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Novel Benzothiazole Based Imidazole Derivatives as New Cytotoxic Agents Against Glioma (C6) and Liver (HepG2) Cancer Cell Lines

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ABSTRACT

In this work, some novel *N*-(6-substituted-benzothiazol-2-yl)-2-[[4,5-dimethyl-1-((p-tolyl/4-nitrophenyl)amino)-1*H*-imidazol-2-yl]thio]acetamide derivatives were synthesized and searched for their cytotoxic activities against C6 and HepG2 tumor cells. Among all compounds, the most active compound was determined as compound **7**. It was calculated IC_{50} value about 15.67 µg/mL through C6 tumor cell lines and also compound **2**, **4**, **5**, **6** were observed as good cytotoxic agents against HepG2 tumor cells. Findings about antiproliferative activity studies have encouraged the acquirement of new similar compounds in undergoing studies.

Keywords: Imidazole, Benzothiazole, Cytotoxicity, Antiproliferative Activity

INTRODUCTION

Cancer is the second leading cause of death after heart disease throughout the world. A great amount of anticancer drugs are discovered and still have been designed nowadays for cancer treatment[1]. Today, treatments involving cytotoxic drugs are used in a widespread manner because of increasing in cancer incidence[2]. Compounds containing imidazole and benzothiazole moiety have shown a wide range of biological properties including anticancer, antiviral, antitubercular, antimicrobial, antidiabetic, anti-inflammatory activities. These broad thera-

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peutic properties of imidazole and benzothiazole related drugs have encouraged the medicinal chemists in order to synthesize novel chemotherapeutic agents[3-16].

Dr. Malcolm Stevens, a researcher of Cancer Research UK Group at Nottingham University demonstrated the potential of benzothiazole (NSC 674495) and related compounds as anticancer agents. Phortress (NSC 710305) was the lead compound in this work. This lead compound has shown activity against breast tumors, regardless of estrogen receptor status, and against lung, ovarian, colon and renal cancer cells[17].

In a previous study of our research group, synthesized imidazole derivatives showed antiproliferative activity among the sixty tumor cell line, UO-31 derived from renal cancer against tested compound with the growth percentage 69.91 % respectively[18]. Moreover, compounds containing imidazole ring were determined to exhibite high potency anticancer activity against human hepatocellular carcinoma, human colon carcinoma, breast and adeno carcinoma, in recent studies[8,19].

In accordance with these study, *N*-(6-substituted-benzothiazol-2-yl)-2-[[4,5-dimethyl-1-((p-tolyl/4-nitrophenyl)amino)-1*H*-imidazol-2-yl]thio]acetamide derivatives **(2a-j)** were synthesized by two steps and structure of the compounds were clarified by spectroscopic techniques. Cytotoxicity of the compounds was determined by MTT assay against C6 (rat glioma) and HepG2 (human liver) cell lines.

METHODOLOGY

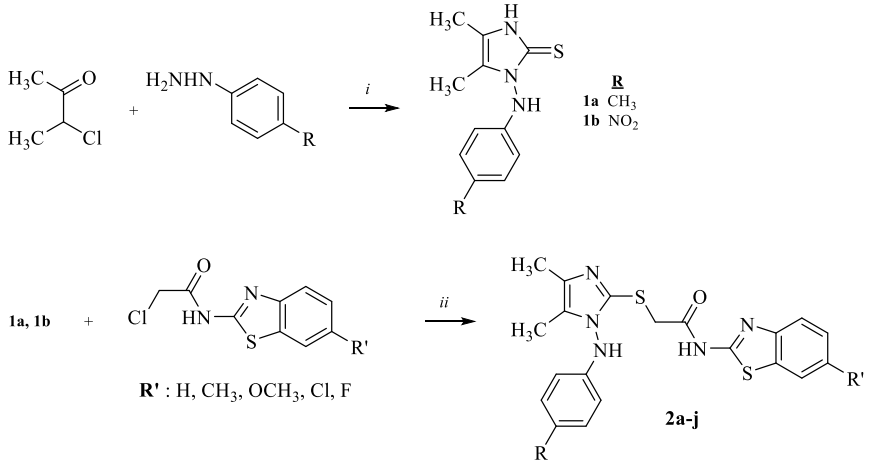
Chemistry

Melting points were determined on d by MP90 digital melting point apparatus (Mettler Toledo, OH) and were uncorrected. Spectroscopic data were recorded on the following instruments: a Bruker Tensor 27 IR spectrophotometer; a ^{1}H NMR (nuclear magnetic resonance) Bruker DPX- 300 FT-NMR spectrometer, ^{13}C NMR, Bruker DPX 75 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA); M+1 peaks were determined by Shimadzu LC/MS ITTOF system (Shimadzu, Tokyo, Japan). Elemental analyses were performed in a Perkin Elmer EAL 240 elemental analyser for C, H and N.

General procedure for the synthesis of final compounds (2a-j)

Firstly, equimolar quantities of **1a** or **1b** (3 mmol) in acetone (35 mL) and equimolar potassium carbonate were stirred and continued to mixing by adding various 2-chloro-*N*-(benzothiazol-2-yl)acetamide derivatives. After completed stirring at room temperature for 3-4 h, the solution was checked by TLC in 1:1

ethanol/EtOAc. The solvent was removed under reduced pressure, and then water (100 mL) and brine added to the residue. The mixture solution was filtered off and air-dried. The obtained solid was dissolved in ethanol and decolorizing activated charcoal was added to solution and boiled finally. After filtering off the charcoal by filter paper, the residue was purified by recrystallization from ethanol (Scheme 1).



Scheme 1: The synthesis of the compounds. Reactants, reagents, conditions: *i :* AcOH, reflux; *ii :* K_2CO_3, acetone, r.t., 3-4 h.

N-(Benzothiazol-2-yl)-2-[[4,5-dimethyl-1-(p-tolylamino)-1H-imidazol-2-yl]thio]acetamide (2a):

Yield 76 %; mp 178 °C. IR ν_{max} (cm^{-1}): 3250 (N-H), 1689 (C=O), 1598-1375 (C=C, C=N), 1280-1163 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.89 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 4.09 (s, 2H, CH_2CO), 6.35 (d, J=8.37 Hz, 2H, Ar-H), 6.99 (d, J=8.25 Hz, 2H, Ar-H), 7.31 (t, J=7.47 Hz, 1H, Ar-H), 7.44 (t, J=7.47 Hz, 1H, Ar-H), 7.75 (d, J=7.92 Hz, 1H, Ar-H), 7.98 (d, J=7.71 Hz, 1H, Ar-H), 9.00 (s, 1H, NH), 12.78 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.27, 13.56, 20.56, 35.63, 112.69, 121.07, 122.19, 124.03, 125.62, 126.60, 129.46, 130.13, 132.12, 139.85, 145.02, 168.90. For $C_{21}H_{21}N_5OS_2$ calculated: (%) C 59.55, H 5.00, N 16.53; found: (%) C 59.60, H 4.96, N 16.61. HRMS (*m/z*): $[M+H]^+$ calcd: 423.55; found 424.13.

N-(6-Methylbenzothiazol-2-yl)-2-[[4,5-dimethyl-1-(p-tolylamino)-1H-imidazol-2-yl]thio]acetamide (2b):

Yield 72 %; mp 206 °C. IR ν_{max} (cm^{-1}): 3346 (N-H), 1689 (C=O), 1598-1380 (C=C, C=N), 1276-1124 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.89 (s, 3H, CH_3),

2.06 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.08 (s, 2H, CH_2CO), 6.35 (d, J=8.43 Hz, 2H, Ar-H), 6.99 (d, J=8.10 Hz, 2H, Ar-H), 7.25 (d, J=7.28 Hz, 1H, Ar-H), 7.64 (d, J=8.25 Hz, 1H, Ar-H), 7.77 (d, J=7.92 Hz, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 9.00 (s, 1H, NH), 12.78 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.27, 13.56, 20.58, 21.44, 35.55, 112.69, 120.73, 121.79, 125.61, 127.93, 129.46, 130.14, 132.10, 133.52, 139.89, 145.01, 168.33. For $C_{22}H_{23}N_5OS_2$ calculated: (%) C 60.39, H 5.30, N 16.00; found: (%) C 60.34, H 5.25, N 16.07. HRMS (*m/z*): $[M+H]^+$ calcd: 437.58; found 438.14.

N-(6-Methoxybenzothiazol-2-yl)-2-[[4,5-dimethyl-1-(p-tolylamino)-1H-imidazol-2-yl]thio]acetamide (2c):

Yield 75 %; mp 224 °C. IR ν_{max} (cm^{-1}): 3289 (N-H), 1670 (C=O), 1602-1398 (C=C, C=N), 1267-1056 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.89 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.07 (s, 2H, CH_2CO), 6.35 (d, J=8.43 Hz, 2H, Ar-H), 6.97-7.05 (m, 3H, Ar-H), 7.58 (d, J=2.55 Hz, 1H, Ar-H), 7.64 (d, J=8.82 Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 12.65 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.26, 13.56, 20.58, 35.50, 56.06, 105.21, 112.69, 115.41, 121.70, 125.72, 129.47, 130.14, 132.10, 133.36, 139.88, 145.01, 156.62, 168.16. For $C_{22}H_{23}N_5O_2S_2$ calculated: (%) C 58.26, H 5.11, N 15.44; found: (%) C 58.30, H 5.16, N 15.49. HRMS (*m/z*): $[M+H]^+$ calcd: 453.58; found 454.14.

N-(6-Chlorobenzothiazol-2-yl)-2-[[4,5-dimethyl-1-(p-tolylamino)-1H-imidazol-2-yl]thio]acetamide (2d):

Yield 72 %; mp 214 °C. IR ν_{max} (cm^{-1}): 3288 (N-H), 1697 (C=O), 1546-1400 (C=C, C=N), 1286-1101 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.89 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.09 (s, 2H, CH_2CO), 6.34 (d, J=8.43 Hz, 2H, Ar-H), 6.98 (d, J=8.13 Hz, 2H, Ar-H), 7.46 (dd, $J_{1,2}$=8.61, 2.22 Hz, 1H, Ar-H), 7.74 (d, J=8.64 Hz, 1H, Ar-H), 8.13 (d, J=2.16 Hz, 1H, Ar-H), 8.99 (s, 1H, NH), 12.89 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.27, 13.57, 20.58, 35.56, 112.68, 121.93, 122.29, 125.64, 126.96, 128.09, 129.47, 130.13, 132.13, 133.67, 139.80, 145.00, 147.92, 159.10, 168.73. For $C_{21}H_{20}ClN_5OS_2$ calculated: (%) C 55.07, H 4.40, N 15.29; found: (%) C 55.12, H 4.46, N 15.35. HRMS (*m/z*): $[M+H]^+$ calcd: 458.00; found 458.09.

N-(6-Fluorobenzothiazol-2-yl)-2-[[4,5-dimethyl-1-(p-tolylamino)-1H-imidazol-2-yl]thio]acetamide (2e):

Yield 72 %; mp 212 °C. IR ν_{max} (cm^{-1}): 3317, 3286 (N-H), 1689 (C=O), 1543-1398 (C=C, C=N), 1294-1136 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.88 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.09 (s, 2H, CH_2CO), 6.35 (d, J=8.43 Hz, 2H, Ar-H), 6.98 (d, J=8.16 Hz, 2H, Ar-H), 7.29 (td, $J_{1,2}$=8.70, 2.64

Hz, 1H, Ar-H), 7.76 (q, J=8.70 Hz, 1H, Ar-H), 7.90 (dd, $J_{1,2}$=8.40, 2.67 Hz, 1H, Ar-H), 8.98 (s, 1H, NH), 12.82 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.27, 13.57, 20.58, 35.51, 108.49, 108.84, 112.69, 114.38, 114.56, 114.89, 122.14, 122.26, 125.63, 129.46, 130.13, 131.13, 139.83, 145.00, 145.74, 157.53, 158.19, 159.33, 160.71, 168.59. For $C_{21}H_{20}FN_5OS_2$ HRMS (*m/z*): $[M+H]^+$ calcd: 441.54; found 442.12.

N-(Benzothiazol-2-yl)-2-{[4,5-dimethyl-1-[(4-nitrophenyl) amino]-1H-imidazol-2-yl]thio}acetamide (2f):

Yield 69 %; mp 126 °C. IR ν_{max} (cm^{-1}): 3323, 3288 (N-H), 1689 (C=O), 1595-1350 (C=C, C=N, NO_2), 1288-1111 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.92 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 4.11 (s, 2H, CH_2CO), 6.56 (d, J=8.61 Hz, 2H, Ar-H), 7.31 (td, $J_{1,2}$=8.10, 1.11 Hz, 1H, Ar-H), 7.44 (td, $J_{1,2}$=7.20, 1.26 Hz, 1H, Ar-H), 7.75 (d, J=7.92 Hz, 1H, Ar-H), 7.96 (d, J=7.23 Hz, 1H, Ar-H), 8.12 (d, J=7.08 Hz, 2H, Ar-H), 10.25 (s, 1H, NH), 12.68 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.13, 13.57, 35.95, 111.63, 121.08, 122.20, 124.08, 125.48, 126.63, 131.92, 132.67, 139.24, 140.39, 148.97, 152.90, 158.16, 168.12. For $C_{20}H_{18}N_6O_3S_2$ HRMS (*m/z*): $[M+H]^+$ calcd: 454.52; found 455.12.

N-(6-Methylbenzothiazol-2-yl)-2-{[4,5-dimethyl-1-[(4-nitrophenyl) amino]-1H-imidazol-2-yl]thio}acetamide (2g):

Yield 68 %; mp 95 °C. IR ν_{max} (cm^{-1}): 3298 (N-H), 1683 (C=O), 1595-1327 (C=C, C=N, NO_2), 1271-1111 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.92 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.08 (s, 2H, CH_2CO), 6.55 (t, J=9.27 Hz, 2H, Ar-H), 7.19-7.31 (m, 1H, Ar-H), 7.61 (d, J=8.22 Hz, 1H, Ar-H), 7.74 (s, 1H, Ar-H), 8.07-8.15 (m, 2H, Ar-H), 10.23 (s, 1H, NH), 12.31 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.13, 13.57, 21.44, 34.04, 36.38, 61.43, 111.66, 117.86, 120.65, 121.27, 121.75, 125.48, 126.62, 126.86, 127.86, 132.65, 132.76, 133.39, 140.36, 153.03, 169.04. For $C_{21}H_{20}N_6O_3S_2$ HRMS (*m/z*): $[M+H]^+$ calcd: 468.55; found 469.12.

N-(6-Methoxybenzothiazol-2-yl)-2-{[4,5-dimethyl-1-[(4-nitrophenyl)amino]-1H-imidazol-2-yl]thio}acetamide (2h):

Yield 67 %; mp 122 °C. IR ν_{max} (cm^{-1}): 3253 (N-H), 1683 (C=O), 1597-1328 (C=C, C=N, NO_2), 1261-1059 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.92 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.09 (s, 2H, CH_2CO), 6.55 (d, J=8.52 Hz, 2H, Ar-H), 7.02 (dd, $J_{1,2}$=8.40, 2.58 Hz, 1H, Ar-H), 7.75 (d, J=2.55 Hz, 1H, Ar-H), 7.63 (d, J=7.35 Hz, 1H, Ar-H), 8.11 (d, J=8.40 Hz, 2H, Ar-H), 10.34 (s, 1H, NH), 12.43 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.15, 13.57, 35.99, 56.08, 105.18, 111.63, 115.39, 121.66, 125.47, 126.62, 132.65, 133.25,

139.24, 140.37, 143.08, 152.95, 156.25, 156.60, 167.88. For $C_{21}H_{20}N_6O_4S_2$ HRMS (*m/z*): $[M+H]^+$ calcd: 484.55; found 485.12.

N-(6-Chlorobenzothiazol-2-yl)-2-{[4,5-dimethyl-1-[(4-nitrophenyl) amino]-1H-imidazol-2-yl]thio}acetamide (2i):

Yield 72 %; mp 115 °C. IR ν_{max} (cm^{-1}): 3254 (N-H), 1683 (C=O), 1595-1328 (C=C, C=N, NO_2), 1288-1053 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.92 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 4.11 (s, 2H, CH_2CO), 6.55 (d, J=8.40 Hz, 2H, Ar-H), 7.45 (dd, $J_{1,2}$=8.61, 2.22 Hz, 1H, Ar-H), 7.73 (d, J=8.67 Hz, 1H, Ar-H), 8.08-8.12 (m, 3H, Ar-H), 10.29 (s, 1H, NH), 12.78 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.14, 13.57, 35.99, 111.61, 121.92, 122.27, 125.51, 126.60, 126.96, 128.11, 132.69, 133.63, 139.12, 140.36, 152.91, 168.39. For HRMS (*m/z*): $[M+H]^+$ calcd: 488.97; found 489.52.

N-(6-Fluorobenzothiazol-2-yl)-2-{[4,5-dimethyl-1-[(4-nitrophenyl) amino]-1H-imidazol-2-yl]thio}acetamide (2j):

Yield 75 %; mp 121 °C. IR ν_{max} (cm^{-1}): 3282 (N-H), 1683 (C=O), 1597-1328 (C=C, C=N, NO_2), 1267-1051 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.93 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 4.11 (s, 2H, CH_2CO), 6.53-6.59 (m, 2H, Ar-H), 7.28 (td, $J_{1,2}$=9.12, 2.70 Hz, 1H, Ar-H), 7.75 (q, J=9.00 Hz, 1H, Ar-H), 7.88 (dd, J=8.73, 2.67 Hz, 1H, Ar-H), 8.10 (d, J=9.33 Hz, 2H, Ar-H), 10.33 (s, 1H, NH), 12.71 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 8.16, 13.57, 35.94, 108.47, 108.83, 111.60, 114.57, 114.89, 122.14, 122.25, 125.52, 126.59, 132.68, 133.08, 139.13, 140.35, 145.70, 152.93, 157.54, 158.17, 160.72, 168.24. For $C_{20}H_{17}FN_6O_3S_2$ HRMS (*m/z*): $[M+H]^+$ calcd: 472.51; found 473.12.

MTT assay

To find cytotoxic activity of the compounds against C6 (rat glioma) and HepG2 (human liver) cell lines according to the reported data, MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was performed[20-21]. C6 and HepG2 and cells were cultured in 96-well flat-bottom plates at 37 °C for 24h (2 x 104 cells per well). Then by waiting for 24 h drug incubation, 20 µL MTT solution (5 mg/mL MTT powder in PBS) was added to each well and incubated about 2 h. After dissolving formazan crystals in 200 µL DMSO, the absorbance was read with the aid of ELISA reader (OD570nm). According to medium control, the percentage of viable cells was calculated and for all experiments, measurements were carried out in triplicate[22].

RESULTS AND DISCUSSION

Chemistry

Novel *N*-(6-substituted-benzothiazol-2-yl)-2-[[4,5-dimethyl-1-((p-tolyl/4-nitrophenyl)amino)-1*H*-imidazol-2-yl]thio]acetamide derivatives **(2a-j)** were procured by reacting of *N*-(6-substituted-benzothiazol-2-yl)-2-chloroacetamide derivatives with compounds **(1a-1b)** in the presence of K_2CO_3 in acetone. The synthesized compounds were yielded in a range of % 67-% 76. Melting points of final compounds were calculated between 95 °C and 212 °C. The results of IR spectral analysis showed that characteristic streching bands were observed at 3250 cm^{-1}-3346 cm^{-1} and 1294 cm^{-1}-1051 cm^{-1} in respect of N-H and C-N single bonds, at about 1697 cm^{-1} and 1670 cm^{-1}-1328 cm^{-1} belonging to C=O and C=C, C=N, NO_2 double bonds. In the ^{1}H-NMR spectra of the compounds, peaks of methyl groups hydrogens were observed at between 1.89 ppm and 2.19 ppm whereas protons of N-H were seen at 9.00 ppm and 12.78 ppm range. Aromatic hydrogens and acetyl group hydrogens were seen in order 6.34 ppm-8.15 ppm and 4.08 ppm. ^{13}C-NMR spectroscopic data displayed signals of aliphatic carbons which were assigned at 8.26 ppm-61.43 ppm and signals of aromatic carbons were seen at between 105.18 ppm-169.04 ppm. $[M+H]^+$ peaks of the molecular weights of the compounds were observed at expected values in mass spectroscopy.

Cytotoxicity

Cytotoxicity of compounds **(2a-j)** were evaluated by using MTT assay against C6 (rat glioma) and HepG2 (human liver) tumor cell lines. As shown in Table 1, IC_{50} values were calculated among 15-500 μg/mL values. IC_{50} values of the compounds **5**, **6** and **7** were found values of 16 μg/mL, 19 μg/mL and 15 μg/mL as having high cytotoxic activity because of higher values even more than cisplatin against C6 tumor cell lines. Among all compounds, the most active compound was determined as compound **7**. Its IC_{50} value was calculated as 15.67 μg/mL since that value for cisplatin was defined as 23.0 μg/mL. Compound **8** possessed IC_{50} value greater than 500 μg/mL were considered to be non-toxic. Studies against HepG2 tumor cell lines showed that compound **2**, **4**, **5**, **6** were good cytotoxic agents according to their IC_{50} values in contrast with the value of cisplatin. While these compounds had strongest cytotoxicity, IC_{50} values for compound **8**, **9**, **10** could not be calculated on account of needing high tested concentration as more than 500 μg/mL against HepG2 tumor cells. Accordingly, findings from that cytotoxicity studies displayed that synthesized novel benzothiazole based imidazole derivatives could be considered as new cytotoxic agents.

Table 1. IC_{50} values of the compounds against C6 and HepG2 tumor cell lines

Comp.	C6	HepG2
1	27.0±1.41	50.0±5.0
2	20±2.0	26.33±1.53
3	32.67±6.43	275.0±35.36
4	22.0±3.61	29.33±1.15
5	16.33±2.31	31.67±7.23
6	19.50±2.12	28.67±1.15
7	15.67±2.52	58.33±2.89
8	>500	>500
9	24.33±4.04	>500
10	19.33±2.31	>500
Cisplatin	23.0±1.73	46.67±7.64

REFERENCES

1. Baroniya, S.; Anwer, Z.; Sharma, P. K.; Dudhe, R.; Kumar, N. Recent advancement in imidazole as anti cancer agents: A review. *Pharm. Sin.* **2010**, *1(3),* 172-182.

2. Hoppe-Tichy, T. Current challenges in European oncology pharmacy practice. *J. Oncol. Pharm. Pract*. **2010**, *16*, 9-18.

3. Katritzky, A. R. *Rees. Comprehensive Heterocyclic Chemistry*. **1984**, *5*, 469-498. W. Meyer, Ber. Dtschn. Chem. Ges.;1883; 16; 1465.

4. Grimmet, R. M. Imidazole and Benzimidazole Synthesis. *Academic Press,* San Diego, **1997**.

5. Brown, E. G. Ring Nitrogen and Key Biomolecules. *Kluwer Academic Press,* Dortrecht, **1998.**

6. Pozharskii, A. F. Heterocycles in Life and Society. *John Wiley & Sons*. **1997**.

7. Gilchrist, T. L. Heterocyclic Chemistry. *The Bath Press,* Oxford, **1985**.

8. Congiu, U.; Cocco, M. T.; Onnis, V. Design, synthesis, and in vitro antitumor activity of new 1,4-diarylimidazole-2-ones and their 2-thione analogues. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 989-993.

9. Venkatesan, A. M.; Agarwal, A.; Abe, T.; Ushirogochi, H. O.; Santos, D.; Li Z.; Francisco, G.; Lin, Y. I.; Peterson, P. J.; Yang, Y.; Weiss, W. J.; Shales, D. M.; Mansour, T. S. 5,5,6-Fused tricycles bearing imidazole and pyrazole 6-methylidene penems as broad-spectrum inhibitors of β-lactamases. *Bioorg. Med. Chem*. **2008**, *16,* 1890-1902.

10. Nakamura, T.; Kakinuma, H.; Umemiya, H.; Amada, H.; Miyata, N.; Taniguchi, K.; Bando, K.; Sato, M. Imidazole derivatives as new potent and selective 20-HETE synthase inhibitors. *Bioorg. Med. Chem. Lett*. **2004**, *14,* 33-336.

11. Su Han, M.; Kim, D. H. Effect of zinc ion on the inhibition of carboxypeptidase A by imidazole-bearing substrate analogues. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1425-1427.

12. Roman, G.; Riley, J. G.; Vlahakis, J. Z.; Kinobe, R. T.; Brien, J. F.; Nakatsu, K.; Szarek, W. A. Heme oxygenase inhibition by 2-oxy-substituted 1-(1*H*-imidazol-1-yl)-4-phenylbutanes: effect of halogen substitution in the phenyl ring. *Bioorg. Med. Chem*. **2007**, *15*, 3225-3234.

13. Bbizhayev, M. A. Biological activities of the natural imidazole-containing peptidomimetics

n-acetylcarnosine, carcinine and L-carnosine in ophthalmic and skin care products. *Life Sci.* **2006**, *78*, 2343-3234.

14. Nantermet, P. G.; Barrow, J. C.; Lindsey, S. R.; Young, M.; Mao, S.; Carroll, S.; Bailey, C.; Bosserman, M.; Colussi, D.; McMasters, D. R.; Vacca, J. P.; Selnick, H. G. Imidazole acetic acid TAFIa inhibitors: SAR studies centered around the basic P(1)(') group. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2141-2145.

15. Adams, J. L.; Boehm, J. C.; Gallagher, T. F.; Kassis, S.; Webb, E. F.; Hall, R.; Sorenson M.; Garigipati, R.; Griswold, D. E.; Lee, J. C. Pyridinylimidazole inhibitors of p38: cyclic N-1 imidazole substituent enhance p38 kinase inhibition and oral activity *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2867-2870.

16. Bhandari, K.; Srinivas, N.; Keshava, G. B. S.; Shukla, P. K. Tetrahydronaphthyl azole oxime ethers: the conformationally rigid analogues of oxiconazole as antibacterials. *Eur. J. Med. Chem.* **2009**, *44*, 437-447.

17. Ali, R.; Siddiqui, N. Biological aspects of emerging benzothiazole: A short review. *J. Chem.* **2013**, *2013,* 1-12.

18. Yurttas, L.; Duran, M.; Demirayak, S.; Gencer, H. K.; Tunalı, Y. Synthesis and initial biological evaluation of substituted 1-phenylamino-2-thio-4,5-dimethyl-1H-imidazole derivatives. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6764-6768.

19. Wang, X.Q.; Liu, L.X.; Li, Y.; Sun, C.J.; Chen, W.; Li, L.; Zhang, H.B.; Yang, X.D. Design, synthesis and biological evaluation of novel hybrid compounds of imidazole scaffold-based 2-benzylbenzofuran as potent anticancer agents. *Eur. J. Med. Chem.* **2013**, *62*, 111-121.

20. Mossman, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to proliferation and cytotoxicity assays. *J. Immunol. Methods*, **1983**, *16*, 55-63.

21. Keiser, K.; Johnson, C.C.; Tipton, D.A. Cytotoxicity of mineral trioxide aggregate using human periodontal ligament fibroblasts. *J. Endod.,* **2000**, *26*, 288-291.

22. Yurttas, L.; Demirayak, S.; Akalın Ciftci, G. Cytotoxic, antiproliferative and apoptotic effects of new benzimidazole derivatives on A549 lung carcinoma and C6 glioma cell lines. *Anticancer Agents Med. Chem.* **2015**, *15*, 1174-1184.

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