Synthesis, Characterization and Antioxidant Activity of 2-Aryl Benzimidazole Derivatives

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A B S T R A C T

Objective: To synthesize benzimidazole derivatives, characterize them by 1H NMR and ATIR techniques and evaluate their antioxidant activity.

Methods: In the present study 19 benzimidazole derivatives were synthesized by reacting O-phenylenediamine as the primary reactant with different aromatic aldehydes and benzoic acids. Reactions were monitored using thin layer chromatography technique, and the newly synthesized derivatives were characterized by ATIR and 1H NMR techniques. The antioxidant assay was performed using ABTS (2,2’-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) method and DPPH (2,2-diphenyl-1-picrylhydrazyl) method.

Results: Compounds BNZ-1, BNZ-2, BNZ-3, BNZ-9, and BNZ-10 showed comparable antioxidant activity to ascorbic acid at higher dose.

Conclusion: The synthesized benzimidazole derivatives have significant radical scavenging potential.

Keywords: Antioxidant, benzimidazole, O-phenylenediamine, Polyphosphoric acid

A R T I C L E I N F O

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INTRODUCTION

Free radicals are unstable/unpaired electrons in their outermost shell and may become highly reactive.1 Reactive oxygen species (ROS) are generated from molecular oxygen/nitrogen through Electron Transport Chain (ETC), cytochrome P450, and other cellular, subcellular functions.2 Free radicals play an important role in a cell's life and death.3 They affect beneficial metabolic and cellular processes adversely and play a key role in the development of pathological conditions of the body like cell damage and homeostatic disruption causing diseases including diabetes, cirrhosis, cancer and cardiovascular diseases. In healthy individuals, it is normally balanced by the endogenous antioxidant system.5 If the endogenous antioxidants fail to overcome the production of the reactive oxygen species, then exogenous antioxidants would be necessary to balance redox status.6 All antioxidants generally influence the redox status, thereby protecting cells against Reactive Oxygen Species (ROS).7 Antioxidants are molecules that help to protect cells from oxidative stress.8 Antioxidants are either present naturally in various types of food (fruits and vegetables) or taken as dietary supplements.9 They play a defensive role against ROS toxicity in our body. Thus antioxidants are considered as scavengers of free radicals.

Enzymes like Catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase directly/indirectly contribute to defense against the generated ROS. The nonenzymatic antioxidants like glutathione, vitamin E and C, uric acid, albumin, bilirubin, N-Acetylcysteine, melatonin are the scavengers of ROS and RNS actually.10

MATERIALS AND METHODS

Experimental
All chemicals and solvents were supplied by Sigma Aldrich, Merck, and CDH under a certificate of purity. The melting range of the synthesized compounds was measured by Scientech-2211 digital auto melting/boiling point apparatus. Proton magnetic resonance (1H NMR) spectra were recorded on Bruker 400 MHz NMR spectrometer using CDCl3 as a solvent. Chemical shifts were reported in parts per million relative to internal standard tetramethylsilane (TMS). IR spectra were recorded on Bruker-Alpha 1005151/06 ATIR spectrophotometer. Reaction progress was checked by TLC using Merck Silica
gel coated glass plates. The solvent system used was n-Hexane: Ethyl acetate in the ratio of 2:3.

**Synthetic procedures:**

**By using substituted aromatic carboxylic acid and 5-substituted O-phenylenediamine:**

0.01 mol of 5-substituted-o-phenylenediamine was dissolved in toluene and stirred with heat till completely dissolved. This solution was taken in a round bottom flask (RBF). The Poly phosphoric acid was heated to 60°C and added slowly with stirring to 5-substituted-o-phenylenediamine solution. Finally 0.01 mol of substituted aromatic carboxylic acid was added into the reaction mixture. RBF was fitted to reflux for about 8 to 10 hours at 120 to 150°C temperature at 300RPM.

To check the completion of reaction, TLC analysis of the compounds was done on Silica gel G 60 coated plates. The mobile phase was n-hexane and ethyl acetate in the ratio of 2:3. The spots obtained were visualized in UV-chamber.

![Synthetic procedure](image)

**By using Substituted Aromatic aldehydes and 5-substituted-O-phenylenediamine**

0.01 mol of 5-substituted-o-phenylenediamine was dissolved in 30 ml of ethanol with continuous starring in RBF. Added 3.0 gram of Sodium meta-bisulfate in RBF. Finally 0.01 mol of substituted aromatic aldehyde was added in reaction mixture and fitted to reflux for 4 to 6 hours at the 80 to 90°C temperature and 300RPM.

To check the completion of reaction TLC analysis of the compounds was done on Silica gel G 60 coated plates. The mobile phase was n-hexane and ethyl acetate in ratio of 2:3. The spots obtained were visualized in UV-chamber.

After completion of reaction, reaction mixture was cooled and to this ethyl ether was added to form a precipitate. The crude product was filtered and washed several times with ethyl ether until solid compound was obtained.

![Synthetic procedure](image)

| Name   | Structure | IUPAC Name                                      |
|--------|-----------|-------------------------------------------------|
| BNZ 1  | ![Structure](image) | 2-[(5-(4-fluorophenyl)pyridin-3-yl)]-1H-benzimidazole |
| BNZ2  | ![](image1) | 2-(5-methyl-3-phenyl-1,2-oxazolidin-4-yl)-1H-benzimidazole |
|-------|-------------|----------------------------------------------------------|
| BNZ3  | ![](image2) | 4-(2,3-dihydro-1H-inden-2-yl)-3-ethyl-5-methyl-1,2-oxazolidine |
| BNZ4  | ![](image3) | 4-(5-chloro-1H-benzimidazol-2-yl)quinolin-2-ol |
| BNZ5  | ![](image4) | 5-chloro-2-(5-methyl-3-phenyl-1,2-oxazol-4-yl)-1H-benzimidazole |
| BNZ6  | ![](image5) | 2-[5-(4-fluorophenyl)pyridin-3-yl]-5-nitro-1H-benzimidazole |
| BNZ7  | ![](image6) | 4-(5-nitro-1H-benzimidazol-2-yl)pyridine-2,6-diol |
BNZ8

2-(2-chloropyridin-4-yl)-5-nitro-1H-benzimidazole

BNZ9

4-(5-nitro-1H-benzimidazol-2-yl)quinolin-2-ol

BNZ10

4-(5-nitro-1H-benzimidazol-2-yl)-9H-fluoren-9-one

BNZ11

2-(3-ethyl-5-methyl-1,2-oxazol-4-yl)-5-nitro-1H-benzimidazole

BNZ12

2-(5-methyl-3-phenyl-1,2-oxazol-4-yl)-5-nitro-1H-benzimidazole

BNZ13

2-(5-methylthiophen-2-yl)-5-nitro-1H-benzimidazole
| BNZ14 | 2-(5-methylfuran-2-yl)-5-nitro-1H-benzimidazole |
| BNZ15 | N,N-diethyl-4-(5-nitro-1H-benzimidazol-2-yl)aniline |
| BNZ16 | 2,6-dimethoxy-4-(5-nitro-1H-benzimidazol-2-yl)phenol |
| BNZ17 | 4-bromo-2-(5-nitro-1H-benzimidazol-2-yl)phenol |
| BNZ18 | 5-nitro-2-{5-[3-(trifluoromethyl)phenyl]furan-2-yl]-1H-benzimidazole |
| BNZ19 | [5-(5-nitro-1H-benzimidazol-2-yl)furan-2-yl]methanol |
Table 2: Physical data of synthesized compounds

| Name  | Molecular formula | Molecular weight | Melting point °C | Yield (%) | Solubility                  | state | RF Value |
|-------|-------------------|------------------|------------------|-----------|----------------------------|-------|----------|
| BNZ1  | C_{18}H_{24}N_{2}F | 289.28           | 185-187          | 74        | Chloroform, Ethanol, Methanol | Solid | 0.90     |
| BNZ2  | C_{17}H_{22}N_{2}O | 279.33           | 189-191          | 71        | Chloroform, Ethanol, Methanol | Solid | 0.79     |
| BNZ3  | C_{17}H_{20}N_{2}O | 231.33           | 184-186          | 73.5      | Chloroform, Ethanol, Methanol | Solid | 0.82     |
| BNZ4  | C_{16}H_{18}ClN_{2}O | 295.72         | 189-191          | 66        | Chloroform, Ethanol          | Solid | 0.90     |
| BNZ5  | C_{17}H_{23}ClN_{2}O | 309.75          | 198-200          | 55        | Chloroform, Ethanol, Methanol | Solid | 0.74     |
| BNZ6  | C_{16}H_{20}F_{3}O | 334.33           | 196-198          | 74.2      | Chloroform, Ethanol, Methanol | Solid | 0.79     |
| BNZ7  | C_{19}H_{22}N_{2}O_{4} | 272.21          | 192-193          | 76        | Chloroform, Ethanol, Methanol | Solid | 0.75     |
| BNZ8  | C_{17}H_{21}ClN_{2}O_{2} | 274.66         | 191-193          | 63        | Chloroform, Ethanol, Methanol | Solid | 0.86     |
| BNZ9  | C_{16}H_{19}N_{2}O_{2} | 306.27          | 206-208          | 68.4      | Chloroform, Ethanol, Methanol | Solid | 0.70     |
| BNZ10 | C_{20}H_{19}N_{2}O_{4} | 341.31           | 204-205          | 69        | Chloroform, Ethanol, Methanol | Solid | 0.73     |
| BNZ11 | C_{17}H_{22}N_{2}O_{3} | 272.25           | 188-190          | 64.6      | Chloroform, Ethanol, Methanol | Solid | 0.66     |
| BNZ12 | C_{17}H_{22}N_{2} | 320.30           | 207-209          | 62        | Chloroform, Ethanol          | Solid | 0.88     |
| BNZ13 | C_{17}H_{20}N_{2} | 259.28           | 201-203          | 67.4      | Chloroform, Ethanol, Methanol | Solid | 0.66     |
| BNZ14 | C_{17}H_{20}N_{2}O | 243.21           | 215-216          | 61        | Chloroform, Ethanol, Methanol | Solid | 0.67     |
| BNZ15 | C_{17}H_{20}N_{2}O_{2} | 310.35          | 211-213          | 66        | Chloroform, Ethanol, Methanol | Solid | 0.90     |
| BNZ16 | C_{18}H_{20}N_{2}O_{3} | 315.28           | 220-222          | 65.3      | Chloroform, Ethanol          | Solid | 0.79     |
| BNZ17 | C_{17}H_{20}BrN_{2}O_{3} | 334.12          | 181-183          | 58        | Chloroform, Ethanol, Methanol | Solid | 0.82     |
| BNZ18 | C_{18}H_{19}F_{3}N_{2}O_{3} | 373.28          | 182-184          | 59        | Chloroform, Ethanol, Methanol | Solid | 0.91     |
| BNZ19 | C_{17}H_{20}N_{2}O_{4} | 259.21           | 179-180          | 65        | Chloroform, Ethanol, Methanol | Solid | 0.71     |

Table 3: Spectral study of synthesized compounds

| Name  | IR spectra                                      | 1H-NMR spectra                                        |
|-------|------------------------------------------------|------------------------------------------------------|
| BNZ1  | 1710.98v (C=O), 1690.08 v (C=N), 1515.41 v (C-C), 1411.45v (C=C), 1058.96 v (C-O-C), 754.78 v (Ar C-H), 686.54 v (C-S) | δ 8.20-8.05 (d, 2H, Ar-H), 7.52 (t, 2H, Ar-H), 7.33-6.99 (m, 4H, Ar-H), 3.66 (m, 1H, CH), 1.57 (d, 3H, CH3) |
| BNZ2  | 2303.91 v (C=N), 1665.11 v (C=N), 1585.15 v (C-C), 1431.68 v (C=C), 759.19 v (Ar C-H), 645.11 v (C-S) | δ 8.25-8.12 (d, 2H, Ar-H), 7.56 (t, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H), 7.02 (t, 1H, Ar-H) |
| BNZ3  | 1607.75 v (C=N), 1515.50 v (C-C), 1465.28 v (C-C), 1050.58 v (C-F), 745.14 v (Ar C-H), 692.81 v (C-S) | δ 8.32-8.00 (d, 2H, Ar-H), 7.88 (s, 1H, Ar-H), 7.52 (t, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 5.08 (s, 1H, OH), 3.99 (s, 3H, CH3) |
ANTIOXIDANT ACTIVITY:

The anti-oxidant activity was assessed by DPPH method and ABTS method as described by Mensor et al.10

DPPH assay

The DPPH radical is one of the few stable organic nitrogen radicals, which bears a deep purple color. It is commercially available. Because of a strong absorption band centered at about 520 nm, the DPPH radical has a deep violet color in solution, and it becomes colorless or pale yellow when neutralized. This assay is based on the measurement 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 assays are based on the loss of the DPPH color at 517 nm after reaction with the test compounds; the reaction is monitored by UV-Visible spectrophotometer.

Procedure:

0.01M solution of DPPH was prepared in methanol. Methanolic solutions of all the compounds in the...
concentration ranges of 40μg/ml, 60μg/ml, 80μg/ml and 100μg/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 assay mixture were kept in a dark and cool place for 30 min. immediately after that the absorbance of the DPPH solution without sample, DPPH solution with sample and ascorbic acid with DPPH were recorded at 517 nm on a UV-Visible spectrophotometer. The antioxidant activity was measured using the formula.

\[
\% \text{ Scavenging or Inhibition} = \left( \frac{ Ao - As }{ Ao } \right) \times 100
\]

Where,

\( Ao \) = Absorbance of the DPPH solution without sample

\( As \) = Absorbance of DPPH solution with sample

**ABTS assay**

The assay is based on the ability of different compounds to scavenge 2, 2-azino-bis (ethylbenzthiazoline-6-sulfonic acid) radical cation. ABTS radicals have a characteristic absorbance at 734 nm. This absorbance decreases when the radical is reduced by any antiradical compound. The decrease in the absorbance can be measured using a UV-Vis spectrophotometer at 734 nm.

**Procedure**

7 mole ABTS stock solution in water was prepared. To it 2 mole solution of potassium persulfate was added in 1:1 ratio (volume/volume). This reaction mixture was left undisturbed in a dark place for about 16 h for generation of the radicals. This solution was further diluted using methanol so that it has a stable absorbance of 0.700±0.05 at 734 nm. Methanolic solutions of all compounds including ascorbic acid were prepared in the concentration ranges of 40μg/ml, 60μg/ml, 80μg/ml and 100μg/ml. Absorbance of the test sample, blank (methanol) and the standard solutions were taken immediately at 734 nm. The antioxidant activity of the samples was determined using the equation

\[
\% \text{ E} = \left( \frac{ Ac - At }{ Ac } \right) \times 100
\]

Where,

\( E \) = Anti-oxidant activity

\( Ac \) = Absorbance of the ABTS solution

\( At \) = Absorbance of the test compounds

**RESULTS**

| Name  | Dilutions (µg/ml) | 40µg/ml | 60µg/ml | 80µg/ml | 100µg/ml |
|-------|-------------------|---------|---------|---------|----------|
| BNZ 1 | 48.02%            | 58.02%  | 69.02%  | 85.03%  |
| BNZ2  | 49.02%            | 59.02%  | 71.33%  | 82.36%  |
| BNZ3  | 53.02%            | 67.02%  | 78.25%  | 88.53%  |
| BNZ4  | 38.02%            | 46.56%  | 59.02%  | 71.02%  |
| BNZ5  | 46.32%            | 59.20%  | 67.02%  | 77.82%  |
| BNZ6  | 36.06%            | 44.02%  | 55.02%  | 68.02%  |
| BNZ7  | 43.02%            | 52.36%  | 63.74%  | 76.36%  |
| BNZ8  | 44.02%            | 51.02%  | 66.02%  | 76.02%  |
| BNZ9  | 48.03%            | 56.77%  | 68.02%  | 81.32%  |
| BNZ10 | 51.02%            | 66.53%  | 76.33%  | 86.33%  |
| BNZ11 | 44.03%            | 48.56%  | 58.03%  | 69.36%  |
| BNZ12 | 25.02%            | 36.33%  | 48.02%  | 63.02%  |
| BNZ13 | 33.18%            | 43.25%  | 53.03%  | 67.02%  |
| BNZ14 | 26.02%            | 35.38%  | 46.33%  | 62.55%  |
| BNZ15 | 43.35%            | 59.07%  | 62.33%  | 71.04%  |
| BNZ16 | 41.04%            | 58.06%  | 64.36%  | 69.03%  |
| BNZ17 | 44.53%            | 54.05%  | 61.02%  | 71.55%  |
| BNZ18 | 39.41%            | 52.45%  | 65.01%  | 74.03%  |
| BNZ19 | 33.32%            | 39.36%  | 42.02%  | 56.55%  |
| Ascorbic acid | 64.49% | 71.33% | 86.010% | 92.34% |
Table 5: Percentage scavenging of ABTS radical by compounds and ascorbic acid

| Name  | Dilutions (µg/ml) |
|-------|-------------------|
|       | 40µg/ml | 60µg/ml | 80µg/ml | 100µg/ml |
| BNZ 1 | 38.45%   | 56.23%   | 67.23%   | 79.02%   |
| BNZ2  | 40.21%   | 58.32%   | 64.58%   | 78.52%   |
| BNZ3  | 36.75%   | 45.02%   | 56.02%   | 75.32%   |
| BNZ4  | 38.35%   | 48.56%   | 58.23%   | 70.32%   |
| BNZ5  | 10.33%   | 11.02%   | 19.23%   | 29.56%   |
| BNZ6  | 35.23%   | 43.23%   | 51.23%   | 63.01%   |
| BNZ7  | 33.22v   | 42.02%   | 52.12%   | 61.23%   |
| BNZ8  | 16.21%   | 15.02%   | 18.23%   | 26.23%   |
| BNZ9  | 26.32%   | 34.23%   | 42.03%   | 58.23%   |
| BNZ10 | 33.21%   | 44.25%   | 58.36%   | 64.36%   |
| BNZ11 | 34.21%   | 43.45%   | 53.65%   | 64.35%   |
| BNZ12 | 29.63%   | 38.56%   | 51.36%   | 61.35%   |
| BNZ13 | 24.23%   | 33.23%   | 48.23%   | 63.45%   |
| BNZ14 | 19.33%   | 26.12%   | 47.23%   | 58.23%   |
| BNZ15 | 31.22%   | 46.23%   | 55.32%   | 69.32%   |
| BNZ16 | 33.02%   | 44.12%   | 63.45%   | 79.54%   |
| BNZ17 | 36.57%   | 53.12%   | 67.21%   | 79.03%   |
| BNZ18 | 22.33%   | 32.31%   | 49.56%   | 68.33%   |
| BNZ19 | 18.33%   | 26.33%   | 39.32%   | 51.32%   |
| Ascorbic acid | 511.02% | 58.63% | 71.40% | 90.01% |

DISCUSSION

Gale CR. et al. (2016) on his studies on benzimidazole showed that better antioxidant activity is due to the electronegative substituent at position-5(methoxy), position-4(nitro), position-2(2-methoxy-4-hydroxy). Likhar Rupali et al. (2016) in her studies showed that the compounds which showed good antioxidant activity contain electronegative group at position-3(aminoo), position-4(chloro) and position-2(hydroxyl group with bigger ring). Buettner GR. et al. (2017) in his research on benzimidazole showed that comparable good antioxidant activity is due to the electronegative substituent at position-1(-OCH3), position-4(-NH2), position-2(-C6H4CHF2). Pawar PY et al. (2017) has published that the compounds which showed good antioxidant activity contains electronegative group at position-5 and 6(Cl), position-4(-CH3) and position-2(isoquinoline ring). Kashif MK, et al. (2018) in his studies on benzimidazole showed that better antioxidant activity is due to the electron withdrawing substituent at position-3(-C2H5), position-4(-NO2), position-2(quinoline ring).

To assess the free radical scavenging activity of synthesized benzimidazole compounds, DPPH and ABTS assays were conducted, and the results are indicated in table 4 and 5 respectively. From the results, it is clear that the efficacy of BNZ-1, BNZ-2, BNZ-3, BNZ-9, and BNZ-10 as antioxidant agents was better in DPPH assay and compound BNZ-1, BNZ-2, BNZ-3, BNZ-16, and BNZ-17 in ABTS assay.

The pharmacophore of compound BNZ-1 have fluoro group and compound BNZ-2 and BNZ-3 have amino group, compound BNZ-9 have nitro group with hydroxyl group, compound BNZ-10 have keto group with amino group. Compound BNZ-16 have methoxy group and compound BNZ-17 have halide group which infers that all attached groups are electronegative and in concurrence with previous studies, our research also says that presence of electro negativity is the major contributing factor towards antioxidant activity.

CONCLUSION:-

In this research, 19 new benzimidazole derivatives were synthesized using well recognized synthetic protocols. The synthesized compounds were characterized using ATIR and 1HNMR techniques and were screened for their antioxidant potential.

Results suggest that compounds BNZ-1, BNZ-3, BNZ-9 and BNZ-10 are the efficient scavengers of DPPH and BNZ-1, BNZ-2, BNZ-3, BNZ-16, BNZ-17 are the efficient scavengers of ABTS radicals. From the structure-activity perspective, the position of the electron donating functional groups on the benzimidazole core may promote the expected antioxidant activity. Further derivatization of these substances will result in more selective antioxidant agents.

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