JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Synthesis and antimicrobial evaluation of some novel N-substituted-2-phenyl benzimidazole derivatives

[1]Shaikh Risal, [2] Mr. Ankit Diwan, [3]Dr. Kuldeep Ganju
Sagar Institute of Pharmacy and Technology, Bhopal, M.P. India

Abstract : Benzimidazole is a heterocyclic aromatic compound. This bicyclic organic compound is fused ring of benzene and imidazole. Benzimidazole derivatives are versatile nitrogen containing heterocylic compound which have long been known as promising class of biologically active compounds possessing wide variety of biological and pharmacological activities like antibacterial, anti-inflammatory , anti-ulcer, anti-diabetic etc. Scientists have elucidated that benzimidazole system posses the variable sites like position 2 and 5 which can be suitably modified to yield potent therapeutic agent. This research paper covers the synthesis and antibacterial activities of different derivatives of phenyl benzimidazole.

Keywords **– Heterocyclic, Aromatic, Benzimidazole, antibacterial, anti-inflammatory, anti-ulcer etc**

1. INTRODUCTION

Design of novel and newer potent molecules has been the thirst of researchers worldwide. An important approach towards this incorporates the modification of the existing molecules with established biological actions utilizing the various approaches for drug designing. Heterocyclic compounds either of synthetic or natural origins have found applicability in several physiological neurotransmitters as well as in the modulators of certain neurotransmission processes1 .

Heterocyclic compounds containing two nitrogen atoms oriented in, 1-3 position are gifted with wide spectrum of biological actions. A plethora of sulphur and nitrogen possessing compounds are found in the biological and non-biological systems2 . Amongst the heterocyclic compounds containing sulphur and nitrogen, the six and five membered heterocycles have gathered the maximum interest, owing to their biological and industrial applications3 .

1.1 Benzimidazole Ever since its discover, the research and developments of benzimidazole-based compounds have been quite a rapidly developing and increasingly active area owing to their wide potential applications as medicinal drugs, agrochemicals, man-made materials, artificial acceptors, supramolecular ligands, biomimetic catalysts, and so on 4

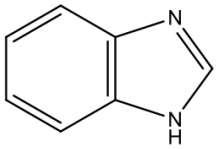


Figure 1. Benzimidazole nucleus

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and privileged structure in medicinal chemistry. It plays a very important role with plenty of therapeutic activities such as: antiulcers, antihypertensives, analgesic, anti-inflammatory, anti-viral, antifungals, anticancers, and antihistaminics.5 This compound is bicyclic in nature which consists of the fusion of benzene and imidazole6

Benzimidazole nucleus is a constituent of many bioactive heterocyclic compounds that are of wide interest because of their diverse biological and clinical applications. Moreover, benzimidazole derivatives are structural isosters of naturally occurring nucleotides, which allows them to interact easily with the biopolymers of the living System7 .

The benzimidazole ring system as a nucleus from which to develop potential chemotherapeutic agents was established in the 1950s when it was found that 5, 6- dimethyl-l-(a-D-ribofuranosyl) benzimidazole is an integral part of the structure of the vitamin B12. Modifications in the position 2 and 5 of the molecule provide a number of active drugs.

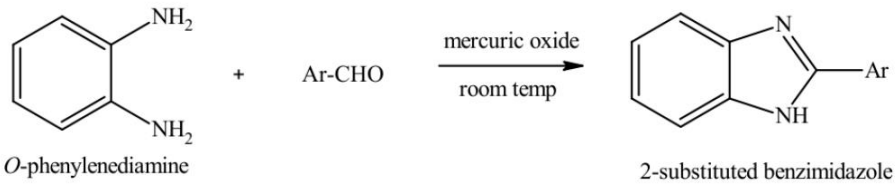
1.2 Synthetic methods for benzimidazoles

Synthesis of Benzimidazole can be possible from various starting material viz.

- ✓ O-phenylene diamine
- ✓ O-nitroarylamines and O-dinitroarenes
- ✓ O-substituted-N-benzylidene aniline
- ✓ Amidine
- ✓ Using green chemistry
- ✓ Miscellaneous

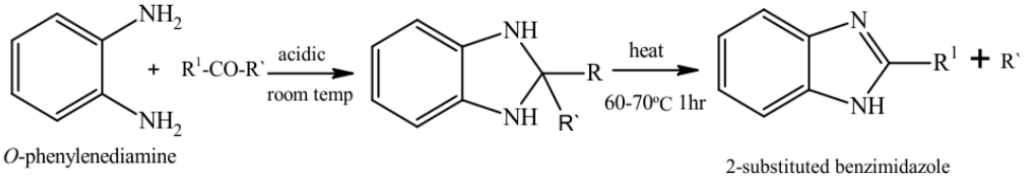
1.2.1 From O-phenylene diamine:

Benzimidazole can be synthesized by the reaction of O-phenylene diamine with Carboxylic acids and its derivatives; various substitute aldehydes, ketones, urea, aminoethers and lactones. The reaction between O-phenylenediamine and aryl aldehydes in the presence of the oxidising agents like- cupric acetate, mercuric oxide, chlorine, lead tetra acetate, manganese dioxide, Nickel peroxide at room temperature. This synthetic method is ecofriendly and gives good yield of about 85%.



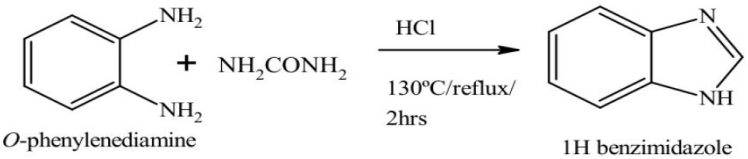
O-phenylenediamine 2-substituted benzimidazole

When O-phenylenediamine is reacted with aromatic aldehydes in the presence of acidic medium at 50ºC to 65ºC, it yields an intermediate 2- (benzylideneamino) aniline which is converted into 2-substituted benzimidazole by treating with reducing agents which gives 78% yield. O-phenylenediamine reacted with the substituted ketones in the presence of acidic medium at room temperature gives a 2, 2-disubstituted-benzimidazoles, which on heating 60 to 70ºC for 1 h, breaks down into 2-substituted benzimidazole and a hydrocarbon.



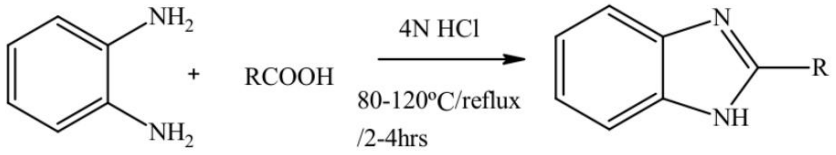
O-phenylenediamine 2-substituted benzimidazole

O-phenylenediamine reacts with urea in the presence of hydrochloric acid at 130ºC for 2 h gives a 78% yield of benzimidazole



O-phenylenediamine 1H benzimidazole

O-phenylenediamine was refluxed with formic acid under the acidic conditions (4N HCl) at 120ºC for 2 to 4 h to give 75% yield of benzimidazole



O-phenylenediamine 2 subtituted benzimidazole

1.3 Antimicrobials

The mechanism of action of most of the antimicrobial agents is not completely understood. However, the classification based on the proposed mechanism of action is most acceptable.

- ✓ **Agents that inhibit synthesis of or activate enzymes that disrupt bacterial cell wall to cause cell death and often cell lysis.**
- ✓ **Agents that exert their action by inhibiting cell membrane function via altering the permeability, resulting in leakage of intracellular macromolecules and ions, leading to cell damage and cell death**
- ✓ **Antimicrobial action through inhibition of protein synthesis**
- ✓ **Inhibition of protein synthesis by inhibiting binding of aminoacyl tRNA**
- ✓ **Antimicrobial action through interference with DNA-RNA synthesis**
- ✓ **Antimicrobial action through inhibition of cell metabolism (By preventing synthesis of folic acid)**

2. EXPERIMENTAL WORK

The scheme for the synthesis of the benzimidazoles was designed for reported methods and modified for synthesis of derivatives(figure 4.1) The entire synthetic scheme was performed in three distinct steps:

- ✓ Synthesis of 2-(4-nitrophenyl)-1H-benzo[d]imidazole
- ✓ Synthesis of 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole
- ✓ Synthesis of 1-benzyl-5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole derivatives

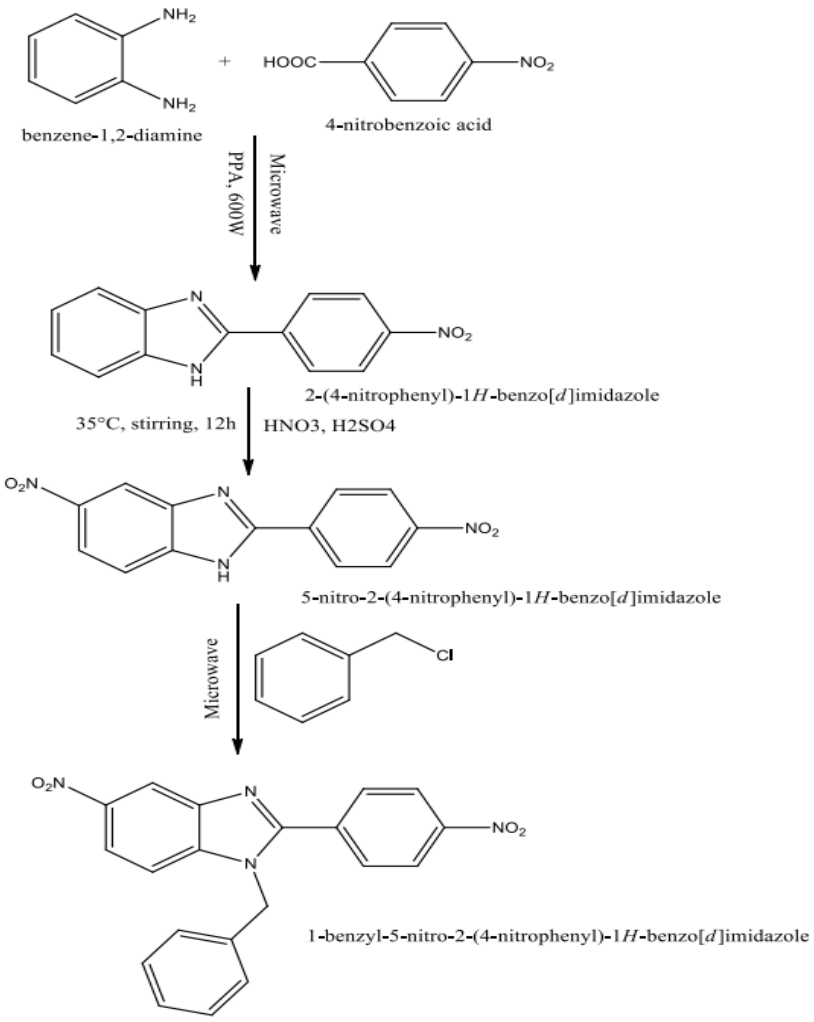


Figure 4.1Scheme for synthesis of benzimidazole derivatives

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

O-phenylene diamine 1.08 g (0.01 M), 4-nitro benzoic acid 1.69 g (0.01 M) and poly phosphoric acid 10 g was properly mixed with glass rod in a beaker. The mixture was irradiated in the microwave oven for 8 min 30 sec at 600 W. The completion of reaction was monitored by TLC, after irradiation the mixture was poured into ice cold water and then slowly neutralized with sodium hydroxide to pH 8. The precipitate was collected by filtration, dried and recrystallized from ethanol.

2.2 Synthesis of 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole

Conc. HNO3 (7.5 ml) was placed in 3-necked round bottom flask fitted with a mechanical stirrer. The flask was immersed in ice cold water and added slowly Conc. H2SO4 (7.5 ml) down the condenser with slow stirring. After the addition, 2-(4- nitrophenyl)-1H-benzimidazole 6.69 g (0.028 M) was added in a portion over a period of 1 h at such a rate that the temperature did not exceed 35º C. After continuous stirring for 12 h, the reaction mixture was poured very slowly over crushed ice with vigorous stirring. The formed product was filtered, washed with cold water and recrystallized from ethanol. The reaction was checked for completion by TLC using (methanol:dichloromethane, 1:1) as the solvent system.

2.3 General method for the synthesis of 1-benzyl-5-nitro-2-(4-nitrophenyl)-1Hbenzo[d]imidazole derivatives

In a 100 ml beaker, 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (0.01mol), benzyl chloride (0.01mol) and sodium hydroxide (0.01mol) were placed. 5 ml ethanol was added to this mixture and stirred. The mixture was heated in a microwave oven at 120W power and irradiated for 45 to 180 seconds. The reaction mixture was allowed to cool to obtain the product. The product was filtered, dried and recrystallized from ethanol to obtain the substituted final product. The reaction was checked for completion by TLC using (methanol:chloroform, 2:8) as the solvent system.

2.3.1 Synthesis of 1-benzyl-5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole, BZI1

In a 100 ml beaker, 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (0.01mol), benzyl chloride (0.01mol) and sodium hydroxide (0.01mol) were placed. 5 ml ethanol was added to this mixture and stirred. The mixture was heated in a microwave oven at 100W power and irradiated for 45 to 180 seconds. The reaction mixture was allowed to cool to obtain the product. The product was filtered, dried and recrystallized from ethanol to obtain the substituted final product. The reaction was checked for completion by TLC using (methanol:chloroform, 2:8) as the solvent system.

2.3.2 Synthesis of 5-nitro-1-(4-nitrobenzyl)-2-(4-nitrophenyl)-1Hbenzo[d]imidazole, BZI2

In a 100 ml beaker, 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (0.01mol), 4- nitro benzyl chloride (0.01mol) and sodium hydroxide (0.01mol) were placed. 5 ml ethanol was added to this mixture and stirred. The mixture was heated in a microwave oven at 100W power and irradiated for 45 to 180 seconds. The reaction mixture was allowed to cool to obtain the product. The product was filtered, dried and recrystallized from ethanol to obtain the substituted final product. The reaction was checked for completion by TLC using (methanol:chloroform, 2:8) as the solvent system.

2.3.3 Synthesis of 4-((5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazol-1- yl)methyl)phenol, BZI3

In a 100 ml beaker, 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (0.01mol), 4- hydroxy benzyl chloride (0.01mol) and sodium hydroxide (0.01mol) were placed. 5 ml ethanol was added to this mixture and stirred. The mixture was heated in a microwave oven at 100W power and irradiated for 45 to 180 seconds. The reaction mixture was allowed to cool to obtain the product. The product was filtered, dried and recrystallized from ethanol to obtain the substituted final product. The reaction was checked for completion by TLC using (methanol:chloroform, 2:8) as the solvent system.

2.3.4 Synthesis of 1-(4-chlorobenzyl)-5-nitro-2-(4-nitrophenyl)-1Hbenzo[d]imidazole, BZI4

In a 100 ml beaker, 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (0.01mol), 4- chloro benzyl chloride (0.01mol) and sodium hydroxide (0.01mol) were placed. 5 ml ethanol was added to this mixture and stirred. The mixture was heated in a microwave oven at 100W power and irradiated for 45 to 180 seconds. The reaction mixture was allowed to cool to obtain the product. The product was filtered, dried and recrystallized from ethanol to obtain the substituted final product. The reaction was checked for completion by TLC using (methanol:chloroform, 2:8) as the solvent system.

2.3.5 Synthesis of 1-(4-bromobenzyl)-5-nitro-2-(4-nitrophenyl)-1Hbenzo[d]imidazole, BZI5

In a 100 ml beaker, 5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (0.01mol), 4- bromo benzyl chloride (0.01mol) and sodium hydroxide (0.01mol) were placed. 5 ml ethanol was added to this mixture and stirred. The mixture was heated in a microwave oven at 100W power and irradiated for 45 to 180 seconds. The reaction mixture was allowed to cool to obtain the product. The product was filtered, dried and recrystallized from ethanol to obtain the substituted final product. The reaction was checked for completion by TLC using (methanol:chloroform, 2:8) as the solvent system.

2.4 Physicochemical Characterization of the synthesized compounds

2.4.1 Determination of melting point

The melting point determination of each of the synthesized compounds was carried out instrumentally using open capillary method and is uncorrected. Briefly, the dried compounds were filled in capillary tubes sealed from one end and inserted into the heating head of the melting point apparatus. Temperature was gradually increased and melting point was recorded when the last trace of crystal in the capillary was in the molten state. The procedure was carried in duplicate for each sample to confirm the melting point.

2.4.2 Determination of solubility

In order to determine solubility of the synthesized compounds, 1 mg of the compound was weighed and shaken with 1 mL of solvent (non-polar to polar) taken in test tubes. Shaking was continued until no further amount of the solute was able to dissolve despite of vigorous and prolonged stirring.

2.4.3 Infra-red Spectrum study

The samples were dried completely and mixed with IR grade potassium bromide previously dried in an oven. The dispersion was the fed on to the sample holder of the IR spectrophotometer and spectrum was obtained.

2.4.4 H-NMR spectrum study

The samples were dissolved in deuteriated chloroform and filled in the NMR tubes. NMR spectrum was recorded at 300 MHz

2.4.5 Mass spectrum study

The samples were dissolved in appropriate solvent and injected into the interface of the LC-MS/MS system. The spectrum of mass fragmentation were obtained and interpreted thereafter.

2.5 Antibacterial acivity

The compounds synthesized during the present investigation were screened for their antibacterial activity. The antibacterial tests were conducted on four common microorganisms viz. Bacillus subtilis, Streptococcus aureus, Escherichia coli and Salmonella, which are the representative types of gram positive and gram-negative organisms respectively. The antibacterial activity of the compounds was assessed by disc diffusion.

2.5.1 Preparation of Nutrient broth:

- ✓ Nutrient broth powder – 37.2 g
- ✓ Distilled water - 1000 ml

Nutrient broth was prepared by dissolving all the ingredients and adjusting the pH adjusted to 7.2 and autoclaved at 15 lbs pressure for 20 min in an autoclave. One day before the testing, the microorganisms were sub-cultured into sterile nutrient broth and incubated at 37°C for 24 h. The culture growth thus obtained was used as inoculum for the antibacterial testing.

2.5.2 Preparation of nutrient agar media'

The nutrient agar media was prepared by using the following ingredients.

- ✓ Nutrient agar – 28.6 g
- ✓ Distilled water - 1000 ml

The specified amount of nutrient agar powder was dissolved by heating on a water bath. and the volume of final solution is made up to 1000 ml with distilled water. The above prepared nutrient agar media was sterilized by autoclave at 121°C for 20 minutes at 15 lbs pressure.

2.5.3 Preparation of test solution

20 mg of the synthesized compounds were dissolved separately in 20 ml methanol. 1 ml of this solution was diluted to 10 ml with methanol. 0.5 ml (50 µg) and 1 ml (100 µg) of this solution was further diluted upto 2 ml by addition of methanol to obtain a solution of 25 and 50 µg/ml strength. These sample solutions were sterilized test tubes. These test compounds (25, 50 and 100 µg/ml) were soaked on small circular disc of 5 mm.

2.5.4 Preparation of standard solution

Ciprofloxacin was used as the standard drug at concentration of 50 and 100µg/ml prepared in distilled water

2.5.5 Procedure of antibacterial testing

The sterilized media (nutrient agar) was cooled to 45°C with gentle shaking for uniform cooling and then inoculated with 18-24 h old bacterial subculture under aseptic conditions in a laminar air flow bench and mixed well by gentle shaking. This was poured in to sterile Petri dishes and allowed to set. After solidification all the Petri dishes were transferred to laminar flow unit and the test sample discs were carefully kept on the solidified media by using sterilized forceps. These Petri dishes were kept in the laminar air flow unit undisturbed for one-hour diffusion at room temperature and then for incubation at 37°C for 24 h in an incubator. The extent diameter of inhibition after 24 h was measured as the zone of inhibition in millimeters (mm).

3. RESULTS AND DISCUSSION

3.1 Chemistry

Synthesis of the desired compounds was carried out by utilizing the scheme depicted in figure 4.1. The scheme was optimized by varying the molar concentrations of the reactants and the reaction time in order to achieve maximum yield for the compounds.

The Rf value obtained from TLC, melting point and percent yield of the synthesized compounds is depicted in Table 3.1.

Table 3.1 TLC, melting point and percent yield

Compound code	Microwave time (sec)	Color	Rf Value	Melting Point	% Yield
BZI_1	45	Pale Yellow	0.56	293-295°C	61
BZI_2	180	Yellow	0.67	268-271°C	57
BZI_3	150	Pale Yellow	0.51	276-278°C	64
BZI_4	75	Brown	0.72	284-287°C	67
BZI_5	105	Yellow	0.75	290-293°C	59

The solubility characteristics (qualitative) of the synthesized compounds is various solvents is presented in Table 3.2. The results reveal the all the compounds had variable solubility in the solvents.

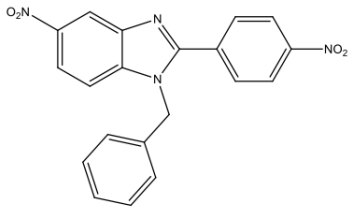
Table 3.2 Solubility Profile of the Synthesized Compounds

Compound	Solubility Profile			
	Water	Methanol	Chloroform	DMSO
BZI_1	Insoluble	Soluble	Soluble	Soluble
BZI_2	Insoluble	Soluble	Soluble	Insoluble
BZI_3	Insoluble	Soluble	Soluble	Insoluble
BZI_4	Insoluble	Soluble	Soluble	Insoluble
BZI_5	Insoluble	Soluble	Soluble	Insoluble

The spectral studies (NMR, Mass and IR) were conducted to confirm the structure of the synthesized compounds. The spectra were obtained for the samples and the interpretation of each spectrum was carried out to ascertain the formation of desired bonds and incorporation of the functional groups.

The FTIR spectra of all the compounds exhibited stretching and bending vibrations for CH, C=N, C-N whereas N-O, C-O, C-Cl and C-Br stretching peaks were prominent in the corresponding compounds. The peak for OH stretching was evident in compound 5c. The proton NMR spectra yielded shifts for aromatic protons as wellas the CH2 proton of the benzyl group. The proton for OH was almost merged with the CH2 proton. The mass spectra revealed molecular ion peaks and isotopic peaks corresponding to the molecular mass of the compounds.

Compound BZI_1



IUPAC Name - 1-benzyl-5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole

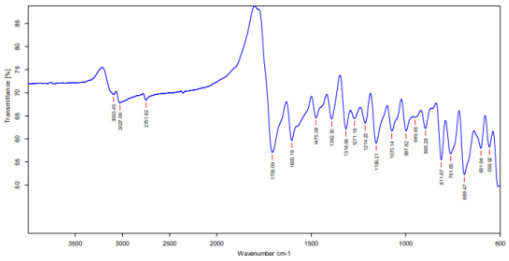


Figure 3.1 FTIR spectrum of BZI_1

R (cm-1): 2751 (C-H stretching), 1706 (C=N stretching), 1603 (C=C stretching), 1475 (C-H bend), 1316 (C-N stretching)

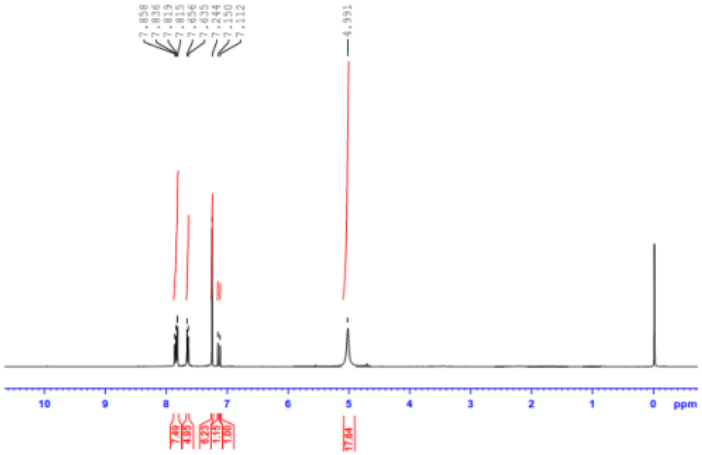


Figure no. 3.2 1HNMR Spectrum of BZI_1

HNMR (δ ppm): 7.1-7.8 (CH, aromatic), 4.99 (CH2), 8.01 (CH, adj to NO2)

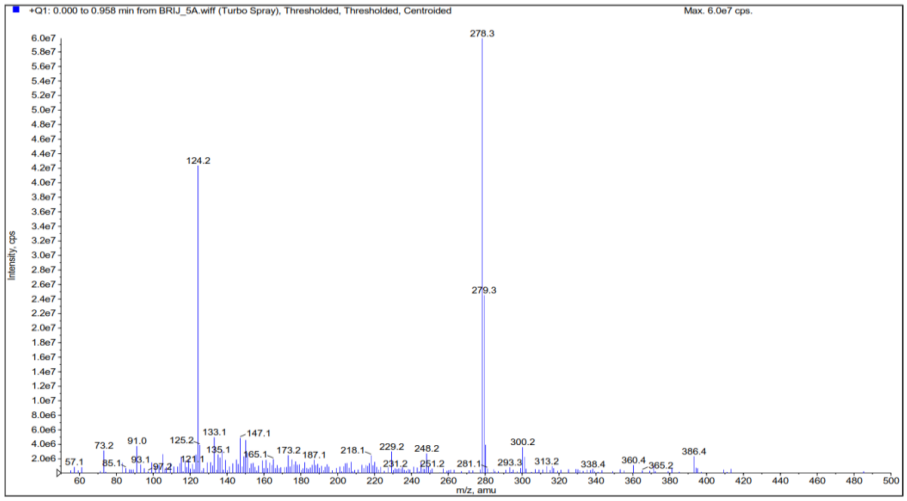
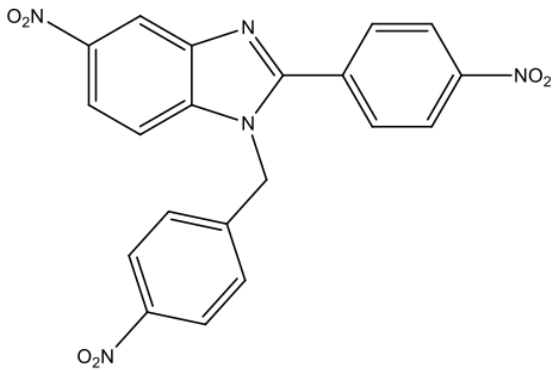


Figure 3.3 Mass spectrum of BZI1

Mass (m/z): 376.4 (M++2 peak)

Compound BZI$_2$



IUPAC Name - 5-nitro-1-(4-nitrobenzyl)-2-(4-nitrophenyl)-1H-benzo[d]imidazole

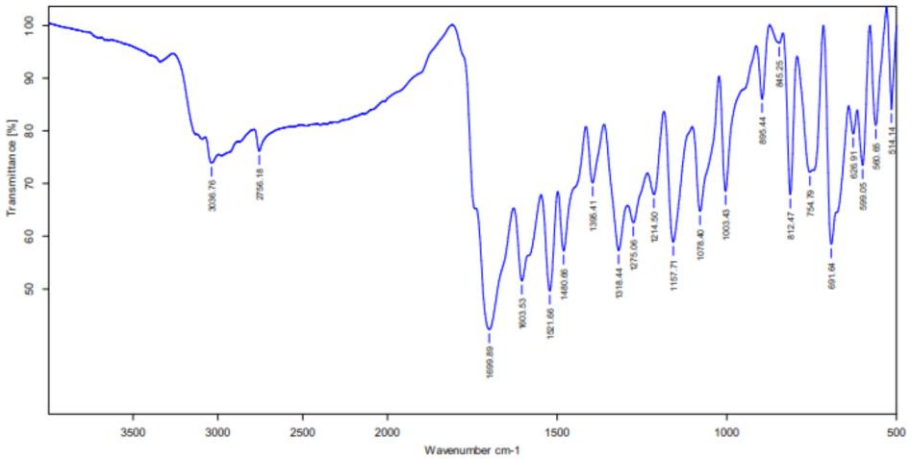


Figure 3.4 FT-IR spectrum of BZI2

IR (cm-1): 2756 (C-H stretching), 1699 (C=N stretching), 1603 (C=C stretching), 1521 (N-O stretching), 1480 (C-H bend), 1318 (C-N stretching)

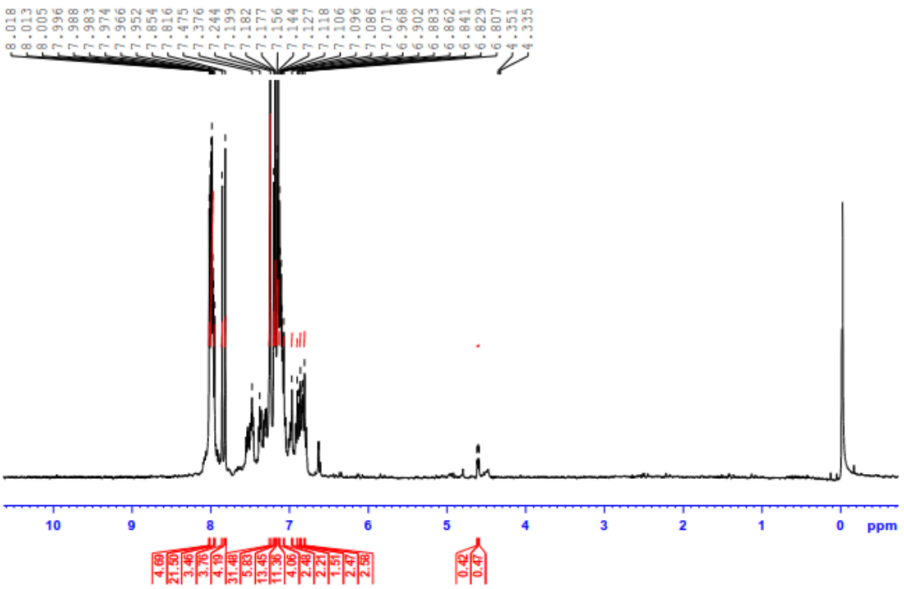


Figure 3.5 1HNMR spectrum of BZI2

1HNMR (δ ppm): 6.8-7.9 (CH, aromatic), 8.01 (CH, adj to NO2), 4.35 (CH2)

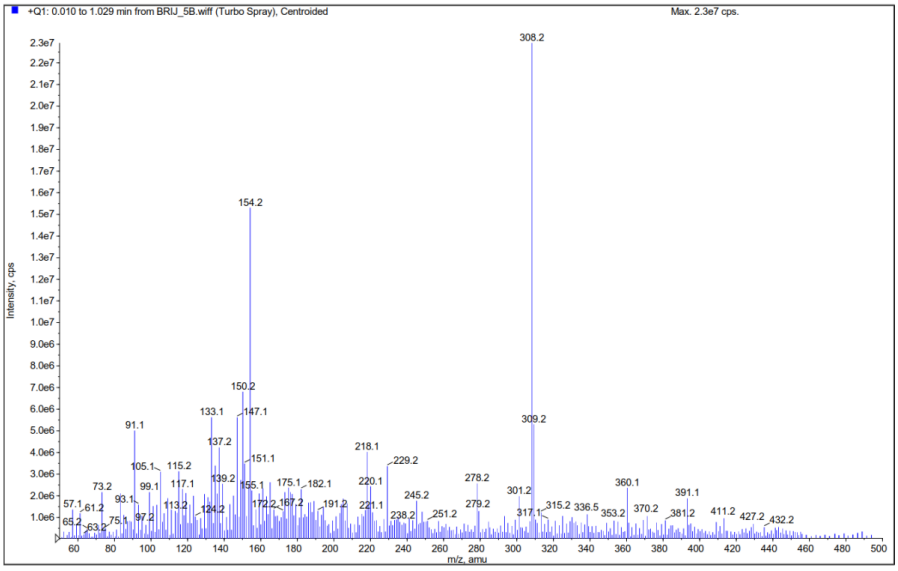
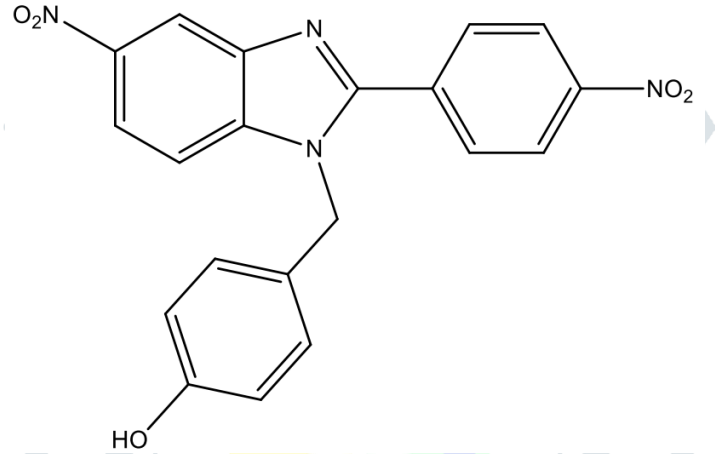


Figure 3.6 Mass spectrum of BZI2

Mass (m/z): 420.2 (M+1 peak)

Compound BZI3



IUPAC Name- 4-((5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazol-1- yl)methyl)phenol

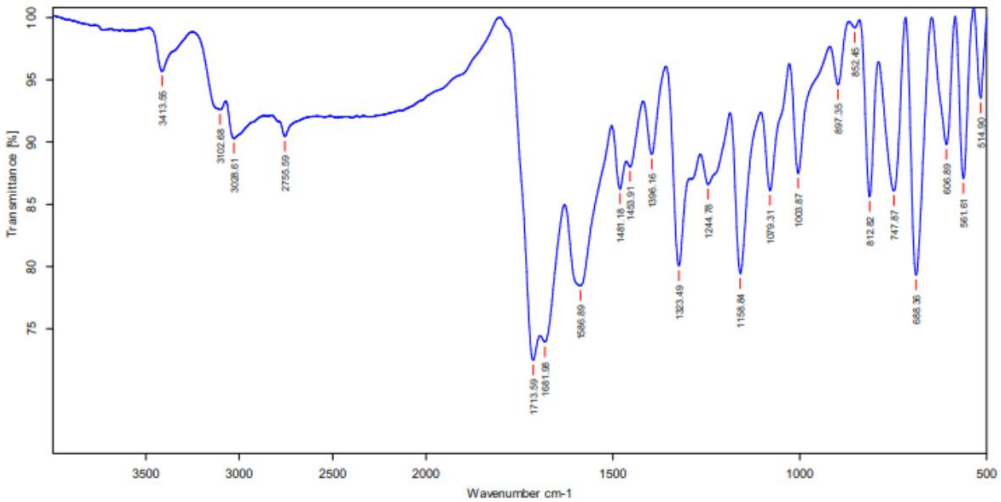


Figure 3.7 FT-IR spectrum of BZI3

IR (cm-1): 3413 (O-H stretching), 2755 (C-H stretching), 1713 (C=N stretching), 1586 (C=C stretching), 1481 (C-H bend), 1323 (C-N stretching), 1079 (C-O stretching)

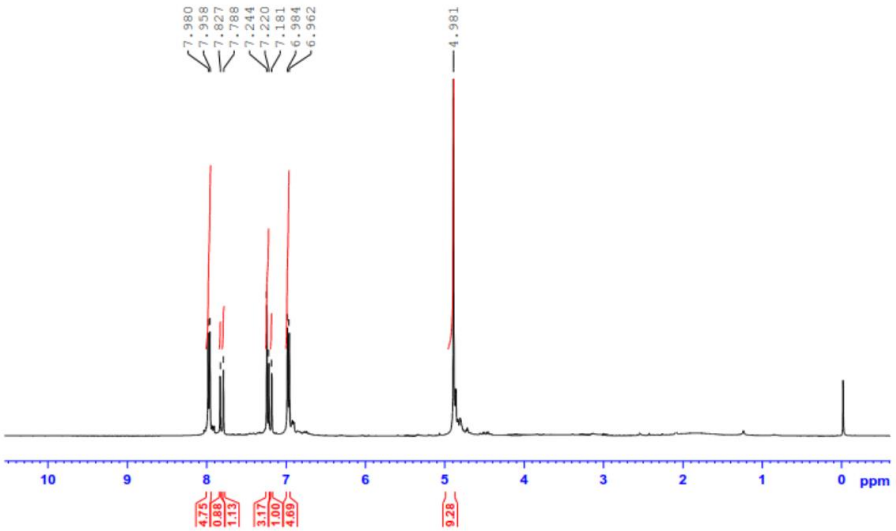


Figure 3.8 1HNMR spectrum of BZI3

1HNMR (δ ppm): 7.1-7.9 (CH, aromatic), 6.9 (CH, adjacent to OH), 4.99 (OH, CH2)

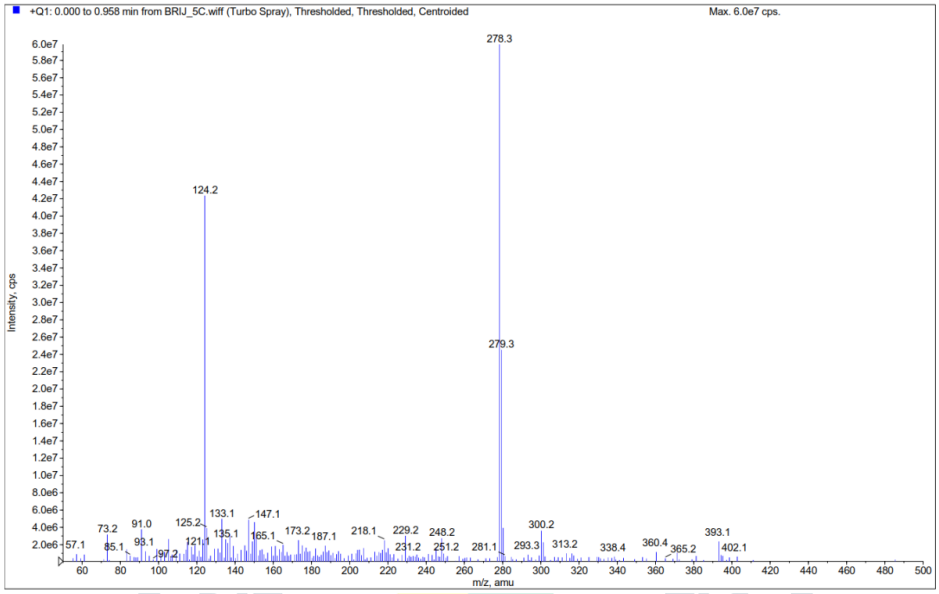
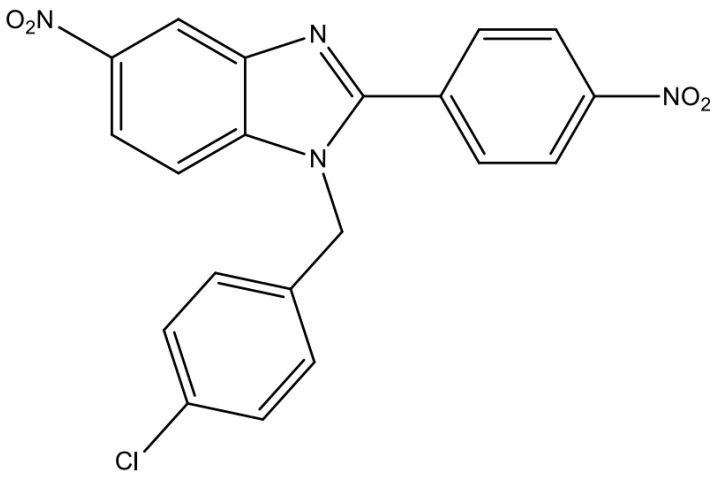


Figure 3.9 Mass spectrum of BZI3

Mass (m/z): 390.4 (M+ peak)

Compound BZI4



IUPAC Name - 1-(4-chlorobenzyl)-5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole

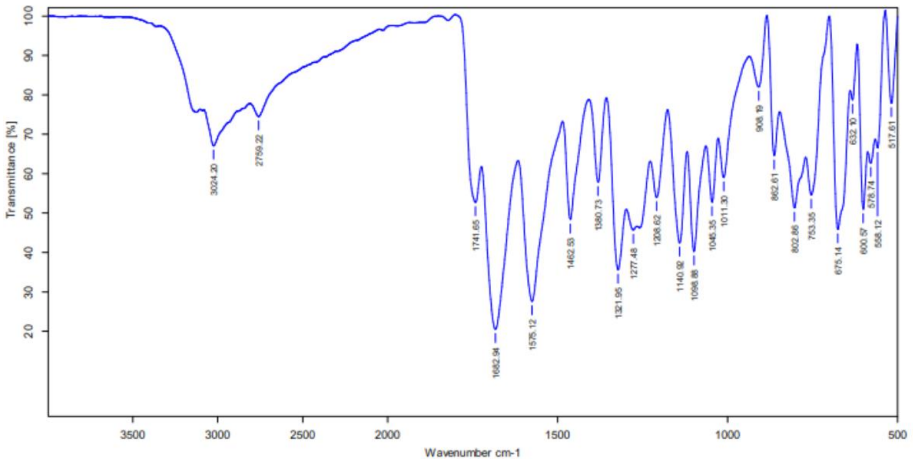


Figure 3.10 FT-IR spectrum of BZI4

IR (cm-1): 2759 (C-H stretching), 1682 (C=N stretching), 1575 (C=C stretching), 1462 (C-H bend), 1321 (C-N stretching), 802 (C-Cl stretching)

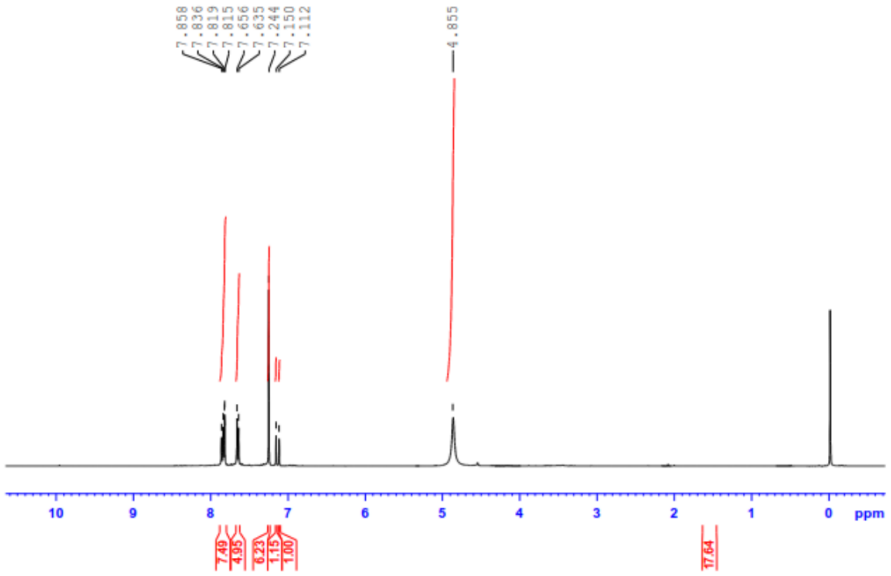


Figure 3.11 1HNMR spectrum of BZI4

1HNMR (δ ppm): 7.1-7.8 (CH, aromatic), 4.85 (CH2)

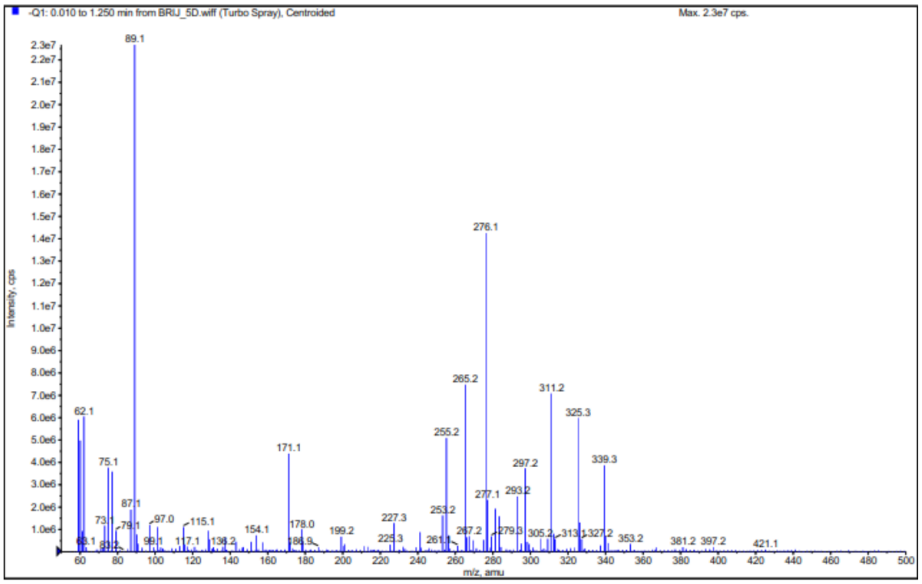
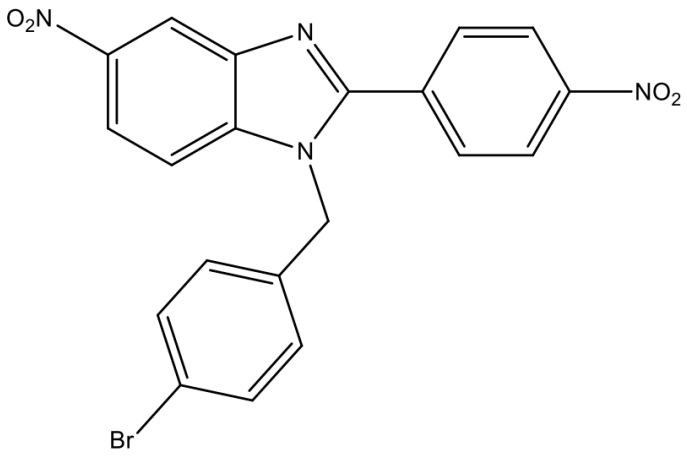


Figure 3.12 Mass spectrum of BZI4

Mass (m/z): 408.7 (M+ peak)

Compound BZI5



IUPAC Name - 1-(4-bromobenzyl)-5-nitro-2-(4-nitrophenyl)-1H-benzo[d]imidazole

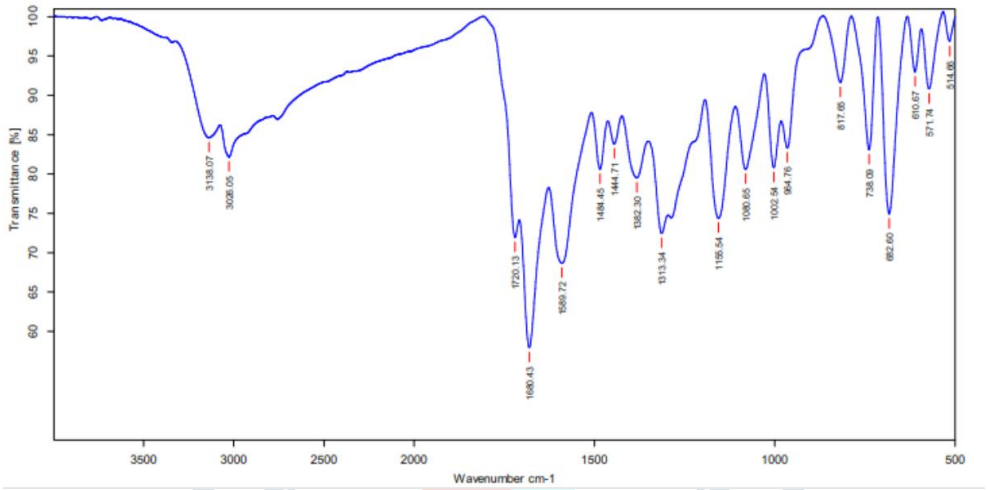


Figure 3.13 FT-IR spectrum of BZI5

IR (cm-1): 3026 (C-H stretching), 1680 (C=N stretching), 1589 (C=C stretching), 1484 (C-H bend), 1313 (C-N stretching), 682 (C-Br stretching)

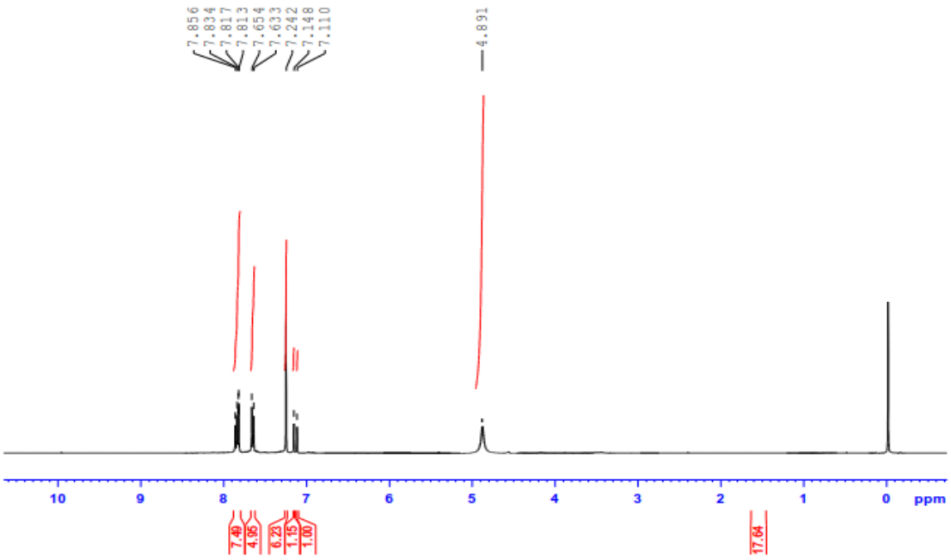


Figure 3.14 1HNMR spectrum of BZI5

1HNMR (δ ppm): 7.1-7.8 (CH, aromatic), 4.89 (CH2)

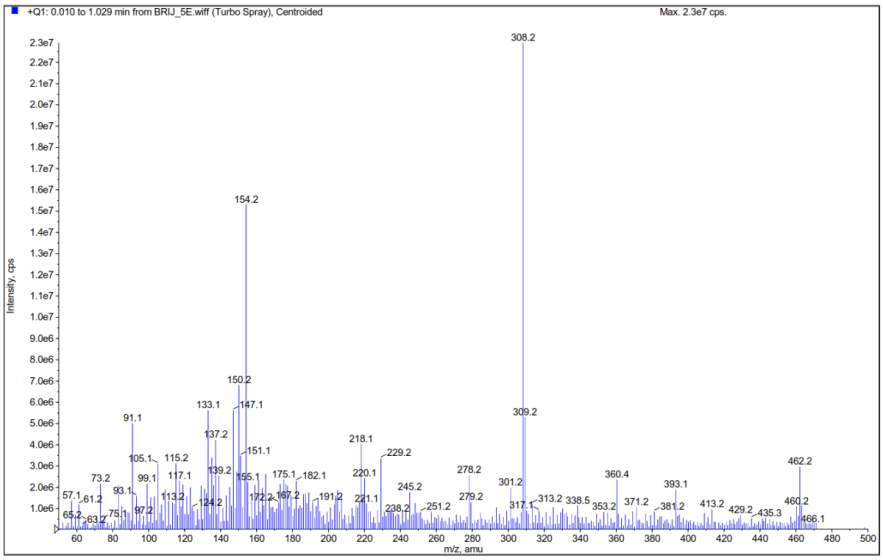


Figure 3.15 Mass spectrum of BZI5
Mass (m/z): 454.1 (M+1 peak)

3.2 Antibacterial Action

The antibacterial activity of the synthesized benzimidazoles was determined measuring the zone of inhibition in the agar plate. Three concentrations of the synthesized compounds were tested for antibacterial action against ciprofloxacin as the standard drug for antibacterial action. The zone of inhibition of the test compounds is presented in table 3.3

Table 3.3 Antibacterial activity of synthesized compounds

Compound code	Zone of Inhibition (mm)*											
	B. subtilis			S. aureus			E.coli			Salmonella		
	25µ g	50µ g	100µ g	25µ g	50µ g	100µ g	25µ g	50µ g	100µ g	25µ g	50µ g	100µ g
BZI_1	4	6	7	4	7	10	6	8	12	7	10	13
BZI_2	6	9	13	5	9	14	10	15	**23**	9	15	**24**
BZI_3	9	15	**24**	8	16	**25**	6	9	13	6	8	13
BZI_4	6	9	13	5	9	14	10	16	**25**	9	16	**24**
BZI_5	6	8	12	6	10	13	11	14	**23**	10	15	**23**
Ciprofloxacin	15	**21**	**33**	13	**22**	**27**	15	**23**	**35**	16	**22**	**36**

*Below 12 mm – poor activity; 13-18 mm – moderate activity & above 18 mm – good activity

The results revealed that the antibacterial action of the synthesized compounds was dose dependent. The compounds were mild to moderately antibacterial. The presence of electron withdrawing groups in the compounds favored antibacterial activity against gram negative bacteria (BZI2, BZI4 & BZI5) whereas electron donating group favored activity against gram positive bacteria (BZI3). Compound 5a did not exhibit significant antibacterial action as compared to the control (DMF).

The lack of significant activity in BZI1 signifies the importance of the substitution of ring attached to 1-position of benzimidazole nucleus for antibacterial action. The positional effect of the substitution on this ring was though not studied

4. SUMMARY AND CONCLUSION

4.1 SUMMARY

The objective of the present investigation was to synthesize novel benzimidazole derivatives using microwave irradiation and evaluating them for antibacterial action. The synthesis was accomplished in three steps. While the first step and third step were performed by microwave method, the second step that involved a conventional method of nitration.

The synthesized compounds were obtained in 57-67% yield and were insoluble in water and soluble in methanol and chloroform. The FTIR spectra of all the compounds exhibited stretching and bending vibrations for CH, C=N, C-N whereas N-O, C-O, CCl and C-Br stretching peaks were prominent in the corresponding compounds. The peak for OH stretching was evident in compound 5c. The proton NMR spectra yielded shifts for aromatic protons as well as the CH2 proton of the benzyl group. The proton for OH was almost merged with the CH2 proton. The mass spectra revealed molecular ion peaks and isotopic peaks corresponding to the molecular mass of the compounds.

The antibacterial activity of the synthesized compounds was determined using zone of inhibition method against gram positive (S. aureus, B. subtilis) and gram negative bacteria (E. coli, Salmonella). The presence of electron withdrawing groups in the compounds favored antibacterial activity against gram negative bacteria (BZI2, BZI4 & BZI5) whereas electron donating group favored activity against gram positive bacteria (BZI2). Compound BZI1 did not exhibit significant antibacterial action as compared to the control (DMF).

4.2 CONCLUSION

Microwave irradiation provides a quick approach to synthesize organic compounds. The benzimidazole derivatives synthesized using microwave irradiation was obtained in good yields in a very low reaction time. The synthesized compounds exhibited mild to moderate antibacterial action against gram negative and gram positive bacteria. The study of a congeneric series of benzimidazole derivatives, determining it IC50 values and performing QSAR analysis would be highly helpful in designing newer antimicrobial compounds that would overcome the problems of resistance to antibiotics by the microbes.

5. REFERENCE

1. Belagali SL, Harish K, Boja P, Himaja M. Synthesis and biological studies of 5(p-chlorophenyl)-furan-2-carbony peptides and 4-[2'-(5'-formyl)- furyl]benzoyl peptides. Indian J Chem 1998; 37B: 370.
2. Bansal RK. Heterocyclic chemistry. Synthesis, reactions and mechanism, New Dehli; Wiley Eastern Ltd. 1990.
3. Sammes PG. Compressive organic chemistry of heterocyclic compounds. Oxford; Pergammon press; part 20-1, 1971.
4. Zhang L, Pend X-M, Damu GLV, Geng RX, Zhou C-H. Comprehensive review in current developments of imidazole based medicinal chemistry. Med Res Rev 2014; 34(2): 340-437.
5. Molina P, T´arraga A, Ot´on F. Imidazole derivatives: A comprehensive survey of their recognition properties. Org Biomol Chem 2012; 10: 1711– 1724.
6. Srestha N, Banerjee J, Srivastava S. A review on chemistry and biological significance of benzimidazole nucleus. IOSR J Pharm. 2014; 4(12): 28-41.
7. Narasimhan B, Sharma D, Kumar P. Benzimidazole: a medicinally important heterocyclic moiety. Medicinal Chemistry Research. 2012; 21(3): 269-283.
8. Seth SD. General Principles of Antimicrobial Action. In: Textbook of Pharmacology, Seth SD, Seth V (Eds), 3rd Ed, Elsevier India, New Delhi, 2009.
9. Z. Wang, X. Deng, S. Xiong, R. Xiong, J. Liu, L. Zou, X. Lei, X. Cao, Z. Xie, Y. Chen, Y. Liu, X. Zheng, G. Tang, Design, synthesis and biological evaluation of chrysin benzimidazole derivatives as potential anticancer agents, Nat. Prod. Res. 32 (24) (2018) 2900–2909.
10. G.R. Morais, E. Palma, F. Marques, L. Gano, M.C. Oliveira, A. Abrunhosa, H. V. Miranda, T.F. Outeiro, I. Santos, A. Paulo, Synthesis and biological evaluation of novel 2-aryl benzimidazoles as chemotherapeutic agents, J. Heterocyclic Chem. 54 (1) (2017) 255–267.
11. Y.M. Shaker, M.A. Omar, K. Mahmoud, S.M. Elhallouty, W.M. El-Senousy, M. M. Ali, A.E. Mahmoud, A.H. Abdel-Halim, S.M. Soliman, H.I. El Diwani, Synthesis, in vitro and in vivo antitumor and antiviral activity of novel 1- substituted benzimidazole derivatives, J. Enzyme Inhib. Med. Chem. 30 (5) (2015) 826–845.
12. A.H. Alanazi, Md.T. Alam, M. Imran, Design, molecular docking studies, in silico drug likeliness prediction and synthesis of some benzimidazole derivatives as antihypertensive agents, Md. Imranl. Indo American J. of Pharmaceutical Sci. 4 (04) (2017) 926–936.
13. R. Kankate, A. Pangare, R. Kakad, P. Gide, V. Nathe, Synthesis and biological evaluation of benzimidazolyl biphenyl derivatives as antihypertensive agents, Int. J. Chem. Concepts 2 (2) (2016) 111–119.
14. R. Sharma, A. Bali, B. Chandhari, Synthesis of methanesulphonamidobenzimidazole derivatives as gastro-sparing antiinflammatory agents with antioxidant effect, Bioorg. Med. Chem. Lett. 27 (2017) 3007–3013.
15. P. Sethi, Y. Bansal, G. Bansal, Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents, Med. Chem. Res. 27 (1) (2017) 61–72.
16. N. Gohary, M. Shaaban, Synthesis and biological evaluation of a new series of benzimidazole derivatives as antimicrobial, antiquorum-sensing and antitumor agents, Eur. J. Med. Chem. 131 (2017) 255–262.
17. L.R. Singh, S.R. Avula, S. Raj, A. Srivastava, G.R. Palnati, C.K.M. Tripathi, M. Pasupuleti, K.V. Sashidhara, Coumarin–benzimidazole hybrids as a potent antimicrobial agent: synthesis and biological elevation, J. Antibiotics 70 (9) (2017) 954–961.
18. O. Ajani, D. Aderohunmu, S. Olorunshola, C. Ikpo, I. Olanrewaju, Facile synthesis, characterization and antimicrobial activity of 2-alkanamino benzimidazole derivatives, Oriental J. Chem. 32 (1) (2016) 109–120.
19. A. Kapoor, N. Dhiman, Synthesis and evaluation of 2-aryl substituted benzimidazole derivatives bearing 1,3,4-oxadiazole nucleus for antimicrobial activity, Der. Pharmacia Lett. 8 (12) (2016) 97–104.
20. S.R. Archie, B. Das, M.S. Hossain, U. Kumar, A.S.S. Rauf, Synthesis and antioxidant activity of 2-substituted-5-nitro benzimidazole derivatives, Int. J. Pharm. Pharm. Sci. 9 (1) (2017) 308–310.
21. S.N. Abd, F.M.A. Soliman, Synthesis, some reactions, cytotoxic evaluation and antioxidant study of novel benzimidazole derivatives, Der Pharma Chemica 7 (4) (2015) 71–84.
22. H. Yang, Y. Ren, X. Gao, Y. Gao, Synthesis and anticoagulant bioactivity evaluation of 1,2,5-trisubstituted benzimidazole fluorinated derivatives, Chem. Res. Chin. Univ. 32 (6) (2016) 973–978.
23. F. Wang, Y.-J. Ren, Design, synthesis, biological evaluation and molecular docking of novel substituted 1-ethyl-1H-benzimidazole fluorinated derivatives as thrombin inhibitors, J. Iran. Chem. Soc. 13 (2016) 1155–1166.
24. R. Kenchappa, D. Yadav, Bodke, S. Telkar, M. Sindhe, Antifungal and anthelmintic activity of novel benzofuran derivatives containing thiazolo benzimidazole nucleus: of novel substituted 1-ethyl-1H-benzimidazole fluorinated derivatives as thrombin inhibitors, J. Iran. Chem. Soc. 13 (2016) 1155–1166.
25. https://go.drugbank.com/drugs/DB00518, assessed on 26/12/2023
26. https://pubchem.ncbi.nlm.nih.gov/compound/Enviradene; assessed on 26/12/2023
27. https://go.drugbank.com/drugs/DB00338; assessed on 26/12/2023
28. https://go.drugbank.com/drugs/DB04812; assessed on 26/12/2023
29. https://go.drugbank.com/drugs/DB00796; assessed on 26/12/2023
30. https://go.drugbank.com/drugs/DB00637; assessed on 26/12/2023
31. https://go.drugbank.com/drugs/DB06769; assessed on 26/12/2023