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Microwave Synthesis, Characterization, and Antioxidant Activity of New Dihydrobenzimidazoquinazoline Compounds

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Abstract: *Four new benzimidazoquinazolines were synthesized by microwave-enhanced and classical heating methods. Microwave assisted method produced excellent yields (92-98%) within very short reaction time. All compounds were characterized by spectroscopic and elemental analysis. Antioxidant activity for the target analogues were performed. Some of the compounds showed excellent antioxidant activities against both of the studied antioxidant DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ radicals.*

Keywords: *Microwave,dihydrobenzo[4,5]imidazo[1,2-c]quinazolin, antioxidant.*

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I. Introduction

Heterocyclic compounds occupy a central position in medicinal and organic chemistry, with considerable attention concentrating on their syntheses [1]. Quinazoline derivatives, which belong to the *N*-containing heterocyclic compounds, have caused universal interest due to broad and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives. In turn, benzimidazole derivatives are important nitrogen-comprising heterocycles which constitute useful intermediates in organic synthesis. Benzimidazole and quinazoline containing compounds display a broad range of therapeutic activities, including antimicrobial, antitumor, anti-inflammation, anti-viral, anticytotoxin, anti-spasm, anti-tuberculosis and are also used as inhibitors of PI3-kinase 6 and the potent antistaphylococcal agents with dual inhibitory mechanisms against DNA gyrase [2-8].Given the several interesting properties of these two moieties, it is postulated that introduction of benzimidazole group into the quinazoline system would be a useful strategy for designing a new class of drugs which appreciably, will influence the biological activity. Notwithstanding, many previous literature reported the pharmaceutical properties of quinazoline-fused benzimidazole skeleton. Figure 1 illustrates the attractive fused scaffold consisting of both benzimidazole and quinazoline.

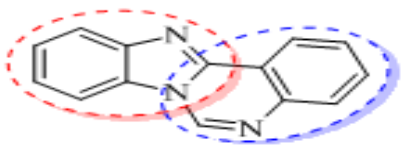

Figure 1: Benzimidazoquinazoline scaffold.

The imbalance of antioxidant mechanisms inside human bodies leads to the progression of oxidative stress and numerous diseases, especially various chronic and age-related ones such as carcinogenesis, inflammation, and atherogenesis. As important supplements to the scavenging mechanisms, antioxidants (both naturally occurring and synthetic) have been widely applied in pharmaceuticals, foods, and cosmetics [9]. Therefore there is growing request to design and synthesise new antioxidants for pharmaceutical use. In this article we study the syntheses and characterization of four new dihydrobenzimidazoquinazolines using microwave-assissted and classical heating techniques. Antioxidant activities for those compounds are studied as well.

II. Materials and Methods

2.1 Materials

All chemicals used in this project were commercially available and of analytical grade and used as received without any additional purifications. Glacial acetic acid was purchased from J.T. Baker/USA. Silica gel aluminum plates 60 F254, analytical grade methanol, 1-butanol, and Mueller-Hinton agar were purchased from Merck/Germany. 2-(2-aminophenyl)-1*H*-benzimidazole,*o*-tolualdehyde, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), trans-cinnamaldehyde, hydrocinnamaldehyde, potassium persulphate, (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox), 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma-Aldrich. Ethyl acetate, *n*-hexane, toluene, and DMSO were obtained from Fisher Scientific/UK. Tetracycline was purchased from Bioanalysis/Turkey, nystatin from Bio Basic/Canada, and quinine sulphate from BDH/UK. To dry the solvents, 3Å molecular sieves were used from Acros organics/USA.

2.2 Instrumentation

The microwave assisted synthesis was carried out using single mode benchtop CEM microwave reactor and the reaction profile was followed using Synergy software.Melting points of samples were determined by using Barnstead Electrothermal. ^{1}H-NMR (400 and 500 MHz) and ^{13}C-NMR (100 and 125 MHz) spectra were analyzed by aid of JEOL JNM ECA 400 and 500. CHN elemental analysis were performed by LECO TruSpec Micro CHNS and mass spectrum of targeted compounds were measured by aid of GCMS QP5050A (Shimadzu).Fourier Transform Infrared (FTIR) spectra were analyzed using IR Tracer-100 (Shimadzu) and 100 FTIR Spectrometer (PerkinElmer). The absorbance of the radical-samples mixture were obtained by Thermo Scientific ELISA reader. In addition, UV-Vis absorbance maxima and emission maxima (photoluminescence, PL) of samples were obtained at 25°C by running UV-1650 PC (UV-Visible spectrophotometer, Shimadzu) and Perkin Elmer LS 55 Fluorescence Spectrometer, respectively. Finally, the optical activities were obtained by using Autopol VI, Automatic Polarimeter manufactured by Rudolph Research Analytical/Hackettstown.

2.3 Synthesis and characterization

Four dihydro-benzimidazoquinazoline derivatives were synthesized according to the following two protocols as shown in Figure 2

a. General microwave-assisted method

The microwave-assisted synthesis was conducted according to Negi *et al*., 2015 [10] with some modifications. In a 10-mL microwave vials, aldehydes (1.2 mmol) were dissolved in methanol (1 mL) and added dropwise to 2-(2-aminophenyl)-1H-benzimidazole (1 mmol, 0.21 g) which was dissolved in methanol (5 mL), followed by two drops of glacial acetic acid. The solution was irradiated with stirring in a single-mode benchtop CEM microwave (USA) for 5-20 min at 102°C and the reaction was monitored using Synergy software. TLC was performed to check the reaction progress and completion. After 5 min., the vial was cooled down to room temperature, dried in vacuum oven, and washed with suitable solvent to provide the final pure product. Crystals were grown by slow evaporation of butanol or toluene to give crystalline solid with yield of 92-98%.

b. General classical heating method

The conventional reflux method was performed according to Kapoor *et al*., 2011 [11] with slight modifications. In a 50-mL round bottom flask, aldehydes (1.2 mmol) derivatives was dissolved in methanol (1mL) and then added dropwise to 2-(2-aminophenyl)-1H-benzimidazole (1 mmol, 0.21 g) which was dissolved in hot methanol (15 mL), followed by two drops of glacial acetic acid. The prepared mixture was heated to reflux with stirring at 95°C for 45-240 min over an oil bath. The reaction progress was monitored every fifteen minutes to check the reaction development. Then, it was cooled down to RT after its completion as evidenced by TLC. The target crystals obtained after vacuum drying, and vigorously washing of the crude product with

suitable solvents to produce the precipitate which was recrystallized from butanol or toluene to furnish shiny crystals of 55-83% yield.

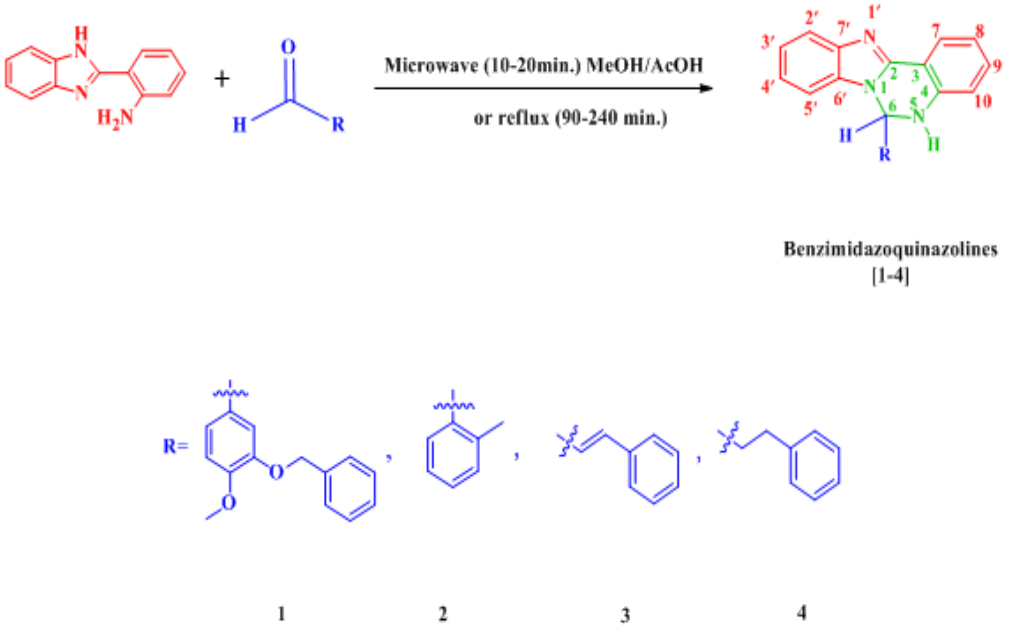

Figure 2: General scheme for synthesis of dihydro-benzimidazoqunazolines [1-4].

Synthesis of 6-(3-(benzyloxy)-4-methoxyphenyl)-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*] quinazoline [1]

Following the microwave-assisted method (a) using 3-benzyloxy-4-methoxybenzaldehyde (0.29 g, 1.2 mmole), new compound **1a** was obtained and characterized directly without any further purification as an off white solid (0.38 g, 92%), while following the conventional heating method (b) the same compound **1b** was obtained in 0.23 g, 55% ; m.p.:204-205°C; R_f:0.66 in hexane: ethyl acetate (1:1) solvent system.$[\alpha]_D^{20}$ =+40.1 (c=0.01, DMSO).FTIR UATR (cm^{-1}) υmax: 3188 (**N-H** stretching), 3103(**=C-H** sp^2 stretching), 2956 (**-C-H** sp^3 stretching), 1614 (**C=N** stretching), 1517 (**C=C** aromatic stretching),1393 **N-H** bending), 1305 (**C-N** stretching), 1250 (**C-O** stretching), 735 (**C-H** aromatic out of plane bending).^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 3.71 (s, 3 H, **CH_3**), 4.95 (d, *J*=1.4 Hz, 2 H, **CH_2**), 6.74 (dd, *J*=2.0, 8.3Hz, 1 H, **H-6"**), 6.9 (ddd, *J*=1.0,7.3, 8.0 Hz, 1H, **H-8**),6.9 (d, *J*=8.0 Hz, 1 H, **H-10**), 6.89-6.92 (m, 2 H, **H-6, 5"**), 7.02 (d, *J*=8.1, 1 H, **H-5'**), 7.06 (ddd, *J*=1.2, 7.6, 8.4,1 H, **H-3'**), 7.16(ddd, *J*=1.5, 8.4, 8.4,1 H, **H-4"**), 7.17 (d, *J*=2.0 Hz,1H,**H-2"**), 7.26 (ddd, *J*=1.0,7.3,8.0 Hz, 1 H, **H-9**), 7.29 - 7.36 (m, 5 H, **H-4',2'", 3'", 5'",6'"**), 7.49 (s, 1 H, **N-H**), 7.64 (d, *J*=8.4 Hz, 1 H, **H-2'**), 7.94 (dd, *J*=1.0, 8.0 Hz, 1 H, **H-7**).^{13}C NMR (125 MHz, *DMSO-d6*) δ ppm55.6 (**CH_3**), 67.9 (**CH_2**), 69.9 (**C-6**), 110.6 (**C-5'**), 111.9 (**C-6"**), 112.0 (**C-2"**), 114.8 (**C-3**), 118.2 (**C-8**), 118.6 (**C-2'**), 118.9 (**C-10**), 122.0 (**C-5"**), 122.1 (**C-4"'**), 124.6 (**C-1"'**), 127.9 (**C-3', 2'", 6'"**), 128.4 (**C-4', 3'", 5'"**), 131.6 (**C-9**), 132.5 (**C-7**), 132.9 (**C-1"**), 136.6 (**C-6'**), 143.4 (**C-4**), 143.9 (**C-7'**), 147.0 (**C-3"**), 147.6 (**C-4"**), 149.7 (**C-2**). MS: DIMS *m/z*: 433 (M^+, 22%), 220 ($[C_{14}H_{10}N_3]^+$, 25), 194 ($[C_{13}H_{10}N_2]^+$, 100), 91 ($[C_6H_5N]^+$, 47). Anal. Calcd. for $C_{28}H_{23}N_3O$: C, 80.55; H, 5.55; N, 10.06%. Found: C, 80.60; H, 5.82; N, 9.95%. UV-Vis in DMSO λ_{max}, nm (ε, L $mole^{-1}$ cm^{-1}): 360(ε, 0.300 ×10^4), 305 (ε, 0.424 ×10^4).

Synthesis of new 6-(*o*-tolyl)-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*] quinazoline [2]

Following the microwave-assisted method (a) using *o*-tolualdehyde (138.76 µL, 1.2 mmole), new compound **2a** was obtained and characterized directly without any further purification as an off white solid (0.29 g, 96%), while following the conventional heating method (b) the same compound **2b** was obtained in 0.26 g, 83% ; m.p.: 196-197°C; R_f:0.56 in hexane: ethyl acetate (2:1) solvent system.$[\alpha]_D^{20}$ =+4.1 (c=0.01, DMSO). FTIR UATR (cm^{-1}) υmax: 3149 (**N-H** stretching), 2928 (**-C-H** sp^3 and **=C-H** sp^2 stretching), 1788 (ortho-substitution of benzene ring), 1605 (**C=N** stretching), 1476 (**C=C** aromatic stretching and **N-H** bending), 1277 (**C-N** stretching), 729 (**C-H** aromatic out of plane bending). ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 2.48 (s, 3H, C**H_3**), 6.60 (d, *J*=8.0 Hz, 1 H, **H-5'**), 6.82 (ddd, *J*=7.9, 7.4, 1.0 Hz, 1H, **H-8**), 6.85 (d, *J*=8.7 Hz, 1H, **H-10**), 6.95

- 7.00 (m, 2 H, **H-4', 4"**), 7.10 - 7.15 (m, 2 H, **H-3', 5"**), 7.16 (d, *J*=1.4 Hz, 1H, **H-6**), 7.24 (ddd, *J*= 8.7, 7.4, 1.6 Hz, 1 H, **H-9**), 7.26 - 7.31 (m, 2 H, **H-3",6"**), 7.32 (s, 1 H, N-**H**), 7.65 (d, *J*=8.0 Hz, 1 H, **H-2'**), 8.00 (dd, *J*=7.9, 1.6 Hz, 1 H, **H-7**). ^{13}C NMR (125 MHz, *DMSO-d*$_6$) δ ppm 18.6 (**C**H$_3$), 66.8 (**C**-6), 110.3 (**C**-5'), 111.5 (**C**-2"), 114.7 (**C**-6"), 118.0 (**C**-5"), 118.6 (C-3"), 121.9 (**C**-2'), 122.0 (**C**-10), 124.6 (**C**-4"), 126.3 (**C**-7), 126.8 (**C**-9), 129.1 (**C**-4), 131.2 (**C**-4'), 131.5 (**C**-3'), 132.8 (C-3), 136.0 (**C**-1"), 136.8 (**C**-6'), 143.3 (**C**-7'), 144.0 (**C**-4), 147.6 (**C**-2). MS: DIMS *m/z*: 311 (M^+, 39%), 220 ($[C_{14}H_{10}N_3]^+$, 20), 194 ($[C_{13}H_{10}N_2]^+$, 100). Anal. Calcd. for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49%. Found: C, 80.50; H, 5.78; N, 13.75%. UV-Vis in DMSO λ_{max}, nm (ε, L mole^{-1} cm^{-1}): 361 (ε, 0.196 ×10^4), 305 (ε, 0.301 ×10^4).

Synthesis of new (*E*)-6-styryl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*] quinazoline [3]

Following the microwave-assisted method (a) using cinnamaldehyde (151.04 µL, 1.2 mmole), new compound **4a** was obtained and characterized directly without any further purification as a white solid (0.31 g, 97%), while following the conventional heating method (b) the same compound **4b** was obtained in 0.27 g, 83%; m.p.: 268-269^{o}C; R$_f$: 0.35 in hexane: ethyl acetate (2:1) solvent system.$[\alpha]_D^{20}$ = -195.0 (c=0.01, DMSO). FTIR UATR (cm^{-1}) υmax: 3250 (**N-H** stretching), 3059 (=**C-H** sp^2 and –**C-H** sp^3), 1616 (**C=N** stretching), 1510 and 1476 (**C=C** aromatic), 1450 (**N-H** bending), 1319 (**C-N** stretching), 733 (**C-H** bending out of plane for aromatic). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 6.46 (dd, *J*=15.4, 7.8 Hz, 1H, **H-1**"), 6.65 (dd, *J*=7.7, 1.6 Hz, 1H, **H-6**), 6.83 (ddd, *J*=7.8, 7.0, 1.0 Hz, 1H, **H-8**), 6.86 (dd, *J*=15.4, 7.8 Hz, 1H, **H-2"**), 6.92 (d, *J*=8.3 Hz, 1H, **H-10)**, 7.14 - 7.34 (m, 6H, **H-2'", 3"', 4"', 5"', 6"', N-H**), 7.36 - 7.46 (m, 3H,**H-9, 3', 4')**, 7.56 - 7.63 (m, 1H, **H-2')**, 7.63 - 7.70 (m, 1H, **H-5**'), 7.94 (dd, *J*=7.8, 1.4 Hz, 1H, **H-7**). ^{13}C NMR (100 MHz, *DMSO-d*$_6$) δ ppm, 67.3 (**C-6**), 110.4 (**C-2'**), 111.7 (**C-3**), 115.0 (**C-10**), 118.1 (**C-8**), 118.6 (**C-5'**), 122.0 (**C3'**), 122.1 (**C4'**), 124.6 (**C-7**), 126.1 (**C-4"'**), 126.8 (**C-3"',5"'**), 128.4 (**C-2"**), 128.7 (**C-2'", 6"'**), 131.6 (**C-1"**), 131.9 (**C-9**), 132.6 (**C-6'**), 135.1 (**C-1"'**), 142.9 (**C-7'**), 143.9 (**C-4**), 146.3 (**C-2**). DIMS *m/z*: 323(M^+, 60%), 320 ($[C_{22}H_{14}N_3]^+$, 64), 244 ($[C_{16}H_{10}N_3]^+$, 23), 220 ($[C_{14}H_{10}N_3]^+$, 28), 194 ($[C_{13}H_{10}N_2]^+$, 100), 160 ($[C_{10}H_{12}N_2]^+$, 15), 91 ($[C_6H_5N]^+$, 16). Anal. Calcd. for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 12.99%. Found: C, 81.59; H, 5.38; N, 12.78%. UV-Vis in DMSO λ_{max}, nm (ε, L mole^{-1} cm^{-1}): 360 (ε, 0.133 ×10^4), 303 (ε, 0.263 ×10^4), 292 (ε, 0.292 ×10^4), 265 (ε, 0.336 ×10^4).

Synthesis of new 6-phenethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*] quinazoline [4]

Following the microwave-assisted method (a) using hydrocinnamaldehyde (158.01 µL, 1.2 mmole), new compound **3a** was obtained and characterized directly without any further purification as a white solid (0.31 g, 98%), while following the conventional heating method (b) the same compound **3b** was obtained in 0.27 g, 82%; m.p.: 239-240^{o}C; R$_f$: 0.31 in hexane: ethyl acetate (2:1) solvent system.$[\alpha]_D^{20}$ = -18.2 (c=0.01, DMSO). FTIR UATR (cm^{-1}) υmax: 3252 (**N-H** stretching), 2947 (-**C-H** sp^3 stretching), 1614 (**C=N** stretching), 1504 and 1474 (**C=C** aromatic), 1449 (**N-H** bending), 1310 (**C-N** stretching), 735 (**C-H** bending out of plane for aromatic).^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 1.92 - 2.04 (m, 1H, **H**$_A$), 2.10 (dt, *J*= 14.7, 8.0 Hz, 1H, **H**$_B$), 2.65 (t, *J*=8.0 Hz, 2H, **H-1"**), 6.05 - 6.15 (m, 1H, **H-6**), 6.81 (t, *J*=7.8 Hz, 1H, **H-8**), 6.94 (d, *J*=8.3 Hz, 1H, **H-10**), 7.09 (s, 1H, N-**H**), 7.10 - 7.30 (m, 8H, **H-9, 3', 4', 2"', 3"', 4"', 5"', 6"'**), 7.46 - 7.56 (m, 1H, **H-2'**), 7.58 - 7.69 (m, 1H, **H-5'**), 7.89 (d, *J*=7.8 Hz, 1H, **H-7**).^{13}C NMR (100 MHz, *DMSO-d*$_6$) δ ppm, 29.9 (**C**H$_{A,B}$), 37.3 (**C-1"**), 65.2 (**C-6**), 109.9 (**C-2'**), 112.0 (**C-3**), 115.1 (**C-10**), 118.0 (**C-8**), 118.6 (**C-5'**), 122.0 (**C-3'**), 122.0 (**C-4'**), 124.6 (**C-4"'**), 125.9 (**C-7**), 128.0 (**C-3"', 5"'**), 128.4 (**C-2"', 6"'**), 131.6 (**C-9**), 132.5 (**C-1"'**), 140.7 (**C-6'**), 143.0 (**C-7'**), 143.7 (**C-4**), 146.4 (**C-2**).MS: DIMS *m/z*: 325(M^+, 6%), 323 ($[C_{22}H_{17}N_3]^+$, 29), 246 ($[C_{16}H_{12}N_3]^+$, 8), 220 ($[C_{14}H_{10}N_3]^+$, 100), 194 ($[C_{13}H_{10}N_2]^+$, 10), 91 ($[C_6H_5N]^+$, 12). Anal. Calcd. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N,12.91%. Found: C, 80.82; H, 5.81; N, 12.78%. UV-Vis in DMSO λ_{max}, nm (ε, L mole^{-1} cm^{-1}): 358 (ε, 0.226 ×10^4), 304 (ε, 0.360 ×10^4).

2.4 Antioxidant Activity

2.4.1 DPPH$^•$ Scavenging Activity

DPPH$^•$ scavenging activity of all the derivatives were conducted according to Chan *et al*. 2013a [12]. In a ninety-six well microplate, 50 µL of diluted samples in DMSO were reacted with 195 µL of 0.2 mM DPPH$^•$ (methanolic solution) in triplicate. The reaction mixture was kept in the dark at ambient room temperature for 1 h. Following that, the absorbance of radical-antioxidant mixture was read at 540 nm with the aid of Thermo Scientific microplate ELISA reader/UK. The antiradical activity of the derivatives was expressed in milligram Trolox equivalent per gram of the sample (mg TE.g^{-1}).

2.4.2 ABTS$^{•+}$ Scavenging Activity

ABTS$^{•+}$ scavenging activity of all studied samples were performed according to the previous study which was done by Chan *et al*. 2013b [13] with some modifications. Briefly, ABTS$^{•+}$ was generated by adding 10 mL of 7 mM ABTS to 10 mL of 2.45 mM potassium persulfate and kept in dark place at RT for 24 h. Then,

$ABTS^{\bullet+}$ solution was diluted to the absorbance of 1.40 ± 0.05 at 734 nm at room temperature with the aid of UV-vis spectrophotometer (UV-1700, Shimadzu/Japan). Subsequently, 180 µL of $ABTS^{\bullet+}$ solution was added to 20 µL of samples in a ninety-six well microplate. After 1h of incubation at RT, the absorbance was recorded at 734 nm using microplates ELISA reader. The analysis was conducted in triplicates and the scavenging activity of the compounds were expressed in milligram trolox equivalent per gram of the sample (mg $TE.g^{-1}$).

2.5 Statistical Analysis

Antioxidant values were expressed as mean ± SD of three replicates for all samples. The significant differences of the mean values were analyzed by one way ANOVA followed by Tukey HSD *posthoc* test at 95% confidence level for multiple comparison using Minitab 16 Statistical Analysis Software (Minitab Inc., State College, PA, USA). Values were considered to be statistically significant when $p<0.05$.

III. Results and Discussion

3.1 Synthesis and Characterization

Conventional reflux and microwave synthesis were used to synthesis the target compounds. 2-(2-Aminophenyl)-1*H*-benzimidazole was condensed with different aldehydes to produce dihydro-benzimidazoquinazoline derivatives. By using microwave-assisted method, the compounds were synthesized in excellent yield (92-98%) within very short reaction time (5-15 min.). Moreover, reaction time was reduced by 86-93% and the product percentage yield was increased by10-16% as summarized in Table 1. In addition, using of microwave condensation gave very pure products that can be used for characterization directly after simple filtration and rinse with suitable solvent without extra purification steps.

Table 1: Reaction time and % yield of dihydro-benzimidazoquinazoline [1-4] under conventional reflux and microwave irradiation.

Compounds	**Classical reflux**		**Microwave assisted**		**Increase in Yield (%) MW/CR***	**Decrease in Reaction time (%) MW/CR****
	Yield (%)	Time	Yield (%)	Time		
1	55	180	92	15	10	93
2	83	190	96	15	13	92
3	83	35	97	5	14	86
4	82	45	98	5	16	89

*: Microwave over Classical Reflux increase in yield (%)= $MW\ yield\ (\%) - CR\ yield\ (\%)$

**: Microwave over Classical Reflux decrease in reaction time= $\frac{CR\ time - MW\ time}{CR\ time} \times 100$

The probable reaction mechanism is shown in Figure 3. the reaction started by activation of carbonyl group of analdehyde via protonation step, followed by the attacking of the nucleophilic amine on to the protonated carbonyl carbon to form the intermediate **III** which was then protonated under the acidic reaction conditions to produce carbinolamine intermediate **IV.**Carbinolamine was in equilibrium with iminium cation **V** that formed by losing of water molecule. Presumably, the imine carbon was quite electrophilic and proceeded to react with the basic secondary amine of the benzimidazol ring to form a new ring after loss of a proton. Interestingly, the cyclized compound was obtained instead of the expected Schiff base **VI** under the same reaction conditions which means that the position of *ortho*amino group of the parent amine is the main reason behind cyclization process and benzimidazoquinazoline creation. Presumably, Schiff base could be the initial compound, but it react further to create benzimidazoquinazoline and this is applicable for all aldehydes. In the future, the R group in the amine can be changed to decrease its reactivity hoping to allow the isolation of the Schiff base compounds.

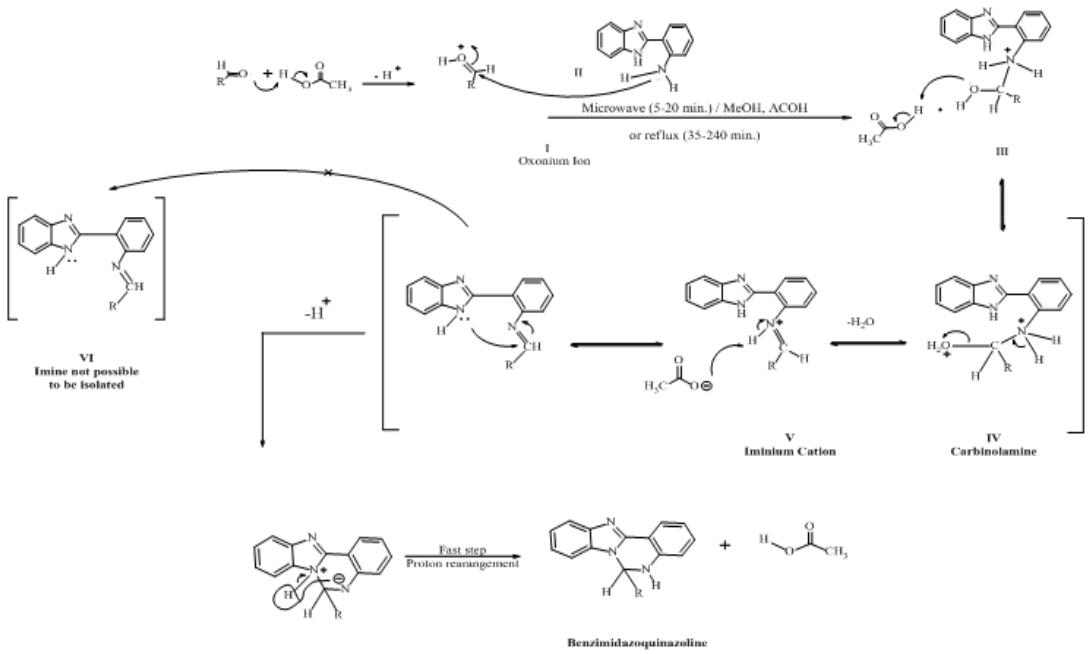

Figure 3: Plausible mechanism for formation of 6-substitutyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline.

Characterization of dihydro-benzimidazoquinazolines **1-4** was performed using ^{1}H NMR, ^{13}C NMR, FTIR, GC-MS, UV-Vis spectroscopy, as well as elemental analysis. Table 2 summarizes the physical and elemental analysis of synthesized compounds. From the table, melting points results confirm the purity of the compounds since they melted within one to two degree Celsius which means that they were free from impurities. Moreover, the calculated CHN values were in agreement with the experimental results.

Table 2: Physical and elemental analysis of compounds [1-4].

Compounds	**Molecular Formula**	**Molecular weight**	**Melting point °C**	**Elemental analysis % found (calculated)**		
				%C	**%H**	**%N**
1	$C_{28}H_{23}N_3O$	417.18	204-205	80.60 (80.55)	5.82 (5.55)	9.95 (10.06)
2	$C_{21}H_{17}N_3$	311.14	196-197	80.50 (81.00)	5.78 (5.50)	13.75 (13.49)
3	$C_{22}H_{17}N_3$	323.14	268-269	81.59 (81.71)	5.38 (5.30)	12.78 (12.99)
4	$C_{22}H_{19}N_3$	325.16	239-240	80.82 (81.20)	5.81 (5.89)	12.78 (12.91)

The ^{1}H NMR spectra for all synthesized benzimidazoquinazoline displayed the most important resonances in the range of 7.09-7.49 ppm for the N-H proton and 6.05- 7.16 ppm for the proton H-6 (Table 3) which confirm the cyclisation process and formation of the new diazine ring instead of the expected Schiff base formation under the same reaction conditions. Furthermore, regarding a comparative point of view, dihydrobenzimidazoquinazoline compounds did not display any singlet peak in the range of 8.5-9 ppm for the –N=C-H azomethine distinctive functional group. All this evidence combined has confirmed that there is no Schiff base formation. Table3 summarizes the N-H and H-6 peak chemical shifts for all derivatives in this family. For the aliphatic derivative 4, there are another distinctive peaks specific for that compounds which are protons H_A and H_B which resonated as multiplet at1.61-1.72 and doublet of triplet at 1.80 ppm. This is due tothe adjacency of aliphatic chain (sp^3) to chiral center C-6 (Table 3).Figure 4 depict the ^{1}H NMR spectrum of compound **4**.

Table 3: Important protons and carbon in ^{1}H NMR and ^{13}C NMR spectra of dihydro-benzimidazoquinazolines [1-4].

Compound		Chemical shifts of ^{1}H and ^{13}C NMR (δ,ppm)				
R=		**N-H**	**H-6**	**H_A**	**H_B**	**C6**
1		7.49 (s)	6.89-6.92 (m)			69.6
2		7.32 (s)	7.16 (d,*J*=1.4)	-	-	66.8
3		7.14 - 7.34 (overlap)	6.65 (dd, *J*=7.7, 1.6)			67.3
4		7.09 (s)	6.05-6.15 (m)	1.61-1.72	1.80	65.2

- : not detected.

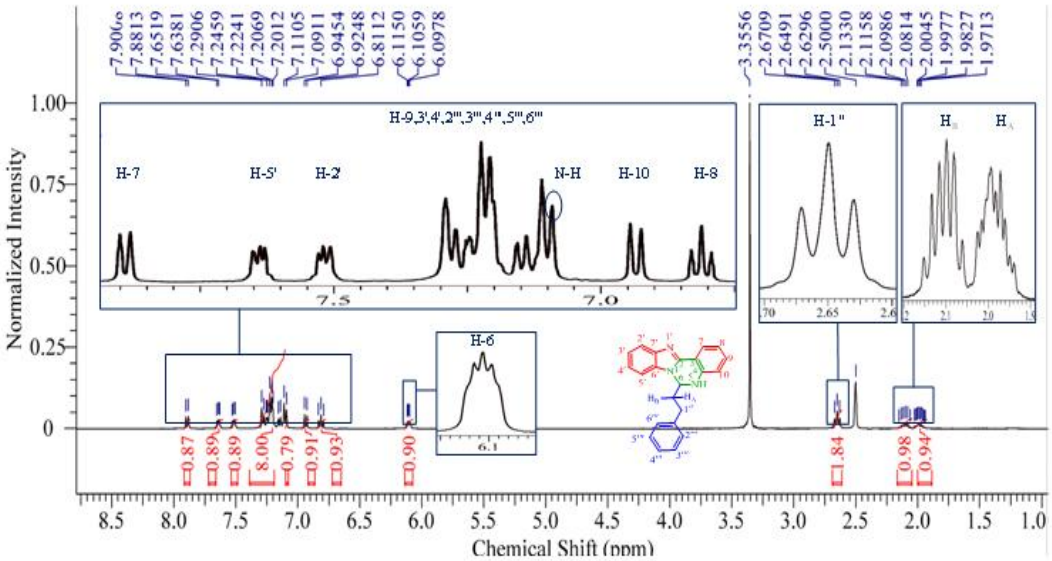

Figure 4: ^{1}H-NMR spectrum of 6-phenethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline [4].

The ^{13}CNMR spectra for those benzimidazoquinazolines showed the most significant peak in the aliphatic region between 65.2 ppm to 69.6 ppm assigned for C-6 in all benzimidazoquinazoline derivatives which affirm the cyclisation and formation of the target analogues. If not, the characteristic carbon peak for azomethine compounds (C=N) will appear at 165 to 170 ppm. Table 3 highlights the main carbons in the ^{13}CNMR spectra of the prepared benzimidazoquinazolines [1-4] with their chemical shifts. For instance, in benzimidazoquinazoline 4, C-6 peak appeared at 65.2 ppm. This compound also displayed another signals at different chemical shifts as shown in Figure 5.

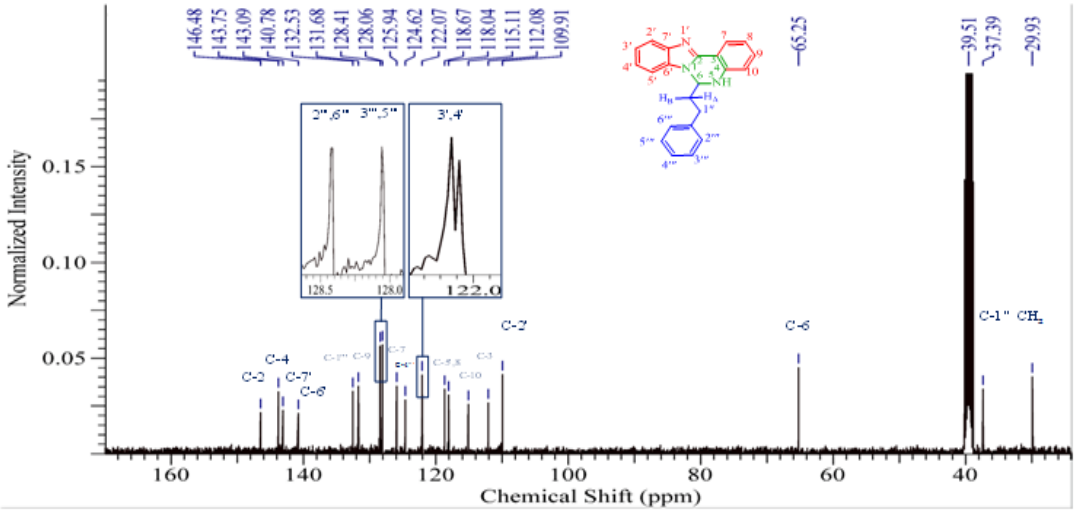

Figure 5: ^{13}C-NMR of 6-phenethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline [4].

The studied dihydro-benzimidazoquinazoline compounds were analyzed using Fourier Transform Infrared spectroscopy (FTIR) to identify what functional groups are present in each particular derivatives. FTIR spectra for all aromatic dihydro-benzimidazoquinazoline family exhibit the most important absorption bands around 3149-3252 and 1393-1476 cm^{-1} which belongs to **N-H** stretching and bending vibrations, respectively. These two bands prove that the secondary NH group of new diazine ring were formed. The most important functional group are summarized in Table 4. Figure 6 depicts the FTIR spectrum for compound 4.

Table 4: Infraredfrequencies of the major functional groups.

Compounds	N-H stretching	=C-H sp2 stretching	-C-H sp3 stretching	C=N stretching	C=C aromatic stretching	N-H bending	C-N stretching	C-O stretching	C-H aromatic
1	3188	3103	2956	1614	1517	1393	1305	1250	735
2	3149	2928		1605	1476		1277	-	729
3	3250	3059		1616	1510, 1476	1450	1319	-	733
4	3252	-	2947	1614	1504, 1474	1449	1310	-	735

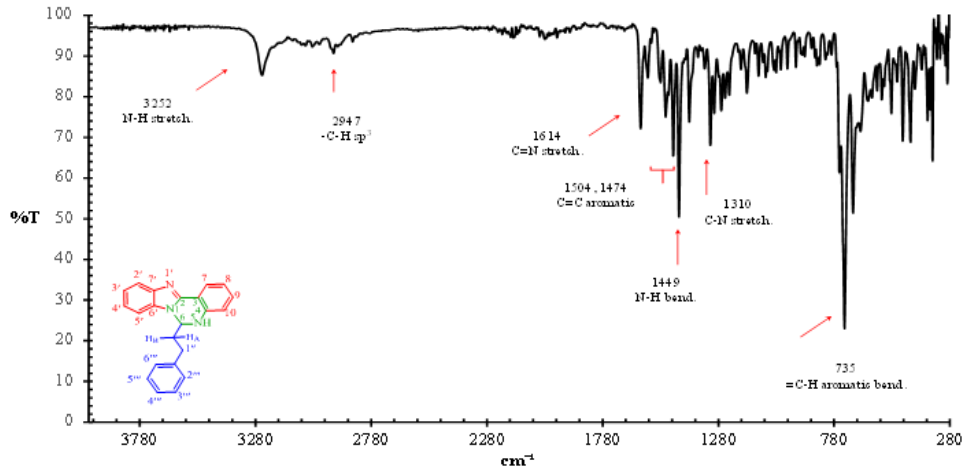

Figure 6: FTIR spectrum of 6-phenethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline [4].

Mass spectroscopy (GCMS) was also run for target compounds and the results revealed that the molecular weights of the compounds were equal to the theoretical molecular weight. For instance, the GCMS fragmentation spectrum is shown in Figure 7.

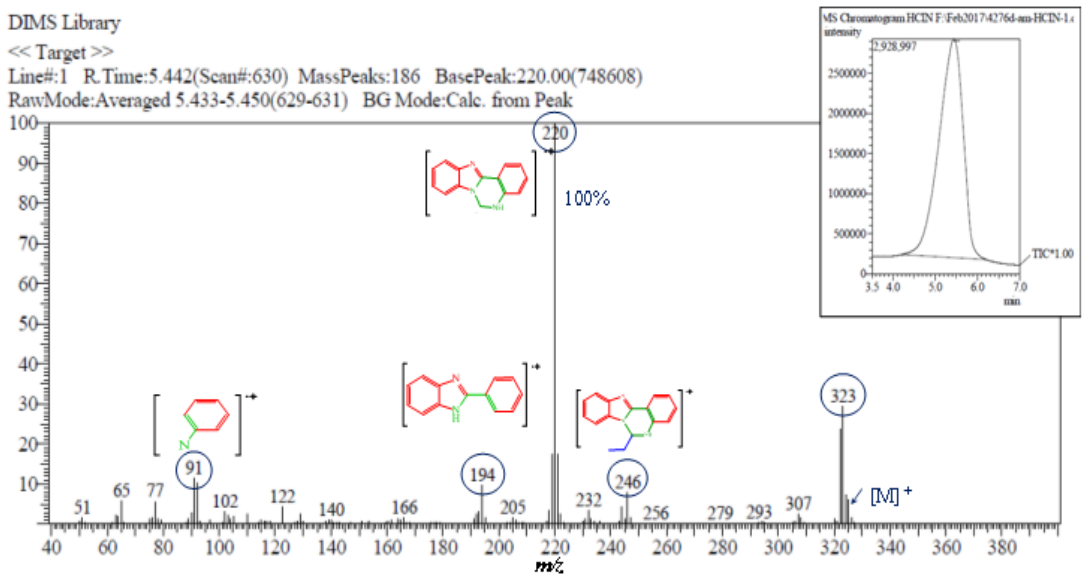

Figure 7: GCMS fragmentation spectrum of 6-phenethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline [4].

UV-Vis absorption for allbenzimidazoquinazolines were run at $1X10^{-4}$ M in DMSO solvents and the results spectra showed that all of them got one to three bands in the range of 264 to 305 nm. This was due to the$\pi\rightarrow\pi^*$ transitionsfrom the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). In addition, there is a broad band appear at lower wavelength between 350-361 nm for $n\rightarrow\pi^*$ transitions of non-bonding electrons. Figure 8 illustrates the UV-Vis spectrum of compound 4.

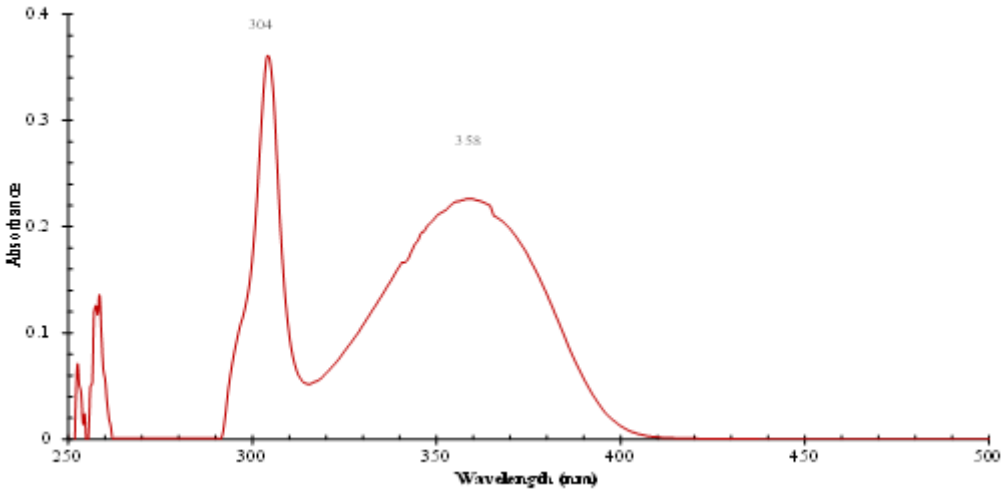

Figure 8: UV-Vis spectrum of 6-phenethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-c]quinazoline [4].

3.2 Antioxidant Activity

Antioxidant activity of studied compounds was evaluated by $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ as fast and reliable methods to determine the radical scavenging activity of dihydrobenzimidazoquinazolines. $ABTS^{\bullet+}$ scavenging activities for studied benzimidazoquinazolines were excellent with highest activity for compound **2** (923.18±47.28 $mgTE.g^{-1}$), Table 5. For $DPPH^{\bullet}$ scavenging activities, they were moderate and lower than those of $ABTS^{\bullet+}$ with highest activity for derivative **2** as well (22.48±0.87 $mgTE.g^{-1}$). Generally, $ABTS^{\bullet+}$scavenging activities were better than$DPPH^{\bullet}$ due to the structure difference for the two radical. $DPPH^{\bullet}$ is nitrogen center radical and this is the main obstacle for its reaction [14]. On the contrary, the $ABTS^{\bullet+}$is not sterically hindered

compound and can easily react as a potent reductant. Review of previous literature disclose many of studies resulted with superiority of $ABTS^{\bullet+}$ on $DPPH^{\bullet}$ scavenging activities for plant extracts as well as synthesized compounds [15-18].Therefore, compound 2 showed the best scavenging activities amongst all derivatives in both of the tests. Its reactivity could also be attributed to the electron donating by inductive effect (+I-effect) methyl group which can stabilize the formed radical after hydrogen atom donation to either $DPPH^{\bullet}$ or $ABTS^{\bullet+}$.

Table 5: DPPH and ABTS scavenging activities of compounds 1-4.

Compounds	Scavenging activity (mg trolox equiv/g sample)			
	$DPPH^{\bullet}$		$ABTS^{\bullet+}$	
	Mean±SD	Relative Standard Deviation (RSD %)	Mean±SD	Relative Standard Deviation (RSD %)
1	13.27±1.93	10.54	480.01±22.81	4.75
2	22.48±0.87	3.90	923.18±47.28	5.12
3	13.95±0.33	2.36	382.70±32.11	8.39
4	21.66±0.39	1.80	613.46±40.74	6.64

IV. Conclusion

Four new 6-substituted-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline compounds were successfully synthesized in excellent yield within few minutes using the microwave-assisted method. All studied benzimidazoquinazolines were very pure and characterized directly by spectroscopic and elemental analysis without any purification. The antioxidant activities for the compoundswere evaluated by two simple methods $DPPH^{\bullet}$ and $ABTS^{\bullet+}$. Some of the compounds show excellent antioxidant activity and these can be good candidate for further pharmaceutical applications.

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