Synthesis of Aryl and Aliphatic 2-Substituted Benzimidazole Derivatives

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Abstract-Benzimidazole is a category of heterocyclic aromatic compounds formed form the fusion of six membered benzene with five membered imidazole ring. The current research focuses on the synthesis of aryl and aliphatic 2-substituted benzimidazole derivatives. The synthetic compounds exhibit a wide range of biological activities, including Anti-Bacterial and Anti-Oxidative properties.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound which enjoys the attention as a versatile Pharmacophore in medicinal chemistry. The benzimidazole ring is one of the privileged scaffolds for the development and synthesis of novel molecules of therapeutic value [1]. This nitrogen containing heterocyclic moiety exhibits a diverse range of biological activities like antimicrobial, anticancer, anthelmintic, anti- convulsant, antioxidant, anti-inflammatory, anti-fungal, anti- psychotic, antihistaminic, antiviral [2].

Chemistry:

Benzimidazole is a six-membered bicyclic heteroaromatic compound in which benzene ring is fused to the 4 and 5 positions of the imidazole ring [3]. Benzimidazole ring contains two nitrogen atoms placed at position 1 and 3 which exhibit amphoteric nature, that is possessing both acidic and basic characteristics [4] (Figure 1).

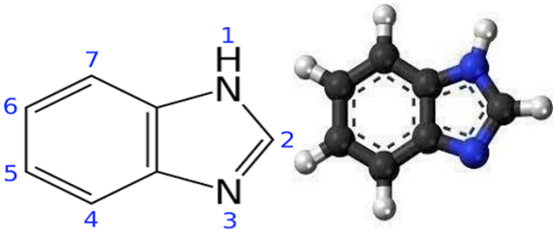


Figure 1

Benzimidazole ring exists in two equivalent tautomeric forms, in which the hydrogen atom can be located on either of the two nitrogen atoms [5] (Figure 2).

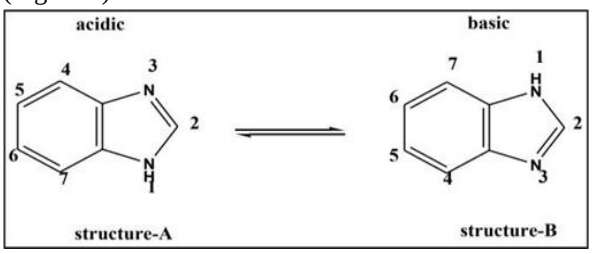


Figure 2

Physical Properties:

Benzimidazoles exists as small Tabular crystals. Its molecular formula is C7H6N2 and molecular weight is 118.053 g/mol. It is in whitish colour and odor is characteristics. It has melting point 170.5-171.50C and boiling point is 360. It is freely soluble in alcohol, sparingly soluble in ether. Practically insoluble in benzene, petroleum ether. Soluble in aqueous solutions of acids and strong alkalis [6]. There is a high melting point for benzimidazoles. The melting point is lowered by the introduction of replacement at position 1.

The melting point of a number of simple benzimidazoles are

Benzimidazole	170^0c
1-methyl benzimidazole	61^0c
2-methyl benzimidazole	176^0c
2-phenyl benzimidazole	294^0c
2(3H)-benzimidazole	308^0c

Table 1

The dipole moment of benzimidazole have been determined, the value that have been obtained 3.93D (in dioxane) and 4.08D.

Acidic/basic nature – The acidic properties of benzimidazole like those of imidazole seem to be due to stabilization of the ion by resonance (Figure 3) [7].

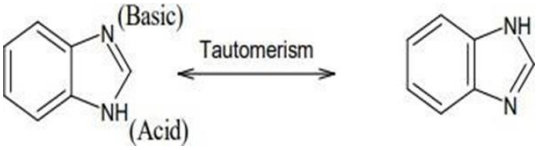


Figure 3

PKa value – The PKa value of benzimidazole is 12.8 and 5.6 (for the conjugate acid)

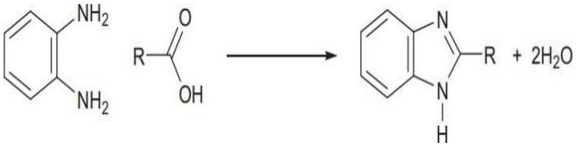
PKa = 5.30 for 2-methyl benzimidazole

PKa = 12.33 for 2-amino benzimidazole.

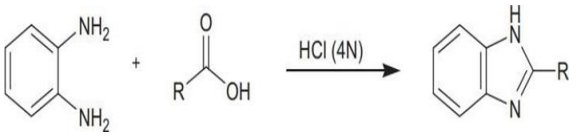
The ring of the benzimidazole compound is extremely stable. Concentrated sulfuric acid, heated hydrochloric acid, alkylation, oxidation, and breaking of the benzene ring have no impact on benzimidazole. Reactions involving benzimidazoles substituent groups only occur under intense condition.

LITERATURE REVIEW

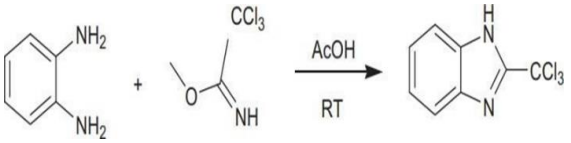
Literature survey has revealed that o-phenylenediamine reacts readily with most carboxylic acids to give 2-substitued benzimidazoles, usually in very good yield. The reaction is carried out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated temperature, or by heating in a sealed tube.



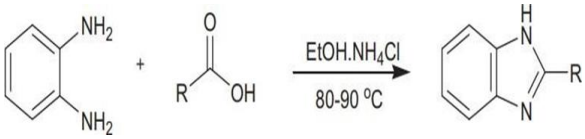
Phillips (1951) method involves the condensation of o-diaminobenzenes with carboxylic acid and its derivatives, including heating the reagents together in the presence of concentrated hydrochloric acid, this is the most common synthetic method for the preparation of a wide range of benzimidazoles [6].



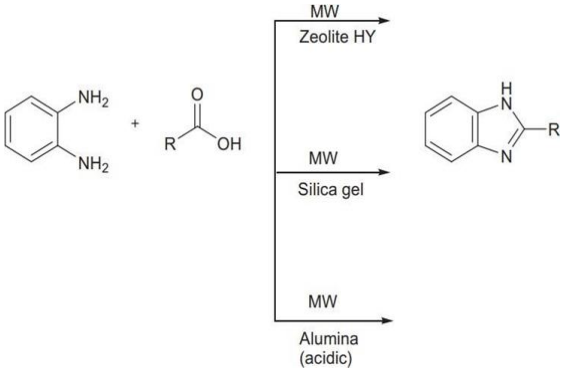
Hollan et al (1967), who have reported the reaction of the appropriate imidate ester (trichloroacetamidate) with o-phenylenediamine or its salt give the 2-trichloromethyl benzimidazole only at room temperature, and this is an important precursor for 2-carboxylic benzimidazoles [8].



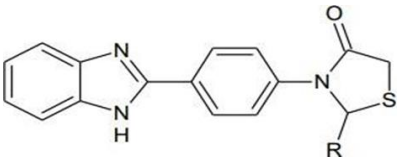
Rithe et al (2015), have reported various of 2-substituted benzimidazole derivatives in moderate to good yield have been prepared in 1-spot reaction by condensation of o-phenylenediamine (0.01 mol) and different aromatic acids (0.01 mol) in the presence of ammonium chloride as catalyst at 80-900C. the reaction is green and economically viable [9].



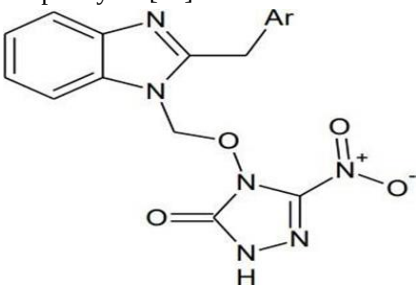
Saberi (2015) has reported synthesis of 2-benzimidazoles under microwave irradiation and solvent free conditions which is catalyzed by alumina, silica gel and zeolite HY as shown in figure, o-phenylenediamine (2 mmol) and 50mg of alumina or silica gel or zeolite were mixed thoroughly in a mortar. The reaction mixture was then irradiation in a domestic microwave oven for 5 to 9 min at 160-560 W [21].



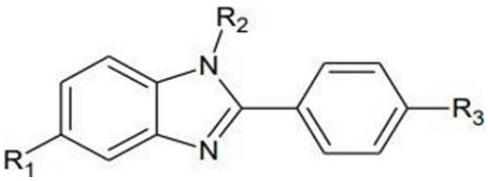
Panneer selvan et al (2011), synthesized a novel series of 2-substituted benzimidazole derivatives by equimolar quantities of o-phenylenediamine (0.01 mol) and p-aminobenzoic acid (0.01 mol) in presence of 4N HCl (20 ml) was refluxed for 30 min [22].



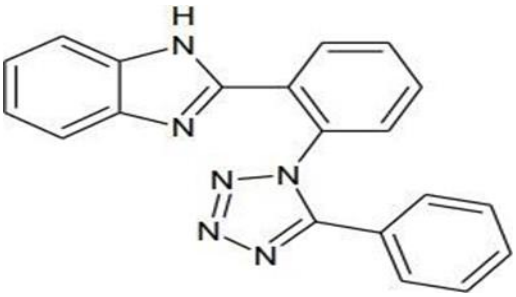
Maste M. M. et al (2011), synthesized some benzimidazoles acetic acid derivatives as well as derivatives associated with 1,2,4 triazolone derivatives and was investigated for their biological actives. All the compounds screened for anti-tubercular and anti-microbial activities by standard methods. Result reveals the compounds shows promising anti-tubercular activities at both the concentrations compared to standard drug streptomycin [23].



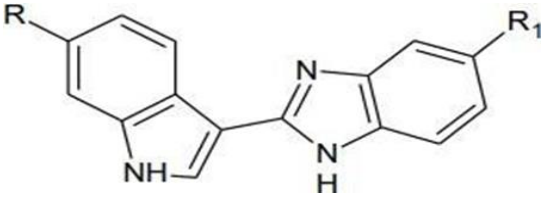
Hamdan S. Al-Ebaisat (2011), synthesized a set of novel benzimidazole compounds. The biological activity of these compounds as fungicides was tested against the commercially known fungicides (C. albicans, patient isolate C. glabrata and C. krusei). The biological activity of two compounds was found to be comparable to that of the commercially available fungicides [24].



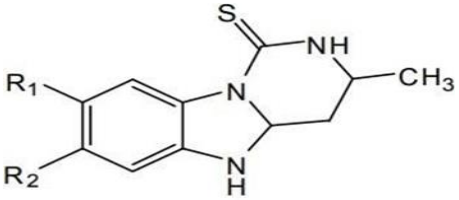
Ahamed A. Jafar et al (2009), synthesized benzimidazole derivatives and screened them for anti-microbial activity. They synthesized 1H-tetrazol-1-yl) phenyl)-1H-benzo[d] imidazole by a series of conventional methods. Antimicrobial activity against bacteria and fungi was studied. The result of preliminary biological tests showed that of these compounds possess good biological activity [25].



Y. Radha et al (2011), synthesized characterized and evaluated some benzimidazole derivatives for antimycobacterial, cytotoxic and diureticactivity. Novel benzimidazole derivatives possessing two different structural moieties, pyridinyloxyphenyl benzimidazoles and indolyl benzimidazole were synthesized [26].

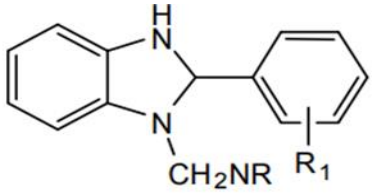


Sondhi et al, (2002) has synthesized some novel pyrimido[1,6-a] benzimidazole derivatives. These derivatives were screened for anti- inflammatory, analgesic and anti-amoebic activity [27].



$R_1 = NO_2$
$R_2 = H$

Leonard et al, (2006) has synthesized some new phenyl benzimidazole derivatives. These derivatives were screened for anti- inflammatory activity. The compound was showed maximum (5.4%) inhibition of edema at doses of 50mg/kg [28].



(1c; R=dimethylamine, R_1=Cl)

Synthesized Derivative Compounds for A-Series

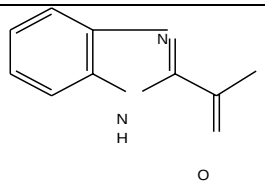
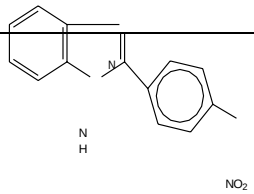
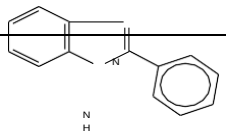
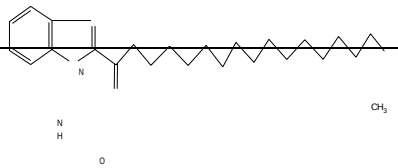
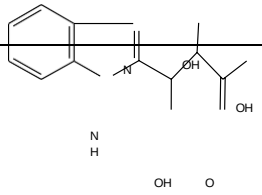
S.No.	Comp. code	Name	Structure
1	A_1	1-(1H-benzo[d]imidazol-2-yl) ethanone	
2	A_2	2-(4-nitrophenyl)-1H-benzo[d]imidazole	
3	A_3	2-phenyl-1H-benzo[d]imidazole	
4	A_4	1-(1H-benzo[d]imidazol-2-yl) heptadecan-1-one	
5	A_5	3-(1H-benzo[d]imidazol-2-yl)-2,3-dihydroxypropanoic acid	

Table 2

Experimental Studies:
Chemicals:
o-Phenylene diamine, Formic acid, HCl and Sodium hydroxide.

Principle:
The condensation of o-phenylene diamine with formic acid or the equivalent trimethyl orthoformate benzimidazole is typical example for Phillips reaction. 2-substituted benzimidazoles can be prepared using different carboxylic acid.

Procedure:
1. To the round bottom flask containing o-phenylene diamine and catalytic amount of hydrochloric acid add formic acid.
2. Heat the contents at 1000C by placing on a water bath for 3 hrs.
3. Cool and add sodium hydroxide solution slowly with constant stirring until the mixture becomes alkaline.
4. Filter and wash the residue with ice cold water.
5. Dry and recrystallize the product.
6. Dissolve the product in boiling water, add chloroform and heat for 15 minutes.
7. Filter in hot condition, cool to 100C, filter and wash with cold water.
8. The melting range of pure benzimidazole is 171-1720C.

Identification and Characterization:
The compounds synthesized were identified and characterized by following methods such as:
- Melting point determination
- Thin layer chromatography
- Mass Spectroscopy
- Nuclear magnetic resonance spectroscopy (1HNMR and 13C NMR)

Melting point determination
The melting point of organic compound was determined by Thiele's melting pointtube (capillary tube method). The determination of melting point is the most important and easy way of differentiating this physical constant of one compound from other.

Thin layer chromatography
TLC is an important method for synthetic chemistry to infer the formation of the compound based on the Rf values since different compound will have different Rf values. Mobile Phase was used for Scheme 1 and Scheme 2 Ethyl Acetate: n- Hexane (2:8).

Mass Spectroscopy
Mass spectrometry is an analytical technique that utilize the degree of deflection of charged particles by a magnetic field to find the relative masses of molecular ions and fragments. It is a powerful method because it provides a great deal of information and can be conducted on tiny samples. Mass Spectrometry has a number of applications in organic chemistry. They are:
- Determining molecular mass
- Finding out the structure of an unknown substance
- Verifying the identity and purity of a known substance
- Providing data on isotopic abundance

The Mass Spectra of the compounds were carried out in BrukerAMX 400MHZ at LIALA IMPLEX, Vijayawada. The solvent used was dueterated dimethyl sulfoxide.

BIOLOGICAL EVALUATION
Biological evaluation for synthesized compounds by in-vitro studies.
- Anti-Bacterial Activity
- Anti-Oxidative Activity

Anti-Bacterial Activity:
Method:
Cup plate method was used to carry out this study.

Principle:
The cup plate method depends on diffusion of antibiotic from a cup through a solidified agar layer in a petri-dish or petri-plate to an extent such that growth added microorganism is prevented entirely in zone around cup or cylinder containing a solution of antibiotic.

Cultivation of Microorganism:
The following microorganisms were used to study the antibacterial activity. Escherichia coli – Gram negative bacteria
Standard: Streptomycin (1000 mg) Solvent: DMF

(Dimethylformamide)
All the test compounds were tested at 250 µg, 500 µg, and 1000 µg.

Preparation of media:
Composition of nutrient agar medium Beef extract – 10g
Peptone – 10g Sodium chloride – 5g Agar – 20g
Purified water – 1000ml pH 7.2± 0.2
The medium was prepared by dissolving the specified quantity of dehydrated medium in purified water by heating on water bath and were dispensed in 100ml volume conical flask. The conical flask was closed with cotton plugs and were sterilized by autoclavinat

121oc (15 lb psig) for 15 min.
the contents of the conical flasks were poured aseptically into sterile petri-dishes are allowed to solidify. These sterilized medias were used to subculture the bacterial culture.

Procedure:
Each petri-dish was filled to a depth of 4-5 mm with a nutrient agar medium that was previously inoculated with suitable inoculums of suitable test organism, and then allowed to solidify. The petri-dish were specially selected with flat bottom and were placed on level surface so as to ensure that the layer of medium is in uniformthickness. The petri-dishes were sterilized at 160- 170oc in hot air oven for 30 mins before use. Small sterile borer to uniform size was placed approximately at 10 cm height, having an internal diameter of approximately at 6-8 mm and made of aluminium(or)stainless steel. Each plate was divided in to four equal portions alongthe diameter. To each portion one cylindrical cavity was made in medium with the help of sterile borer. Three cavities for test compounds and one cavity for the standard. The petri-dishes were incubated at 37oc for 18 hours. Diameter of the zoneof inhibition was measured and the average diameter foe each sample was calculated. The diameter obtained by the test sample was compared with that produced bystandard streptomycin.

Anti-Bacterial activity

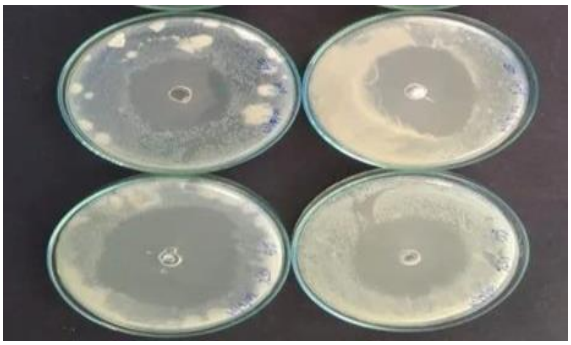


FIGURE 4

Anti-Oxidant Activity:
Oxidative stress has been in numerous patho-physiological conditions including cancer. Conventional medical treatment has its own side effects besides the high cost. A simple but effective way of preventing cancer may be to prevent oxidative damage. By virtue of their of their anti-oxidant property. They also prevent cell growth by inhibiting the proteins responsible for cell growth.
One important mechanism of membrane damage is injury by free radicals, particularly by activated species, it is final common pathway of cell injury in such variousprocesses as chemical and radiation injury, oxygen and other gaseous toxicity, cellularaging, microbial killing by phagocytic cells, inflammatory damage, tumor destruction by macrophages and other.
The current study deals with free radicals scavenging activity of above mentioned derivatives. The objective of the study was to investigate the antioxidant potential of these derivatives, to understand their beneficial role in cancer therapy different derivatives showed antioxidant activity when compared to ascorbic acid.

Various methods of Anti-Oxidant Activity [53]:
- DPPH Free Radical Scavenging Assay
- Superoxide Scavenging Assay
- Iron Chelating Assay

DPPH free Radical Scavenging Assay:
The DPPH radical is one of the few stable organic nitrogen radicals, which bears a deep purple colour. It is commercially available. Because of a strong absorption band centred at about 520 nm, the DPPH radical has a deep violet colour in solution, and it becomes colourless or pale yellow when realized.

This assay is based on the measurements of the reducing ability of anti- oxidants towards DPPH. The ability can be evaluated by electron spin resonance (EPR) or by measuring the decrease in its absorbance. Anti- oxidant assay are based on the loss of the DPPH colour at 517 nm. After reaction with the test compounds, the reaction is monitored by UV-Visible spectrophotometer.

Principle:
1,1 Diphenyl 2-Picryl Hydrazyl is a stable (in powder form) free radical with red colour which turns yellow when scavenged. The DPPH assay uses this character to show free radical scavenging activity. The scavenging reaction between (DPPH) and an antioxidant (HA) can be written as,
(DPPH) + (H-A) → DPPH-H + (A)
Antioxidants reacts with DPPH AND REDUCE IT TO DPPH-H and as consequence the absorbance decreases. The degree of discolouration indicates the scavenging potential of the antioxidant compounds or extracts in terms of hydrogen donating ability.

Reagent preparation:
0.1 mm DPPH solution was prepared by dissolving 4 mg of DPPH in 100 ml of ethanol.
Procedure:
M solution of DPPH was prepared in methanol. Methanolic solutions of all the compounds in the concentration ranges of 40 µg/ml, 60 µg/ml, 80 µg/ml and 100 µg/ml were prepared.

Similarly, solutions of ascorbic acid in the same concentration ranges were prepared as standard. 1 ml of DPPH solution was added to 1 ml of the sample solution as well as ascorbic acid. The volume was finally made up to 3 ml using methanol. The test tubes containing the absorbance of the DPPH solution without sample, DPPH solutionwith sample and ascorbic acid with DPPH were recorded at 517 nm on a UV-Visible spectrometer. The antioxidant activity was measured using the formula [52].

Percentage inhibition of free radicals DPPH (% of DPPH radical scavenging) was calculated by using the following equation [54]:
Percentage inhibition = (1- Asample/Ablank) × 100
Physical and spectral characterization of synthesized derivative compounds:
A total of 05 compounds were synthesized and recrystallized by appropriate solvents. They were identified and characterized by various spectral method. All the compounds characterization were shown in the table

Characterization of synthesized Derivative compounds of A-SERIES

Comp .code	Mol. Formul a	Mol. Weight (g/mole)	M.P(℃)	%yield	Rf value
A1	C9H8N2O	160.17	167-170℃	83.75%	0.41
A2	C13H9N3O2	239.23	165-170℃	78.53%	0.53
A3	C13H10N2	194.23	160-164C^{O}	72.62%	0.57
A4	C24H38N2O	370.30	162-171℃	65.12%	0.67
A5	C10H10N2O4	222.06	155-163℃	54.37%	0.71

Table 3

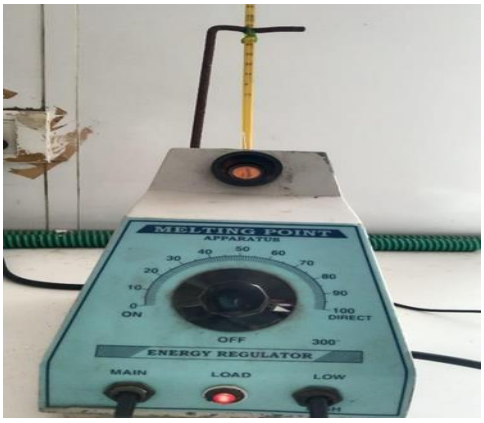


Figure 5

RESULT AND CONCLUSION

All the synthesized compounds derivatives of 2-substituted Benzimidazole Derivatives were evaluated with Physical, spectral Characterization and its Biological evaluation respectively.
All the synthesized derivatives of 2-substituted Benzimidazole Derivative Compounds were evaluated with Physical, spectral Characterization and its Biological activity by appropriate Methods. All the 05 compounds were evaluated with in-vitro Anti-oxidant by DPPH Free Radical Scavenging

Assay and Anti-bacterial activity by Cup plate Method were compare with appropriate reference drugs.

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