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SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS POTENTIAL AS ANTIMICROBIAL AGENTS BY USING MICROWAVE IRRADIATION METHOD

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Abstract:
The main aim of the project is 2-substituted benzimidazole derivatives were prepared by the microwave induced reaction between O-Phenylene diamine and various aromatic aldehydes and aromatic acids. The synthesized compounds have been characterized and confirmed by TLC, elemental analysis, FTIR spectroscopy and screened for their antibacterial activity. • Prepared by the reaction of orthophenylene diamine with equivalent of aromatic acid and dilute 4N HCl. The mixture was refluxed with condenser in synthetic microwave oven at 100° Watts for 5-10 minutes. The mixture was cooled and added 10% NaOH solution till the reaction mixture was neutralized. Then the mixture was separated by vaccum evaporation techinque, dried and calculate the percentage yield. Find out the melting point range and characterize the products using thin layer chromatography, FTIR spectroscopy to confirmm its purity. All the synthesied compounds was screened for invitro antimicrobial activity. the current research shows a rapid, clean, and environmentally sustainable method of the microwave-assisted synthesis of 2-substituted benzimidazoles. The proposed method reduces the reaction time and energy consumption, making developing the process industrially appropriate. The synthesized compounds were recrystallized from ethanol and characterized by thin layer chromatography (TLC), Melting point, FT-IR studies. The synthesized compounds were screened for antimicrobial activity.

Key words: *Synthesis, Biological Evaluation, 2-Substituted Benzimidazole Derivatives, FT IR, TLC*

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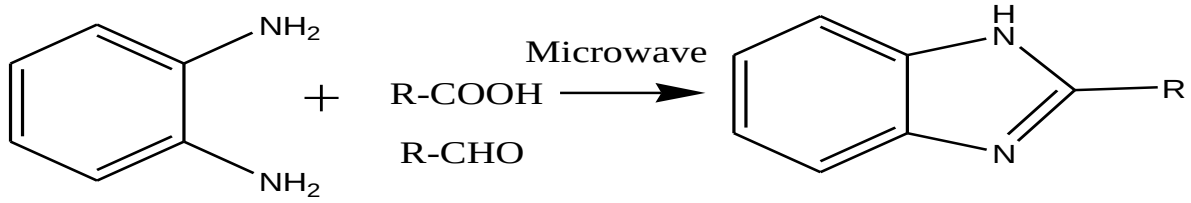
INTRODUCTION:

The biological application of benzimidazole nucleus is discovered way back 1944, when Woolley speculated that benzimidazoles resemble purine-like structure and elicit some biological application [1]. Hence benzimidazole structure found isosters of naturally occurring nucleotides, which allows them to contact easily with the biopolymers of the living system. Later, Brink discovered 5,6-dimethylbenzimidazole as a degradation product of vitamin B12 and subsequently found some of its analogs having vitamin B12-like activity [2, 3]. These initial study reports emerged to explore various decorated benzimidazole motif discoveries by the medicinal chemist. Over the few decades of active research, benzimidazole has evolved as an important heterocyclic nucleus due to its wide range of pharmacological applications. Hence, it's worth to understand the basic chemistry and structure of such a wonderful molecule. Benzimidazole is formed by the fusion of benzene and imidazole moiety, and numbering system according to the IUPAC is depicted in Figure 1. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2,5 (or 2,6)-dimethylbenzimidazole by the reduction of 2-nitro-4-methylacetanilide [4]. Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize, and this may be depicted in Figure 1. This basic "6 + 5" heterocyclic structure is shared by another class of chemical compounds existing in nature shown in Figure 2. Among the members of this group of molecules are well-known building blocks for biopolymers, such as adenine and guanine, two of the five nucleic acid bases, uric acid, and caffeine. From this basic structural similarity, it is not too surprising that benzimidazole nucleus has emerged biologically as an important pharmacophore with a privileged structure in medicinal chemistry. Nowadays it is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. The pharmacological application of benzimidazole analogs found potent inhibitors of various enzymes involved and therapeutic uses including as antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine, and also neurological, endocrinological, and ophthalmological drugs [5, 6, 7, 8, 9, 10, 11, 12, 13].

The main aim of the project is 2-substituted benzimidazole derivatives were prepared by the microwave induced reaction between O-Phenylene diamine and various aromatic aldehydes and aromatic acids. The synthesized compounds have been characterized and confirmed by TLC, elemental analysis, FTIR spectroscopy and screened for their antibacterial activity.

SCHEME



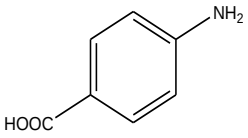
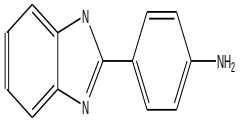
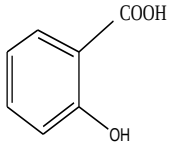
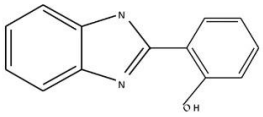
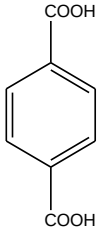
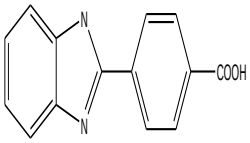
O-Phenylene diamine

Benzimidazole

PROCEDURE

- Prepared by the reaction of orthophenylene diamine with equivalent of aromatic acid and dilute 4N HCl.
- The mixture was refluxed with condenser in synthetic microwave oven at 100° Watts for 5-10 minutes.
- The mixture was cooled and added 10% NaOH solution till the reaction mixture was neutralized.
- Then the mixture was separated by vaccum evaporation techinque, dried and calculate the percentage yield.
- Find out the melting point range and characterize the products using thin layer chromatography, FTIR spectroscopy to confirmm its purity.
- All the synthesied compounds was screened for invitro antimicrobial activity.

Table1: Synthesized Compounds

COMPOUND	STRUCTURE	PRODUCT	MELTING POINT	%YEILD
PARA AMINO BENZOIC ACID			**170°**	**71%**
SALICYLIC ACID			**187°**	**64.5%**
TEREPHTHALIC ACID			**180°**	**66%**

CHEMICAL EVALUTION

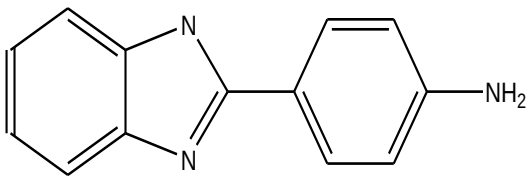
A. **Determination of Rf value by thin layer chromatography**

- Rf value of synthesized compounds and the intermediates were determined by Thin Layer Chromatography on glass plates using silica gel-G as absorbent (stationary phase), Chloroform and Methanol as solvent (mobile phase)
- The differences in Rf value between starting compound and product were indicative of the conversion of starting compound into the product.

B. **Fourier transform Infrared Spectroscopy Analysis**

- Fourier transform infrared spectroscopy (FTIR) is a technique which is used to obtain infrared spectrum of absorption, emission, and photoconductivity of solid, liquid, and gas.
- It is used to detect different functional groups in Compound. FTIR spectrum is recorded between 4000 and 400 cm^{-1}.

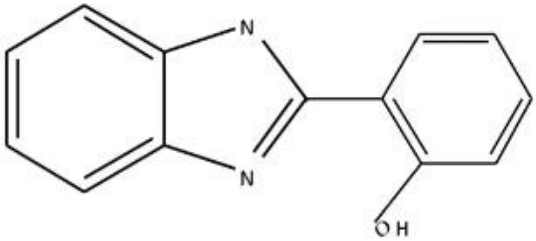
4-(1H-benzimidazol-zyl) benzamide:-



FTIR Spectroscopy

- The structures of the synthesized compounds were confirmed using FTIR.
- An absorption peak obtained at 3212 cm-1 has helped in confirming the presence of -NH in vicinity to the carbonyl group.
- The presence of aromatic C-H linkage is confirmed by the peak obtained at 3045 cm-1.
- A sharp peak at 2101 cm-1 helped to assign the presence of –C=C bond group.
- The presence of -C=N in the Benzimidazole nucleus was also confirmed by the presence of a sharp absorption band at 1680 cm-1.

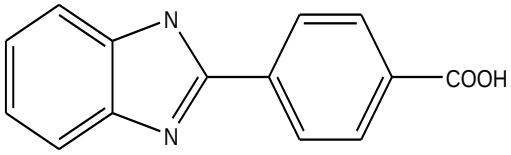
Benzimidazolium salicylate :-



FTIR Spectroscopy

- The structures of the synthesized compounds were confirmed using FTIR.
- An absorption peak obtained at 3209 cm-1 has helped in confirming the presence of -NH in vicinity to the carbonyl group.
- The presence of aromatic C-H linkage is confirmed by the peak obtained at 3050 cm-1.
- A sharp peak at 2102 cm-1 helped to assign the presence of –C=C bond group.
- The presence of -C=N in the Benzimidazole nucleus was also confirmed by the presence of a sharp absorption band at 1659 cm-1.

4-(1H-benzimidazol-zyl) benzoic acid :-



FTIR Spectroscopy

- The structures of the synthesized compounds were confirmed using FTIR.
- An absorption peak obtained at 3281cm-1 has helped in confirming the presence of -NH in vicinity to the carbonyl group.
- The presence of aromatic C-H linkage is confirmed by the peak obtained at 3058 cm-1.
- A sharp peak at 2430 cm-1 helped to assign the presence of –C=C bond group.
- The presence of -C=N in the Benzimidazole nucleus was also confirmed by the presence of a sharp absorption band at 1678 cm-1.

Pharmacological Evaluation

Antimicrobial Activity

All synthesized compounds were screened for in vitro antibacterial activity against one-gram positive strain of bacteria (S. aureus) and one-gram negative strain of bacteria (E. coli) by cup plate method

Cup Plate Method

The nutrient agar medium was prepared by dissolving commercially available agar in distilled water.

- Immediately it was then autoclaved and cooled to 45 - 50 °C. The nutrient agar medium was inoculated aseptically with 0.5ml of strains of S. aureus and E. coli at room temperature.
- Into each sterile Petri dish about 15ml of inoculated molten agar medium was poured. The plates were left at room temperature for solidification. After solidification, the cups of 6mm diameter Petri dish and were made by scooping out the medium with the sterilized corn borer from Petri dish and were labeled.
- All the synthesized compounds and reference were dissolved in DMSO to prepare appropriate dilution to get required concentration of 25µg/ml, 50µg/ml and 100µg/ml.
- The solutions of each compound, reference and a control (DMSO) were added separately into each cups. The plates were kept undisturbed for about 24 hours at room temperature.
- After incubation period of 24 hours the diameter of zone of inhibition was measured with the help of antibiotic zone reader.
- Antibacterial activity of compounds against S.aureus (gram positive bacteria).

Table 2: Antibacterial activity of compounds against S. aureus (gram positive bacteria) Zone of inhibition.

concentration	25	50	100
C1	8	11	14
C2	6	10	13
C3	9	17	19
Standard	16	20	23

Table 3: Antibacterial activity of compounds against E. coli (gram negative bacteria). Zone of inhibition.

Concentration	25	50	100
C1	9	11	15
C2	6	12	13
C3	9	10	16
Standard	16	20	23

CONCLUSION:

- In summary, the current research shows a rapid, clean, and environmentally sustainable method of the microwave-assisted synthesis of 2-substituted benzimidazoles.
- The proposed method reduces the reaction time and energy consumption, making developing the process industrially appropriate.
- The synthesized compounds were screened for antimicrobial activity.
- The synthesized compounds were recrystallized from ethanol and characterized by

  thin layer chromatography (TLC), Melting point, FT-IR studies.

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