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SYNTHESIS AND CHARACTERIZATION OF PHENYL LINKED BENZO[*D*]IMIDAZOLE DERIVATIVES

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ABSTRACT:
Benzimidazole is one of the most flexible aromatic heterocycles that encompasses nitrogen and is formed by the fusing of a benzene ring with an imidazole ring, exhibiting flexibility and varied biological activities. It is a versatile pharmacophore in medicinal chemistry which exhibits various therapeutic activities like antimicrobial, antiulcer, antihypertensive, analgesic, antiviral, antifungal, anticancer and antihistaminic. The present article covers the simple synthesis and detailed characterization of benzo[*d*]imidazole derivatives (1–4) through various synthetic routes with good yields.

KEYWORDS: heterocycles, imidazole, benz[*d*]imidazole, synthesis, characterization

INTRODUCTION:

Benzimidazole, also known as 1*H*-benzimidazole and 1,3-benzodiazole, consists of a benzene ring fused with a five-membered imidazole ring is one of the most widely studied nitrogen-based benzo-fused heterocyclic systems. "The first inquiry into the biological activity of the benzimidazole nucleus was well documented in 1944".[i] The core benzimidazole structure plays very important roles in numerous biologically active molecules due to the similarity in its structure with nucleotide found in human body. They exhibits wide range of biological properties[i] such as antiparasitic,[ii] antiulcer,[iii] antihelminthic,[iv] anticoagulant,[v] antimicrobial,[vi] antiinflammatory,[vii] antitumour,[viii] antiretroviral.[ix] The pharmacological activities of benzimidazole compounds can be further enhanced by functionalizing its core structure. This is the most popular method to develop newer drugs to treat various diseases based on the benzimidazole skeleton.

The most common strategy involved in the synthesis of benzimidazole derivatives involved condensation of o-phenylenediamine and carboxylic acids[x] or their derivatives such as nitriles, imidates, or orthoesters.[xi] Using the same strategy, we have synthesized the phenyl linked benzo[*d*]imidazoles (compound 1) by condensing o-phenylenediamine and teraphthalic acid. Other derivatives (compounds 2–4) have prepared by the conventional methods of bromination, nitration and reduction of nitro group.[xii,xiii]

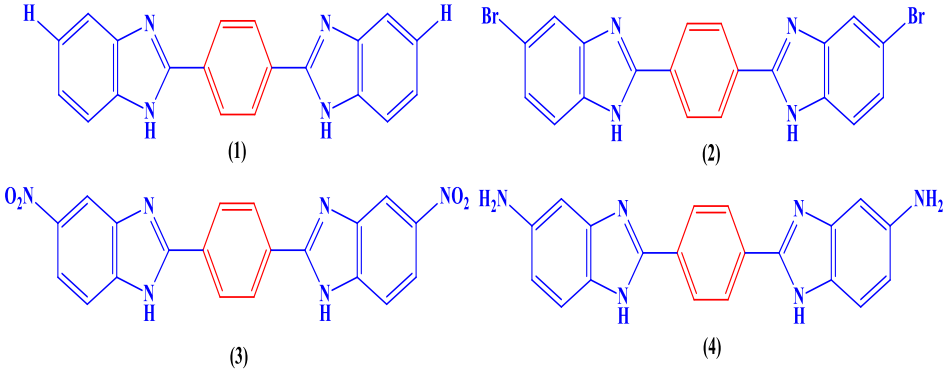


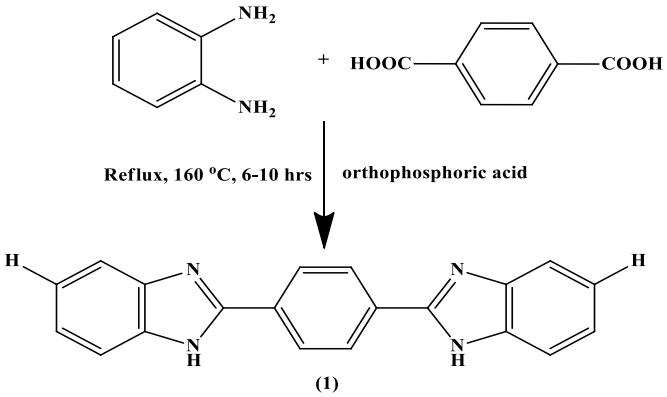
Figure 1. Molecular structures of 1–4.

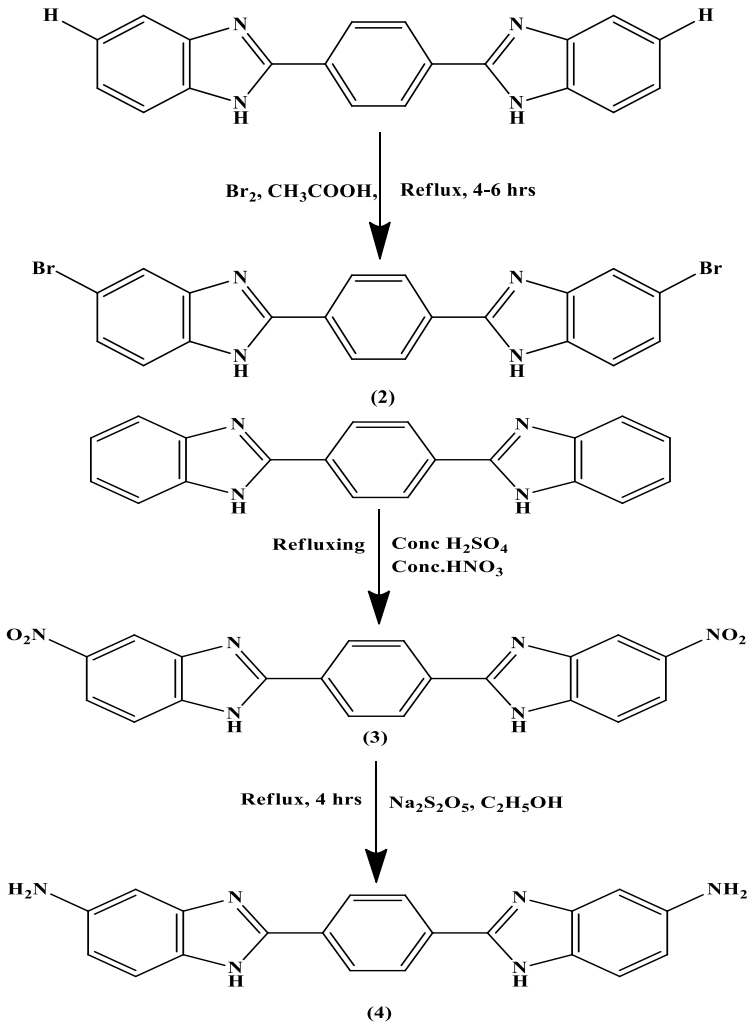
The biological, photophysical, electrochemical, thermal and bioactivities of phenyl linked benzimidazole compounds are not reported in the literature, it would be interesting to know their above properties. Hence in this research article we report synthesis and detailed characterization of novel benzo[*d*]imidazole derivatives (1–4). Further we also believe that synthesized derivatives would have biological activities which can be explored for different types of diseases.

EXPERIMENTAL:

MATERIALS AND METHODS

All of the solvents (HPLC grade) and starting chemicals (AR grade) were sourced from commercial vendors (SD Fine-Chem, Sigma Aldrich and Spectrochem) and were used without any purification. Column chromatography (60–120 mesh) silica gel with eluting solvent system (n–hexane and ethyl acetate) was used for column chromatography. Aluminum Thin layer chromatography (TLC) plates from Merck were used to track the reaction's progress and the purity of the produced compounds. Chemical structures of produced compounds 1–4 were ascertained by FTIR, Mass, ^{1}H NMR, ^{13}C NMR, and elemental analysis. Bruker 300 Ultrashield spectrometer was employed to record ^{1}H and ^{13}C NMR spectra at functional frequencies of 300 MHz and 75 MHz, respectively. Deuterated DMSO (DMSO-d_6) was used as solvent with Tetramethylsilane (TMS) served as an internal reference. Thermo Scientific Polaris Q GC-MS instrument and Perkin Elmer Frontier 91579 were used record mass and FTIR spectras. Elemental analysis was carried on EA Euro-elemental analysis instrument. Melting points are measured in open capillaries and are uncorrected on a Thomas Hoover melting point apparatus.





Scheme: Synthesis of novel benz[*d*]imidazole derivatives

RESULT AND DISCUSSION:

The structure of the synthesized compounds has been confirmed by physical and spectroscopic data such as elemental analyzer, FTIR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra. In the FTIR spectra, the stretching frequency of aromatic –C=N– is formed in the region between ν = 1459–1582 cm^{-1}. The aromatic stretching vibration of C–H appeared at region between ν = 2903–3059cm^{-1}. In the ^{1}H NMR spectra, singlet for two proton of –N–H– has chemical shift in the range of δ = 7.5 to 7.8 ppm. The signals around δ = 6.84–8.38 ppm are assigned by protons of CH=CH of aromatic rings. In the ^{13}C NMR spectra, the carbon of –C=N has chemical shift in the range of δ =148 to 151 ppm

GENERAL PROCEDURE:

Compound 1*:* 1,4-bis(1*H*-benzo[*d*]imidazol-2-yl)benzene

Teraphthalic acid (10 mmol, 1.66 g) and 1,2-diamino benzene (25 mmol, 2.71 g) in 60 cm^{3} ortho phosphoric acid was heated for 9 hour at 160 ^{o}C. The crude solid product obtained purified by column chromatography with eluent solvent system of n−hexane: ethyl acetate: methanol ratio as 20:70:10. Yield: 2.948 g (95.0%) Bluish green solid; Melting Point (open capillary method): >350 ^{o}C; (ν_{max} cm^{-1}): 3390.18, 1656.45, 1589.56, 1472.69, 1289.71, 1006.84, 834.99, 715.43; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 7.817 (s, 4H, -NH-), 7.611-7.593 (m, 6H, Ar-H), 7.291-7.252 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d$_6$): 150.301, 137.689, 137.498, 130.609, 128.320, 123.620, 123.323, 118.485, 115.121; Mass

spectrum (m/z): 310.32 (100%): Elemental Anal. Calcd for $C_{20}H_{14}N_4$: C (77.40%), H (4.55%), N (18.05%) Found: C (77.30%), H (4.60%), N (18.15%).

Compound 2: 1,4-bis(5-bromo-1*H*-benzo[*d*]imidazol-2-yl)benzene
1,4-bis(1*H*-benzo[*d*]imidazol-2-yl)benzene (1 mmol, 0.311 g) and liquid bromine (4 mmol, 0.21 cm^3) in 30 cm^3 acetic acid was heated for 6 hour at 100 ^oC. The crude solid product obtained purified by column chromatography with eluent solvent system of n−hexane: ethyl acetate: methanol ratio as 15:80:05.Yield: 0.354 g (76.0%) Pale yellow solid; Melting Point (open capillary method): >350 ^oC; FTIR (ν_{max} cm^{-1}): 3323.45, 1661.79, 1582.76, 1470.89, 1280.89, 1031.76, 826.67, 715.34, 575.56; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.896 (s, 2H, Ar-H), 7.813 (s, 4H, Ar-H), 7.581 (s, 2H, -NH-), 7.467-7.505 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 151.171, 135.545, 135.118, 130.609, 128.320, 123.651, 121.064, 120.286, 114.693; Mass spectrum (m/z): 467.92 (100%); Elemental Anal. Calcd for $C_{20}H_{12}Br_2N_4$: C (51.31%), H (2.58%); Br (34.14%), N (11.97%) Found: C (51.35), H (2.54%); Br (34.11%), N (12.00%)

Compound 3: 1,4-bis(5-nitro-1*H*-benzo[*d*]imidazol-2-yl)benzene
1,4-bis(1*H*-benzo[*d*]imidazol-2-yl)benzene (1 mmol, 0.311 g) in mixture of Conc. H_2SO_4 (6 cm^3) and HNO_3 (2 cm^3) in 30 cm^3 acetic acid was heated for 6 hour at 40-50 ^oC. The crude solid product obtained purified by column chromatography with eluent n−hexane: ethyl acetate: methanol ratio as 20:70:10. Yield: 0.288 g (72.0%) Pale Green; Melting Point (open capillary method): 350^oC; FTIR (ν_{max} cm^{-1}): 3374.84, 1640.14, 1572.78, 1453.19, 1272.57, 987.21, 814.84, 582.26, 491.54; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 8.601 (d, 2H, Ar-H), 8.139 (dd, 2H, Ar-H), 7.865 (d, 2H, Ar-H), 7.821 (s, 4H, Ar-H), 7.750 (s, 2H, -NH-); ^{13}C NMR (75 MHz, DMSO-d_6): 141.069, 140.069, 139.032, 130.609, 128.320, 119.103, 118.80, 115.220, 114.693; Mass spectrum (m/z): 400.30 (100%); Elemental Anal. Calcd for $C_{20}H_{12}N_6O_4$: C (60.00%), H (3.02%); N (20.99%), O (15.99%); Found: C (60.08%), H (3.05%); N (20.95%), O (15.91%).

Compound 4: 2,2'-(1,4-phenylene)bis(1*H*-benzo[*d*]imidazol-5-amine)
1,4-bis(5-nitro-1*H*-benzo[*d*]imidazol-2-yl)benzene (1 mmol, 0.40 g) and Sodium dithionate (6 mmol) in 30 cm^3 ethanol was heated for 6 hour at 70 ^oC The crude solid product obtained purified by column chromatography with eluent solvent system of n−hexane: ethyl acetate: methanol ratio as 10:80:10. Yield: 0.220 g (65.0%) Red brown solid; Melting Point (open capillary method): 280 ^oC; FTIR (ν_{max} cm^{-1}): 3599.72, 1659.07, 1589.87, 1474.29, 1295.20, 1008.33, 798.92, 597.72; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.818 (s, 4H, ArH), 7.502 (s, 2H, -NH-), 7.423 (d, 2H, Ar-H), 6.927 (s, 2H, Ar-H), 6.623 (d, 2H, Ar-H), 1.842 (s, 4H, -NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): 151.171, 141.191, 136.606 130.609, 129.243, 128.320, 115.166, 111.436, 102.715; Mass spectrum (m/z): 340.12 (100%); Elemental Anal. Calcd for $C_{20}H_{16}N_6$: C (70.57%), H (4.75%); N (24.68%); Found: C (70.55%), H (4.78%); N (24.67%).

CONCLUSION:

In conclusion, we have synthesized phenyl linked benz[*d*]imidazole compounds (1-4) with complete characterization which includes IR, Mass, ^1H NMR, ^{13}C NMR and elemental analysis with good yields. Synthesized derivatives would have promising biological activities, based on literature survey and will be explored and published later. Further we are also planning to functionalize the 5^{th} position of compound 2 and 4 by putting electron donating/withdrawing moieties using palladium catalyzed coupling reactions and their photophysical, electrochemical, theoretical and biological activity studies.

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