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MICROWAVE-ASSISTED SYNTHESIS OF SOME NOVEL BENZIMIDAZOLE COMPOUNDS CONTAINING OXADIAZOLE MOIETY

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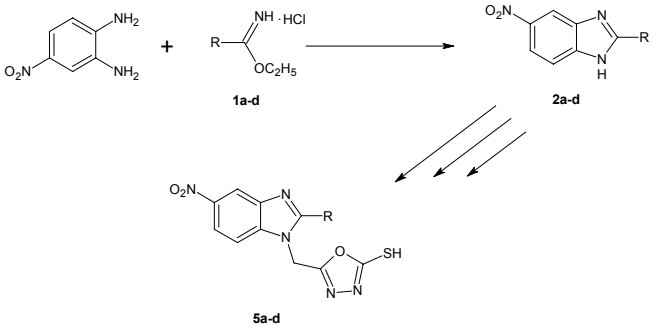
5(6)-Nitro-2-alkyl/aryl-1H-benzimidazoles were obtained from the reaction of iminoester hydrochlorides and 4-nitro-o-phenylenediamine, and converted to their ester and hydrazide derivatives. Hydrazide derivatives were used as a key intermediate to prepare 5-[(2-alkly/arly-5(6)-nitro-1H-benzimidazol-1-yl) methyl]-1, 3, 4-oxadiazol-2-thioles.



INTRODUCTION

N-Heterocycles have attracted scientists' attention due to their numerous pharmaceutical applications.[1-4] Benzimidazole ring takes an important place among these heterocycles because it is found naturally in the structure of vitamin B_{12} and shows similarity with adenine and guanine.[5-6] Also, some benzimidazole derivatives are constituent of important drugs like Imet 3393[7] (anti-cancer), Thiabendazole[8] (anti-helmintic), and Astemizole[7] (antihismaminic).

Another important pharmacophore, 1, 3, 4 oxadiazole nucleus has been incorporated into some important drugs.[9,10] In addition, compounds including benzimidazole and oxadiazole moiety in their structure have been obtained as antimicrobial and anti-cancer agent.[11, 12] The structures of two benzimidazole compounds which are developed for the treatment of breast-cancer have been given in Fig. 1.

Keeping these observations in view, this paper has presented an efficient and simple method for the synthesis of benzimidazole compounds by using microwave irradiation. Four known benzimidazole derivatives **(2a-d)** have been synthesized with this technique and important changes were seen on product yields, times and purities. Also, 1, 3, 4-oxadiazol-2-thiole derivatives have been synthesized effectively.

EXPERIMENTAL

All the chemicals were supplied from Merck, Aldrich and Fluka. Melting points were determined on capillary tubes on a Büchi oil heated melting point apparatus and uncorrected. ^{1}H- and ^{13}C-NMR spectra were performed on Varian-Mercury 200 MHz spectrophotometer in DMSO-d_6 using TMS as internal. The IR spectra were recorded on a Perkin-Elmer

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100 FTIR spectrophotometer as KBr pellets. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer; the experimental values were in agreement (±0.4%) with calculated ones. Mass spectra were recorded on Thermo Scientific Quantum Access max LC-MS spectrophotometer. A mono-mode CEM-Discover microwave was used to carry out microwave reactions in 30 mL microwave process vials with temperature control by infrared detection temperature sensor. All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness).

Synthesis of 5(6)-nitro-2-alkyl/aryl-1H-benzimidazoles **(2a-d)**

Conventional Method. A mixture of 4-nitro-o-phenylenediamine (0.01mol) and corresponding iminoester hydrochloride **(1a-d)** (0.013mol) in methanol (30 mL) were stirred at room temperature for 4 hours. Then the mixture was refluxed for 2 hours. After the reaction was completed, monitored by TLC (EtAc:Hexane, 3:1), the mixture was cooled down to room temperature, the product was precipitated with addition of water. The obtained product was filtered, dried and recrystallized from ethanol-water (1:1).

Microwave Method 4-Nitro-o-phenylenediamine (0.01mol) and corresponding iminoester hydrochloride **(1a-d)** (0.013mol) in methanol (10 mL) were taken in a closed vessel. Then, it was irradiated in microwave at 60 °C and 10 min (hold time) at 300 Watt maximum power. After the reaction was completed (monitored as stated above), the mixture was cooled down to room temperature and taken in a beaker. The product was precipitated by addition of water and purification methods mentioned above were applied.

2-Methyl-5(6)-nitro-1H-benzimidazole (**2a**)

M.p. 225-227 °C (Lit.[17] 225 °C). IR (KBr), ν/cm^{-1}: 3106, 2999, 2972, 1630 1513, 1339; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 12,53 (s, 1H, NH), 8.30 (s, 1H, Ar-H), 7.92 (d, 1H, Ar-H, J=8.6), 7.55 (d, 1H, Ar-H, J=8.6), 2.41 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 20.15, 106.54, 117.90, 119.07, 135.92, 141.13, 145.70, 153.25 ppm. Anal. Calcd. For $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72; Found: C, 54.21; H, 4.01; N, 23.75; ESI-MS: m/z: 178 [M]$^+$.

2-Ethyl-5(6)-nitro-1H-benzimidazole (**2b**)

M.p. 184-185 °C (Lit.[18] 181-182 °C). IR (KBr), ν/cm^{-1}: 3150, 3090, 2982 1625, 1516, 1341. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 12.82 (s, 1H, NH), 8.34 (s, 1H, Ar-H), 8.04 (d, 1H, Ar-H, J=8.6), 7.61 (d, 1H, Ar-H, J=8.6), 2.83 (q, 2H, CH_2, J= 7,4 Hz), 1.21 (t, 3H, CH_3, J= 7,4 Hz) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 10.32, 21.35, 107.21, 117.32, 121.92, 137.49, 141.90, 143.18, 156.11 ppm. Anal. Calcd. For $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98; Found: C, 56.57; H, 4.77; N, 21.95; ESI-MS: m/z: 214 [M+Na]$^+$, 192[M]$^+$.

2-Phenyl -5(6)-nitro-1H-benzimidazole (**2c**)

M.p. 197-199 °C (Lit.[19] 198-199 °C). IR (KBr), ν/cm^{-1}: 3111, 3048, 2992, 1627, 1522, 1338. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 13.63 (s, 1H, NH), 8.52 (s, 1H, Ar-H), 8.34 (d, 1H, Ar-H, J=8.9), 8.07 (d, 1H, Ar-H, J=8.9), 7.87-7.59 (m, 5H, Ar-H) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 105.12, 117.11, 119.43, 125.22, 127.41, 128.15, 130.47, 137.49, 143.10, 145.57, 154.25 ppm. Anal. Calcd. For $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56; Found: C, 65.25; H, 3.81; N, 17.52; ESI-MS: m/z: 240 [M]$^+$.

2-Benzyl-5(6)-nitro-1H-benzimidazole (**2d**)

M.p. 183-185 °C (Lit.[20] 182-184 °C). IR (KBr), ν/cm^{-1}: 3182, 3035, 2972, 1625, 1511, 1341. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 12.93 (s, 1H, NH), 8.45 (s, 1H, Ar-H), 8.25 (d, 1H, Ar-H, J=9.0), 8.02 (d, 1H, Ar-H, J=9), 7.41 (m, 3H, Ar-H), 7.28 (d, 2H, Ar-H, J=7.9), 4.36 (s, 2H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 32.35, 107.32, 112.18, 114.53, 123.71, 128.17, 129.52, 132.45, 138.64, 145.19, 146.13, 156.61 ppm. Anal. Calcd. For $C_{14}H_{11}N_3O_2$: C, 65.27; H, 3.79; N, 17.56; Found: C, 65.25; H, 3.81; N, 17.52; ESI-MS: m/z: 276 [M+Na]$^+$, 254 [M]$^+$.

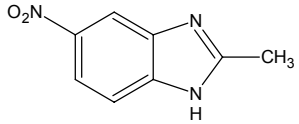
Synthesis of Ethly-(2-alkyl/aryl-5(6)--nitro-1H-benzimidazol-1-il) acetate **(3 a-d)**

Conventional Method. A mixture of **2a-d** (0.01 mol), ethyl bromoacetate (0.01 mol) and dry K_2CO_3 (0.03mol) in acetone (20 mL) were stirred in a room temperature for 10 hours. After the reaction was completed, monitored by TLC (EtAc: Hexane, 4:1), the product was precipitated by addition of water and was filtrated, dried and recrystallized from ethanol to afford the desired product.

Microwave Method. A solution of compound **2a-d** (0.01 mol) in acetone (10 mL) was taken in a closed vessel and dry K_2CO_3 (0.03 mol) was added. The mixture was irritated in microwave at 90 ºC, 5 min (hold time) at 300 Watt maximum power. Then, the mixture was cooled down to room temperature and ethly bromoacetate (0.01mol) was added. Again, it was irradiated in microwave at 90 ºC and 10 min (hold time) at 300 Watt maximum power. After the reaction was completed (monitored as stated above), the mixture was cooled, taken in a beaker and the product was precipitated by addition of water. Purification methods mentioned above were applied to yield the pure product.

Ethyl-(2-methyl-5(6)-nitro-1H-benzimidazole-1-yl)acetate (**3a**)

M.p. 127-128 °C. IR (KBr), ν/cm^{-1}: 3011, 2985, 1749, 1619, 1515, 1337, 1211. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.60 (s, 1H, Ar-H), 8.22 (d, 1H, Ar-H, J=8.6), 7.28 (d, 1H, Ar-H, J=8.6), 4.81 (d, 2H, CH_2), 4.22 (q, 2H, CH_2, J=7.0 Hz), 2.63 (s, 3H, CH_3), 1.23 (t, 3H, CH_3, J=7.0 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.22, 21.17, 43.24, 63.17, 108.21, 112.82, 119.51, 133.12, 140.3, 145.81, 155.19, 169.11 ppm. Anal. Calcd. For $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96; Found: C, 54.77; H, 4.99; N, 15.99; ESI-MS: m/z: 286 [M+Na]$^+$, 264 [M]$^+$.



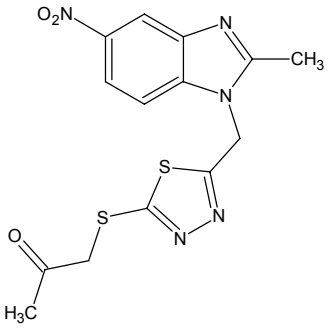


Fig. 1 – The structure of two benzimidazole compounds developed for the treatment of breast cancer.

Ethyl-(2-ethyl-5(6)-nitro-1H-benzimidazole-1-yl)acetate (**3b**)
M.p. 144-145 °C. IR (KBr), ν/cm^{-1}: 3036, 2987, 1741, 1619, 1520, 1334, 1233. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.20 (s,1H, Ar-H), 7.70 (d, 1H, Ar-H, J=8.8), 7.27 (d, 1H, Ar-H, J=8.8), 4.92 (d, 2H, CH_2), 4.23 (q, 2H, CH_2, J= 7.0 Hz), 2.81 (q, 2H, CH_2, J= 7.4 Hz), 1.43(t, 3H, CH_3, J=7.4 Hz), 1.25 (t, 3H, CH_3, J= 7.0 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 10.42, 14.25, 22.13, 45.45, 65.26, 110.42, 113.41, 121.31, 137.91, 142.35, 149.83, 157.48, 170.35 ppm. Anal. Calcd. For $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15; Found: C, 56.33; H, 5.43; N, 15.20; ESI-MS: m/z: 300 [M+Na]$^+$, 278 [M]$^+$.

Ethyl-(2-phenyl-5(6)-nitro-1H-benzimidazole-1yl)acetate (**3c**)
M.p. 84-85 °C. IR (KBr), ν/cm^{-1}: 3065, 2980, 1740, 1617, 1528, 1346, 1215. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.78 (s, 1H, Ar-H), 8.38 (d,1H, Ar-H, J=8.6), 8.19 (d, 1H, Ar-H, J=8.7), 7.98-7.68 (m, 5H, Ar-H), 5.06 (s, 2H, CH_2), 4.31 (q, 2H, CH_2, J= 7.2 Hz), 1.32 (t, 3H, CH_3, J= 7.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.23, 45.56, 65.43, 102.52, 119.11, 121.71, 123.72, 128.48, 129.55, 131.22, 135.21, 145.10, 148.47, 157.21, 168.79 ppm. Anal. Calcd. For $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 19.67; Found: C, 62.77; H, 4.67; N, 19.70; ESI-MS: m/z: 348 [M+Na]$^+$, 326 [M]$^+$.

Ethyl-(2-benzyl-5(6)-nitro-1H-benzimidazole-1-yl)acetate (**3d**)
M.p. 129-130 °C. IR (KBr), ν/cm^{-1}: 3015, 2987, 1741, 1619, 1518, 1341, 1271. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8. 76 (s, 1H, Ar-H), 8.35 (d,1H, Ar-H, J=8.8), 8.19 (d, 1H, Ar-H, J=8.7), 7.57 (m, 3H, Ar-H), 7.36 (d, 2H, Ar-H, J=7.9), 4.74 (d, 2H, CH_2), 4.32 (s, 2H, CH_2), 3.90 (q, 2H, CH_2, J=7.2), 1.2(t, 3H, CH_3, J=7.2) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.43, 35.16, 46.12, 68.33, 103.42, 117.61, 123.71, 125.79, 129.10, 130.15, 133.41, 137.20, 147.21, 149.17, 156.42, 167.89 ppm. Anal. Calcd. For $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; Found: C, 63.70; H, 5.07; N, 12.41; ESI-MS: m/z: 362 [M+Na]$^+$, 340 [M]$^+$.

Synthesis of 2-(2-Alkyl/aryl-5(6)-nitro-1H-benzimidazol-1-il)acetohydrazide **(4a-d)**

Conventional Method. A mixture of **3a-d** (0.01mol) and hydrazine monohydrate (0.02 mol) in ethanol (30 mL) was refluxed for 6 hours. After the reaction was completed, monitored by TLC (Ethyl acetate: Hexane, 3:1), the mixture was cooled down to room temperature and a white solid appeared. This crude product was filtrated, dried and recrystallized from ethanol.

Microwave Method. A solution of **3a-d** (0.01mol) in ethanol (10 mL) and hydrazine monohydrate (0.02mol) were taken in a closed vessel. The mixture was irradiated in microwave at 120 ºC and 10 min (hold time) at 300Watt maximum power. After the reaction was completed (monitored as stated above), the mixture was cooled down to room temperature, taken in a beaker and a white solid appeared. This crude product was filtrated and purification methods mentioned above were applied.

2-(2-Methyl-5(6)-nitro-1H-benzimidazole-1-yl)acetohydrazide (**4a**)
M.p. 237-238 °C. IR (KBr), ν/cm^{-1}: 3300, 3180, 3014, 2975, 1654, 1620 1522, 1340. ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 9.51 (s, 1H, NH), 8.51 (s, 1H, Ar-H), 8.45 (d, 1H, Ar-H, J=8.6), 7.66 (d, 1H, Ar-H, J=8.6), 4.92 (s, 2H, CH_2), 4.32 (s, 2H, NH_2), 2.43 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 14.43, 45.59, 107.53, 110.94, 114.95, 119.05, 142.10, 147.65, 157.80, 166.28 ppm. Anal. Calcd. For $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10; Found: C, 48.19; H, 4.47; N, 28.11; ESI-MS: m/z: 250 [M]$^+$.

2-(2-Ethyl-5(6)-nitro-1H-benzimidazole-1-il)acetohydrazide (**4b**)
M.p. 217-218 °C. IR (KBr, cm^{-1}) ν/cm^{-1}: 3298, 3101, 3056, 2985 1671, 1621, 1522, 1338. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 9.54 (s, 1H, NH), 8.57 (s, 1H, Ar-H), 8.41 (d, 1H, Ar-H, J=8.6), 7.59 (d, 1H, Ar-H, J=8.6) 4.91 (s, 2H, CH_2), 4.35 (s, 2H, NH_2), 2.75 (q, 2H, CH_2, *J*: 7.2 Hz), 1.33 (t, 3H, CH_3, *J*: 7.2 Hz) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 11.65, 20.98, 45.22, 107.62, 117.90, 119.02, 119.28, 135.91, 142.91, 155.60, 163.45 ppm. Anal. Calcd. For $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60; Found: C, 50.21; H, 4.95; N, 26.62; ESI-MS: m/z: 286 [M+Na]$^+$, 264 [M]$^+$.

2-(2-Phenyl-5(6)-nitro-1H-benzimidazole-1-yl)acetohydrazide (**4c**)
M.p. 255-256 °C. IR (KBr), ν/cm^{-1}: 3302, 3091, 3022, 2929, 1669, 1626 1527, 1350. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 9.62 (s, 1H, NH), 8.65 (s, 1H, Ar-H), 8.29 (d, 1H, Ar-H, J=8.8), 8.10 (d, 1H, Ar-H, J=8.8), 7.76-7.58 (m, 5H, Ar-H), 5.03 (s, 2H, CH_2), 4.31 (s, 2H, NH_2) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 48.32, 106.23, 118.73, 119.32, 122.76, 125.37, 127.47, 128.51, 132.69, 135.91, 142.91, 152.10, 166.41 ppm. Anal. Calcd. For $C_{15}H_{13}N_5O_3$: C, 57.87; H, 4.21; N, 22.50; Found: C, 57.87; H, 4.23; N, 22.51; ESI-MS: m/z: 334 [M+Na]$^+$, 312 [M]$^+$.

2-(2-Benzyl-5(6)-nitro-1H-benzimidazole-1-yl)acetohydrazide (**4d**)
M.p. 239-240 °C. IR (KBr), ν/cm^{-1}: 3300, 3106, 1671, 1518, 1350, 1633. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 9.63 (s ,1H, NH), 8.59 (s, 1H, Ar-H), 8.49 (d, 1H, Ar-H, J=8.6), 8.03 (d, 1H, Ar-H, J=8.6), 7.51-7.37 (m, 5H, Ar-H), 5.01 (s, 2H, CH_2), 4.30 (s, 2H, NH_2), 4.22 (s, 2H, CH_2) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 32.21, 49.12, 107.13, 117.74, 119.12, 122.26, 125.77, 127.57, 128.56, 132.99, 133.99, 145.98, 155.13, 168.91 ppm. Anal. Calcd. For $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53; Found: C, 59.05; H, 4.65; N, 21.51; ESI-MS: m/z: 348 [M+Na]$^+$, 326 [M]$^+$.

Synthesis of 5-[(2-alkly/arly-5(6)-nitro-1H-benzimidazol-1-yl) methyl]-1, 3, 4-oxadiazol-2-thiol **(5a-d)**

Conventional Method. A solution of KOH (0.01mol) in water (20 mL) and CS_2 (0.01 mol) was added to solution of **4a-d** (0.01 mol) in ethanol (20 mL) and then, the mixture was refluxed for 4 hours. After the reaction was completed, monitored by TLC (Ethyl acetate: Hexane, 3:1), the mixture was cooled down to room temperature and neutralized with diluted HCl (4N). The mixture was left to cool down and the precipitated product was filtrated, washed with H_2O and recrystallized from ethanol.

Microwave Method. A solution of **4a-d** (0.01 mol) in ethanol (10 mL) and KOH (0.01 mol) in water (5 mL) were taken in a microwave process vial. Then, the mixture was heated under microwave irradiation 300 Watt at 100 ºC, with stirring and air-jet cooling for 5 min. After the mixture was cooled down, CS_2 (0.01 mol) was added to the mixture and then, heated again 300 Watt at 100 ºC. Completion of reaction was achieved in 10 min. as indicated by TLC. Then, the mixture was neutralized with 4 N HCl and left to cool. The precipitated product was filtrate, washed with H_2O and recrystallized from Ethanol.

5-[(2-Methyl-5(6)-nitro-1H-benzimidazole-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (**5a**)
M.p. 249-250 °C. IR (KBr), ν/cm^{-1}: 3021, 2968, 2698, 1618, 1518, 1343, 1250, 1145. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 14.22 (s, 1H, SH), 8.44 (s, 1H, Ar-H), 8.18 (d, 1H, Ar-H, J=8.8), 7.86 (d, 1H, Ar-H, J=8.8), 5.71 (s, 2H, CH_2), 2.42 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 14.29, 43.24, 111.38, 115.09, 118.64, 136.14, 142.14, 143.66, 157.43, 159.50, 178.73 ppm. Anal. Calcd. For $C_{11}H_9N_5O_3S$:

C, 45.36; H, 3.11; N, 24.04; S, 11.01; Found: C, 45.38; H, 3.13; N, 24.05; S, 11.02; ESI-MS: m/z: 292 $[M]^+$.

5-[(2-Ethyl-5(6)-nitro-1H-benzimidazole-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (**5b**)

M.p. 262-263 °C. IR (KBr), ν/cm^{-1}: 3012, 2998, 2692, 1619, 1523, 1340, , 1248, 1155. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 14.02 (s, 1H, SH), 8.54 (s, 1H, Ar-H), 8.26 (d, 1H, Ar-H, J=8.8), 7.89 (d, 1H, Ar-H, J=8.9), 5.83 (s, 2H, CH_2), 2.92 (q, 2H, CH_2, J=7.6), 1.31 (t, 3H, CH_3, J=7.6) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 14.29, 21.35, 45.25, 113.48, 115.31, 117.60, 137.34, 143.54, 145.96, 158.93, 159.10, 179.16 ppm. Anal. Calcd. For $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.63; N, 22.94; S, 10.50; Found: C, 47.23; H, 3.65; N, 22.98; S, 10.50; ESI-MS: m/z: 306 $[M]^+$.

5-[(2-Phenyl-5(6)-nitro-1H-benzimidazole-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (**5c**)

M.p. 267-269 °C. IR (KBr), ν/cm^{-1}: 3015, 2997, 2713, 1617, 1521, 1338, 1252 1141. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 14.23(s, 1H, SH), 8.82 (s, 1H, Ar-H), 8.58 (d, 1H, Ar-H, J=8,6), 8,23 (d, 1H, Ar-H, J=8.6), 7.84-7.43 (m, 5H, Ar-H), 5.82 (s, 2H, CH_2) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 45.33, 106.43, 113.23, 114.91, 112.11, 118.63, 125.33, 127.44, 138.61, 145.14, 147.66, 159.13, 159.96, 178.96 ppm. Anal. Calcd. For $C_{16}H_{11}N_5O_3S$: C, 54.38; H, 3.14; N, 19.82; S, 9.07; Found: C, 54.40; H, 3.13; N, 19.85; S, 9.09; MS ESI-MS: m/z: 368 $[M]^+$.

5-[(2-Benzyl-5(6)-nitro-1H-benzimidazole-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (**5d**)

M.p. 240-241 °C. IR (KBr), ν/cm^{-1}: 3008, 2967, 2717, 1620, 1519, 1341, 1245, 1146. ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 14.21 (s, 1H, SH), 8.90 (s, 1H, Ar-H), 8.69 (d, 1H, Ar-H, J=8,8), 8,23 (d, 1H, Ar-H, J=8.8), 8.00-7.48 (m, 5H, Ar-H), 5.8 (s, 2H, CH_2), 4.36 (s, 2H, CH_2) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 33.17, 45.13, 107.13, 112.73, 117.82, 118.80, 120.23, 126.61, 128.20, 139.32, 141.52, 148.91, 159.53, 160.26, 179.36 ppm. Anal. Calcd. For $C_{17}H_{13}N_5O_3S$: C, 55.58; H, 3.57; N, 19.06; S, 8.73; Found: C, 55.61; H, 3.55; N, 19.05; S, 8.75; ESI-MS: m/z: 368 $[M]^+$.

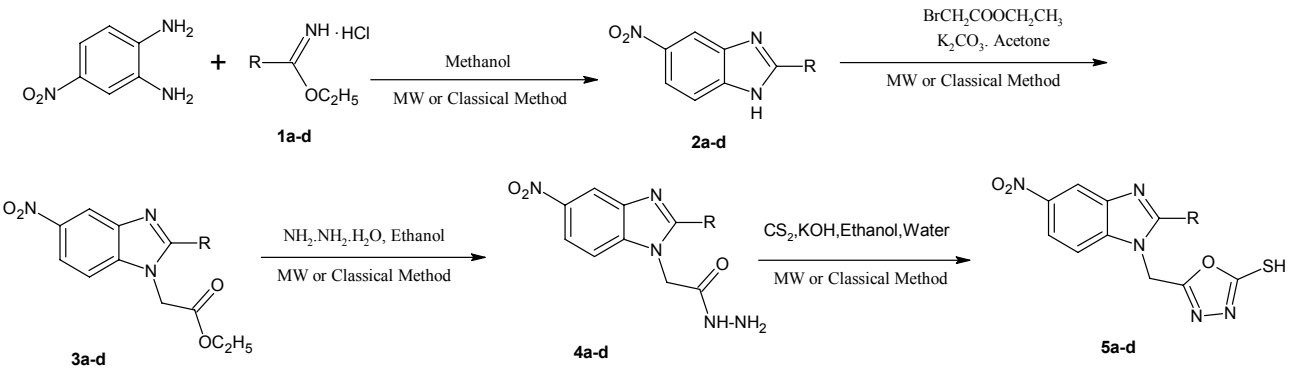
RESULTS AND DISCUSSION

In this search, Iminoester hydrochlorides **(1a-d)** were prepared according to the reported literature procedures.[13-15] To synthesize benzimidazole derivatives, aromatic aldehydes or carboxyl acids are mostly used with o-phenylenediamine derivatives. In this report, a practical method has been proposed for the synthesis of benzimidazole derivatives with using iminoester hydrochlorides **(1a-d)** and 4-nitro-o-phenylenediamine under microwave irradiation.[16] An important improvement has been shown on yields and reaction times on the synthesis of compounds **2a-d** with this technique.

Etoxycarbonylmethylation of compounds **2a-d** with ethyl bromoacetate in absolute acetone in the presence of dry K_2CO_3 afforded the ethyl acetate derivatives **(3a-d)** in good yields. The treatment of compounds **3a-d** with hydrazine hydrate in absolute ethanol resulted in the formation of hydrazide derivatives **(4a-d)**, which were employed as key intermediates for the synthesis of oxadiazole derivatives **(5a-d)**. Finally, compounds **4a-d** were reacted with CS_2 in basic condition to synthesize the target oxadiazole derivatives (Scheme 1). All reaction was carried out by using microwave irradiation and conventional heating and results were compared in Table 1.

Spectroscopic investigations of newly synthesized compounds are accordance with the proposed structure. The IR spectra of compounds **3a-d** showed the C=O and C-O band at 1749-1740 and 1271-1211 cm^{-1} respectively. The ^{1}H- and ^{13}C-NMR spectra of compounds **3a-d** exhibited additional signals derived from the $–CH_2CO_2Et$ group at the related chemical schift values.

The ^{1}H- and ^{13}C-NMR of compounds **4a-d** displayed no signals belonging to the etoxy group; instead, new signals derived from the hydrazide structure were shown at 4.30-4.35 ppm for $–NH\underline{NH_2}$ and 9.63-9.54 ppm for $–\underline{NH}NH_2$. These groups both disappeared by addition of D_2O to DMSO-d_6 solution of these compounds.



R, a:-CH_3, b:-C_2H_5, c:C_6H_5, d:-$CH_2C_6H_5$

Scheme 1 – Synthetic route of compounds **2a-d**, **3a-d**, **4a-d** and **5a-d**.

Table 1

Comparation of yields and reaction times of classical and microwave condition

Compound	Classical conditions		Microwave conditions		
	Time (hr)	Yield (%)	Temperature (°C)	Time (min.)	Yield (%)
2a	10	71 (Lit.[17]: 60)	60	10	87
2b	10	79 (Lit.[18]: 54)	60	10	91
2c	10	80 (Lit.[19]: 70)	60	10	93
2d	10	72 (Lit.[20]: 61)	60	10	88
3a	12	86	90	15	96
3b	12	89	90	15	92
3c	12	79	90	15	95
3d	12	74	90	15	90
4a	6	50	120	10	79
4b	6	43	120	10	70
4c	6	54	120	10	71
4d	6	40	120	10	65
5a	8	63	100	15	75
5b	8	66	100	15	73
5c	8	59	100	15	65
5d	8	55	100	15	70

With the conversion of compounds **4a-d** to 1,3,4-oxadiazol-2-thioles derivatives (**5a-d**), the $-NHNH_2$ signals disappeared; instead, new –SH signal appeared at 14.23-14.02 ppm as singlet in the ^{1}H-NMR spectra. Furthermore, the IR spectrum of compounds **5a-d** showed no signals belonging to $-NHNH_2$ group, While new signal belonging to the –SH group was shown at 2717-2692 cm^{-1}. In ^{13}C-NMR spectra of compounds **5a-d**, the signals belonging to C-2 and C-5 atoms of 1,3,4-oxadiazole ring were shown at 139.32-136.14 and 178.96-179.36 ppm, respectively.

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