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Original Article

SYNTHESIS, CHARACTERIZATION AND ANTIOXIDANT ACTIVITY OF 2-ARYL BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

Objective: To synthesize benzothiazole derivatives, characterize them by ^{1}HNMR and ATIR techniques and evaluate for their antioxidant activity.

Methods: In the present study 12 benzothiazole derivatives were synthesized by reacting 2-chloronitro benzene as the primary reactant with different aromatic aldehydes and benzoic acids. Reactions were monitored using thin layer chromatography technique, and the newly synthesized derivatives were characterized by ATIR and ^{1}HNMR techniques. The antioxidant assay was performed using 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) or ABTS method and 2,2-diphenyl-1-picrylhydrazyl or DPPH method.

Results: The antioxidant activity was found to be better in ABTS assay than DPPH assay. The compounds showed comparable activity to ascorbic acid at 100µg/ml.

Conclusion: It was found that the synthesized benzothiazole derivatives showed significant radical scavenging potential.

Keywords: Antioxidant, Benzothiazoles, 2-chloronitrobenzene, Polyphosphoric acid

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INTRODUCTION

Free radicals play an important role in a cell's life and death. These are unstable/unpaired electrons in their outermost shell and may become highly reactive. Reactive oxygen species (ROS) are generated from molecular oxygen/nitrogen through Electron Transport Chain (ETC), cytochrome P450, and another cellular, sub-cellular functions. They affect beneficial metabolic and cellular processes adversely and play a key role in the development of pathological conditions of the body. In healthy individuals, it is normally balanced by the endogenous antioxidant system. If the endogenous antioxidants fail to overcome the reactive metabolites production, then exogenous antioxidants would be necessary to balance redox status. Antioxidants are the molecules that help to protect cells from oxidative stress [1]. Antioxidants are either present naturally in various types of food (fruits and vegetables) or taken as dietary supplements. They play a defensive role against oxygen free radical toxicity in our body [2]. Thus antioxidants are considered as scavengers of free radicals.

Free radicals are constantly being generated in the body through various mechanisms, and are also being removed by endogenous antioxidant defensive mechanisms that act either by scavenging free radicals, decomposing peroxides, and/or binding with pro-oxidant metal ions. Free radicals lead to cell damage and homeostatic disruption causing diseases including diabetes, cirrhosis, cancer and cardiovascular diseases [3, 4]. The imbalance between antioxidant defenses and free radical production generates oxidative stress which is responsible to damage essential biological entities like nucleic acids, lipids, proteins, producing excess ROS [5]. Thus the balance between the pro-oxidant and antioxidant is very important for the cell survival. All antioxidants generally influence the redox status, thereby protecting cells against Reactive Oxygen Species (ROS).

The cell damage through free radical-mediated reactions is usually protected by enzymatic and nonenzymatic defense mechanisms of the body. Enzymes like Catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase directly/indirectly contributes to defense against the generated ROS.

The non-enzymatic antioxidants like glutathione, vitamin E and C, uric acid, albumin, bilirubin, N-Acetylcysteine, melatoninare the scavengers of ROS and RNS [6] actually.

Classification of antioxidants

Antioxidants are classified in two ways

1. The first way of classification is described by Gutteridge and Halliwell [7].

- Primary antioxidants: involved in the prevention of oxidant formation
- Secondary antioxidants: are the scavengers of ROS.
- Tertiary antioxidants: repair the oxidized molecules through sources like dietary or consecutive antioxidants.

2. The second way of classification is

- Exogenous antioxidants (dietary sources) and
- Endogenous antioxidants.

Endogenous antioxidants

It can be categorized into primary antioxidants and secondary antioxidants. SOD, Catalase and Glutathione peroxidase are the primary antioxidant enzymes which inactivate the ROS into intermediates [8]. Secondary antioxidant enzymes are Glutathione reductase, Glucose-6-Phosphate dehydrogenase, glutathione-S-transferase, and ubiquinone. They work directly to detoxify ROS by decreasing the peroxides level and continuously supplying the NADPH and glutathione for primary antioxidant enzymes to maintain their proper functioning. Copper, iron, manganese, zinc, selenium enhance the activity of antioxidant enzymes [9, 10].

Exogenous antioxidants

These are mainly derived from food and other dietary sources. Several herbs, spices, vitamins, foods, vegetables, etc exhibit antioxidant activities. Various phytochemicals like flavonoids, isoflavones, flavones, anthocyanins, coumarins, lignans, catechins, isocatechins, epicatechin, etc. found in natural foods also show antioxidant properties.

MATERIALS AND METHODS

Experimental

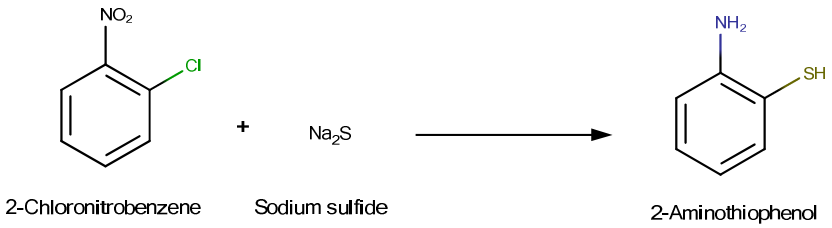
All chemicals and solvents were supplied by Sigma Aldrich, Merck, and CDH under a certificate of purity. The melting range of the synthesized compounds was measured by Scientech-2211 digital auto melting/ boiling point apparatus. Proton magnetic resonance (^{1}HNMR) spectra were recorded on Bruker 400 MHz NMR spectrometer using $CDCl_3$ as a solvent. Chemical shifts were reported in parts per million relative to internal standard tetramethylsilane (TMS). IR spectra were recorded on Bruker-Alpha 1005151/06 ATIR spectrophotometer.

Reaction progress was checked by TLC using Merck Silica gel 60 F-254 coated glass plates. The solvent system used was n-Hexane: Ethyl acetate in the ratio of 2:3.

Synthetic procedures: [11, 12]

Step I: For the synthesis of 2-aminothiophenol

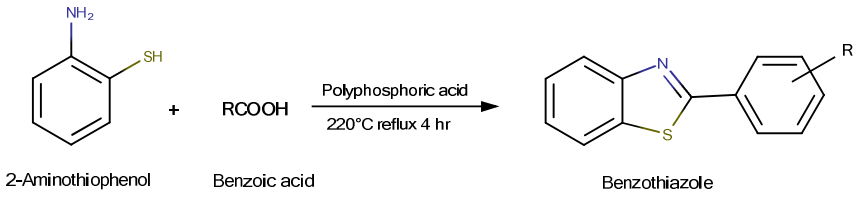
A clear solution of sodium sulphide nonahydrate (4.8g, 0.02M) in water (20 ml) was prepared. 2-chloronitrobenzene (1.28g, 0.008M) was added to it in one single portion, and the mixture was refluxed for 8 h. After 4 h, a small amount of yellow colored oil appeared in the reaction mixture due to the formation of 2-chloroaniline as the by-product. The reaction mixture was cooled after 8 h and then extracted with ether to remove 2-chloroaniline. The aqueous layer containing sodium salt of 2-aminothiophenol was saturated with sodium chloride and then acidified with glacial acetic acid. Addition of acetic acid should be done carefully to get the maximum yield of 2-aminothiophenol.



Step II: For the synthesis of benzothiazoles

- **Using 2-aminothiophenol and benzoic acid (Scheme I)**

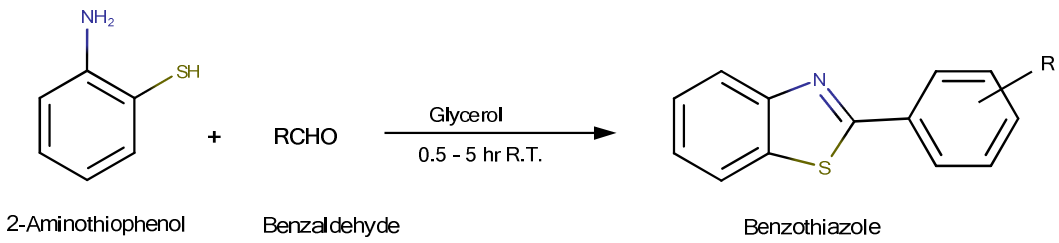
Equimolar quantities of 2-aminothiophenol and substituted benzoic acid were added to 15g of polyphosphoric acid and refluxed for 4 hr at 220˚C. The reaction mixture was cooled and poured into a large volume of rapidly stirred ice cold water. The slurry was made alkaline with 50% sodium hydroxide solution. The progress of the reaction was monitored by TLC, using n-Hexane: Ethyl acetate in the ratio of 2:3 as the mobile phase. During the basification, ice was added to prevent an excessive rise in temperature. The crude product was obtained by extracting the reaction mixture with toluene and subsequent evaporation of the solvent in a rotary vacuum evaporator followed by recrystallization from ethanol.



Scheme I

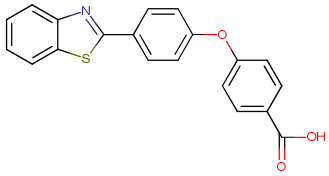
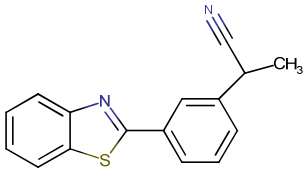
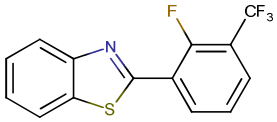
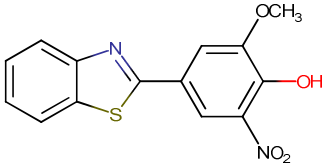
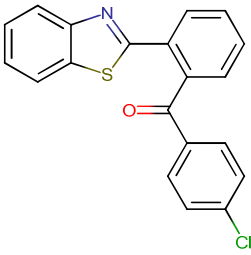
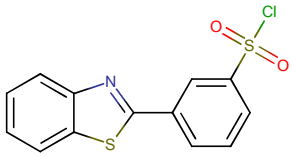
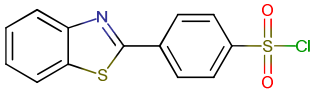
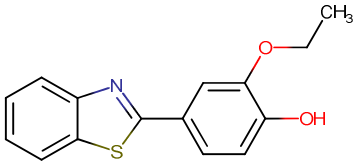
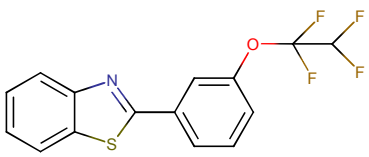
- **Using 2-aminothiophenol and benzaldehyde**

Equimolar quantities of 2-aminothiophenol (1.25 g, 10 mmol) and the appropriate aldehyde (10 mmol) in glycerol (10 ml) were heated until a clear solution was obtained and then left at room temperature for 0.5–5 h (TLC control). The reaction mixture was quenched with water, and the resulting solid product was collected by filtration, dried and recrystallized from ethanol to afford final compounds.



Scheme II

Table 1: List of synthesized compounds

Name	Structure	IUPAC name
BTA-1		4-[4-(1,3-benzothiazol-2-yl) phenoxy] benzoic acid
BTA-2		2-[3-(1,3-benzothiazol-2-yl) phenyl] propanenitrile
BTA-3		2-[2-fluoro-3-(trifluoromethyl) phenyl]-1,3-benzothiazole
BTA-4		4-(benzothiazol-2-yl)-2-methoxy-6-nitrophenol
BTA-5		2-[2-(4-chlorobenzoyl) phenyl]-1,3-benzothiazole
BTA-6		3-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride
BTA-7		4-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride
BTA-8		4-(1,3-benzothiazol-2-yl)-2-ethoxyphenol
BTA-9		2-[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-1,3-benzothiazole

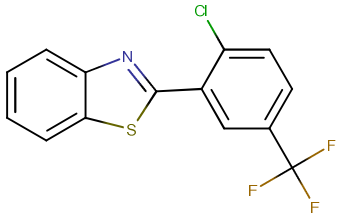
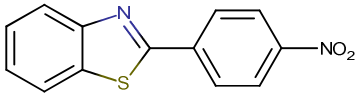
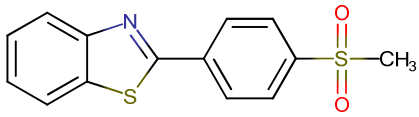
BTA-10		2-[2-chloro-5-(trifluoromethyl) phenyl]-1,3-benzothiazole
BTA-11		2-(4-nitrophenyl)benzothiazole
BTA-12		2-(4-methanesulfonyl phenyl)-1,3-benzothiazole

Table 2: Physical data of synthesized compounds

Name	Molecular formula	Molecular weight	Melting point (˚C)	Yield (%)	Solubility
BTA-1	$C_{20}H_{13}NO_3S$	347.39	121-123	62	Chloroform, DMSO, Ethanol, Methanol
BTA-2	$C_{16}H_{12}N_2S$	264.34	114-120	71	Chloroform, DMSO, Ethanol
BTA-3	$C_{14}H_7F_4NS$	298	115-120	74	Chloroform, DMSO, Ethanol, Methanol
BTA-4	$C_{14}H_{10}N_2O_4S$	303.31	118-121	56	Chloroform, DMSO, Ethanol, Methanol
BTA-5	$C_{20}H_{12}ClNOS$	349.83	115-117	82	Chloroform, DMSO, Ethanol, Methanol
BTA-6	$C_{13}H_{18}ClNO_2S_2$	309.79	116-121	65	Chloroform, DMSO, Ethanol
BTA-7	$C_{13}H_{18}ClNO_2S_2$	309.79	117-119	83	Chloroform, DMSO, Ethanol, Methanol
BTA-8	$C_{15}H_{13}NO_2S$	271.22	125-127	70	Chloroform, DMSO, Ethanol, Methanol
BTA-9	$C_{15}H_8F_4NOS$	327.3	112-116	56	Chloroform, DMSO, Ethanol, Methanol
BTA-10	$C_{14}H_7ClF_3NS$	313.73	115-119	70	Chloroform, DMSO, Ethanol, Methanol
BTA-11	$C_{13}H_8N_2O_2S$	256.28	116-118	54	Chloroform, DMSO, Ethanol, Methanol
BTA-12	$C_{14}H_{11}NO_2S_2$	289.37	120-125	69	Chloroform, DMSO, Ethanol, Methanol

Anti-oxidant activity

The anti-oxidant assay was performed by the method of Mensor *et al.* [13]

DPPH assay

The DPPH radical is one of the few stable organic nitrogen radicals, which bears a deep purple color. It is commercially available. Because of a strong absorption band centered at about 520 nm, the DPPH radical has a deep violet color in solution, and it becomes colorless or pale yellow when neutralized. This assay is based on the measurement of the reducing ability of anti-oxidants towards DPPH. The ability can be evaluated by electron spin resonance (EPR) or by measuring the decrease in its absorbance. Anti-oxidant assays are based on the loss of the DPPH color at 517 nm after reaction with the test compounds; the reaction is monitored by UV-Visible spectrophotometer.

Procedure

0.01m solution of DPPH was prepared in methanol. Methanolic solutions of all the compounds in the following concentration ranges were prepared (40µg/ml, 60µg/ml, 80µg/ml and 100µg/ml). Similarly, solutions of ascorbic acid in the same concentration range were prepared. 1 ml of DPPH solution was added to 1 ml of the sample solution and to ascorbic acid as well. The volume was finally made up to 3 ml using methanol. The test tubes containing the assay mixture were kept at a dark and cool place for 30 min. Immediately after incubation the absorbance of the DPPH solution, blank (methanol), samples and ascorbic acid containing DPPH reagent were recorded at 517 nm on a UV-VIS spectrophotometer. The antioxidant activity was measured using the formula.

% Scavenging or Inhibition = $[(A_o-A_s)/A_o]*100$

Where,

A_o= Absorbance of the DPPH solution without sample

A_s= Absorbance of DPPH solution with sample

ABTS assay

The assay is based on the ability of different compounds to scavenge 2, 2-azino-bis (ethylbenzthiazoline-6-sulfonic acid) radical cation. ABTS radicals have a characteristic absorbance at 734 nm. This absorbance decreases when the radical is reduced by any anti-radical compound. The decrease in the absorbance can be measured using a UV-VIS spectrophotometer at 734 nm.

Procedure

7 mmol ABTS stock solution in water was prepared. To it 2.45 mmol solution of potassium persulfate was added in 1:1 ratio (volume/volume). This reaction mixture was left undisturbed in a dark place for about 16 h for generation of the radicals. This solution was further diluted using methanol so that it has a stable absorbance of 0.700±0.05 at 734 nm. Methanolic solutions of all compounds including ascorbic acid were prepared in the concentration ranges of 40µg/ml, 60µg/ml, 80µg/ml and 100µg/ml. To 0.1 ml of the test solutions, 1 ml of distilled ABTS solutions were added. Absorbance of the test and the standard solutions were taken immediately at 734 nm. The antioxidant activity of the samples was determined using the equation

% E = $[(A_c-A_t)/A_c]*100$,

Where,

E= Anti-oxidant activity

A_c=Absorbance of the ABTS stock solution

A_t= Absorbance of the test compounds

RESULTS AND DISCUSSION

Table 3: Spectral study of synthesized compounds

Name	IR spectra data	^{1}HNMR spectra data ($CDCl_3$)
BTA-1	1710.98ν (C=O), 1690.08 ν (C=N), 1515.41 ν (C-C), 1411.45ν (C=C), 1058.96 ν (C-O-C), 754.78 ν (Ar C-H), 686.54 ν (C-S)	δ11.0 (s, 1H, COOH), 8.32-8.00 (m, 4H, Ar-H), 7.55 (t, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.13 (d, 2H, Ar-H), 6.72 (d, 2H, Ar-H)
BTA-2	2303.91 ν (C≡N),1665.11 ν (C=N), 1585.15 ν (C-C), 1431.68 ν (C=C), 759.19 ν (Ar C-H), 645.11 ν (C-S)	δ 8.20-8.05 (d, 2H, Ar-H), 7.52 (t, 2H, Ar-H), 7.33-6.99 (m, 4H, Ar-H), 3.46 (m, 1H, CH), 1.57 (d, 3H, CH_3)
BTA-3	1607.75 ν (C=N), 1515.50 ν (C-C), 1465.28 ν (C=C), 1050.58 ν (C-F), 745.14 ν (Ar C-H), 692.81 ν (C-S)	δ 8.25-8.12 (d, 2H, Ar-H), 7.56 (t, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H), 7.02 (t, 1H, Ar-H)
BTA-4	3376.99 ν (OH), 1615.35 ν (C=N), 1549.28 ν (C-C), 1468.13 ν (C=C), 1318.19 ν (C-N), 1041.48 ν (C-O-C), 799.98 ν (Ar C-H), 672.07 ν (C-S)	δ 8.32-8.00 (d, 2H, Ar-H), 7.88 (s, 1H, Ar-H), 7.52 (t, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 5.08 (s, 1H, OH), 3.99 (s, 3H, CH_3)
BTA-5	1801.85 ν (C=O), 1650.31 ν (C=N), 1515.40 ν (C-C), 1435.28 ν (C=C), 756.63 ν (Ar C-H), 722.64 ν (C-Cl), 692.40 ν (C-S)	δ 8.03-8.00 (d, 2H, Ar-H), 7.85 (d, 1H, Ar-H), 7.70 (d, 2H, Ar-H), 7.59-7.32 (m, 7H, Ar-H)
BTA-6	1610.16 ν (C=N), 1544.62 ν (C-C), 1409.12 ν (C=C), 1199.10 ν (SO_2Cl), 796.71 ν (Ar C-H), 679.41 ν (C-S)	δ 8.32-8.05 (m, 3H, Ar-H), 7.72 (d, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.55 (m, 3H, Ar-H)
BTA-7	1605.61ν (C=N), 1506.82 ν (C-C), 1439.52 ν (C=C), 1204.16 ν (SO_2Cl), 754.50 ν (Ar C-H), 670.11 ν (C-S)	δ 8.15 (d, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.99 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.54 (t, 2H, Ar-H)
BTA-8	3367.45 ν (OH), 1601.01 ν (C=N), 1508.41 ν (C-C), 1437.38 ν (C=C), 1039.98 ν (C-O-C), 750.17 ν (Ar C-H), 655 ν (C-S)	δ 8.59-8.05 (d, 2H, Ar-H), 7.49 (d, 2H, Ar-H), 6.97-6.68 (m, 3H, Ar-H), 4.65 (s, 1H, OH), 3.97 (m, 2H, CH_2), 1.53 (t, 3H, CH_3)
BTA-9	1728.86 ν (C=N), 1596.70 ν (C-C), 1439.12 ν (C=C), 1192.42 ν (C-F), 832.32 ν (Ar C-H), 722.53 ν (C-S)	δ 8.25 (d, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.56 (t, 2H, Ar-H), 7.21 (t, 1H, Ar-H), 7.04-6.73 (m, 3H, Ar-H)
BTA-10	1698.40 ν (C=N), 1515.09 ν (C-C), 1404.36 ν (C=C), 1077.57 ν (C-F), 789.28 ν (C-Cl), 742.04 ν (Ar C-H), 641.72 ν (C-S)	δ 8.32-8.00 (d, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.55 (t, 2H, Ar-H), 7.40 (d, 1H, Ar-H), 6.72 (d, 1H, Ar-H)
BTA-11	1669.26 ν (C=N), 1586.48 ν (NO_2), 1516.91 ν (C-C), 1417.09 ν (C=C), 752.05 ν (Ar C-H), 657.15 ν (C-S)	δ 8.28-8.04 (m, 4H, Ar-H), 7.73 (d, 2H, Ar-H), 7.51 (t, 2H, Ar-H)
BTA-12	1647.80 ν (C=N), 1523.76 ν (C-C), 1440.49 ν (C=C), 1022.14 (S=O), 802.37 ν (Ar C-H), 690.53 ν (C-S)	δ 8.31-8.09 (d, 2H, Ar-H), 7.97 (d, 2H, Ar-H), 7.68(d, 2H, Ar-H) 7.55 (t, 2H, Ar-H), 2.41 (s, 3H, CH_3)

Antioxidant assay

Table 4: Percentage scavenging of DPPH radical by compounds and ascorbic acid

Compounds	Dilutions (µg/ml)			
	40µg/ml	60µg/ml	80µg/ml	100µg/ml
BTA-1	51.48%	68.70%	74.20%	82.19%
BTA-2	42.69%	56.89%	69.34%	73.53%
BTA-3	32.85%	44.40%	52.65%	61.40%
BTA-4	44.50%	54.60%	66.93%	81.62%
BTA-5	51.12%	63.28%	74.0%	83.30%
BTA-6	32.65%	43.48%	55.90%	68.14%
BTA-7	10.80%	20.67%	37.37%	45.70%
BTA-8	35.87%	55.30%	70.34%	86.01%
BTA-9	16.45%	28.79%	52.18%	63.95%
BTA-10	12.43%	20.70%	27.26%	36.76%
BTA-11	35.14%	51.29%	63.16%	73.33%
BTA-12	31.75%	43.42%	51.33%	63.47%
Ascorbic acid	65.28%	72.14%	86.52%	92.38%

Table 5: Percentage scavenging of ABTS radical by compounds and ascorbic acid

Compounds	Dilutions			
	40µg/ml	60µg/ml	80µg/ml	100µg/ml
BTA-1	36.90%	47.20%	62.80%	76.50%
BTA-2	28.12%	37.17%	48.60%	59.80%
BTA-3	22.40%	36.41%	43.50%	55.20%
BTA-4	30.70%	44.43%	61.70%	74.50%
BTA-5	36.50%	50.20%	67.30%	71.70%
BTA-6	28.60%	34.66%	46.17%	54.02%
BTA-7	12.71%	18.30%	32.52%	43.64%
BTA-8	33.38%	45.50%	62.7%	83.16%
BTA-9	18.57%	29.10%	41.67%	51.80%
BTA-10	14.60%	25.14%	32.70%	43.60%
BTA-11	25.70%	43.12%	60.42%	74.50%
BTA-12	31.38%	43.50%	60.71%	72%
Ascorbic acid	41.80%	53.27%	70.20%	89.47%

The ATIR of the compounds was found to be in accordance with the data reported in the literature [11]. The major peaks were recorded at 1728-1605 cm-1 for C=N group, at 1365-1305 $cm^{-1}$and 722-640 cm^{-1} for C-S group, Absorption peaks for other functional groups were also observed in the respective derivatives. ^{1}HNMR: NMR peak for CH_3 group was found at δ1.53-3.99 ppm. The NMR peak for aromatic hydrogens Ar-H was found to be in the range δ6.99-8.32 ppm

The most common spectrophotometric methods to fig. out the antioxidant power of activity of organic compounds are depending on DPPH and ABTS, which react directly with the antioxidant species under assessment. In the DPPH analysis, the antioxidants are able to decrease the stable DPPH radical to the yellow colored diphenyl-picrylhydrazine. The method is in accordance with the decrease of an alcoholic DPPH solution in the existence of hydrogen giving anti-oxidant, due to the development of the nonradical form, DPPH-H, during the reaction. The ABTS analysis is depending on a single electron exchange, the ABTS radical-cation decolorization, which is in accordance with the decrease of ABTS radicals by antioxidants. To assess the free radical scavenging activity of synthesized benzothiazole compounds, DPPH and ABTS assays were conducted, and the results are indicated in table 4 and 5 respectively.

From the results, it is clear that the efficacy of BTA-1, BTA-4, BTA-8 and BTA-11as antioxidant agents was better in ABTS assay compared to DPPH assay. The compounds BTA-1, BTA-4, and BTA-8 were found to possess comparable activity to ascorbic acid at 100µg/ml. BTA-1 and BTA-5 at 80µg/ml showed better activity than ascorbic acid at 60µg/ml. Compounds having methoxy group (BTA-4 and BTA-11) were more active than those carrying methyl (BTA-12) and ethoxy (BTA-2) functional groups. BTA-1 with acid group functionality was noticed to exert appreciable activity against both DPPH and ABTS radical.

CONCLUSION

In summary, we have efficiently produced twelve new benzothiazole derivatives using well recognized synthetic protocols. The synthesized compounds were characterized using ATIR and ^{1}HNMR techniques and were screened for their antioxidant potential. Results suggested that compounds BTA-1, BTA-4, BTA-5, and BTA-8 are the efficient scavengers of DPPH and ABTS radicals, showing themselves as a device for discovering the further antioxidant molecules. From the structure-activity perspective, the position of the electron withdrawing and electron donating functional groups on the benzothiazole core may promote the expected antioxidant activity. Lastly, it is possible that further derivatization of such substances will be of attention with a desire to get more selective agents.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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