SYNTHESIS OF N-SUBSTITUTED DERIVATIVES OF BENZIMIDAZOLE

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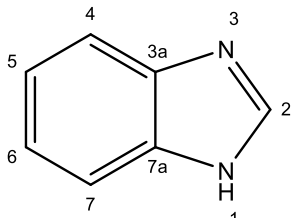
Abstract: Derivatives of Benzimidazole are resembles of purine nucleosides which are found in human body. These are the important heterocyclic organic compounds containing phenyl ring condensed with imidazole ring which possesses wide range of starting material for various compounds. In this article derivatives of benzimidazole prepared by using 4,5-substituted o-phenylene daimine with 3,4,5-trimethoxybenzaldehyde followed by various substitution like $PhCH_2Cl$, $PhCH_2OCH_2Cl$, etc. in presence of sodium hydride, anhydrous methyl nitrile or anhydrous K_2CO_3 in nitrogen atmosphere to get desirable products.

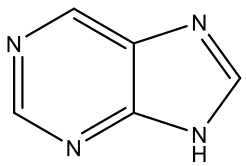
Keywords: Benzimidazole; 4,5-substituted o-phenylene diamine, 3,4,5-trimethoxy benzaldehyde; magnetic stir; NaH/K_2CO_3; N_2 atmosphere.

INTRODUCTION:

Benzimidazole is a bi-heterocyclic organic system contains a benzene ring fused with imidazole ring at 4,5-positions. The first benzimidazole analog 2,6-dimethyl benzimidazole was obtained by reduction of 2-nitro-4-methylacetanilide[1].



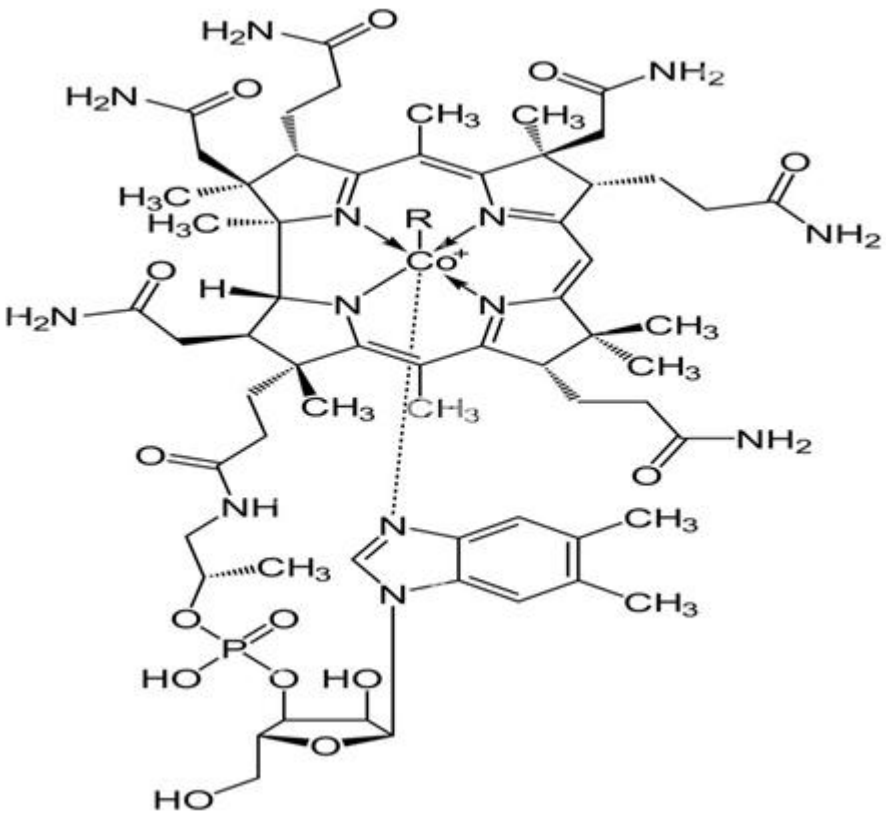
Benzimidazole nucleus



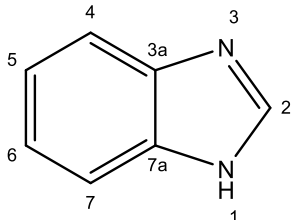
Purine nucleosides

A large number of benzimidazole derivatives exhibited diverse biological and pharmacological activities such as antiviral, antibacterial, antifungal, antiparasitic,

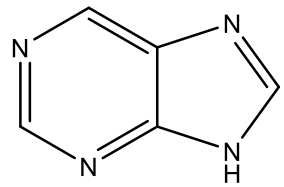
anthelmintic, anticancer, anxieties etc, The activities of these compounds depend upon the substitution on the benzimidazole ring at the position N-1 (or) C-2 or on both. 5, 6-Dimethyl benzimidazole moiety has been shown to be part of the structure vitamin B_{12} as shown below



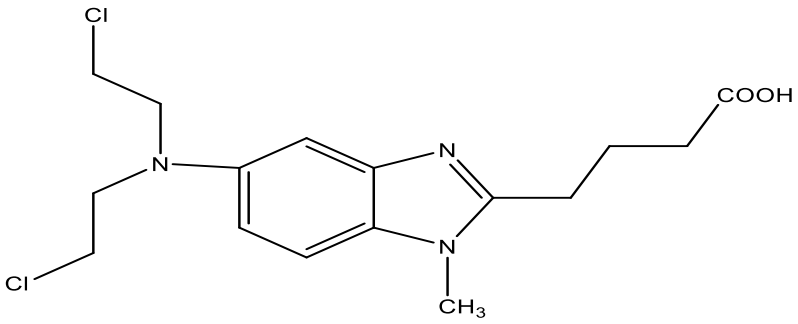
Many commercially available drugs based on the benzimidazole skeleton such as antifungal (carbendazole), anthelmintics (albendazole, mebendazole, fenbendazole, and oxibendazole), proton pump inhibitors (omeprazole), antihypertensives (candesartan and telmisartan), anticancer (bendamustine, nocodazole, and abemaciclib), antiviral(enviradene) and antihistamines(emedastine and clemizole). In this article we planned to modify the benzimidazole nucleus at 2, 4 and 5 –positions to prepare better biological active compounds. The synthesis of benzimidazole derivatives typically involved in the reaction between 4,5-substituted phenylene 1,2 dimine and 4,5,6-trimethoxy benzaldehyde using oxidizing agent sodium metabisuphite in ethanol [2-10].



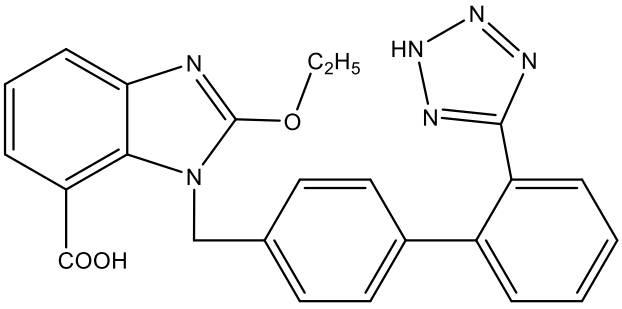
Benzimidazole nucleus



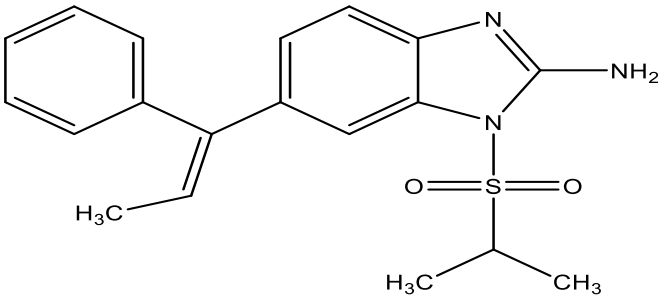
Purine nucleosides



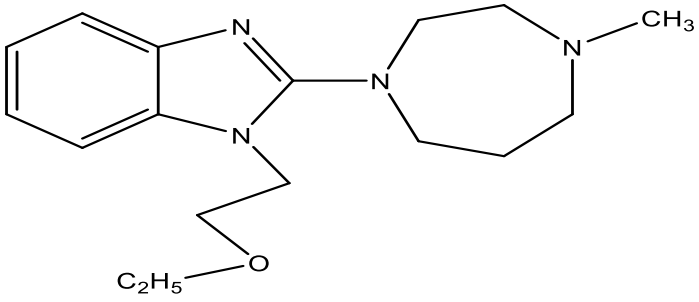
Bendamustine



Candesartan



Enviradene



Emedastine

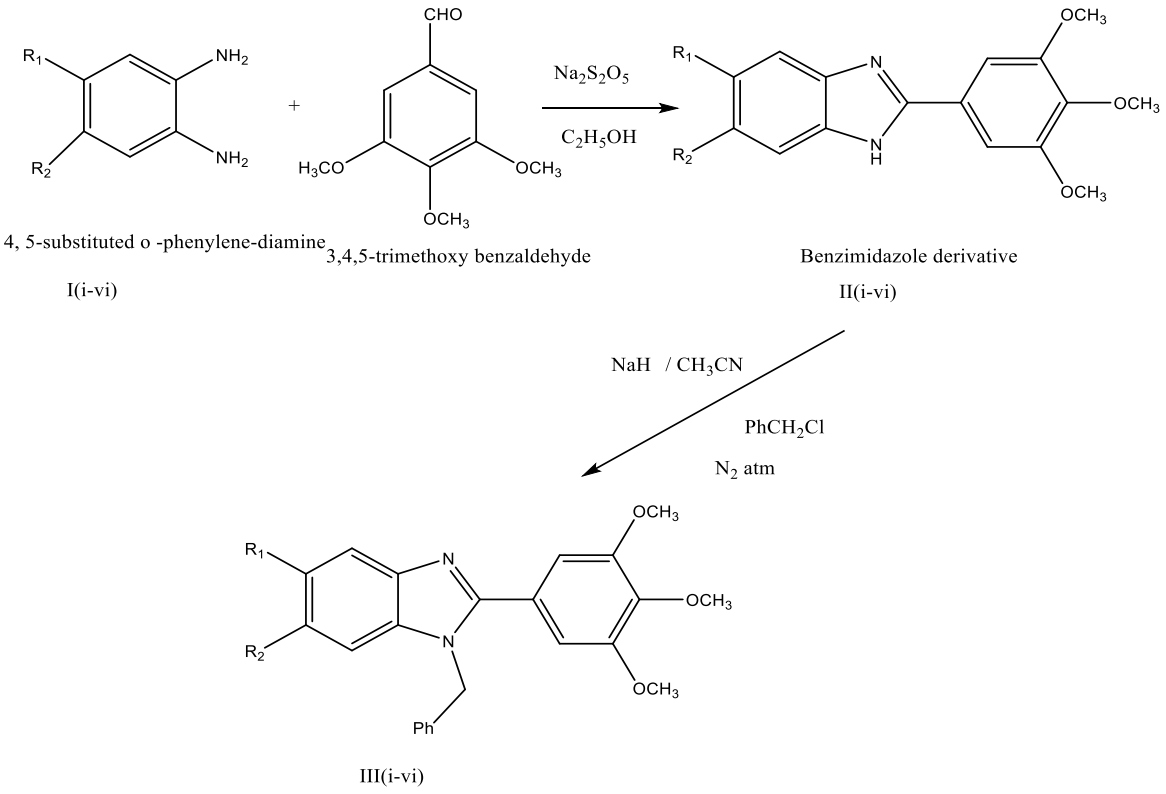
EXPERIMENTAL: Material and Methods

All the reagents and chemicals were purchased from Sigma-Aldrich and used without further purification. Methylnitrile was dried over phosphorus pentoxide and distilled. Melting points were taken in open capillary tubes and are uncorrected. TLC is performed with E. Merck pre-coated silica gel plates (60F-254) with ninhydrin as a spot developing agent. Acme, India silica gel, 60–120 mesh is used for column chromatography. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ^{1}H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectra were recorded $CDCl_3$ solvent containing tetra methyl silane (TMS) as internal references were recorded on Bruker spectrometer; Elemental analyses were performed on a PerkinElmer 2400. Mass spectra were obtained by Water-QTOF ultima spectrometer. Micro analytical data were obtained by elemental-Vario EL-III [11-17].

General methods of preparation of N-benzyl substituted derivatives of 5, 6-substituted 2-(3,4,5-trimethoxyphenyl)-benzimidazole: A mixture of substituted o-phenylene dimine I(i-vi) 0.02 mole, 3, 4, 5-trimethoxybenzaldehyde 0.02 mole and 0.04 mole sodium metabisulphite was added in 30 cm^3 of ethanol. The resulting reaction mixture was stirred using magnetic stirrer at room temperature for about 2-3 hours. The progress of reaction was checked by TLC. After complete completion of reaction, the product was concentrated with vacuum distillation. The solid product II (i-vi) was washed with water and then n-hexane and dried in anhydrous P_2O_5 for overnight. Product was again dried at room temperature and determined the physical constant. Further sodium hydride (0.1mole) was added to the mixture of II(i-vi) dissolved in anhydrous methylnitrile (40 cm^3). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 2 hours. To this benzyl chloride (0.01mole) was added slowly at room temperature. The reaction mixture was heated at 60^{o}C with magnetic stirring for 48 hours. Then the mixture was cooled to room temperature and the

insoluble materials were removed by filteration. Solvent was evaporated and the crube product was purified by silica gel column chromatography using 1:1 $CHCl_3$ and MeOH as eluent gave final product.

SCHEME



4, 5-substituted o -phenylene-diamine I(i-vi)

3,4,5-trimethoxy benzaldehyde

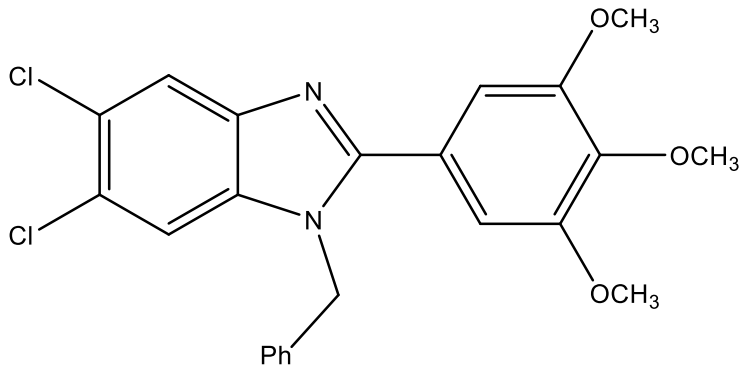
Benzimidazole derivative II(i-vi)

III(i-vi)

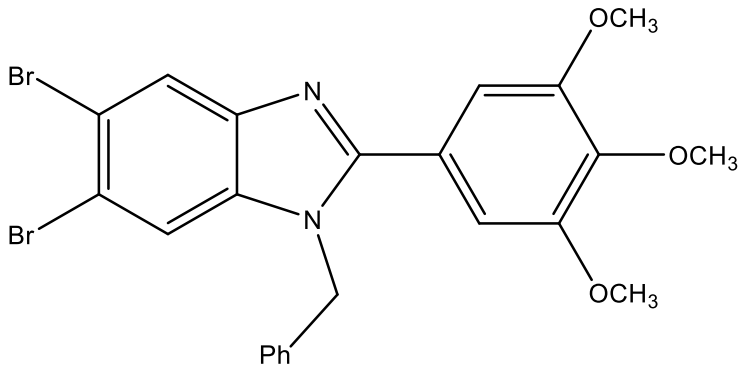
Compound	R_1	R_2
I-III(i)	Cl	Cl
I-III(ii)	Br	Br
I-III(iii)	CH_3	CH_3
I-III(iv)	OCH_3	OCH_3
I-III(v)	OH	H
I-III(vi)	NO_2	H

N-benzyl- 5, 6-dichloro-2-(3, 4, 5-trimethoxyphenyl)-benzimidazole III(i): Colour: Colourless solid. M. P. 132-135ºC, Yield 81.3%. IR (KBr): 3025cm^{-1}(N-CH_2), 1505cm^{-}

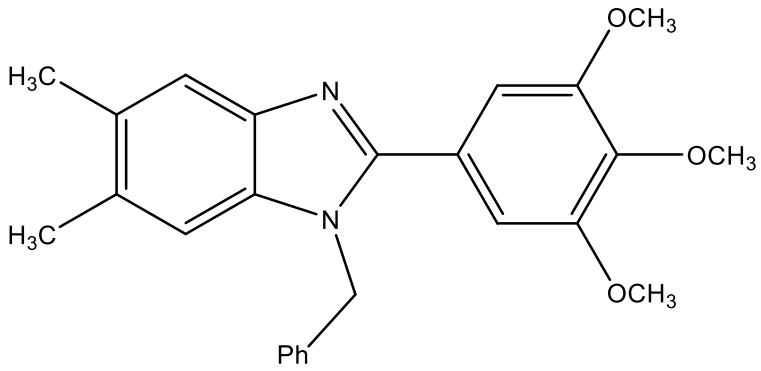
^{1}(C=N), 752cm^{-1}(Ar-Cl) 1395cm^{-1}(Ar-OCH_3).^{1}H- NMR ($CDCl_3$); δ (ppm): 3.71-3.83 (bs, 9H, OCH_3), 6.97 – 8.30 (m, 9H, Ar.-H), 5.79(s, 2H, NCH_2). ^{13}C-NMR ($CDCl_3$); δ (ppm):56.1, 60.8, 139.2, 153.1, 104.6, 124.8, 153.3, 138.4, 117.2, 128.6, 133.7, 52.2, 137.3, 127.6, 128.6, 125.7. Mass (*m/z*): 443.32. Elemental Analysis (%): For $C_{23}H_{20}O_3Cl_2N_2$, Calculated: C, 62.31; H, 4.55; O, 10.83; Cl, 15.99; N, 6.32. Found: C, 62.35; H, 4.51; O, 10.80; Cl, 15.95; N, 6.79.



N-benzyl- 5, 6-dibromo-2-(3, 4, 5-trimethoxyphenyl)-benzimidazole III(ii): Colour: Yellow solid. M. P. 147-149ºC, Yield 78.3%. IR (KBr): 3045cm^{-1}(N-CH_2), 1500cm^{-1}(C=N), 650cm^{-1}(Ar-Br) 1392cm^{-1}(Ar-OCH_3).^{1}H- NMR ($CDCl_3$); δ (ppm): 3.71-3.83 (bs, 9H, OCH_3), 6.97 – 7.76 (m, 9H, Ar.-H), 5.79(s, 2H, NCH_2). ^{13}C-NMR ($CDCl_3$); δ (ppm):56.1, 60.8, 139.2, 153.1, 104.6, 124.8, 153.3, 140.1, 120.9, 120.9, 120.8, 135.4, 52.2, 137.3, 127.6, 128.6, 125.7, 128.6, 127.6. Mass (*m/z*): 532.23. Elemental Analysis (%): For $C_{23}H_{20}O_3Br_2N_2$, Calculated: C, 51.90; H, 3.79; O, 9.02; Br, 30.03; N, 5.26. Found: C, 51.81; H, 3.82; O, 9.05; Br, 30.07; N, 5.25.

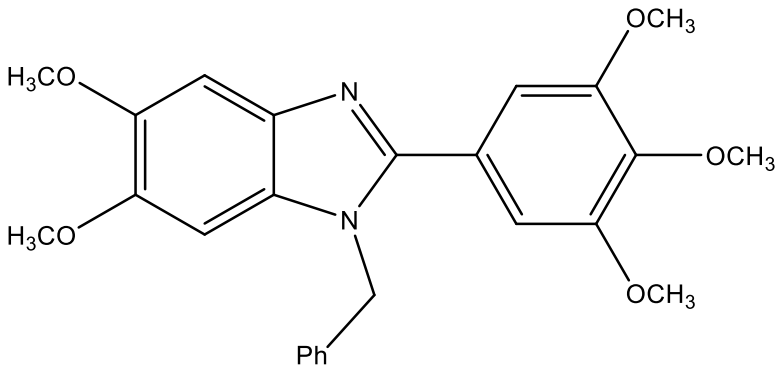


N-benzyl- 5, 6-dimethyl-2-(3, 4, 5-trimethoxyphenyl)-benzimidazole III(iii): Colour: Colourless solid. M. P. 117-119ºC, Yield 69.4%. IR (KBr): 3100cm^{-1}(N-CH_2), 1500cm^{-1}(C=N), 1387cm^{-1} (Ar-OCH_3).^{1}H- NMR ($CDCl_3$); δ (ppm): 2.47(s, 6H, CH_3), 3.71-3.83 (bs, 9H, OCH_3), 6.97 – 7.35 (m, 9H, Ar.-H), 5.79(s, 2H, NCH_2), 2.38-2.47(d, 6H, Ar-CH_3). ^{13}C-NMR ($CDCl_3$); δ (ppm):18.8, 56.1, 60.8, 139.2, 153.1, 104.6, 124.9, 153.3, 135.8, 115.2, 130.3, 133.2, 109.7, 131.1, 52.2, 137.3, 127.6, 128.8, 125.7. Mass (*m/z*): 402.49. Elemental Analysis (%): For $C_{25}H_{26}O_3N_2$, Calculated: C, 70.60; H, 6.51; O, 11.92; N, 6.96. Found: C, 70.51; H, 6.41; O, 12.09; N, 6.99.

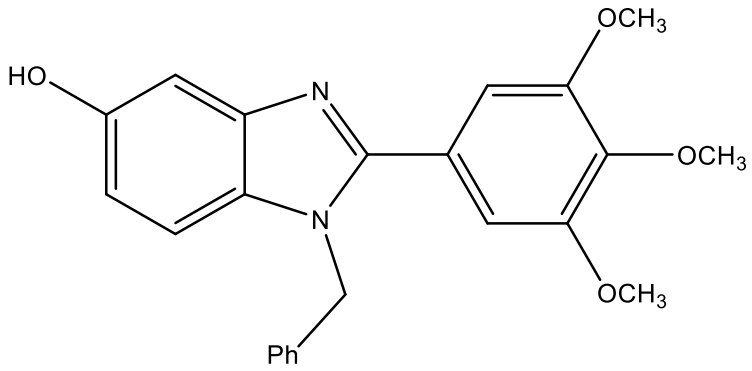


N-benzyl- 5, 6-dimethoxy-2-(3, 4, 5-trimethoxyphenyl)-benzimidazole III(iv): Colour: Colourless solid. M. P. 131-133ºC, Yield 82.7%. IR (KBr): 3105cm^{-1}(N-CH_2), 1500cm^{-1}(C=N), 1387cm^{-1} (Ar-OCH_3).^{1}H- NMR ($CDCl_3$); δ (ppm): 3.71-3.83 (bs, 15H, OCH_3), 6.97 – 7.14 (m, 9H, Ar.-H), 5.79(s, 2H, NCH_2). ^{13}C-NMR ($CDCl_3$); δ (ppm): 56.1, 60.8, 139.2,

153.1, 104.6, 124.8, 153.3, 132.2, 101.8, 142.0, 127.5, 52.2, 137.3, 127.6, 128.6, 125.7. Mass (*m/z*): 434.49. Elemental Analysis (%): For $C_{25}H_{26}O_5N_2$, Calculated: C, 69.11; H, 6.03; O, 18.41; N, 6.45. Found: C, 69.20; H, 6.11; O, 18.32; N, 6.37.

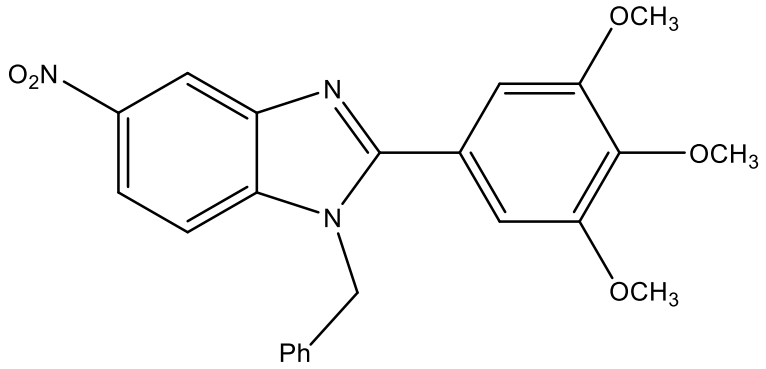


N-benzyl-5-hydroxy-2-(3, 4, 5-trimethoxyphenyl)-benzimidazole III(v): Colour: Orange solid. M. P. 151-153ºC, Yield 74.7%. IR (KBr): 3090cm^{-1}(N-CH_2), 1500cm^{-1}(C=N), 3450cm^{-1}(Ar-OH) 1387cm^{-1}(Ar-OCH_3).^{1}H- NMR ($CDCl_3$); δ (ppm): 3.71-3.83 (bs, 9H, OCH_3), 6.97 – 7.33 (m, 10H, Ar.-H), 9.45(s, 1H, OH), 5.79(s, 2H, NCH_2). ^{13}C-NMR ($CDCl_3$); δ (ppm): 56.1, 60.8, 139.2, 153.1, 104.6, 124.9, 153.3, 140.3, 102.4, 151.7, 111.4, 113.5, 135.0, 52.2, 137.3, 127.6, 128.6, 125.7. Mass (*m/z*): 390.44. Elemental Analysis (%): For $C_{23}H_{22}O_4N_2$, Calculated: C, 70.75; H, 5.68; O, 16.39; N, 7.18. Found: C, 70.61; H, 5.65; O, 16.45; N, 7.29.



N-benzyl- 5-nitro-2-(3, 4, 5-trimethoxyphenyl)-benzimidazole III(vi): Colour: Reddish solid. M. P. 167-169ºC, Yield 83.6%. IR (KBr): 3050cm^{-1}(N-CH_2), 1500cm^{-1}(C=N), 1450cm^{-1}

^{1}(Ar-NO_2) 1402cm^{-1}(Ar-OCH_3).^{1}H- NMR ($CDCl_3$); δ (ppm): 3.71-3.83 (bs, 9H, OCH_3), 6.97 – 8.39 (m, 10H, Ar.-H), 5.79(s, 2H, NCH_2). ^{13}C-NMR ($CDCl_3$); δ (ppm): 56.1, 60.8, 139.2, 153.1, 104.6, 124.9, 153.3, 139.8, 112.9, 144.3, 118.6, 110.4, 148.5, 52.2, 137.3, 127.6, 128.6, 125.7. Mass (*m/z*): 419.44, Elemental Analysis (%): For $C_{23}H_{21}O_5N_3$, Calculated: C, 65.86; H, 5.05; O, 19.07; N, 10.02. Found: C, 65.91; H, 5.10; O, 19.12; N, 10.87.



RESULTS AND DISCUSSION: 2,5,6 -substituted benzimidazole derivatives were prepared in good yields by oxidation reaction of 4,5- substituted o-phenylene dimine I(i-vi) with 3, 4, 5-trimethoxybenzaldehyde using sodium metabisulphite in ethanol. The resulting reaction mixture was stirred using magnetic stirrer at room temperature for about 2-3 hours. The progress of reaction was checked by TLC. After complete completion of reaction, the product was concentrated with vacuum distillation. The solid product II(i-vi) was washed with water and then n-hexane and dried in anhydrous P_2O_5 for overnight. Product was again dried at room temperature and determined the physical constant. The products were recrystallized using hot water. Further compounds II (i-vi) were heated with a mixture of sodium hydride in presence of methylnitrile solvent and benzylchloride under nitrogen atmosphere, gaves III(i-vi) product in good yield. The structures of N-benzyl,2,5,6- substituted benzimidazole derivatives III(i-vi) of were confirmed by IR, ^{1}H- NMR, ^{13}C-NMR and mass spectral data.

CONCLUSION:

We succeeded for the synthesizing of N-benzyl, 2, 5, 6- substituted benzimidazole derivatives III(i-vi) via II(I-VI) in good yields

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