As a result, the antimicrobial activity of Compounds was screened against the most common pathogens. In general, Compound 2b was effective source of active antimicrobial agents.

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