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Research Article

SYNTHESIS, SPECTRAL CHARACTERIZATION AND *IN SILICO* STUDIES OF NOVEL N-MANNICH BASES OF SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS ANALGESIC, ANTIFUNGAL AND POTENT INHIBITORS FOR BREAST CANCER

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ABSTRACT

Objectives: The aim of the present study is to synthesize N-Mannich bases of novel series of substituted benzimidazole derivatives and their *in silico* simulation.

Methods: This study presents research on the synthesis of N-Mannich bases of novel series of substituted benzimidazole derivatives using substituted benzimidazoles as the starting compound. *In silico* simulation and absorption, distribution, metabolism, and excretion prediction of all the compounds are demonstrated by their computational studies.

Results: All synthesized compounds were analyzed using 1hydrogen nuclear magnetic resonance, Fourier transform infrared, and mass spectrometry to validate their structures. *In silico* simulation against the 1C14 as analgesic, 5fsa as antifungal, and 600 k as breast cancer protein database indicated that synthesized compounds have moderate-to-good-binding energy.

Conclusion: Overall, the computational analyses indicate that the derivatives synthesized show encouraging pharmacokinetic characteristics and affinity, positioning them as potential candidates for further advancement as therapeutic agents.

Keywords: Substituted benzimidazoles, Analgesic, Antifungal, Breast cancer, *In silico*, Spectral.

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INTRODUCTION

Benzimidazole, a heterocyclic compound featuring a phenyl ring fused to an imidazole ring, has garnered significant attention due to its diverse pharmacological applications. Recent exploration highlights the significance of the 5, 6-dimethylbenzimidazole moiety as part of the vitamin B1 structure [1]. Substituted benzimidazole derivatives, particularly N-Mannich bases, are of great interest for their varied biological activities, including anticancer, anthelmintic, antiprotozoal, antimicrobial [2-5] anti-inflammatory, analgesic, antiviral, and antiulcer effects [6-9]. This study focuses on the synthesis of N-Mannich bases of substituted benzimidazole using substituted primary or secondary amines and formaldehyde. *In silico* simulation and absorption, distribution, metabolism, and excretion (ADME) prediction of all the compounds are demonstrated by their computational studies [10,11].

MATERIALS

All reagents used for synthesis were analytical-grade commercial products from Sigma Aldrich and were used without further purification. The melting points of the synthesized compounds were determined with an electric melting point apparatus through the open capillary method, expressed in degrees Celsius, and reported as uncorrected. Reaction progress and the purity of the synthesized compounds were monitored using silica gel-G aluminum thin layer chromatography (TLC) plates, employing solvent combinations of differing polarities. Spots were visualized using iodine vapors. 1hydrogen nuclear magnetic resonance (1H-NMR) spectra were obtained with a Bruker AC-F 400 Fourier transform (FT)-NMR spectrometer operating at 400 MHz, with spectra recorded in deuterated chloroform using TMS (δ 0.00 ppm) as an internal standard at room temperature. FT infrared (FT-IR) spectra of the synthesized compounds were recorded on a FT-IR-6600 type A spectrometer, using potassium bromide discs in the range of 4000–350 cm^{-1} at the Institute of Chemical Technology with an Alpha-II/Bruker-Lab India, Mumbai, and mass spectra at NMIMS Mumbai with a Shimadzu liquid chromatography–mass spectrometry. 8040, Maharashtra, India.

METHODS

General preparation method for synthesis of N-Mannich bases of substituted benzimidazole derivatives

Procedure for synthesis of N-Mannich bases of benzimidazole derivatives (B1-B5) (Step I)

To a solution of substituted benzimidazole (0.005 moL) in 10 mL of ethanol, 0.005 moL of a primary or secondary amine and 0.005 moL (0.13 mL) of formaldehyde were added. The mixture was stirred for 30 minutes continuously on a magnetic stirrer. Subsequently, attached reflux condenser, the reaction mixture was heated on water bath for 8–15 hrs. After cooling, the resulting product was filtered, dried, and recrystallized from dimethyl formamide and ethanol. The compounds were further purified using TLC (chloroform ($CHCl_3$): Ethanol, 8:2; 4:1; 7:3) and characterized by determining their melting points (Scheme 1) [12,13].

Ligand preparation

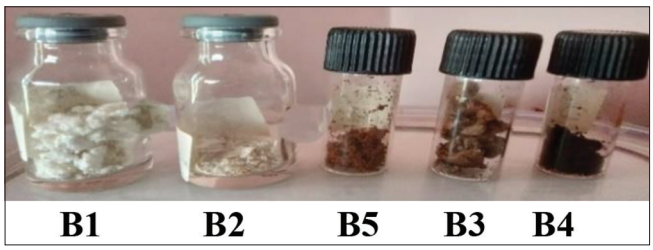
The ligand molecules were selected from previously published studies and relevant databases, ensuring their reliability with the target proteins 1C14, 5FSA, and 600K. The ligand structures were generated using Chem Draw Pro (version 12.0). Protein preparation of the protein structures in protein database (PDB) format (1C14, 5FSA, and 600K) was downloaded from the Protein Data Bank (https://www.rcsb.org/). Following this, *in silico* studies were conducted using Swiss Dock software to evaluate the interactions (binding affinity) between the ligands and the target proteins [14].

Procedure of docking

Virtual screening was performed using SwissDock software for the *in silico* of substituted benzimidazole derivatives with the proteins 1C14, 5FSA, and 600K. The protein structures were loaded into the software and converted to "pdbqt" format. Each of the three-dimensional ligands was uploaded individually, and their geometries were minimized to achieve global energy maxima before conversion to "pdbqt" format. All ligands and the protein were selected simultaneously, and the grid parameters covering the binding pocket were determined. The grid coordinates were set to X: 27 Å, Y: 37 Å, and Z: 34 Å, and the resulting binding affinity was visualized using the same software [14].

Drug likeliness properties

Drug likeness properties of the ligands B1-B5 were assessed using Lipinski's parameters through the Swiss ADME online server (http://www.swissadme.ch/). The ligands' SMILES representations were uploaded to the Swiss ADME web interface, and a Swiss drug design command was executed to generate their ADME characteristics, ensuring that the parameters met acceptable drug-likeness criteria [15]. The Lipinski filter was applied to assess the ligands based on common drug-likeness properties, including lipophilicity, water solubility, total polar surface area, gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, and skin penetration [15,16]. These parameters help in predicting the drug's pharmacokinetics and potential effectiveness. In addition, the BOILED-egg model was used to further predict ADME and drug-likeness properties. This model specifically evaluates GI absorption and BBB permeability of the compounds. The representation in the BOILED-egg plot is divided into several zones like the yellow zone indicates a high likelihood of BBB permeability, suggesting that the molecule may cross the blood–brain barrier efficiently. The white zone corresponds to good GI absorption, indicating that the compound is likely to be absorbed well in the GI tract and red dots in the model represent molecules that are not affected by P-glycoprotein (P-gp) extrusion, suggesting they are not subject to efflux from the central nervous system. This visualization and analysis help to predict whether the compounds would exhibit favorable GI absorption and BBB penetration, critical factors for their potential efficacy and bioavailability as drug candidates [17]. The analysis focused on key 2-dimensional molecular descriptors etc. for the drug likeliness which is described in Table 1. These parameters help evaluate the potential for the synthesized compounds to be viable drug candidates based on their physicochemical properties. The findings are summarized and discussed in relation to their implications for bioavailability and therapeutic efficacy.



Spectral data of synthesized compounds

Compound B1

IR Spectra (cm^{-1}): C=C Aromatic 1600.03, C-N aryl 1334.5, CH_2 1488.78.

MS: m/z: 426 [M^+].

H^1NMR ($CDCl_3$) δ ppm: Aromatic-H 7.053–7.069 (multiplet, 4H), Heterocyclic –CH_2 2.504–2.529 (quartet, 2H), Heterocyclic –H 7.606 (singlet, 1H), Aromatic-H 6.8–6.9 (multiplet, 5H), Aromatic-H 7.083–7.498 (multiplet, 5H), Aromatic-H 7.513–7.590 (multiplet, 5H).

Compound B2

IR Spectra (cm^{-1}): C=C Aromatic 1487.81, CH_2 1463.21, CH_3 1336.71, C-N aryl 1281.47.

MS: m/z: 440 [M^+].

H^1NMR ($CDCl_3$) δ ppm: Aromatic-H 7.1 (singlet, 2H), Aromatic-H 7.2 (singlet, 2H), Aromatic-H 7.3 (singlet, 2H), Aromatic-H 7.4 (singlet, 2H), Heterocyclic –CH_3 4.4 (singlet, 3H), Heterocyclic –CH_2 J=2.3–2.6 (doublet, 2H), Aromatic-H 5.098 (singlet, 2H), Aromatic 7.5 (singlet, 2H), Aromatic 7.6 (singlet, 2H).

Compound B3

IR Spectra (cm^{-1}): C=C Aromatic 1487.81, -CH_2 1472.38, C-N aryl 1365.35, C-O 1032.69.

MS: m/z: 519, Mol. Wt.: 546.

H^1NMR ($CDCl_3$) δ ppm: Aromatic-H 7.666–7.681 (multiplet, 4H), Heterocyclic –CH_2 2.59–2.64 (singlet, 2H), Aromatic-H 7.554–7.570 (multiplet, 5H), Aromatic-H 7.132–7.318 (multiplet, 5H), Aromatic-H 7.589–7.664 (multiplet, 5H).

Compound B4

IR Spectra (cm^{-1}): C=C Aromatic 1599.26, -CH_2 1449.24, -CH_3 1365.35, C-N aryl 1258.22, C-H Stretching 2813.63, C-O 1033.66.

MS: m/z: 399[M^+].

H^1NMR ($CDCl_3$) δ ppm: Aromatic-H 7.060–7.074 (multiplet, 4H), Heterocyclic-H 7.043–7.059 (multiplet, 3H), Heterocyclic –CH_2 2.50–2.507 (singlet, 2H), Aromatic-H 7.076 (singlet, 1H), Aromatic –CH_3 3.208–3.3961 (multiplet, 6H), Aromatic –CH_2 2.511–2.515 (singlet, 2H), Aromatic-H 7.082–7.262 (multiplet, 5H), Aromatic-H 7.277–7.308 (multiplet, 2H).

Compound B5

IR Spectra (cm^{-1}): C=C Aromatic 1620.88, -CH_2 1454.06, -CH_3 1380.78, C-N aryl 1270.19, C-Cl stretching 769.458.

MS: m/z: 340 [M^+].

H^1NMR ($CDCl_3$) δ ppm: Aromatic-H 7.372–7.431 (multiplet, 4H), Aromatic-H 7.434–7.451 (multiplet, 4H), Heterocyclic –CH_2 2.36–2.51 (singlet, 2H), Aromatic-H 7.462–7.508 (multiplet, 5H), Heterocyclic –CH_3 3.3 (singlet, 3H), Aromatic-H 7.519–7.539 (multiplet, 3H).

RESULTS AND DISCUSSION

In view of our ongoing research focused on the development of new synthetic novel N-Mannich bases substituted benzimidazole, the present study aims to design, synthesize, and *in silico* studies of a novel series N-Mannich bases substituted benzimidazole using substituted benzimidazoles as the starting compound. The purity of the compounds was estimated by TLC. All the newly synthesized compounds were characterized with the spectral data obtained from 1H-NMR, FT-IR, and mass data of proposed structures. The synthesis of the target was executed by following the single step as outlined in Scheme 1. The starting compounds such as benzimidazole, 2-methyl benzimidazole, 2-(1, 3-benzodioxole benzimidazole) and 2-(2-chlorophenyl benzimidazole) (1) in ethanol, primary, or secondary amine (2), and formaldehyde were added. The mixture was stirred for 30 min and then refluxed for 5–6 h in good yields. The IR spectrum of all synthesized compounds, respectively, such as, B1 shows an absorption band at 1334.5 cm^{-1} characteristic of the C-N aryl group, B2 shows an absorption band at 1463.21 cm^{-1} characteristic of the –CH_2 group, B3 shows an absorption band at 1032.69 cm^{-1} C-O group, B4 shows an absorption band at 2813.63 cm^{-1} C-H stretching group, and B5 shows an absorption band at 769.458 cm^{-1} C-Cl stretching. Thus, these signals clearly demonstrate the formation of the target molecule. The mass spectrum exhibits the molecular ion peak *m/z* at 426 (B1), 440 (B2), 399 (B4), and 340 (B5). Mass spectrum for B3 shows a peak *m/z* at 519 where the M^+ is absent for the same. The *in silico* study demonstrated promising binding energies for newly synthesized compounds against the targets *Escherichia coli* enoyl reductase-NAD+-Triclosan (PDB ID: 1C14) described in Table 2, Sterol

Table 1: Selected *in silico* physicochemical and pharmacokinetic parameters for oral bioavailability of synthesized compounds

S. No.	Code	GI absorption	BBB penetration	P-glycoprotein substrate	Log Kp (cm/s) epidermis penetration	iLOGP	Drug likeness (Lipinski's rule of five	Water Solubility
1	B1	Low	No	No	−4.40	3.19	Yes; 1 violation	Sparingly soluble
2	B2	Low	No	No	−4.20	3.52	Yes; 1 violation	Sparingly soluble
3	B3	Low	No	No	−4.08	3.60	No; 1 violation	Soluble
4	B4	High	Yes	Yes	−4.99	3.62	Yes; 1 violation	Sparingly soluble
5	B5	High	Yes	Yes	−5.82	3.23	Yes; 0 violation	Sparingly soluble

Table 2: Physical characterization data of synthesis of N-Mannich bases substituted benzimidazole (B1-B5)

S. No.	Compound code	Molecular formula	Molecular weight g/moL	Melting point (°C)	% Yield	RF values	TLC Solvent	Reaction time (in hours)	Colour
1	B1	$C_{29}H_{22}N_4$	426	278–280	72.18	0.67	$CHCl_3$: Ethanol, 8:2	14	White
2	B2	$C_{30}H_{24}N_4$	440	236–238	88.97	0.86	$CHCl_3$: ethanol, 8:2	15	Slight white
3	B3	$C_{36}H_{26}N_4O_2$	546	256–258	73.26	0.48	$CHCl_3$: Ethanol, 4:1	12	Light brown
4	B4	$C_{25}H_{25}N_3O_2$	399	272–274	83.58	0.72	$CHCl_3$: ethanol, 8:2	8	Dark brown
5	B5	$C_{19}H_{21}ClN_4$	340	230–232	84.23	0.32	$CHCl_3$: ethanol, 7:3	14	Light brown

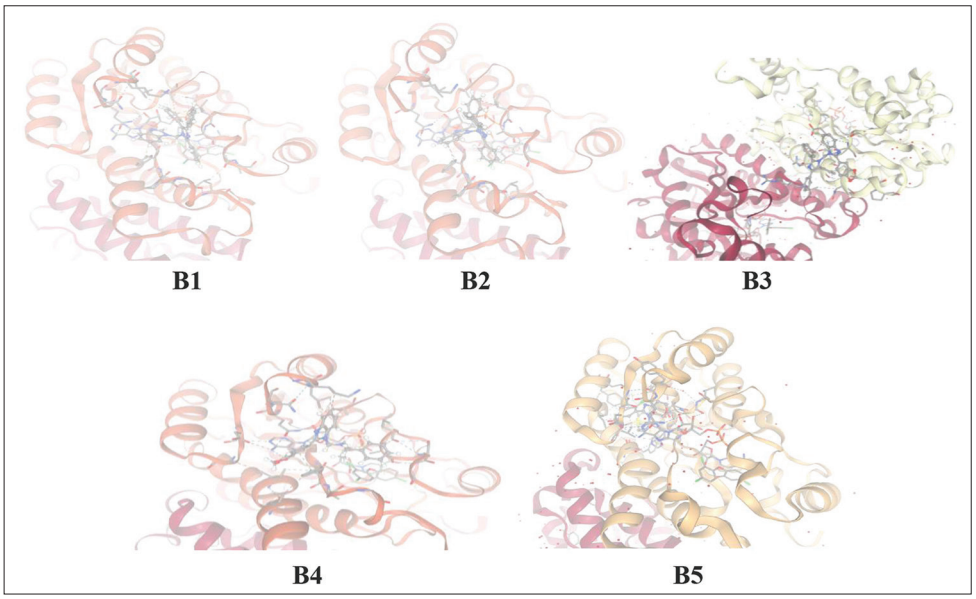


Fig. 1: 3D overlay of docked poses of the synthesized compounds in active site of protein database ID: 1C14

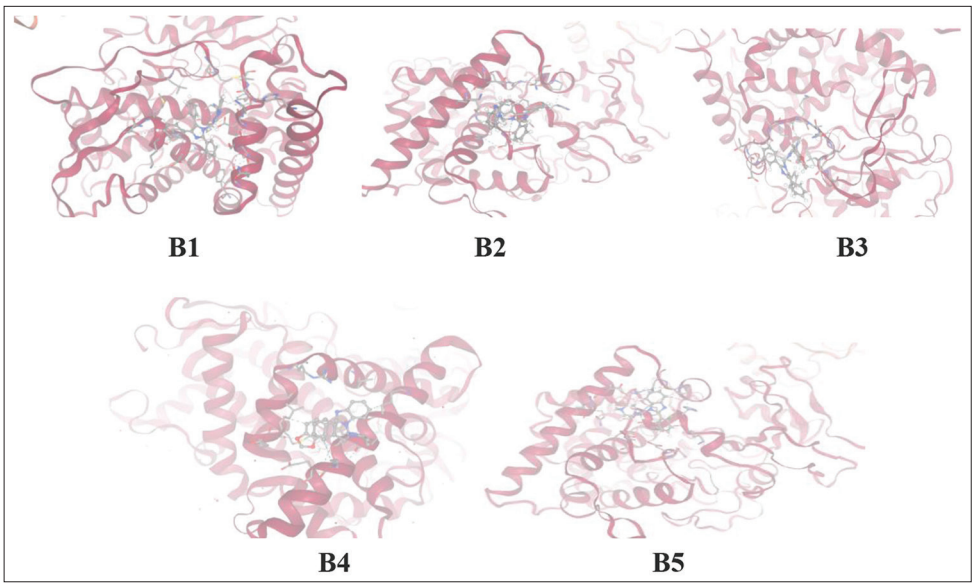
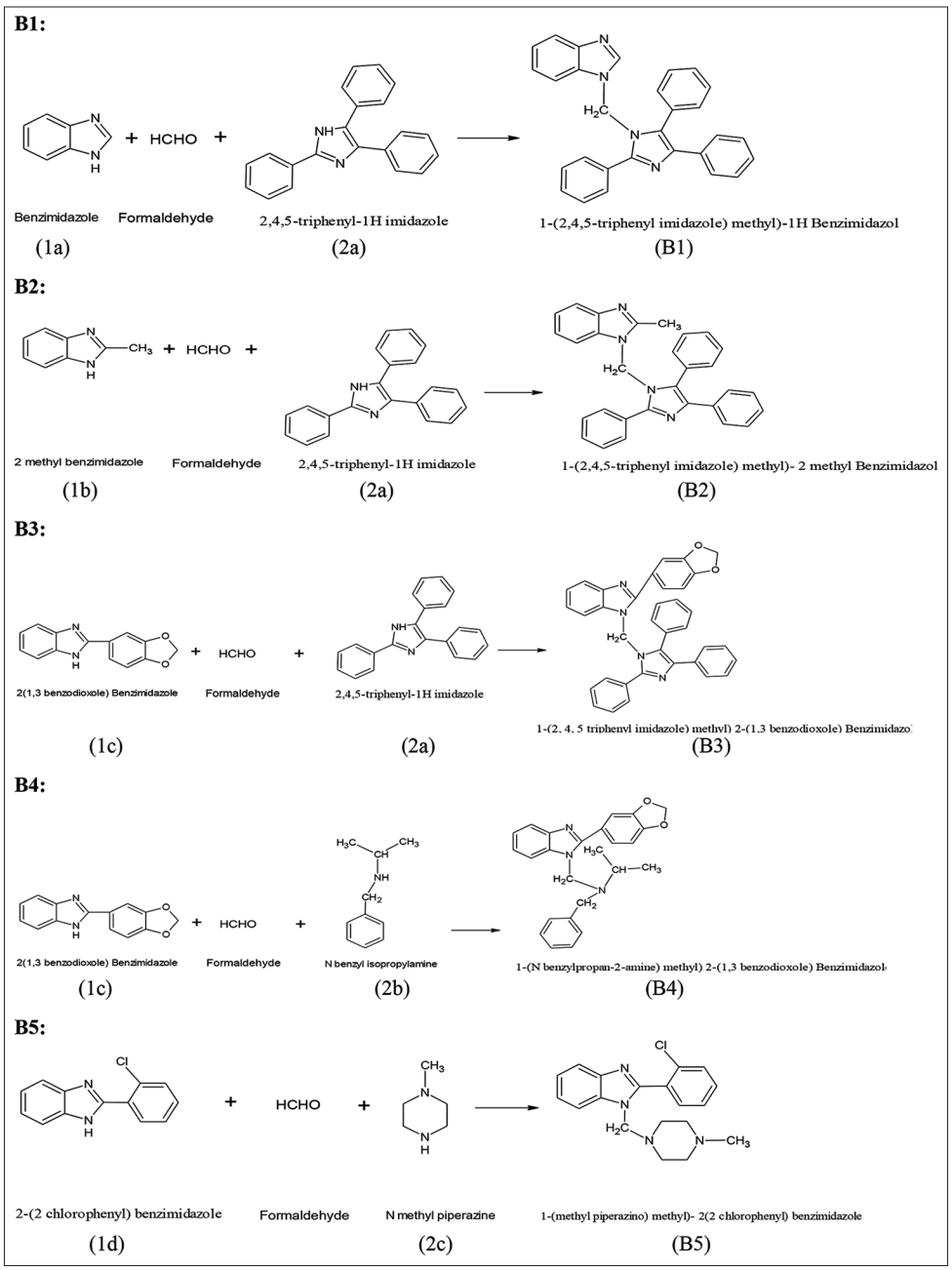


Fig. 2: 3D overlay of docked poses of the synthesized compounds in active site of protein database ID: 5fsa

14-alpha demethylase (PDB ID: 5FSA) in Table 3, and BCl-2 (PDB ID: 600K) in Table 4. The *in silico* results, detailed in Tables 3-5, suggest that these compounds may serve as effective or may be moderate-to-good analgesic, antifungal, and anticancer agents, particularly as inhibitors of the breast cancer cell line. In addition, physicochemical, pharmacokinetic, and ADME properties were evaluated using the Swiss ADME online tool, with results summarized in Table 1. The analyses indicated that the synthesized substituted benzimidazoles possess moderate-to-good physicochemical properties, and the bioavailability radar suggests they have favorable characteristics for oral bioavailability, as most compounds may be fall within the optimal pink region of the radar and egg plot for all synthesized compounds possibility of being absorbed by the GI tract (Fig. 4). The BOILED-Egg model was employed to calculate the ADME and drug-likeness properties of the ligands using the Swiss ADME online server. In addition, Lipinski's Rule of 5 was applied to assess the drug-likeness of the ligands, focusing on key parameters such as molecular weight, lipophilicity, hydrogen bonding capacity, and polar surface area, which are critical for drug development. The results from the docking studies were analyzed to explore the binding affinities between the target protein and the ligands. Key factors such as binding affinity scores were examined to evaluate the stability and strength of the protein–ligand binding interactions. Negative binding affinities indicate stable and favorable interactions between the receptor and ligand, suggesting effective binding. Overall, these computational studies demonstrate that the synthesized benzimidazole derivatives exhibit promising pharmacokinetic properties and affinity, making them strong candidates for further development as therapeutic agents. Their favorable drug-likeness profiles and potential efficacy underline their viability for future experimental validation and clinical testing.

Synthetic scheme

Synthetic scheme for N-Mannich bases of substituted benzimidazole (B1-B5).



Scheme 1: Synthetic scheme for N-Mannich bases of substituted benzimidazole (B1-B5) *in silico* result

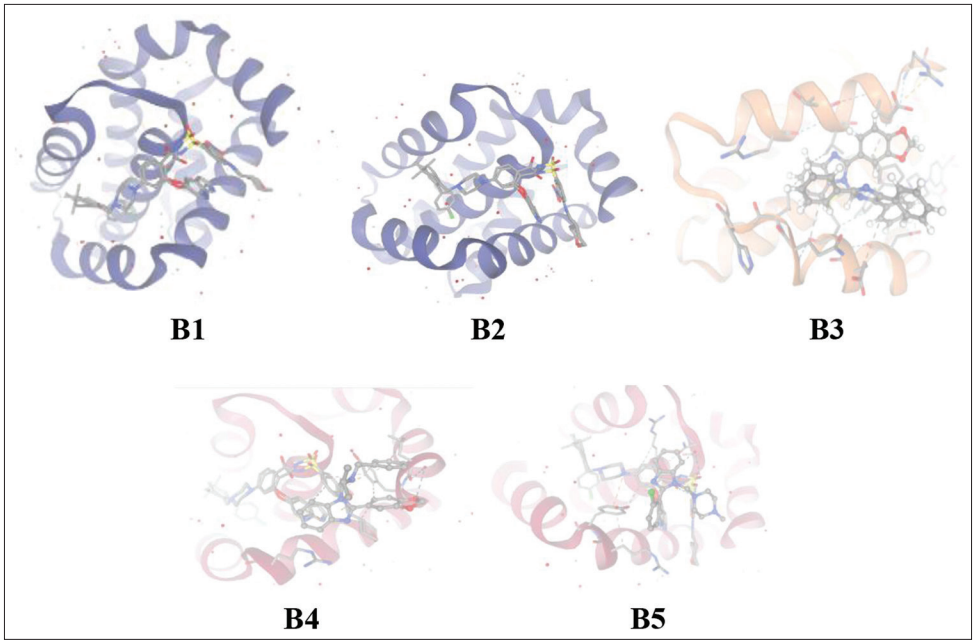


Fig. 3: 3D overlay of docked poses of the synthesized compounds in active site of protein database ID: 600k BCl-2

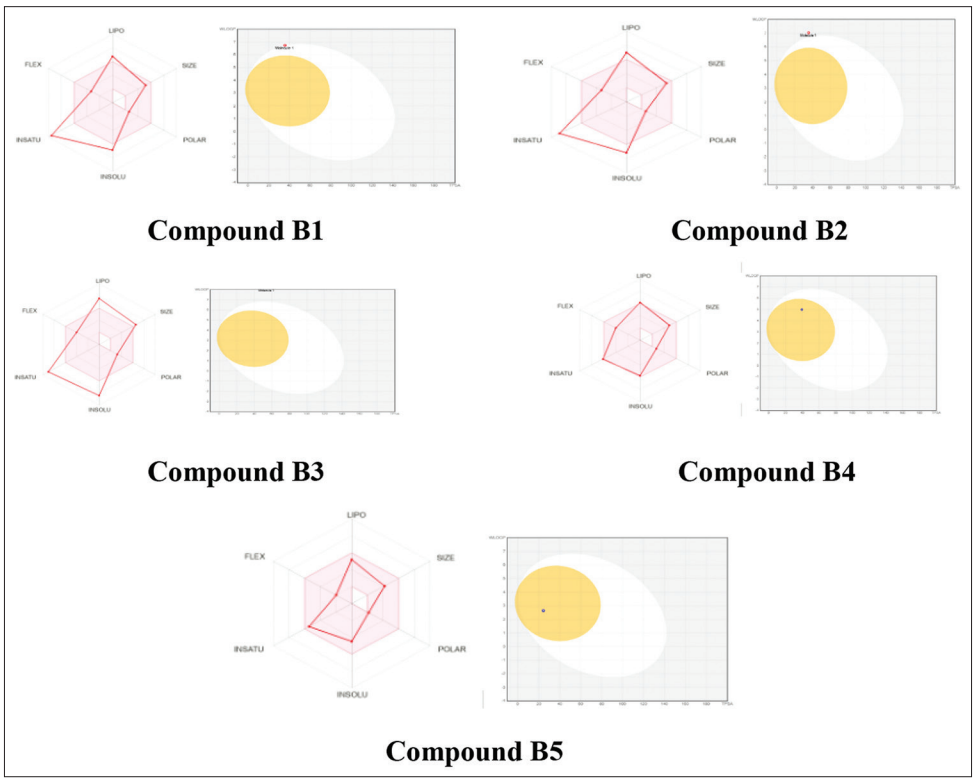


Fig. 4: Left: Oral availability prediction chart: A colored zone is a suitable physicochemical space for oral bioavailability. Right: Boiled egg plot: To show the possibility of being absorbed by the GI tract by the SwissADME software

***In silico* Result**

A technique that is becoming more important for realizing the basis of protein–ligand interaction (affinity) is molecular docking [17]. This present study was performed to determine the binding affinities (Kcal/mol) shown in Tables 2- 4 and 3D overlay of docked poses of synthesized compounds are expressed in the Figs. 1-3 respectively of the ligands with the groups present in the active site of 1C14, 5fsa and 600k. The degree of the interaction between the ligand and the protein is indicated by the binding affinity of the protein–ligand complex. The docking results showed that ligands B1-B5 have better binding affinities >−6.2 KcaL/moL except compound B4 (47.1018 KcaL/moL) for 5fsa target protein. The binding affinities of compounds B3 and B4 have come out as the highest (−7.8 and −7.9 KcaL/moL, respectively) for the 1C14 target protein. Compounds B1 and B5 (−7.2 KcaL/moL, respectively) for 1C14 target protein, B1 (−7.0 KcaL/moL, respectively) for 5fsa target protein, and B3 (−7.0 KcaL/moL, respectively) for 600k target protein have also good binding affinities.

Table 3: *In silico* validation results of synthesized compounds (B1-B5)

S. No.	Compound	Binding Energy (KcaL/moL)
1	B1	−7.0663
2	B2	−6.3470
3	B3	−6.4811
4	B4	47.1018
5	B5	−6.4602

Table 4: *In silico* (5fsa) validation results of synthesized compounds (B1-B5)

S. No.	Compound	Binding energy (KcaL/moL)
1	B1	−6.9697
2	B2	−6.2176
3	B3	−7.0621
4	B4	−6.8537
5	B5	−6.3399

Table 5: *In silico* (600k) validation results of synthesized compounds (B1-B5)

S. No.	Compound	Binding energy (KcaL/moL)
1	B1	−7.2541
2	B2	−7.1986
3	B3	−7.8515
4	B4	−7.9546
5	B5	−7.2865

SwissADME results

The compounds observed in the range of the pink area of the RADAR plot are ingestible. ADME properties of all compounds B1-B5 are shown in Table 1. Oral bioavailability radar and boiled egg plot for interpretation of GI absorption of compounds B1, B2, B3, B4, and B5 are depicted in Fig. 4. They are sparingly soluble to highly soluble in water and are anticipated to absorb well via the GI tract. Only two compounds B4 and B5 were established to be BBB permeable and predicted as P-gp substrates and it was estimated that all synthesized compounds would be skin permeable because of their medium Log Kp values. Lipinski's rule of 5 was employed to evaluate the results of ADME properties. Compound B5 has 0 violations from this rule and the rest of the compounds (B1, B2, B3, and B4) have 1 violation from the Lipinski rule, which for orally active medicines is acceptable [17]. Since all the compounds follow the Lipinski rule of 5 with 0 or 1 violation, so all of them can act as efficient orally active drugs. Thus, from the above results, we may conclude that most of these compounds have better to moderate drug-likeness and ADME properties among which compound B5 is the best drug candidate because it follows the Lipinski rule of 5 with 0 violation and also has binding affinity against the target protein.

CONCLUSION

Novel N mannich bases of substituted benzimidazole derivatives were successfully synthesized. The target novel N-mannich bases of substituted benzimidazole derivatives were synthesized by conventional way, 8-15 hours was required to complete the reaction. The synthesized compounds B1 to B5 were screened for *in silico* studies. The molecular docking results demonstrated moderate-to-good binding affinity for all the pdb databases. Finally, the *in silico* physicochemical, pharmacokinetics, and ADME predictions displayed that the synthesized novel N-Mannich bases of substituted benzimidazoles are may be promising candidates for the optimization in further innovation as analgesic and antifungal agents and breast cancer cell line inhibitors. Therefore, in the search of the new generation of active compounds, it may worthwhile to explore the possibility in this area by making or introducing different functional groups as substituted primary or secondary amine moieties or substituted benzimidazole moieties which may result in better pharmacological agents with higher potency.

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AUTHOR'S CONTRIBUTION

Ms. Bhagyashri D. Jadhav prepared and designed the original draft. Dr. Sushil Narkhede provides valuable inputs toward designing of the manuscript. All authors read and approve the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

FUNDING

Nil.

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