https://doi.org/10.48047/AFJBS.6.10.2024.6901-6909

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Synthesis of Benzimidazole as potent Antimicrobial scaffold

Vishant Goel[*1], Dr. Nasiruddin Ahmad Farooqui[2], Praveen Kumar[3]

Article History

Volume 6 issue 10, 2024
Received:01 June 2024
Accepted: 30 June 2024
doi:
10.48047/AFJBS.6.10.2024.6901-6909

Abstract:
The chemical substances in our environment are rising day by day. Only some of them are degraded, but most of them are non-degradable. These non-degradable substances produce pollutions which cause instability, harm or discomfort to the ecosystem as pollutions and create a risk to the environment. To reduce the possibility of a system we must reduce the risk not by altering the effect but by the cause. Thus, green chemistry (GC) concept was introduced, and it is a rapidly emerging field of chemistry. The GC is the design of chemical products and procedures that decrease or remove the use and production of harmful substances. In recent years, various heterocyclic compounds have appeared owing to the extensive varieties of their pharmacological activities. Benzimidazole is a heterocyclic aromatic compound. It is a vital and advantaged structure in medicinal chemistry and plays a role with ample therapeutic activities like analgesic, anti-inflammatory, antiulcer, antihypertensive, antibacterial, antiviral, antifungal, anticancer and antihistaminic. Because of its value, the processes for their synthesis have become a focus of synthetic chemists. The subbed benzimidazoles are summed up in this survey to give knowledge about their natural amalgamation utilizing ecofriendly techniques that locate better scaffolds to cure the several microbial attacks.
Keywords: Antimicrobial activity, antiulcer, green chemistry heterocyclic chemistry.

Introduction:

Green chemistry (GC) is an invention, design, and application of chemical products and procedures to decrease or to abolish the use and creation of hazardous substances for the living environments. The GC starts with the theory of design and looks for the kind of product and also how we are going to design its manufacturing and uses. The impact of chemical compounds and chemical methods must be considered as design criteria. Hazard concerns for early material and final products must also be included in the performance criteria. From the start of the 1990s, the ideas of GC started to have a more global view. The purpose was to initiate an option carried out in the chemical industry and procedures more benign to the environment. A committee of experts was convened from many industrial countries to advise the areas of research and development for GC applications. The areas proposed for focus under the GC values were the following. They

were selected with an emphasis on economic concerns and for their future input to sustainable development [1-7].

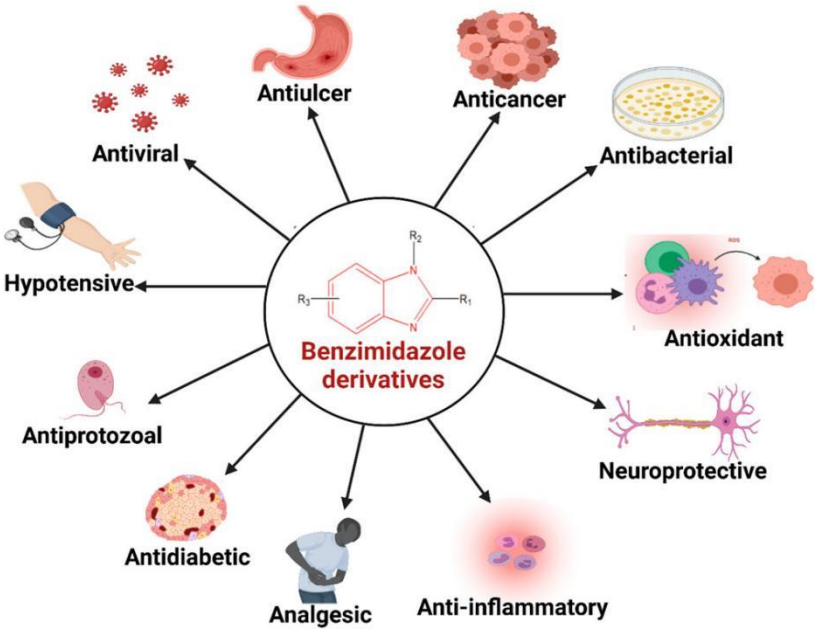
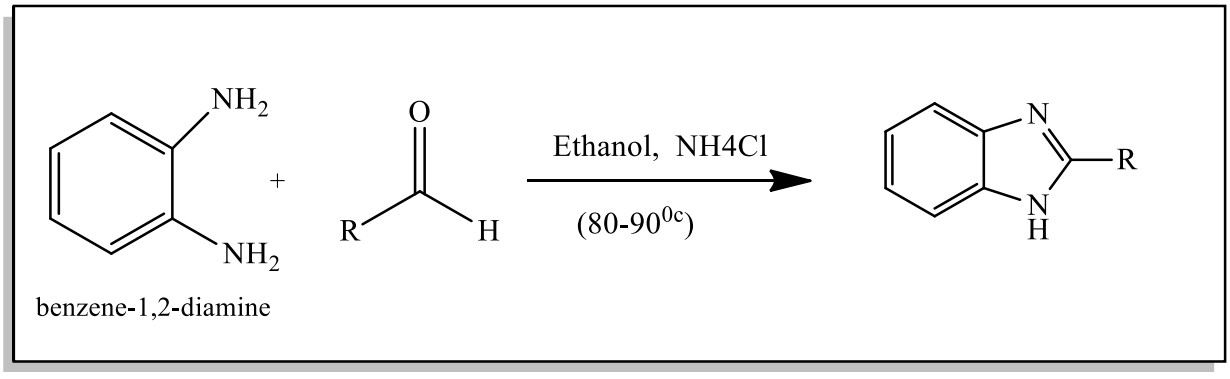


Fig.1 Diversity of Benzimidazole potential

Material Methods:

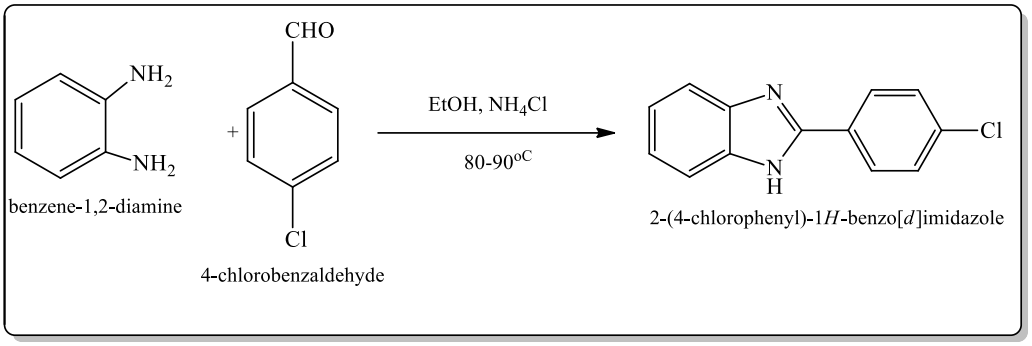
Benzimidazole and its subordinates are natural mixtures that have been arranged utilizing green strategies rather than the customary modern or substance techniques. Microwave innovation (MW) was utilized to set up derivatives subordinates by gathering aldehydes with o-phenylenediamine within the sight of explicit measures of acidic corrosive. Benefits of this technique are that the response times are short, they utilize non-harmful solvents, and give significant returns of the items.

Here I am synthesizing novel 2-aminobenzimidazole 0C and presumed that this strategy was a green and prudent with ammonium chloride with temperature 80 to 90^{OC}

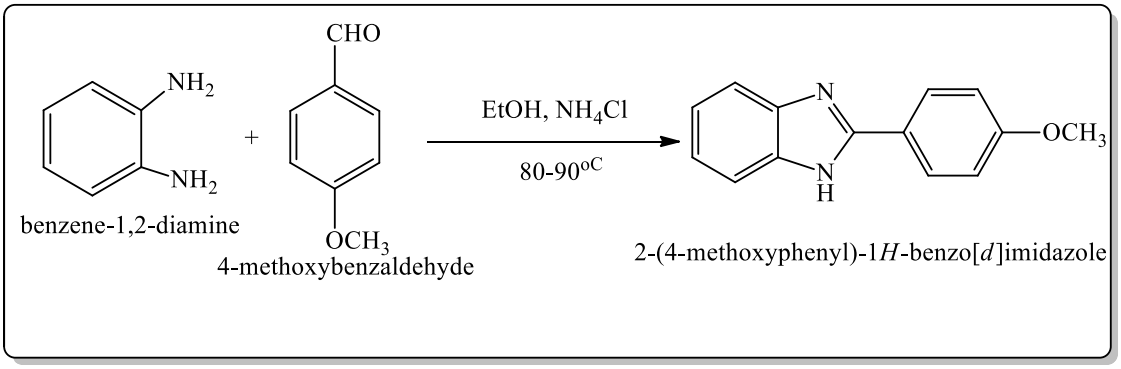


To the combination of O-Phenylenediamine (1g, 0.92mmol) and p-chlorobenzaldehyde (.125g, 92mmol) in 4ml of ethyl alcohol was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by tender loving care (

ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response combination was filled super cold water and item was hastened gives light yellow in variety. The strong item separated by recrystallization from ethanol to acquired unadulterated item.

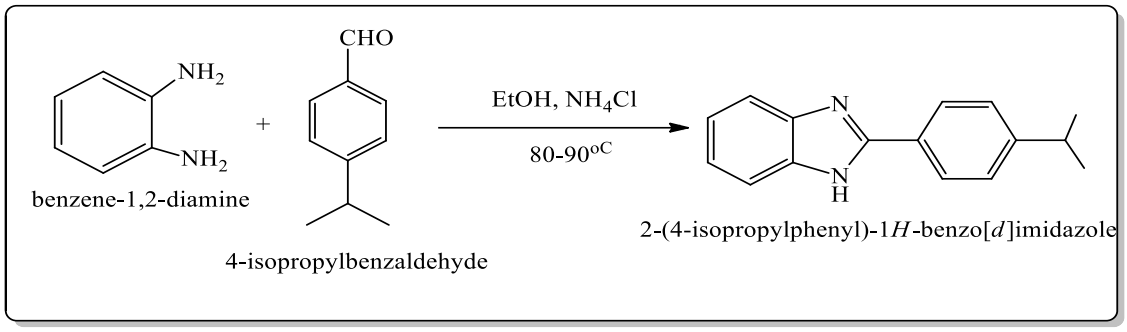


1. **Synthesis of 2-(4-methoxy phenyl)-1*H*-benzo[d]imidazole:**
   To the combination of O-Phenylenediamine (1g, 0.92mmol) and p-methoxybenzaldehyde (.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by attention (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response blend was filled super cold water and item was encouraged gives light yellow in variety. The strong item sifted by recrystallization from ethanol to got unadulterated item.



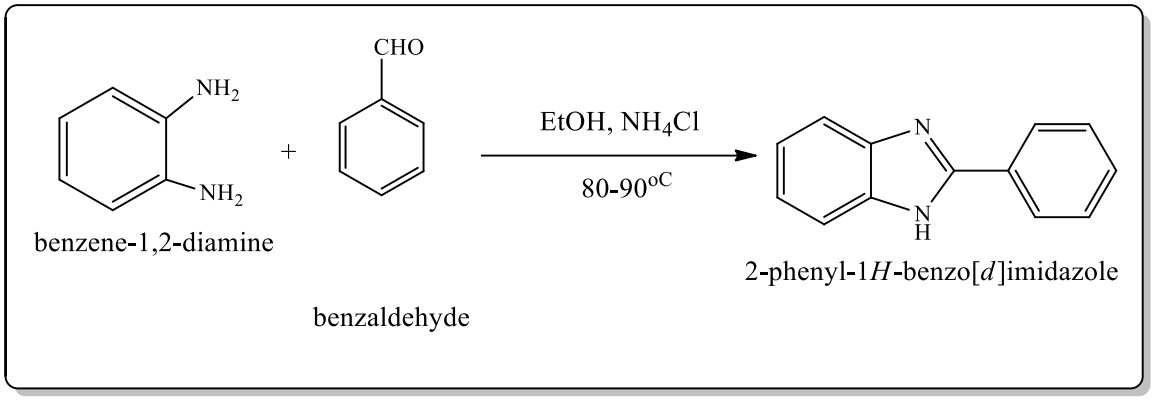
2. **Synthesis of 2-(4-isopropyl phenyl) derivatives**

Procedure: To the combination of O-Phenylenediamine (1g, 0.92mmol) and P-isopropyl benzaldehyde (.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by tender loving care (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response blend was filled super cold water and item was accelerated gives light yellow in variety. The strong item separated by recrystallization from ethanol to acquired unadulterated item.



3. Synthesis of 2-Phenyl-1*H*-benzo imidazole

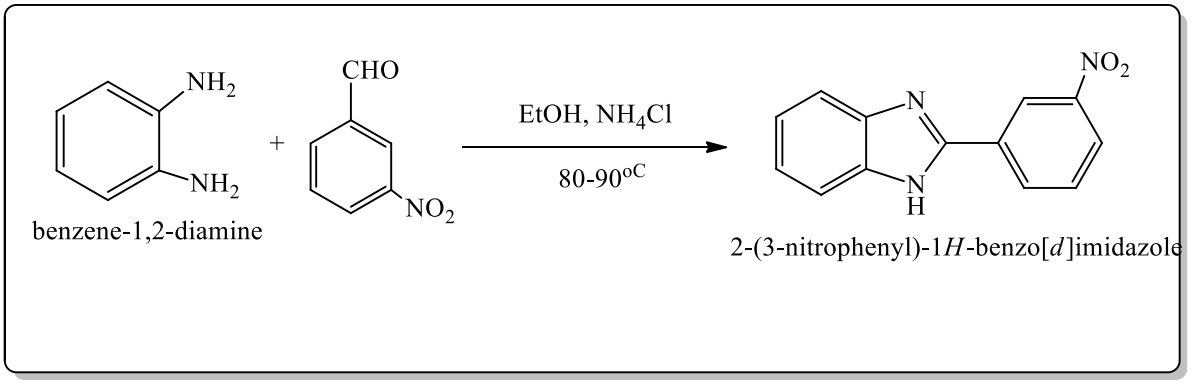
Procedure: To the combination of O-Phenylenediamine (1g, 0.92mmol) and P-isopropylbenzaldehyde (.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by tender loving care (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response combination was filled super cold water and item was encouraged gives light yellow in variety. The strong item separated by recrystallization from ethanol to acquired unadulterated item.



4. Synthesis of 2-(3-nitrophenyl)1-H-benzo[d] imidazole

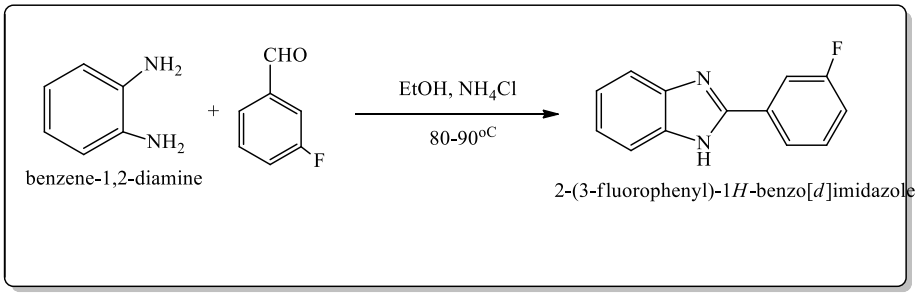
Procedure: To the combination of O-Phenylenediamine (1g, 0.92mmol) and P-isopropylbenzaldehyde (.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by attention (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response

blend was filled super cold water and item was hastened gives light yellow in variety. The strong item separated by recrystallization from ethanol to got unadulterated item.



6.Synthesis of 2-(3-flourophenyl)-1-*H-benz[d]imidazole*

Procedure: To the combination of O-Phenylenediamine (1g, 0.92mmol) and m-nitrobenzaldehyde (.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend blended for 80-90 min. at 80Oc. The response was affirmed by tender loving care (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response combination was filled super cold water and item was hastened gives light yellow in variety. The strong item separated by recrystallization from ethanol to acquired unadulterated item. Colourless solid. Yield 74%. m.p. 272-75°C. IR (KBr): 3030, 1428, 1380, 1275, 970, 754 cm-1; 1H-NMR (500 MHz, DMSO-d6): δ 13.07 (s,1H, NH), 8.38 (S, 1H), 8.19 (d, 1H), 7.71(m, 2H), 7.5 (m, 2H and 7.2 (s, 2H);



`7. **Synthesis of 2-(2-chloro-3-flourophenyl)-1H-benzo[d]imidazole**

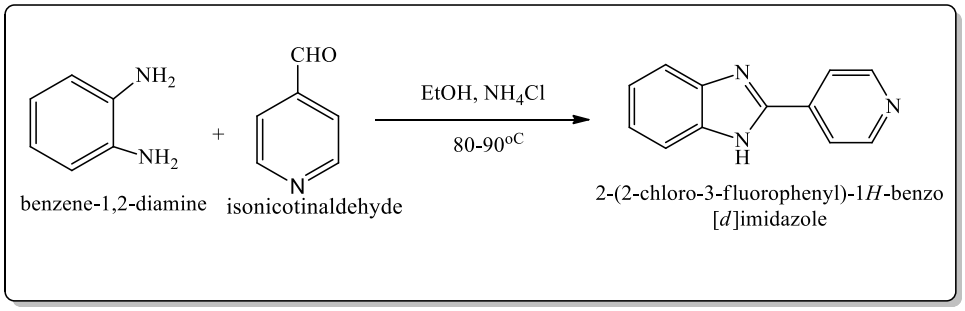
Procedure: To the combination of O-Phenylenediamine (1g, 0.92mmol) and 2-chloro-3-phenylbenzaldehyde (0.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by tender loving care (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response combination was filled super cold water and item was hastened gives light yellow in

variety. The strong item sifted by recrystallization from ethanol to acquired unadulterated item.

Colourless solid. Yield 74%. m.p. 272-75°C. IR (KBr): 3030, 1428, 1380, 1275, 970, 754 cm-1; White solid. Yield 80%. m.p. 235-43°C. IR (KBr): 3009, 1429, 1380, 1260, 970, 727 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 12.96 (s, 1H, NH), 7.6-7.66 (m, 3H), 7.5 (d, 1H) and 7.23 (d, 2H);

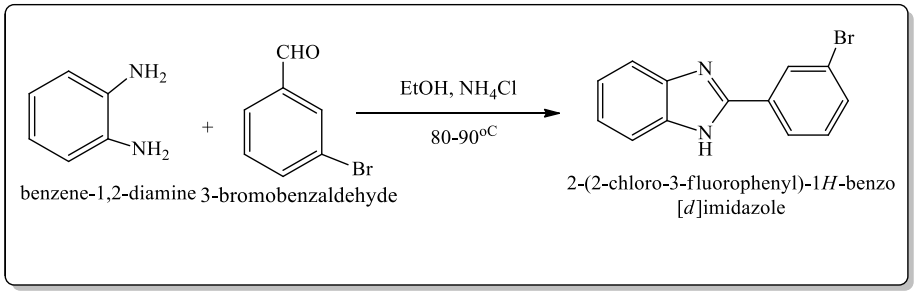
8. **Synthesis of 2-(2-chloro-3-flourophenyl)-1H-benzo[d]imidazole**

Procedure: To the combination of O-Phenylenediamine (1g, 0.92mmol) and 2-chloro-3-isonicotinaldehyde (0.125g, 92mmol) in 4ml of ethyl liquor was added to ammonium chloride (0.15g, 30mol%) Coming about blend mixed for 80-90 min. at 80Oc. The response was affirmed by attention (ethyl acetic acid derivation: Hexane, 1:2 v/v). After that response blend was filled super cold water and item was hastened gives light yellow in variety. The strong item separated by recrystallization from ethanol to acquired unadulterated item.



9. **Synthesis of 2-(2-chloro-3-flourophenyl)-1H-benzo[d]imidazole**

Procedure: To the mixture of O-Phenylenediamine (1g, 0.92mmol) & 3-bromobenaldehyde (0.125g, 92mmol) in 4ml of ethyl alcohol was added to ammonium chloride (0.15g, 30mol%) Resulting mixture stirred for 80-90 min. at 80^{Oc}. After this further workup was done.



Antimicrobial activity: Following bacteria were selected for in-vitro study.

1) ***Staphylococcus aureus (ATCC No. 29737)*: Gram-positive**
2) ***Staphylococcus epidermidis (ATCC No. 12228): Gram-positive***
3) ***Escherichia coli (ATCC No. 8739)*: Gram negative**

Materials: Designed molecules were made during this study different antimicrobial activity. All laboratory grade chemicals were used for the studies. Antimicrobial activity was evaluated by utilizing various methods viz. Agar streak dilution, Agar diffusion, Turbidimetric and Serial dilution method.

Agar diffusion method can be performed in three ways.

- *Agar Cup-Plate Method*
- *Paper disc diffusion method and*
- *Agar ditch-plate technique*

For the purpose, Agar Cup-Plate Method was utilized.

Culture medium chemical composition and its preparation: Nutrient agar medium used and chemical composition of the medium was,

1) 0.5 percent peptone (1.0 gm)
2) 0.5 percent sodium chloride (0.5 gm)
3) 0.3 percent beef extract (or yeast extract) (0.3 gm)
4) Distilled water 100 ml
5) pH 7.6
6) 1.5 percent agar (2.0 gm)

Pre-weighed ingredients were dissolved in distilled water and PH maintained 7.6 followed by addition of agar powder. The 25 ml of medium was distributed among different test tubes and were plugged by cotton-wool and test tubes containing medium were sterilized at a temperature of 121.5°C and pressure 15 psi for 15 minutes.

Antibacterial susceptibility testing:

On a water bath, Nutrient agar broth was melted and heated to 45ºC with slow vibration The molten nutrient agar was then inoculated with one day old culture and mixed well by mild shaking before transferring to the previously sterilized. Medium poured in petri dishes was allowed to set (one and half hour). Afterwards each petri dishes were punched with a sterile cup borer and cleansing out the punched part of agar forming “cups” on the agar surface. Then these “cups” were filled with test solution using sterile micropipette. The plates were marked properly. The percentages of inhibition were calculated to evaluate antibacterial activities of for each compound in, shown in Tables 1-4.

In-vitro antibacterial activity of all the compounds was performed at concentration of 1000 ppm against organisms ***Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli*** One-week old cultures were used for this study. The compounds to be tested were suspended (1 milligram/mL or 1000 ppm) in a previously sterilized Potato Dextrose Agar (PDA) medium separately.

$$Percentage\ of\ inhibition = 100\left(1 - \frac{y}{x}\right)$$

Where X = Area of colony in control plate, Y = Area of colony in test plate.

The percentage (%) data are shown in all tables as follows;

Symbol	Zone	% percentage	Activity

(+)	Small clearing	<50%	Minor
(++)	Medium clearing	51-55%	Moderate
(+++)	Large clearing	56-60%	High
(++++)	Very large clearing	>60%	very high

Table 1: Antibacterial activity of standard used as positive control

Sample	% Zone of Inhibition @ 1000 ppm		
	Gram (+)ve		**Gram (-)ve**
	Staphylococcus aureus	***Staphylococcus epidermidis***	***Escherichia coli***
Vancomycin	++++	++++	Not tested
Ciprofloxacin	Not tested	Not tested	++++

Table 2: Antibacterial activity of test compounds (PMR1- PMR12)

Sample	% Zone of Inhibition @ 1000 ppm		
	Gram (+)ve		**Gram (-)ve**
	Staphylococcus aureus	***Staphylococcus epidermidis***	***Escherichia coli***
V1	++	+++	++
V2	++	+	+++
V3	+++	++	+++
V4	++	+	++
V5	+	+++	+++
V6	++	+++	++
V7	+++	++	+++
V8	+	++	+

CONCLUSION AND FUTURE INDICATION OF GREEN SYNTESIS

The benzimidazoles are one of the main classes of engineered natural mixtures, because of the huge organic job they play in the readiness of different medications and anti-toxins. In this way, the strategies for union of benzimidazole subordinates turned into a significant concentration for the readiness of numerous other natural mixtures that showed particular restorative viability when tried, the main substance and green science techniques utilized for planning several same subsidiaries, connected with valuable and negative parts of every arrangement strategy. An outline of the organic exercises of benzimidazole subsidiaries has likewise different applications, for example, anticancer, mitigating, anticonvulsant, anticoagulant, and others. From the abovementioned, the extraordinary significance of benzimidazole subsidiaries in the improvement of medication throughout the last couple of year is proven the valuable contribution of Benzimidazole derivatives in medicine.

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