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ARTICLE

Synthesis, Characterization and Biological Activities of Substituted 1-[Benzothiazol-(1*H*)-2-yl]-3-phenyl-prop-2-en-1-ones

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ABSTRACT

A series of *ortho* and *para* substituted 1-[benzothiazol-(*1H*)-2-yl]-3-phenyl-prop-2-en-1-one derivatives were synthesized from 2-acetyl benzothiazole and *ortho* and *para*-substituted benzaldehye using ethanol as solvent. The synthesized compounds were characterized by UV-visible, FT-IR, ^{1}H NMR and mass spectrometry. Antioxidant activities of synthesized compounds have been evaluated by DPPH free radical scavenging activity using ascorbic acid as standard. The standard solution and 1-[benzothiazol-(*1H*)-2-yl]-3-phenylprop-2-en-1-ones compounds were prepared with different concentrations. Anticancer activity of 1-[benzothiazol-(*1H*)-2-yl]-3-phenylprop-2-en-1-one and 1-[benzothiazol-(*1H*)-2-yl]-3(4-chlorophenyl)prop-2-en-1-one were assigned by MTT assays.

KEYWORDS

Benzothiazoles, DPPH, Free radical, Antioxidant acitivity, Anticancer activity..

INTRODUCTION

Chalcones are chemical compounds associated with pharmacological activities. In recent years, there has been an immense awareness among the scientists toward the design of new drugs, which consumes less time, highly potent and lower cost to prepare an effective drug molecule against various health problems. Chalcone is one of the secondary metabolites that has been proved to have some biological activities such as antimicrobial [1], antifungal [2], anticancer [3], antimalarial [4], antioxidant [5], antitumor [6], anti-inflammatory [7] and antidepressant [8]. Chalcones are α,β-unsaturated ketones possessing aryl or aliphatic moieties between carbonyl and vinyl parts. They possess multi-prolonged activities due to methylene and carbonyl moieties in their structure [9].

A large number of therapeutic agents are synthesized with the help of benzimidazole nucleus. During recent years there have been some interesting developments in the biological activities of benzothiazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. Antioxidants have the ability of protecting organisms from damage caused by free-radical induced oxidative stress [10].

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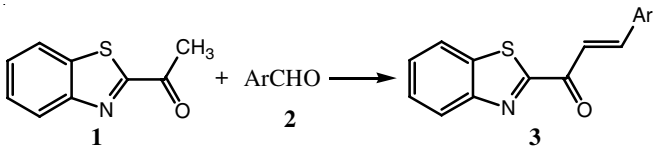
Cancer has been a major public health threat since the beginning of the 21st century. It progresses in different organs and systems of body and has no certain ethiopathology. In fact chemotherapy is the most popular therapeutic method. Therefore there is a need to develop new anticancer drugs having better efficiency and broad spectrum activity [10]. The present work describes the synthesis of some chalcone analogs, evaluation of antioxidant activity by DPPH scavenging method and anticancer activity by MTT assay method.

EXPERIMENTAL

The reagents and solvents used were of AR grade. All chemicals were purchased from Merck Specialities Pvt. Ltd. and HiMedia Laboratories Pvt. Ltd. The spectra were recorded on JEOL DRX 300 or DPX 300 NMR spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C NMR spectra), JEOL SX 102/DA-6000 mass spectrometer for ESI mass spectra and Nicolet 400D FTIR spectrometer. Melting points were uncorrected. Elemental analysis was done at the Central Drug Research Institute, Lucknow, India.

General procedure for the synthesis of *ortho*- and *para*-substituted 1-[benzothiazol-(*1H*)-2-yl]-3-phenyl-prop-2-en-1-one (3a-i): The synthesis of *ortho*- and *para*-substituted 1-[benzo-thiazol-(*1H*)-2-yl]-3-phenyl-prop-2-en-1-one derivatives (**3a-i**) were synthesized from 2-acetylbenzothiazole and *ortho/para*-substituted benzaldehydes in the presence of base using ethanol as solvent (**Scheme-I**).



1 2 3

Ar = Phenyl (**3a**); 2-Chloro-phenyl (**3b**); 4-Chloro-phenyl (**3c**); 2-Hydroxy-phenyl (**3d**); 4-Hydroxy-phenyl (**3e**); 2-Methoxy-phenyl (**3f**); 4-Methoxy-phenyl (**3g**); 2-Methyl-phenyl (**3h**); 4-Methyl-phenyl (**3i**)

Scheme-I: Synthetic route of compound **3**

1-[Benzothiazol-(*1H*)-2-yl]-3-phenyl-prop-2-en-1-one (3a): Yield 68.5 %, m.p. 187-189 °C; Elemental analysis %: calcd. (found) for $C_{23}H_{16}N_4OS_2$ (molar mass: 265.33): C 72.49 (72.43); H, 4.21 (4.18); N, 5.32 (5.28); IR (KBr, ν_{max}, cm^{-1}): 3295, 3141, 2359, 1638, 1561, 1514, 1401, 1239, 813, 762, 644, 503; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.114-7.444 (m, 2H, 2ArH); 7.477 (d, 3H, 1.8 Hz, 1ArH, 2 CH); 7.496-7.546 (m, 1H, 1ArH); 7.548-7.703 (m, 2H, 2ArH); 7.762 (d, 24 Hz, 1H, 1ArH); 7.991 (d, 6 Hz, 1H, 1ArH); 8.161 (d, 5.7 Hz, 1H, 1ArH). ^{13}C NMR; (75 MHz, $CDCl_3$) δ: 39.17, 39.37, 39.59, 39.79, 40, 40.21, 40.42, 77.01, 77.36, 77.56, 77.68, 109.69, 121.47, 137.34, 144.09, 160.61. UV-visible spectrum; λ_{max} = 280 nm.

1-[Benzothiazol-(*1H*)-2-yl]-3-(2-chloro-phenyl)-prop-2-en-1-one (3b): Yield 55.1 %, m.p. 157-159 °C; Elemental analysis %: calcd. (found) for $C_{17}H_{11}N_4OS_2Cl$ (molar mass: 299.78): C, 64.45 (64.11); H, 3.36 (3.36); N, 4.65 (4.67); IR (KBr, ν_{max}, cm^{-1}): 3426, 3173, 2957, 2867, 1601, 1545, 1402, 1313, 1223, 1086, 1009, 822, 718, 676, 629, 493; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: δ 7.239 (t, 12.6 Hz, 4H, 4ArH); 7.338 (d, 3.9 Hz, 6H, 4ArH, 2CH); ESI-MS:299 (M^+)

1-[Benzothiazol-(*1H*)-2-yl]-3(4-chloro-phenyl)-prop-2-en-1-one (3c): Yield 59.6 %, m.p. 158-161 °C; Elemental analysis %: calcd. (found) for $C_{17}H_{11}N_4OS_2Cl$ (molar mass: 299.78): C, 64.45 (64.11); H, 3.36 (3.36); N, 4.65 (4.67); IR (KBr, ν_{max}, cm^{-1}): 3436, 3293, 3156, 2358, 1613, 1401, 1234, 1111, 1068, 813, 760, 641, 503; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 7.440-6.952 (m, 10H, 8ArH, 1CH).

1-[Benzothiazol-(*1H*)-2-yl]-3-(2-hydroxy-phenyl)-prop-2-en-1-one (3d): Yield 66.4 %, m.p. 115-117 °C; Elemental analysis %: calcd. (found) for $C_{18}H_{14}N_4O_2S_2$ (molar mass: 281.33): C, 68.32 (68.31); H, 3.95 (3.94); N, 5.00 (4.98); IR (KBr, ν_{max}, cm^{-1}): 3382, 3137, 1613, 1494, 1401, 1223, 752, 693; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 4.004 (t, *J* = 1.95 Hz, 1H, OH); 6.575 (s, 1H, 1CH); 7.503-6.604 (m, 8H, 8ArH).

1-[Benzothiazol-(*1H*)-2-yl]-3(4-hydroxy-phenyl)-prop-2-en-1-one (3e): Yield 68.9 %, m.p. 257-59 ºC; Elemental analysis %: calcd. (found) for $C_{18}H_{14}N_4O_2S_2$ (molar mass: 281.33): C, 68.32 (68.31); H, 3.95 (3.94); N, 5.00 (4.98); IR (KBr, ν_{max}, cm^{-1}): 3772, 3292, 3029, 2912, 2856, 2726, 2583, 1835, 1902, 1639, 1595, 1556, 1310, 1238, 970, 942, 908, 786, 758, 819; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 5.011 (s, 1H, OH); 7.043 (d, *J* = 16.8 Hz, 3H, 3ArH); 7.106-7.574 (m, 3H, 3ArH); 8.139 (d, *J* = 6.3 Hz, 1H, 1ArH); 8.176 (d, *J* = 14.4 Hz, 1H, 1ArH).

1-[Benzothiazol-(*1H*)-2-yl]-3-(2-methoxy-phenyl)-prop-2-en-1-one (3f): Yield 64.3 %, m.p. 139-141 °C; Elemental analysis %: calcd. (found) for $C_{17}H_{14}N_2O_2$ (molar mass: 295.36): C, 69.10 (69.13); H, 4.43 (4.44); N, 4.75 (4.74); IR (KBr, ν_{max}, cm^{-1}): 3739, 3621, 3433, 3295, 3130, 2357, 1640, 1598, 1562, 1401, 1306, 1240, 641; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 2.351 (s, 3H, OCH_3); 7.440-7.207 (m, 8H, 8ArH).

1-[Benzothiazol-(*1H*)-2-yl]-3(4-methoxy-phenyl)-prop-2-en-1-one (3g): Yield 57.2 %, m.p. 140-143 ºC; Elemental analysis %: calcd. (found) for $C_{17}H_{14}N_2O_2$ (molar mass: 295.36): C, 69.10 (69.13); H, 4.43 (4.44); N, 4.75 (4.74); IR (KBr, ν_{max}, cm^{-1}): 3424, 3132, 2358, 1617, 1562, 1490, 1401, 1211, 1087, 1020, 819, 756, 724, 501; ^{1}H NMR: (300 MHz, $CDCl_3$) δ : 1.740 (s, 3H, OCH_3); 7.440-7.207 (m, 10H, 8ArH, 2CH).

1-[Benzothiazol-(*1H*)-2-yl]-3-(2-methyl-phenyl)-prop-2-en-1-one (3h): Yield 63.5 %, m.p. 126-128 °C; Elemental analysis %: calcd. (found) for $C_{17}H_{14}N_2O$ (molar mass: 279.36): C, 73.10 (73.09); H, 4.68 (4.69); N, 5.02 (5.01); IR (KBr, ν_{max}, cm^{-1}): 3331, 3007, 2923, 2856, 1807, 1740, 1645, 1589, 1500, 1461, 1081, 998, 880, 763, 730, 702; ^{1}H NMR: (300 MHz, $CDCl_3$) δ : 2.285 (s, 3H, $3CH_3$); 7.440-7.207 (m, 10H, 8ArH, 1CH).

1-[Benzothiazol-(*1H*)-2-yl]-3-(4-methyl-phenyl)-prop-2-en-1-one (3i): Yield 58.8 %, m.p. 127-130 °C; Elemental analysis %: calcd. (found) for $C_{17}H_{14}N_2O$ (molar mass: 279.36): C, 73.10 (73.09); H, 4.68 (4.69); N, 5.02 (5.01); IR (KBr, ν_{max}, cm^{-1}): 3456, 3129, 1633, 1401, 535; ^{1}H NMR: (300 MHz, $CdCl_3$) δ : 1.245 (s, 3H, $3CH_3$); (d, *J* = 6.878 Hz, 1ArH); 7.446-7.080 (m, 9H, 8ArH, 1CH).

Antioxidant activity

DPPH free radical scavenging activity: The free radical scavenging capacity was determined using DPPH method. The DPPH solution (10^{-5} M) was prepared by using 1 mg in 250

mL methanol. Benzothiazole solutions of different concentrations 0.1, 0.25, 0.5, 0.75 and 1 mM were prepared. DPPH solution (2.8 mL, 10^{-5} M) was mixed with benzothiazole sample solution (0.1 mL) and decolourization was measured at 517 nm after incubation for 30 min in the dark (spectrophotometer). The control DPPH solution was prepared which contain the same volume without any synthesized compounds and 0.05 mL methanol was used as the blank. Ascorbic acid was used as a reference standard and dissolved in DPPH.

The antioxidant capacity of the compound was expressed as the free radical scavenging activity (IC_{50}) of DPPH radical. Test solutions were prepared with sample solutions of different concentrations and their absorbance were found out at 517 nm. Similarly, the absorbance was found out for BHA solutions also. From the absorbance values, the percentage inhibition was calculated by using the following equation:

$$\text{Inhibition } (\%) = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

Then the % of inhibition was plotted against concentrations for different samples and ascorbic acid. The standard ascorbic acid shows the IC_{50} value of 284 µM.

Anticancer activity: A549 (lung carcinoma) cell line was initially procured from National Centre for Cell Sciences (NCCS), Pune, India and maintained Dulbecos modified Eagles medium (Gibco, Invitrogen). The cell lines was cultured in 25 cm^2 tissue culture flask with DMEM supplemented with 10 % FBS, L-glutamine, sodium bicarbonate and antibiotic solution containing: penicillin (100 U/mL), streptomycin (100 µg/mL) and amphoteracin B (2.5 µg/mL). Cultured cell lines were kept at 37 ºC in a humidified 5 % CO_2 incubator (NBS Eppendorf, Germany). The viability of cells were evaluated by direct observation of cells by inverted phase contrast microscope and followed by MTT assay method.

The percentage of growth inhibition was calculated using the formula:

$$\text{Cell inhibition } (\%) = 100 - \frac{Abs_{sample}}{Abs_{control}} \times 100$$

Non-linear regression graph was plotted between % Cell inhibition and log concentration. IC_{50} was determined using GraphPad Prism software.

RESULTS AND DISCUSSION

The structures of all the compounds were established on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

The antioxidant results (Table-1) shows that among the synthesized compounds, compound **3a** and **3c** have very low IC_{50} value (41 and 49 µM) means excellent antioxidant activity. While compounds **3b**, **3e**, **3f**, **3h** and **3i** have have good antioxidant activity.

The compounds which have highest antioxidant activities **3a** and **3c** were screened for their anticancer activity against MCF-7 cell lines by MTT method. It was found that compound **3a** was the most active derivative against the lung cancer cell line with IC_{50} of 38.5 µg/mL and compound **3c** exhibited an IC_{50} of 49.1 µg/mL.

TABLE-1
ANTIOXIDANT ACTIVITY IC_{50} VALUE OF SYNTHESIZED COMPOUNDS (**3a-i**)

Compd.	IC_{50} value (µM)	Compd.	IC_{50} value (µM)
3a	41	**3f**	61
3b	111	**3g**	305
3c	49	**3h**	54
3d	271	**3i**	91
3e	184	Ascorbic acid	284

Conclusion

A viable route and suitable reaction conditions to synthesize 1-[benzothiazol-(*1H*)-2-yl]-3-phenyl-prop-2-en-1-ones (**3a-i**) is reported. The compounds were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectra. These synthesized compounds were also assessed for the antioxidant and anticancer activities. It was found that compound **3a** exhibited the highest antioxidant and anticancer activities.

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