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Sustainable Chemistry of Benzimidazole and its Derivatives: An Eco-Friendly Method for Producing Effective Antimicrobials

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वित्त पोषण नीति-
'शोध उत्कर्ष' एक स्वतंत्र पत्रिका है। इसे किसी भी सार्वजनिक, वाणिज्यिक या गैर-लाभकारी संगठन से कोई वित्तीय सहायता, अनुदान या फंडिंग प्राप्त नहीं होती है।

Abstract
Certain compounds, such as benzimidazole hydrazone, have been created to evaluate their efficacy against bacteria since medical drugs containing benzimidazole and hydrating agents are significant antimicrobials. Using elemental analysis, 1H-NMR measurements, infrared radiation, and ES-MS spectrum evidence, the chemical composition of the novel produced compounds was elucidated. Following the evaluation of the synthetic chemicals, it was found that the addition of standard Schiff bases and particular substance clusters inserted beneath either benzimidazole nuclear structures along with an altered nucleus (-Cl, -NO_2, OCH_3, -Br) increases the ability to kill bacteria. Each variation performed well against Gram-positive bacteria but poorly against germs with Gram-negative DNA. Several of the recently synthesized chemicals showed modest effectiveness when tested against fungus.
Keywords: benzimidazole, antimicrobials, thiabendazole, Thin Layered Chromatography.

Introduction:

"Environmental chemistry" (GC) is the study and development, aesthetics, and use of chemical products and processes to reduce or eliminate the production and use of hazardous materials for living environments. In order to plan its production and uses, the GC starts with creative theory and looks for the kind of thing being developed and our course of action. The impacts of chemicals and chemical processes must be considered in design requirements. [1]. Potential risks for both raw materials and completed items must be included in the effectiveness requirements. Around the start of the 1990s, the ideas of GC started to take on a broader global scope. The goal was to develop an eco-friendly alternative for the production of chemicals and related procedures. A committee of experts from many developed countries was brought together to offer advice on the areas of research and development for GC applications. Based on the GC values, the following areas were recommended for focus. Their choice was mostly influenced by economic issues and their capacity to promote ecologically friendly growth. [2].

Heterocyclic compounds have a crucial role in the science of medicine since they are used to treat the great majority of diseases. Benzimidazole is an insurance purine-analogue pharmacophore with a variety of therapeutic uses. activity, is distinct from the heterocycles discussed above [3]. The power source benzimidazole ring complex is a very common heterocyclic pharmacophore in nature. These elements are sometimes called

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to as "fortunate" due to the extremely varied occurrence of psychoactive compounds. The main focus is on the biological effects of the benzimidazole antagonist and its structural stability biochemistry molecules, which are also well-known. A variety of commercialized benzimidazole drugs are depicted in Fig. 1 [4].

Table.1 Compound detail and substituents

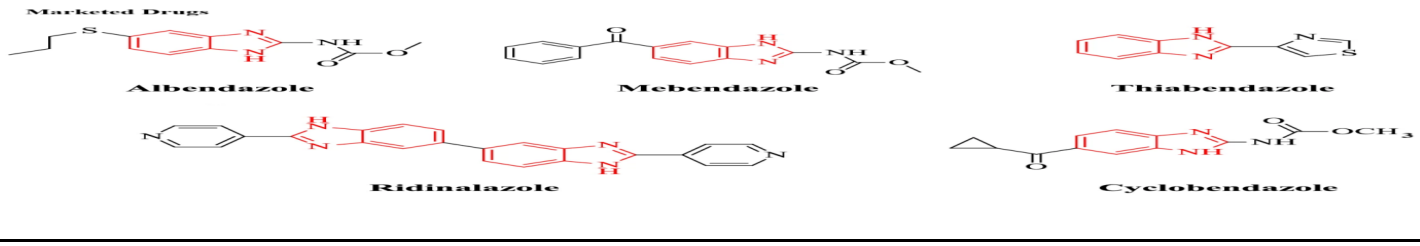


Fig. 1 Marksted drugs of benzimidazole

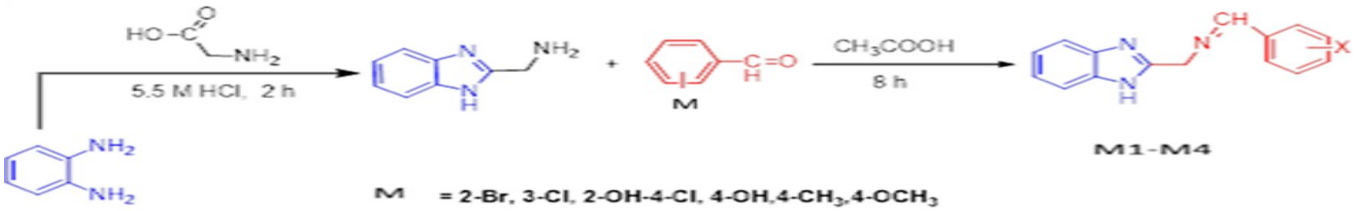
Procedure:

Synthesis Procedure of M1-M4

Step-1 In the beaker, add o-phenylenediamine (0.65g), glycine (0.9g), and 12ml of 5.5mol/L HCl in that order. The molar ratio of o-phenylenediamine and glycine is 2:1. There is a 1:10 molar ratio. To fully dissolve, stir it evenly, place it in a microwave oven set to 2450MHz, and irradiate it six times at an output power of 220W, each lasting one minute. In a microwave oven with a 220W output power, the fully dissolved solution was exposed to intermittent radiation ten times, for five minutes each time, followed by ten minutes of rest. To get 2-aminomethylbenzimidazole dihydrochloride, recrystallize the crude product with 100% ethanol, then dissolve it in water. 2-aminomethylbenzimidazole is obtained by ethanol/water recrystallization after cooling to 3–5°C to finish the crystallization process [5-6].

Step-2 Equimolar amounts of benzaldehyde derivatives (3-Br, 3-Cl, 2-OH-4Cl, 4-OH, 4-CH3) and 2-aminomethylbenzimidazole in 1 milliliter of water should be added to a beaker, placed in a microwave oven set to 2450 MHz, and exposed to 200 W of radiation for 30 to 2 minutes. Thin Layered Chromatography indicates the completion of the process. A crude reaction mixture was obtained by filtration and recrystallized from methanol [7].

Scheme



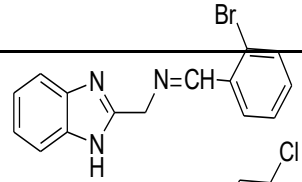
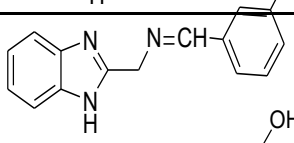
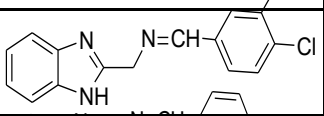
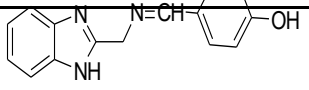
Compound code	Structure	X (Substituent)	Chemical name	R_f value	mass
X1		2-Br	(1H-Benzoimidazol-2-ylmethyl) -(2-bromo-benzylidene)-amine	0.81	315.20 Exact Mass: 313.02
X2		3-Cl	(1H-Benzoimidazol-2-ylmethyl) -(3-chloro-benzylidene)-amine	0.57	270.81 Exact Mass: 269.07
X3		3-OH,4-Cl	5-[(1H-Benzoimidazol-2-ylmethylimino)-methyl]-2-chloro-phenol	0.69	286.1 Exact Mass: 285.07
X4		4-OH	4-[(1H-Benzoimidazol-2-ylmethylimino)-methyl]-phenol	0.75	252.1 Exact Mass: 251.11

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Table.2 Physical Characterization Data of Compounds (M1-M4)

C. C	Chemical For-mula	% Yield	Colour	M.P(°C)	Solubility
M1	$C_{15}H_{12}BrN_3$	72%	Dark brown	293-295	Methanol, Ethanol
M2	$C_{15}H_{12}ClN_3$	86%	Light yellow	162-164	Methanol, Ethanol
M3	$C_{15}H_{12}ClN_3O$	67%	Light brown	128-130	Methanol, Ethanol
M4	$C_{16}H_{15}N_3$	74%	Pale yellow	236-238	Methanol, Ethanol

CHARACTERIZATION OF DATA (SYNTHESIZED COMPOUNDS)

(1H-Benzoimidazol-2-ylmethyl) -(2-bromo-benzylidene)-amine [M1]-Molecular formula: C15H12BrN3, 1H NMR (300 MHz, δ ppm/), dark brown color, Rf-value: 0.81, yield: 72%, m.p.: 293-295°CMeOD: 8.30 (s, 1H, CH), 7.94 (m, 3H, Ph-H), 7.51 (m, 2H, Ph-H), 7.43 (m, 2H, Ph-H), 7.23 (m, 1H, NH), 5.03 (s, 1H, NH), 4.92 (s, 2H, CH2); IR (KBr, cm-1): 3345.76 N–H (benzimidazole ring), 1586.96 C=C (aromatic ring), 3049.87 (Aromatic C–H), and 2895.97 Ele. Ana. Calculated: C, 57.3; H, 3.9; Br, 25.4; N, 13.4 Ele; aliphatic C–H (benzylic CH_2), 837.68 Ph–H out-of-plane bending (para-substituted), 570.36 (C–Br stretch). Ana. Found: Br, 25.1; N, 14.1; C, 56.2; H, 3.9. MS (ESI) m/z: Cal. 315.20 + [M+H] Mass Exact: 313.02.

(1H-Benzoimidazol-2-ylmethyl) -(3-chloro-benzylidene)-amine [M2]-Yellow, Rf-value: 0.57, yield: 83%, m.p: 153-155°C, molecular formula: C15H12ClN3, 1H NMR (300 MHz, δ ppm/MeOD): 8.21 (s, 1H, CH), 7.93 (m, 2H, Ph-H), 7.61 (m, 2H, Ph-H), 7.32 (m, 4H, Ph-H), 4.31 (s, 1H, NH), 4.33 (s, 2H, CH2); IR (KBr, cm-1): 3010.12 (br, N–H stretching, benzimidazole), 1622.26 (s, C=N imine stretching), 1589.37 (m, aromatic C=C), 3048.78 (m, aromatic C–H), 2894.47 (w, aliphatic C–H), 785.47(m, aromatic C–H out-of-plane bend, para-substituted ring), Ele. Ana. Calculated: C, 66.8; H, 4.5; Cl, 13.1; N, 15.58 Ele. Ana. C, 66.6; H, 4.4; Cl, 13.2; N, 15.5; MS (ESI) m/z: [M+H] + Cal. 270.81; Exact Mass: 269.07 were discovered.

5-[(1H-Benzoimidazol-2-ylmethylimino)-methyl]-2-chloro-phenol [M3]-brown, chemical formula: C15H12ClN3O, yield: 67%, m.p: 130-131°C, Rf-value: 0.69, 1H NMR (300 MHz, δ ppm/MeOD): 8.13 (s, 1H, CH), 7.82 (m, 2H, Ph-H), 7.31 (m, 2H, Ph-H), 7.11 (m, 2H, Ph-H), and 7.02 (m,1H).Ph-H) 5.32 (s, 1H,NH), 4.94 (s, 2H, CH2), 4.86 (s, 1H,OH); IR (KBr, cm-1): 3315.94 (br, N–H stretching, benzimidazole), 3464.89 (br, O–H stretching, phenol), 1619.95 (s, C=N imine stretching), 1576.53 (m, aromatic C–C stretching), 3045.67 (m, Ph–H out-of-plane bending), 674.76 (m, C–Cl stretching); Ele. Ana. Calculated: C, 63.1; H, 4.2).

4-[(1H-Benzoimidazol-2-ylmethylimino)-methyl]-phenol [M4]-Molecular formula: C15H13N3O, light brown, Rf-value: 0.75, yield: 61%, m.p: 179-181°C, 1H NMR (300 MHz, δ ppm/MeOD): 8.34 (s, 1H, CH), 7.73 (m, 2H, Ph-H), 7.42 (m, 2H, Ph-H), 6.81 (m, 2H, Ph-H), 5.22 (s, 1H, NH), 4.93 (s, 2H, CH2), and 4.74 (s, 1H, OH); IR (KBr, cm-1): 3316.98 (br). Ele. Ana. Found: C, 71.7; H, 5.2; N, 16.7; O, 6.3; MS (ESI) m/z: [M+H] + Cal. 252.1 Ele. Ana. Calculated: C, 72.1; H, 5.2; N, 16.7; O, 6.3 251.11 is the exact mass.

Table 3. Benzimidazole derivatives' physicochemical characteristics

Compound Codes	Num. heavy atoms	Num. arom. heavy atoms	Molar Re-fractivity	Log S (ESO L)	Solubility(mg/ml)_	Fraction Csp3
M1	19	15	81.74	-4.35	1.41e-02 mg/ml	0.07
M2	19	15	79.05	-4.03	2.49e-02 mg/ml	0.07
M3	20	15	81.07	-3.88	3.12e-04 mg/ml	0.07
M4	19	15	76.06	-3.30	1.27e-01 mg/ml	0.07

SAR of synthesized compound-Substituted molecules in the "4" or "5" positions of the benzimidazole nucleus might increase the antibacterial activity of compounds (M1-M4), which are examples of benzimidazole hybrids [8]. The antibacterial activity of benzimidazole hybrids may be increased when a para- or ortho-substituted phenyl group is present in the "1" position[9].

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The Schiff bases bridge, which connects the substituted benzine ring with benzimidazole, strengthens the antibacterial effect [10].
The inclusion of additional heterocycles in the molecule, which are grafted on benzimidazole and Schiff bases connected with substituted benzine nuclei, increases the antibacterial activity of the compounds [11].

The antibacterial activity of the compounds is increased when special groups, such as -F, -chlorine, -bromine, $-CF_3$, $-NO_2$, -CN, -CHO, -OH, and other heterocycles in the molecule, are grafted on the benzimidazole and Schiff bases connected with modified benzine nuclei [12].

Evaluation of antimicrobial activity

The experiment was conducted using the disc diffusion technique [], using Gentamycine and Ampicelline as recommended, with some modifications for the chemical compounds generated. The created chemical compounds were tested against strains of bacteria and fungus, including Bacillus cereus, a kind of Escherichia coli, Saccharomyces cerevisiae, and Aspergillus niger. The Whatman A 5-mm-diameter filter paper disc (number 1) was sterilized by autoclaving it at 121°C for 15 minutes. The disinfected disks have been treated with many chemicals (600 µg/disk). The topmost layers of agar plates were uniformly inoculated with the culture medium of the investigated pathogens. To ensure sufficient diffusion, the dishes were incubated for one hour at 5 °C after the saturated discs were placed on the medium with the proper spacing. They were then placed in an incubator that was set at 28 °C for 72 hours for yeast and fungus and 37 °C for 24 hours for bacteria. We examined the zones of inhibition that the various substances caused in the microorganisms. The results of the initial diagnostic test are shown in Table 4 [13-16].

Table.4. Outcome of the investigated substances' antibacterial efficacy

Compound No.	*Bacillus cereus*	*Escherichia coli*	*Saccharomyces cerevisae*	*Aspergillus niger*
Gentamycine	+++	+++	-	-
M1	+++	++	++	++
M2	+++	-		+
M3	++	+++	++	+
M4	++	-	-	-

Symbolic key:

+++ indicates excessive activity (inhibition region > 12 mm).
++ indicates moderate activity levels (inhibition region 9–12 mm).
+ (suppression region 6 - 9 mm) = partially active
Inactive = - (inhibition the region < 6 mm)

Docking molecules

The binding interactions between synthetic ligands and the Enterobacter cloacae enzyme (PDB ID: 6NP3) were investigated using molecular docking simulations. Autodocking 4.2 was used for docking, while BIOVIA Discovery Studio was used to view binding modes.
Strong interactions with the active site were indicated by binding affinities ranging from –6.6 to –7.8 kcal/mol. The compounds with the highest binding affinity were M2 (–7.8 kcal/mol), Y4 (–7.7 kcal/mol), and M3 (–7.6 kcal/mol). Excellent docking accuracy was shown by RMSD values of ≤1.45 Å (bottom bound) [17].

Table-5. The synthetic benzimidazole compounds' docking score

Ligand	Binding Affinity (k.cal)	RMSD lower bound	RMSD upper bound
M1	-7.5	0.0	0.0
M2	-7.8	0.0	0.0
M3	-7.6	0.0	0.0
M4	-7.7	0.0	0.0

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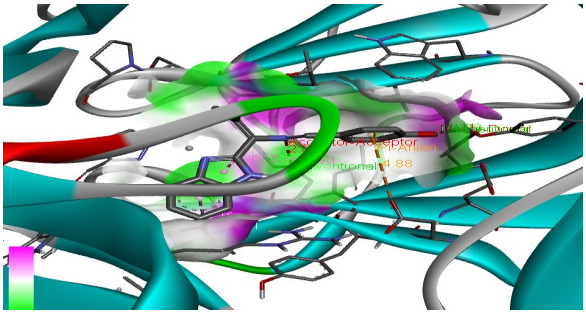

Fig. 2. M3 interaction in three dimensions

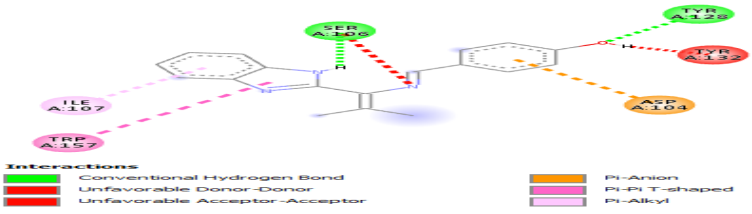

Fig. 3. Two-dimensional compoundM3 interaction

Important interactions:-The amino acids TYR547, TRP629, and TRP157 exhibit π–π stacking; ILE76, TYR105, and LYS554 exhibit π-alkyl interactions; PHE95, ASP96, and TYR128 exhibit hydrogen bonding; sometimes, π-anion interactions and carbon–hydrogen bonds enhance complex stability.

Table. 6 The docking metric score of synthesized benzimidazole derivatives

Ligand	Binding Affinity (k.cal)	RMSD lower bound	RMSD upper bound
M1	-6.6	1.45	1.96
M2	-7.0	0.0	0.0
M3	-7.4	0.0	0.0
M4	-7.2	0.0	0.0

Where: RMSD. , Root Mean Square Deviation

Conclusion:-Sustainable chemistry describes an ensemble of rules designed to minimize or eliminate the consumption or synthesis of potentially harmful compounds throughout the conceptualization, manufacture, and usage of chemical-based items. As we develop new chemical-based syntheses, we will take into account the use of hazardous chemicals and the handling of potentially hazardous substances. Both the basic environmental issues related to these processes and the possibility that hazardous materials need particular disposal must be considered. Benzimidazoles, the most important nuclei in many drugs, are used in a variety of applications and are very beneficial to mankind. Twelve previously unknown medications that have been identified as benzimidazoles have been produced, and their chemical composition has now been confirmed. When compared to the investigated microorganisms, the previously synthesized compounds performed somewhat better biologically than the standard of reference prescription drugs. The structures of the recently synthesized benzimidazoles were confirmed by their spectrum observations (IR, 1H NMR, 13C NMR, and MS spectra). Among most of these new medicines, chemicals M1, M2, and K1, K2 showed the greatest antibacterial activity when compared to the reference drug.

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