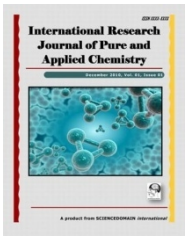

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Facile Synthesis and Characterization of New 2,3-Disubstituted Benzimidazole Derivatives

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Authors' contributions

This work was carried out in collaboration between the authors. Author OOA designed the scheme, the protocol for synthetic pathway and wrote the first draft. Author EKE carried out the synthesis and compounds purification. Author AEO managed the analysis of the study and spectroscopic evaluation. Author AOA did the collation of the data and editing of the write-up. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Benzimidazoles are known to represent a class of medicinally important compounds which are extensively used as antibacterial agents. Hence, a series of five 2-substituted benzimidazole precursors (1a-e) were synthesized via [4 + 1] condensation and imino compound (1f) by simple condensation in the presence of Conc. HCl as catalyst. Synthetic modification of *N*-1 position was achieved in order to obtain new 5-chloro-2,4-dinitrophenyl bearing 1,2-disubstituted benzimidazole 2a-e and 2f, and 3-chlorobenzyl bearing 1,2-disubstituted benzimidazole 3a-e and 3f in good to excellent yields using a facile approach. The chemical structures of all synthesized compounds were confirmed using spectroscopic means such as UV-visible, IR, Mass spectra, ^{1}H and ^{13}C NMR as well as C, H, N elemental analytical data.

Keywords: Heterocycle; benzimidazole; cycloaddition; carboxylic acid; spectroscopy.

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1. INTRODUCTION

Benzimidazole is a benzo-fused imidazole which constitutes an important class of heterocyclic compound for new drug development. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12} [1]. It is an important pharmacophore and a privileged structure in medicinal chemistry. Recent research has shown that benzimidazole derivatives, in general, are of great importance in therapeutics. Fused imidazole derivatives have occupied a prominent place in medicinal chemistry because of their significant properties as therapeutics in clinical applications [2]. It is also known that 5,6-dinitrobenzimidazole can substitute 5,6-dimethylbenzimidazole in the vitamin B_{12} molecule in *Corynebacterium diphteriae* and 2-trifluorobenzimidazoles are potent decouplers of oxidative phosphorylation in mitochondria [3].

Furthermore, the relative ease of preparation and great reactivity of some of benzimidazole derivatives make them promising precursors for preparation of variety of biologically active compounds. Furthermore, benzimidazole moiety is a crucial template in medicinal chemistry because of its wide variety of reported biological and pharmacological activities, some of which include analgesic [4], anthelmintic [5], antiamoebic [6], anticonvulsant [7], antimicrobial [8-10], anti-HIV [11], antihypertensive [12], antiparasitic [13], antiproliferative [14], antiprotozoal [3], anti-inflammatory [15], anticancer [16], antitubercular [17], anti-HBV [18], among others.

2. MATERIALS AND METHODS

2.1 General Conditions

The melting points of the synthesized compounds were determined using a melting point tube on a Stuart melting point apparatus and were uncorrected. The ^{1}H NMR spectra were recorded in either $CDCl_3$ or DMSO-d_6 on NMR Bruker DPX 400 spectrometer operating at 400 MHz. Tetramethyl silane (TMS) was used as internal standard with the deuterium signal of the solvent as the lock and chemical shifts δ recorded in ppm. The ^{13}C NMR spectra were run at 100 MHz frequency. Infrared spectra were recorded using a single beam Nicolet 100 FT-IR Spectrometer while the Mass Spectra were obtained using Waters GCT Premier Spectrometer. The ultraviolet spectra were run on a Genesys spectrophotometer using ethanol as the solvent. The elemental analyses (C, H, N) of the compounds were performed using Flash EA 1112 Elemental Analyzer.

In addition, the pH was monitored and confirmed during acidification by using Portable pH Meter Model PHB4. All drying were conducted at reduced pressure with DHG-9023A Vacuum Oven. The reaction progress was monitored with TLC using $CHCl_3/CH_3OH$ (9:1) solvent system and the developed plates were visualized under UV lamp and/or in iodine tank where necessary. Column chromatographic purifications were carried out on Merck silica gel F (Mesh 200-300). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a RE-2000B Buchi Rotary Evaporator at reduced pressure. At all stage of the experiments, the synthetic protocols were effected in bone dried solvents under nitrogen atmosphere in dried glassware which were wiped with stream flow of nitrogen gas prior to use. Other reagents were used directly after ascertaining the purity condition.

2.2 General Procedure for Disubstitution using 1,5-Dichloro-2,4-dinitrobenzene

Ethanol (20 mL) was added to 1,5-dichloro-2,4-dinitrobenzene (1.18 g, 5.0 mmol) under the influence of magnetic stirrer until a complete solution was attained. The appropriate 2-substituted benzimidazole precursor 1a-e (5.4 mmol) was added cautiously to the solution and the mixture was heated under reflux for 1 h. The resulting solution was allowed to cool for crystallization. The precipitate formed was filtered by suction and dried to afford the corresponding 2,3-disubstituted benzimidazole of 5-chloro-2,4-dintrobenzene 2a-e. Application of this procedure on 1f gave rise to product 2f.

2.2.1 1-(5-Chloro-2,4-dinitrophenyl)-2-phenyl-1H-benzimidazole, 2a

The general procedure was used on 1a (1.05 g, 5.4 mmol) precursor to afford orange needle-like solid 2a (3.28 g, 98.05%). λ_{max} in nm (log ε_{max}): 206 (4.76), 344 (4.04), 527 (3.43), 557 (3.39). IR (KBr, cm^{-1}) v_{max}: 2700 (C-H, aromatic), 1628 (C=C, aromatic), 1582 (C=N), 1168 (NO_2), 855 (C-Cl), 723 (Ar-H). MS-EI: m/z (rel. %): 310.03 (42%), 308.03 (100%), 274.02 (45%), 262.04 (33%), 230.03 (11%), 228.03 (50%), 215.04 (31%), 214.03 (23%), 179.06 (41%), 153.05 (11%), 108.03 (80%), 80.04 (7%), 65.03 (13%).

2.2.2 2-[1-(5-Chloro-2,4-dinitrophenyl)-1H-benzimidazol-2-yl]phenol, $2b_1$

The general procedure was used on 1b (1.13 g, 5.4 mmol) precursor to afford orange needle-like solid $2b_1$ (2.01 g, 97.77%). λ_{max} in nm (log ε_{max}): 206 (5.14), 341 (4.37). IR (KBr, cm^{-1}) v_{max}: 2700 (C-H, aromatic), 1620 (C=C, aromatic), 1579 (C=N), 1170 (NO_2) 800 (C-Cl), 723 (Ar-H). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.76 (s, 1H, Ar-H), 8.95-8.92 (d, *J* = 12 Hz, 2H, Ar-H), 8.44 (s, 1H, Ar-H), 7.19-7.09 (m, 2H, Ar-H), 6.85-6.83 (d, *J* = 8 Hz, 1H, Ar-H), 6.68-6.66 (d, *J* = 8 Hz, 1H, Ar-H), 6.51 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 146.4, 145.5, 134.6, 134.6, 134.0, 133.0, 130.5, 130.5, 130.2, 129.1, 129.1, 128.2, 128.2, 126.3, 126.3, 123.4, 123.4, 117.7, 117.7 ppm. MS-EI: m/z (rel. %): 326.92 (22%), 324.92 (5%), 275.99 (34%), 274.99 (34%), 172.96 (91%), 170.97 (100%), 121.04 (58%), 93.03 (90%), 65.03 (41%), 43.98 (25%).

2.2.3 2-(2-(5-Chloro-2,4-dinitrophenoxy)phenyl)-1-(5-chloro-2,4-dinitrophenyl)-1H-benzimidazole, $2b_2$

The general procedure was used on 1b (0.57 g, 2.7 mmol) precursor to afford orange crystalline solid $2b_2$ (2.33 g, 76.13%). λ_{max} in nm (log ε_{max}): 212 (5.22), 338 (4.48). IR (KBr, cm^{-1}) v_{max}: 2700 (C-H, aromatic), 1610 (C=C, aromatic), 1581 (C=N), 1160 (NO_2), 832 (C-Cl). ^{1}H NMR (400, DMSO-d_6) δ: 9.83 (s, 1H, Ar-H), 8.95-8.92 (d, *J* = 12.0 Hz, 2H, Ar-H), 8.79 (s, 1H, Ar-H), 8.42-8.39 (d, *J* = 12.0 Hz, 2H, Ar-H), 7.77-7.75 (m, 2H, Ar-H), 7.26-7.22 (m, 2H, Ar-H), 7.14 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H). ^{13}C NMR (100 Hz, DMSO-d_6) δ: 171.9, 161.0, 146.2, 145.6, 145.6, 144.9, 134.6 (4 × CH aromatic), 133.9, 133.1, 130.6 (3 × CH aromatic), 130.0, 129.0, 128.5, 126.1, 123.3 (4 × CH aromatic), 118.5, 117.9 ppm. MS-EI: m/z (rel. %): 614.00 (M^+ + 3, 1%), 372.03 (69%), 370.03 (98%), 233.03 (35%), 231.02 (95%), 140.99 (34%), 138.99 (85%), 110.98 (100%), 75.01 (24%).

2.2.4 1-(5-Chloro-2,4-dinitrophenyl)-2-(2-chlorophenyl)-1H-benzimidazole, 2c

The general procedure was used on 1c (1.42 g, 5.4 mmol) precursor to afford orange needle-like solid 2c (1.45 g, 69.13%). λ_{max} in nm (log ε_{max}): 209 (5.21), 341 (4.68). IR (KBr, cm^{-1}) ν_{max}: 2780 (C-H, aromatic), 1600 (C=C, aromatic), 1590 (C=N, aromatic), 850 (C-Cl), 723 (Ar-H). MS-EI: m/z (rel. %): 429.17 (M^+, 9%), 428.16 (M^+ - 1, 98%), 427.16 (M^+ - 2, 26%), 236.08 (100%), 235.09 (21%), 43.98 (8%).

2.2.5 2-Benzyl-1-(5-chloro-2,4-dinitrophenyl)-1H-benzimidazole, 2d

The general procedure was used on 1d (1.12g, 5.4mmol) precursor to afford reddish-brown solid 2d (1.15 g, 56.06%). λ_{max} in nm (log ε_{max}): 206 (5.03), 341 (4.47). IR (KBr, cm^{-1}) ν_{max}: 2850 (C-H, aromatic), 1590 (C=C, aromatic), 1572 (C=N), 1168 (NO_2), 850 (C-Cl), 737 (Ar-H).

2.2.6 1-(5-Chloro-2,4-dinitrophenyl)-2-[(E)-2-phenylethenyl]-1H-benzimidazole, 2e

The general procedure was used on 1e (1.18 g, 5.4 mmol) precursor to afford orange needle-like solid 2e (1.89 g, 89.81%). λ_{max} in nm (log ε_{max}): 215 (5.37), 260 (5.32), 341 (4.59). IR (KBr, cm^{-1}) ν_{max}: 2723 (C-H, aromatic), 1635 (C=C, aromatic), C=N (1580), 1168 (NO_2), 832 (C-Cl), 723 (Ar-H). ^{1}H NMR (400, DMSO-d_6) δ: 7.70-7.68 (d, *J* = 8 Hz, 2H, Ar-H), 7.62 (s, 1H, Ar-H), 7.42-7.37 (m, 5H, Ar-H), 7.31-7.28 (m, 2H, Ar-H), 6.52 (s, 1H, Ar-H), 4.41 (s, 1H), 4.10 (s, 1H).

2.2.7 2-[(E)-({2-[(5-Chloro-2,4-dinitrophenyl)amino]phenyl}imino)methyl]phenol, 2f

The general procedure was used on 1f (1.14 g, 5.4 mmol) precursor to afford dark powdery solid 2f (1.19 g, 76.55%). λ_{max} in nm (log ε_{max}): 218 (5.38), 314 (4.97). IR (KBr, cm^{-1}) ν_{max}: 3500 (OH), 3400, 3380 (NH, two bands), 2738 (C-H, aromatic), 1168 (NO_2), 1600 (C=C, aromatic), 1581 (C=N), 831 (C-Cl), 723 (Ar-H).

2.3 General Procedure for Disubstitution using 3-Chlorobenzyl Substituted

3-Chlorobenzyl chloride (0.625 mL, 5.0 mmol) was put in round bottom flask containing 20 mL of ethanol and stirred for 30 seconds to ensure even miscibility. On adding the appropriate 2-substituted benzimidazole 1a-e (1.18 g, 5.4 mmol), the colour of the solution became darker. The mixture was heated under reflux for 1 h at carefully controlled temperature of 70 – 75ºC. The solution was cooled and allowed to stand overnight to afford coloured solid which was filtered by suction and oven-dried to afford the crystalline solid of the expected product 3a-e. Application of this procedure on 1f gave rise to product 3f.

2.3.1 1-(3-Chlorobenzyl)-2-phenyl-1H-benzimidazole, 3a

The general procedure was used on 1a (1.05 g, 5.4 mmol) precursor to afford dark oily compound 3a (2.91 g, 98.67%). λ_{max} in nm (log ε_{max}): 218 (5.36). IR (KBr, cm^{-1}) ν_{max}: 2884 (C-H, aromatic), 1600 (C=C, aromatic), 1590 (C=N), 803 (C-Cl), 668 (Ar-H). ^{13}C NMR (100 Hz, DMSO-d_6) δ: 166.9, 166.9, 139.7, 137.2, 132.2, 132.1, 132.1, 129.3, 129.2, 129.2, 127.9, 125.6, 125.0, 123.4, 122.2, 122.2, 121.2, 118.6, 118.6, 22.4 (CH_2) ppm.

2.3.2 2-(1-(3-Chlorobenzyl)-1H-benzimidazole-2-yl) phenol, 3b

The general procedure was used on 1b (1.13 g, 5.4 mmol) precursor to afford brown oily compound 3b (2.02 g, 97.82%). λ_{max} in nm (log ε_{max}): 218 (5.38), 229 (5.01). IR (KBr, cm^{-1}) v_{max}: 3422 (OH), 2724 (C-H, aromatic), 1655 (C=C, aromatic), 1599 (C=N), 890 (C-Cl), 723 (Ar-H). ^{13}C NMR (100 Hz, DMSO-d_6) δ: 167.1, 167.1, 139.8, 137.7, 133.0, 131.9, 131.9, 129.3, 129.2, 129.2, 127.5, 125.9, 124.8, 123.6, 122.3, 122.3, 121.1, 118.4, 118.4, 22.4 (CH_2) ppm.

2.3.3 1-(3-Chlorobenzyl)-2-(2-chlorophenyl)-1H-benzimidazole, 3c

The general procedure was used on 1c (1.42 g, 5.4 mmol) precursor to afford dark oily compound 3c (2.76 g, 95.23%). λ_{max} in nm (log ε_{max}): 218 (5.38), 350 (3.72). IR (KBr, cm^{-1}) v_{max}: 2724 (C-H, aromatic), 1635 (C=C, aromatic), 1599 (C=N), 890 (C-Cl), 722 (Ar-H). ^1H NMR (400 Hz, DMSO-d_6) δ: 7.93-7.91 (d, *J* = 8 Hz, 8H, Ar-H), 7.48-7.38 (m, 10H, Ar-H), 2.51 (s, 2H, -CH_2).

2.3.4 2-Benzyl-1-(3-chlorobenzyl)-1H-benzimidazole, 3d

The general procedure was used on 1d (1.12 g, 5.4 mmol) precursor to afford dark oily compound 3d (1.79 g, 96.02%). λ_{max} in nm (log ε_{max}): 212 (5.30). IR (KBr, cm^{-1}) v_{max}: 2724 (C-H, aromatic), 1638 (C=C, aromatic), 1599 (C=N), 869 (C-Cl), 721 (Ar-H). ^1H NMR (400 Hz, DMSO-d_6) δ: 9.77 (s, 1H, Ar-H), 8.94-8.88 (m, 2H, Ar-H), 8.40 (s, 1H), 7.39 (s, 5H, Ar-H), 6.54-6.48 (m, 2H).

2.3.5 1-(3-Chlorobenzyl)-2-styryl-1H-benzimidazole, 3e

The general procedure was used on 1e (1.18 g, 5.4 mmol) precursor to afford dark oily compound 3e (1.71 g, 98.14%). λ_{max} in nm (log ε_{max}): 212 (5.34), 272 (5.28). IR (KBr, cm^{-1}) v_{max}: 2700 (C-H, aromatic), 1636 (C=C, aromatic), 1590 (C=N), 967 (C-Cl), 723 (Ar-H). ^1H NMR (400 Hz, DMSO-d_6) δ: 7.70-7.68 (d, *J* = 8 Hz, 2H, Ar-H), 7.62-7.58 (d, *J* = 16 Hz, 1H, Ar-H), 7.42-7.38 (m, 5H, Ar-H), 7.31-7.28 (m, 2H, Ar-H), 6.56-6.52 (d, *J* = 16 Hz, 1H, Ar-H), 4.41-4.38 (d, *J* = 12 Hz, 1H), 4.10-4.07 (d, *J* = 12 Hz, 1H), 2.51 (s, 2H, CH_2). ^{13}C NMR (100 Hz, DMSO-d_6) δ: 167.5, 167.5, 143.9 (2 × CH aromatic), 140.7, 134.0, 131.1, 130.1 (2 × CH aromatic), 128.9 (3 × CH aromatic), 128.1 (3 × CH aromatic), 126.9, 122.4, 119.2 (2 × CH aromatic), 116.0, 110.5, 56.1 ppm. MS-EI: m/z (rel. %): 343.03 (M^+ - 1, 5%), 342.02 (M^+ - 2, 64%), 340.02 (68%), 262.04 (33%), 171.05 (24%), 170.05 (8%), 143.04 (100%), 115.05 (56%), 89.03 (11%), 77.03 (Ph^+, 8%).

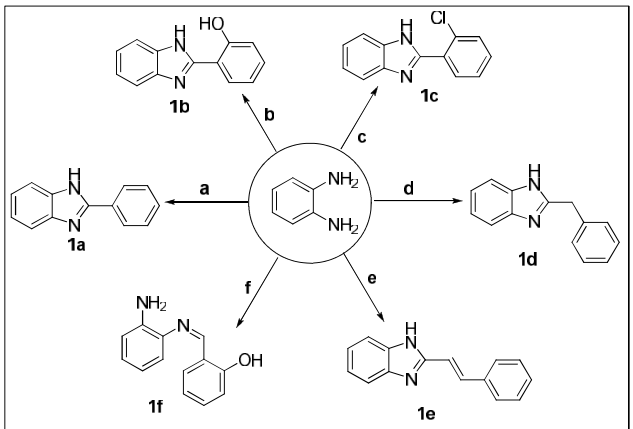
2.3.6 2-((2-(3-Chlorobenzylamino)phenylimino)methyl)phenol, 3f

The general procedure was used on 1f **(**1.14 g, 5.4 mmol) precursor to afford dark oily compound **3f** (1.14 g, 97.85%). λ_{max} in nm (log ε_{max}): 239 (5.42), 284 (5.39), 320 (5.33), 386 (3.62). IR (KBr, cm^{-1}) v_{max}: 3854, 3751 (NH), 3335 (OH), 2885 (C-H, aromatic), 1635 (C=C, aromatic), 1510 (C=N), 803 (C-Cl), 722 (Ar-H).

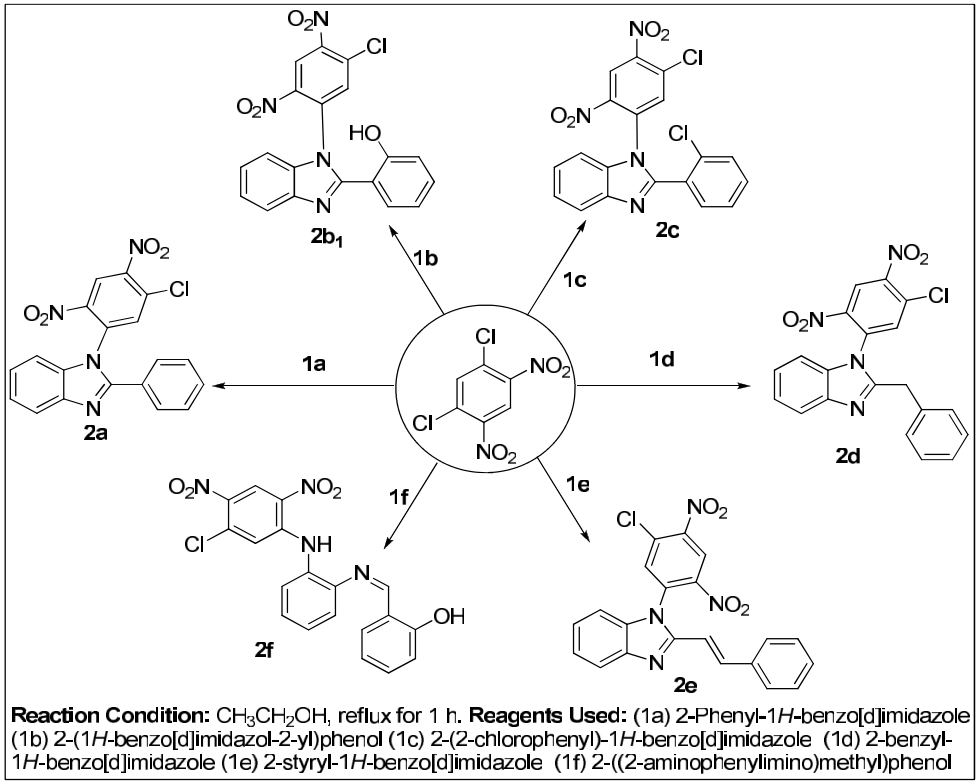
3. RESULTS AND DISCUSSION

In the continuation of our efforts on the synthesis of nitrogen containing heterocyclic compounds for new therapeutic discovery [19-21], we have herein designed and synthesized a new series of 2,3-disubstituted benzimidazole scaffolds. 2-Substituted benzimidazoles 1a-

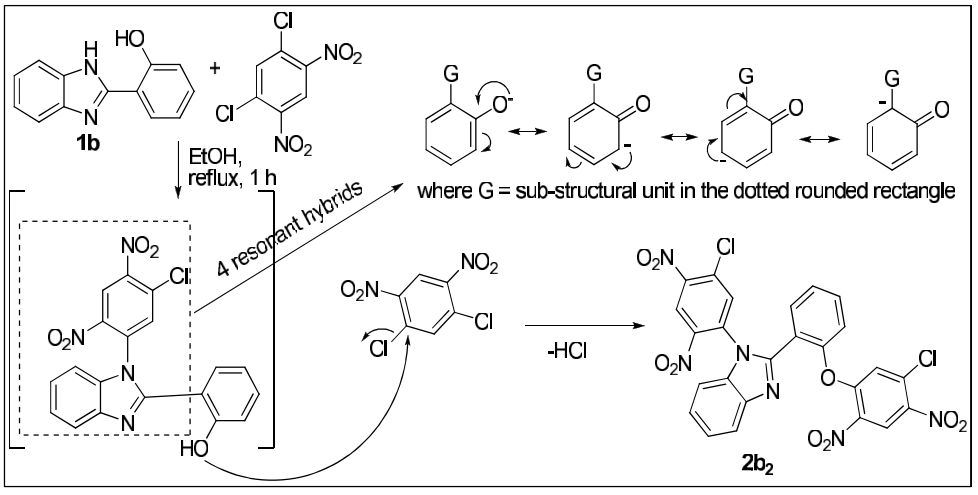
e and imino compound 1f which were used as the main precursors for the synthesis of the new 2,3-disubstituted benzimidazoles, were on their own synthesized by condensation of *o*-phenylenediamine with some carboxylic acids, according to the standard procedure reported by Phillips [22]. In detail, condensation of *o*-phenylenediamine with five different carboxylic acids was herein achieved in the presence of equimolar mixture of concentrated HCl and water by heating under reflux for 3 h (TLC monitored using $CHCl_3/CH_3OH$ (9:1) solvent system). The resulting solutions were worked up by neutralizing with 40% ammonia solution and concentrated by evaporation to one-third its original volume to afford, after cooling, five different 2-substituted benzimidazoles (1a-e) in excellent yield. The condensation with salicyaldehyde as the electron pair acceptor gave rise to an imino compound, 2-[(2-aminophenylimino)methyl]phenol, 1f (Scheme 1). For convenience and the sake of brevity, 1a was used as a representative 2-substituted benzimidazole precursor which was synthetically modified with 1,5-dichloro-2,4-dinitrobenzene in order to achieved the novel 1,2-disubstituted benzimidazole compound 2a as the targeted framework. Thus, the aromatic substitution reaction of 1a with 1,5-dichloro-2,4-dinitrobenzene in the presence of ethanol was achieved by heating the mixture under reflux for 1 h to afford orange needle-like crystal of 2a in excellent yield (98.05%). The procedure was repeated for other 2-substituted benzimidazole 1b-e to afford the corresponding 1,2-disubstituted benzimidazoles 2b-e in improved yields, while utilization of 1f as precursor resulted in formation of 2f (Scheme 2). However, it is worthy to note that only 1b gave two different products $2b_1$ and $2b_2$ based on the molar proportions of the starting materials utilized. In a nutshell, equimolar ratio of 1b and 1,5-dichloro-2,4-dinitrobenzene led to product $2b_1$ in 97.77% yield whereas when ratio of 1b was halved, $2b_2$ was obtained in 76.13% yield. This is due to the fact that, in addition to the substitution at the N-H functionality of 2-substituted benzimidazole, 1b also experienced arylation on the phenolic hydroxyl group at the ortho position of the phenyl ring to give $2b_2$ whose structure was consistent with the assigned ^1H and ^{13}C NMR spectra (Experimental). This unusual reaction in the formation of $2b_2$ was as a result of the resonant stabilization of the phenolate anion conjugate base as shown by the reaction path in Scheme 3. This resonant stabilization caused the equilibrium to shift forward; hence, double arylation was highly favoured.



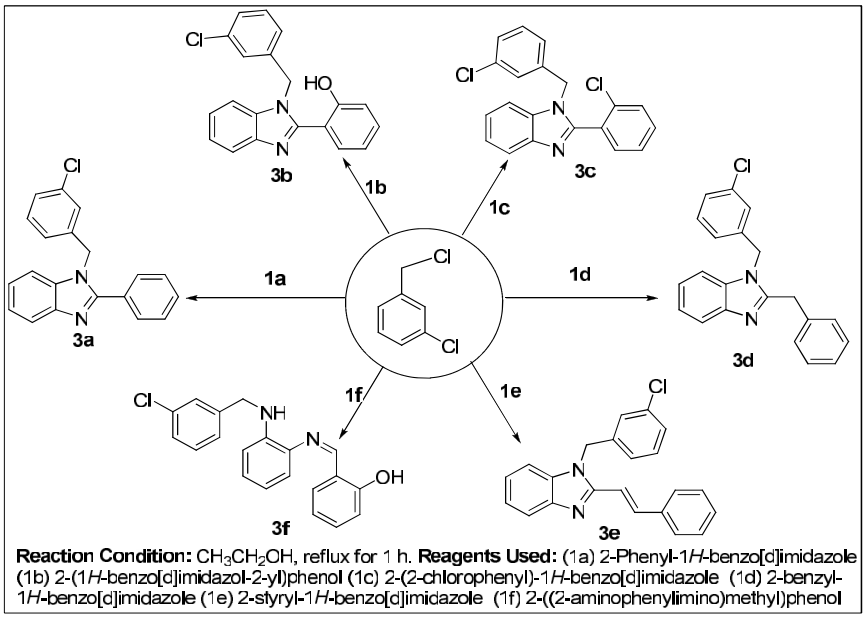
Scheme 1. Synthetic pathway to 2-substituted benzimidazole precursors' 1a-e and imino compound 1f



Scheme 2. 5-Dichloro-2,4-dinitrobenzene bearing 1,2-disubstitutedbenzimidazoles 2a-e and 2f



Scheme 3. Mechanistic justification for the formation of $2b_2$



Reaction Condition: CH_3CH_2OH, reflux for 1 h. **Reagents Used:** (1a) 2-Phenyl-1*H*-benzo[d]imidazole (1b) 2-(1*H*-benzo[d]imidazol-2-yl)phenol (1c) 2-(2-chlorophenyl)-1*H*-benzo[d]imidazole (1d) 2-benzyl-1*H*-benzo[d]imidazole (1e) 2-styryl-1*H*-benzo[d]imidazole (1f) 2-((2-aminophenylimino)methyl)phenol

Scheme 4. 3-Chlorobenzyl bearing 1,2-disubstituted benzimidazoles 3a-e and 3f

In a similar manner, reaction of 1a with 3-chlorobenzyl chloride in the presence of ethanol gave the 1,2-disubstituted benzimidazole 3a in 98.67% yield. Having certified the efficiency of this procedure through reaction optimization study, it was then repeated for the synthetic conversion of the other 2-substituted benzimidazole 1b-e to the targeted corresponding 1,2-disubstituted benzimidazole 3b-e using 3-chlorobenzyl chloride as the electron pair acceptor, whereas, treatment of 1f with 3-chlorobenzyl chloride afforded 3f (Scheme 4). Although, all the products 3a-f were oily substance, they were all produced in excellent yields (95.23 – 98.67%). It is important to note that; although, some 2-substituted benzimidazoles had been synthesized earlier by reaction of *o*-phenylenediamine with some acids such as formic, acetic, propionic, glycolic and mandelic acid [22]; however, the successful synthesis of the disubstituted benzimidazoles 2a-e and 3a-e have never been explored to the best of our knowledge. The result of the physico-chemical properties of all nineteen synthesized heterocyclic compounds is as shown in Table 1. The molecular masses of the compounds ranged from 194.23 to 611.30 which were for the masses of 1a and $2b_2$ respectively. The compounds were obtained in good to excellent yields ranging from 56.06 % to 98.67% which were obtained from the synthesis of 2d and 3a respectively. The melting points of compounds 1a-1f and 2a-2f varied from 73-75ºC to 143-145ºC except compound 1b which did not melt even at 300ºC. The arbitrarily high melting point occurrence in 1b might as a result of the presence of –OH which had tendency for hydrogen bond formation. On the contrary, compounds 3a-f had no melting point value because they were all oily substance at room temperature. The completion of each reaction was monitored by TLC spotting with the R_f values duly calculated to be between 0.16 for compound 1f to 0.6 for compound 3f. Two different solvent systems were used as eluting solvent as seen in Table 1. The result of elemental analysis did not only correlate well with the molecular masses of the compounds but also showed a consistent minimum difference of not more than ±0.05 between % calculated and % found for the carbon, hydrogen and nitrogen of the prepared compounds (Table 1).

Furthermore, apart from physico-chemical data, the structures of newly synthesized compounds were also elucidated by spectroscopic means which include IR, UV, NMR, and mass spectral studies. Generally speaking, from the spectroscopic study, the electronic transition of uv-visible spectra in ethanol gave rise to wavelength (λ_{max}) ranging from 206 nm (4.88) to 557 nm (3.39). The first wavelength (λ_{max}) for all the compounds were found between 206 - 224 nm as a result of $\pi \rightarrow \pi^*$ transition of the compounds indicating the presence of C=C peculiar to benzene nucleus. The uv-visible absorption spectrum of the precursor, 1a, showed a peak at λ_{max} = 224 nm (log ε_{max} = 5.39) and one other bathochromic shift at λ_{max} = 293 nm (log ε_{max} = 4.71). All the wavelength (λ_{max}) above benzenoid region (i.e. between 424 nm to 484 nm) was as a result of $\pi \rightarrow n$ transition and extended conjugation contributed by the C=C. The IR spectra of all the compounds ran in nujol showed absorption bands due to the stretching vibrations of C-H aromatic, C=C of aromatic and Ar-H bending vibration at 2720 - 2724 cm^{-1}, 1589 - 1637 cm^{-1} and 723 - 750 cm^{-1} respectively, while 1a-f showed additional bands at 3160 – 3448 cm^{-1} which were responsible for the N-H stretching vibration. Compounds 1b and 1f had OH broad band at 3500 cm^{-1}. Specifically speaking, using IR spectrum of 1a as representative example of the benzimidazoles, the highest scissors-like twin-band observed at 3320 cm^{-1}, 3325 cm^{-1} depicted the presence of N-H band while CH of aromatic appeared at 2724 cm^{-1}. The absorption bands at 1601 cm^{-1} and 722 cm^{-1} depicted the present of C=C and Ar-H respectively. According to mass spectral data, the molecular ion peaks obtained from all the spectra were consistent with the molecular mass of the proposed structures while some other daughters and base peaks were observed based on some fragmentation patterns.

The mass spectral data of 1a, for instance, showed molecular ion peak at m/z 194.09 (3%) which was in concordance with the molecular mass (194.23) of the compound ($C_{13}H_{10}N_2$) while base peak was observed at m/z 105.02 (100%). A highly intense peak with m/z 122.02 was as a result of (M^+ - Ph) pattern. Other prominent peaks appeared at m/z 108.06, 80.04, 77.02 and 51.01 with relative intensities of 12%, 2%, 68% and 19% respectively due to some fragmentation processes. Specifically, the fragmentation that led to phenylium cation (Ph^+) was responsible for m/z of 77.02, although, with high relative intense (69%).

Table 1. Physico-chemical properties of synthesized compounds

Com no	Molecular formular (Molecular weight)	Yield (%)	Melting point (ºC)	R_f	Elemental analysis: % Calcd. (% Found) C	H	N
1a	$C_{13}H_{10}N_2$ (194.23)	98.12	73-75	0.43[a]	80.93(81.01)	5.19(5.16)	14.42(14.38)
1b	$C_{13}H_{10}N_2O$ (210.23)	71.89	>300	0.40[a]	74.27(74.09)	4.79(4.68)	13.33(13.51)
1c	$C_{13}H_9ClN_2$ (228.68)	86.67	98-100	0.46[a]	68.28(68.19)	3.97(4.02)	12.25(12.34)
1d	$C_{14}H_{12}N_2$ (208.26)	96.52	92-94	0.30[a]	80.74(80.68)	5.81(5.72)	13.45(13.35)
1e	$C_{15}H_{12}N_2$ (220.27)	97.34	68-70	0.43[a]	81.79(81.88)	5.49(5.57)	12.72(12.64)
1f	$C_{13}H_{12}N_2O$ (212.25)	64.83	143-145	0.16[a]	73.56(73.64)	5.70(5.82)	13.20(13.13)
2a	$C_{19}H_{11}ClN_4O_4$ (394.77)	98.05	108-110	0.59[b]	57.81(58.00)	2.81(2.73)	14.19(13.98)
$2b_1$	$C_{19}H_{11}ClN_4O_5$ (410.77)	97.77	95-96	0.30[b]	55.56(55.68)	2.70(2.81)	13.64(13.73)
$2b_2$	$C_{25}H_{12}Cl_2N_2O_9$ (611.30)	76.13	123-124	0.33[b]	49.12(49.20)	1.98(2.06)	13.75(13.88)
2c	$C_{19}H_{10}Cl_2N_4O_4$ (429.21)	69.13	96	0.41[b]	53.17(52.09)	2.35(2.28)	13.05(12.89)
2d	$C_{20}H_{13}ClN_4O_4$ (408.79)	56.06	111	0.29[b]	58.76(58.66)	3.18(3.32)	13.71(13.59)
2e	$C_{15}H_{12}N_2$ (420.27)	89.81	100	0.37[b]	81.79(81.82)	5.81(5.77)	12.27(12.21)
2f	$C_{19}H_{13}ClN_4O_5$ (412.78)	76.55	103-105	0.33[b]	55.28(55.17)	3.17(2.08)	13.57(13.66)
3a	$C_{20}H_{15}ClN_2$ (318.80)	98.67	_	0.33[b]	75.35(75.29)	4.74(4.92)	8.79(8.63)
3b	$C_{20}H_{15}ClN_2O$ (334.80)	97.82	_	0.50[b]	71.75(71.66)	4.52(4.69)	8.37(8.45)
3c	$C_{12}H_{14}Cl_2N_2$ (353.24)	95.23	_	0.50[b]	68.00(67.89)	3.99(4.07)	7.93(8.12)
3d	$C_{21}H_{17}ClN_2$ (332.83)	96.02	_	0.50[b]	75.78(75.89)	5.15(4.97)	8.42(8.36)
3e	$C_{12}H_{17}ClN_2$ (344.84)	98.14	_	0.53[b]	76.63(76.79)	4.97(5.06)	8.12(7.99)
3f	$C_{20}H_{17}ClN_2O$ (336.81)	97.85	_	0.60[b]	71.32(71.30)	5.09(4.91)	8.32(8.23)

Solvent system: [a]chloroform/methanol (9:1), [b]petroleum ether/chloroform (4:6). Com No means Compound Number.

4. CONCLUSION

In summary, a series of new 1,2-disubstituted benzimidazole derivatives 2a-e and 3a-e have been synthesized by elegant and expeditious synthetic modification of 2-substituted benzimidazoles 1a-e which were formerly prepared by a convenient [4+1] condensation reaction. In addition, the synthetic modification of imino compound 1f with 1,5-dichloro-2,4-dinitrobenzene and 3-chlorobenzyl chloride gave compounds 2f and 3f respectively. Benzimidazole is known to be core nucleus of many biologically important compounds. Thus, this work will be very useful for further studies in terms of toxicity effect and Structural Activity Relationship (SAR) in order to establish their biological activities and also help to improve their pharmacological relevance.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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