Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(15):20-26
(http://derpharmachemica.com/archive.html)

Comparative study for the synthesis of new generation of 2(*3H*)-benzothiazolones as antioxidant agents

Hanane Chabane[1*], Mahfoud Messarah[2] and Messaoud Liacha[1]

[1]Laboratory of Organic Synthesis and Biocatalysis, Organic Synthesis and Medicinal Chemistry Group, BADJI Mokhtar-Annaba University, P.O. Box 12 El-Hadjar, Annaba 23000, Algeria
[2]Laboratory of Biochemistry and Environmental Toxicology, Faculty of Sciences, BADJI Mokhtar-Annaba University, P.O. Box 12 El-Hadjar, Annaba 23000, Algeria

---

ABSTRACT

A series of new Schiff bases derived from benzothiazolone moiety were synthesized under thermal and ultrasound irradiation conditions, by reaction of 6-amino-benzothiazolone intermediates with various substituted 2-hydroxybenzaldehydes. The chemical structures of the prepared compounds ***5a-5h*** *were characterized by their melting point, spectral and analytical data. The newly synthesized compounds were in good agreement with the proposed structures. Ultrasound irradiations gave a lower reaction time to offer products* ***5a-5h*** *in higher yields than those obtained by the conventional method where their yields increased from 67-87% to 91-98%. All the compounds were screened for in vitro antioxidant activity. The free radical scavenging activities have been determined by measuring their interaction with the stable free radical 2,2-diphenyl-2-picrylhydrazylhydrate. Result indicated that the 6-(5-Bromo-2-hydroxybenzylideneamino)benzo[d]thiazol-2(3H)-one* ***(5e)*** *showed the most favorable antioxidant activity exhibiting* IC_{50} *of 32.55 µM.*

Keywords: 2(3H)-benzothiazolone, 2-hydroxybenzaldehyde, Schiff bases, synthesis, green chemistry, ultrasound irradiation

---

INTRODUCTION

In recent years, the interest of preventive effects of antioxidative agents, in relation to their therapeutic properties, has increased significantly. The antioxidant activity of a compound is its ability to resist oxidation. Phenolic antioxidant compounds are one of the most important antioxidant agents which can inhibit the oxidative stress in biological system and prevent any damage. Indeed, most of the antioxidants of synthetic or natural origin have hydroxyphenolique groups in their structures and the antioxidant properties are attributable in part to the ability of these compounds to trap free radicals such as the radical hydroxyl ($OH^{\bullet}$) and superoxide ($O_2^{\bullet}$) [1-4]. Previous studies have indicated that free radicals and reactive oxygen species (ROS) including hydrogen peroxide (H_2O_2), extremely reactive hydroxyl, and several other free radicals produced by cells, would cause damage to all biomolecules such as lipids, proteins and DNA resulting in cell damage [5] and subsequently this damage may result in many diseases [6-13].

Schiff base derived from the condensation of substituted salicylaldehydes and primary amines produces interesting oxygen and nitrogen donor Schiff base compounds, and are of very particular interest due to diverse chelating ability [14]. They play important roles in both synthetic and structural research because of their structural diversity and preparative accessibility, also of their importance in medicinal and pharmaceutical field [15]. Salicylaldehyde Schiff base ligands may contain a variety of substituents with different electron-donating or electron-withdrawing groups, and therefore may have interesting chemical and biological properties. They have also been shown to exhibit a broad

range of biological activities including antioxidant [16], antiviral [17], anticancer [18] and others. These activities can be related to the ligand structural arrangements and to the nature of the substituent groups [19]. Additionally, a great deal of interest has been directed towards the bioactivity of 2(3H)-benzothiazolone derivatives as sources of antioxidant. A large number of 2(3H)-benzothiazolone derivatives bearing various substituents at position-3 and 6 have been reported to posses Antifungal [20] and anti-inflammatory as well as analgesic activities which are related to antioxidant property [21-26].

Ultrasound irradiation is a fascinating phenomenon, known to accelerate different types of common reactions used in synthetic organic chemistry efficiently [27,28]. Therefore ultrasound irradiation has been established as an important technique in organic synthesis, which has intrigued many research laboratories worldwide during the last few years [29-35].

In view of the above facts, we were interested in a practical technique for the synthesis of new series of 2-benzothiazolinonyl Schiff bases. Herein, we wish to report our studies toward the coupling of 6-amino-2(3H)-benzothiazolone substrates with substituted salicylaldehyde as the base to produce diverse 2(3H)-benzothiazolone Schiff bases (Figure 1) under conventional and ultrasound irradiation conditions. We also investigated the effect of the nature and the substituent position on the radical scavenging abilities of these novel compounds using the DPPH method.

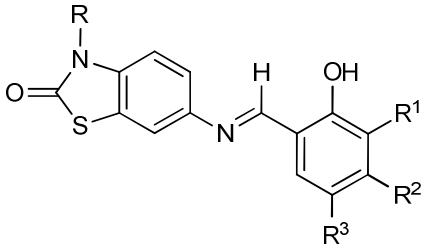


Figure 1 General structure of the synthesized Schiff bases ligands 5a-5h

MATERIALS AND METHODS

All chemicals and solvents that we have used in this study were purchased from Aldrich Chemicals. Melting points have been determined using a SMP3 Stuart Scientific apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were performed $(CD_3)_2SO$ solutions on a Bruker AC 400 spectrometer using dimethylsulfoxide-d_6 with TMS as internal standard, with chemical shifts reported as δ (*ppm*). Analytical thin layer chromatography was performed with commercial silica gel plates 60 F_{254} (Merck) and visualized with UV light, using Ethylacetate/Cyclohexane (8/2, v/v) solvent system as eluent. The experimental Elemental analyses (C, H, N, S) were conducted using the ThermoScientific Flash 2000, their results were found to be in satisfactory agreement (±0.4%) with the calculated values. Ultrasound assisted reactions were carried out using a FUNGILAB ultrasonic bath with a frequency of 40 kHz and a nominal power of 250 W. The reactions were carried out in an open glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL) at room temperature (25°C).

The identity of the known products benzothiazolone derivatives **1**, **2**, **3a**, **3b**, **4a** and **4b** was confirmed by the comparison of their melting points and spectroscopic data with those of authentic compounds available in the literature [36-41].

General procedure for the Synthesis of Schiff bases derivatives (5a-5h)

Conventional technique

Substutued 2-hydroxybenzaldehyde dissolved in boiling ethanol was mixed with a boiling solution of 6-amino-2(3H)-benzothiazolones **4a** and **4b** in the same solvent. The resulting mixture was refluxed at 80 ºC for 1-3h with continuous stirring in the presence of few drop of acetic acid. Progress of the reaction was monitored by TLC. The product which formed was filtered off, washed with ethanol, dried, and recrystallized from ethanol to give the desired Schiff base ligands **(5a-5h)** (Scheme 1).

Ultrasound technique

The procedure was similar to that described in conventional method except that the mixture was capped in an open glass tube and subjected to ultrasonic irradiations (40 kHz and nominal power 250 W) at room temperature under catalyst-free condition for the appropriate time until completion of the reaction (monitored by TLC). The resulting solid was collected by filtration and purified by crystallization from the appropriate solvent.

6-(2-Hydroxy-3-methoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5a)
Orange powder; m.p.: 244-245°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 3.82 (3H, s, O-CH_3), 6.92 (d, J=5 Hz, 1H), 7.17 (m, 2H), 7.37 (d, J=1.5 Hz, 1H), 7.75 (d, J=1.5 Hz, 1H), 8.96 (s, 1H, N=CH, azomethine), 12.01 (s, 1H, N-H), 13.14 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 169.95 (C=O), 162.35 (N=C), 150.30, 147.86, 142.87, 135.43, 124.56, 123.73, 120.54, 119.26, 118.63, 115.50, 115.31, 112.03 (aromatic carbons), 55.87 (OCH_3). Anal. Calcd for $C_{15}H_{12}N_2O_3S$: (%): C, 59.98; H, 4.02; N, 9.32; S, 10.67. Found: C, 59.82; H, 2.94; N, 7.61; S, 8.43.

3-Methyl-6-(2-hydroxy-3-methoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5b)
Yellow powder; m.p.: 200-201°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 3.43 (s, 3H, N-CH_3) 3.83 (s, 3H, O-CH_3), 6.92 (d, J=7.2 Hz, 1H), 7.12 (d, J=7.2 Hz, 1H), 7.21 (d, J=1.2 Hz, 1H), 7.38 (d, J=5.5 Hz, 1H), 7.48 (d, J=1.2 Hz, 1H), 7.83 (d, J=1.2 Hz, 1H), 8.98 (s, 1H, N=CH, azomethine), 13.10 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 168.61(C=O), 162.64 (N=C), 150.31, 147.88, 147.88, 143.42, 136.57, 123.74, 122.41, 120.46, 119.27, 118.66, 115.55, 111.91 (aromatic carbons), 55.89 (O-CH_3), 29.18 (CH_3). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: (%): C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 61.05; H, 4.52; N, 9.17; S, 9.90.

6-(2-hydroxy-4-methoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5c)
Green powder; mp: 253-254°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 3.81 (s, 3H, O-CH_3), 6.49 (d, J=2.4 Hz, 1H), 6.55 (d, J=11.6 Hz, H), 7.14 (d, J=8.4 Hz, 1H,), 7.31 (d, J=8.4 Hz, 1H), 7.49 (d, J=8.8 Hz, 1H), 7.69 (d, J=2 Hz, 1H), 7.86 (s, 1H, N=CH, azomethine), 11.99 (s, 1H, N-H), 13.55 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 169.90 (C=O), 163.48 (N=C), 162.72, 161.57, 143.05, 134.87, 133.90, 124.47, 120.24, 115.05, 113.01, 112.00, 106.78, 100.80 (aromatic carbons). Anal. Calcd for $C_{15}H_{12}N_2O_3S$: (%): C, 59.98; H, 4.02; N, 9.32; S, 10.60. Found: C, 60.31; H, 4.42; N, 9.29; S, 10.54.

3-Methyl-6-(2-hydroxy-4-methoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5d)
Yellow powder; mp: 219-220°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 3.42 (s, 3H, N-CH_3), 3.81(s, 3H, O-CH_3), 6.49 (d, J=2 Hz, 1H), 6.55 (dd, J=11.2 Hz, J=2.4 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H), 7.43 (dd, J=10.8 Hz, J=2.4 Hz, 1H), 7.50 (d, J=8.8 Hz, 1H), 7.77 (d, J=2 Hz, 1H), 8.89 (s, 1H, N=CH, azomethine), 13.52 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 168.56 (C=O), 163.54 (N=C), 145.28, 143.57, 136.12, 135.90, 133.94, 122.12, 120.17, 115.25, 113.01, 111.88, 106.82, 100.80 (aromatic carbons), 55.45 (O-CH_3) 29.15 (CH_3). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: (%): C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 61.23; H, 4.48; N, 9.14; S, 10.14.

6-(5-Bromo-2-hydroxybenzylideneamino)benzo[d]thiazol-2(3H)-one (**5e**)
Yellow powder; m.p.: 282-283°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 6.97 (d, J= 8.8 Hz, 1H), 7.17 (d, J= 8.4 Hz, 1H), 7.36 (dd, J= 10.4Hz, J= 2 Hz, 1H), 7.53 (dd, J= 11.6 Hz, J= 2.4 Hz, 1H), 7.71 (d, J= 2.8 Hz, 1H), 7.73 (d, J= 2 Hz, 1H), 7.78 (d, J= 2 Hz, 1H), 8.94 (s, 1H, N=CH, azomethine), 12.00 (s, 1H, N-H), 12.96 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 169.65 (C=O), 160.43 (N=C), 159.10, 142.80, 135.76, 135.27, 133.68, 124.60, 121.30, 120.47, 119.00, 115.58, 112.07, 109.91 (aromatic carbons). Anal. Calcd for $C_{14}H_9N_2O_2SBr$: (%): C, 48.15; H, 2.60; N, 8.02; S, 9.18. Found: C, 47.94; H, 2.52; N, 7.51; S, 8.90.

3-Methyl-6-(5-bromo-2-hydroxybenzylideneamino)benzo[d]thiazol-2(3H)-one (**5f**)
Beige powder; m.p.: 218-219°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 3.43 (s, 3H, N-CH_3), 7.39 (d, J= 8.4 Hz, 1H), 7.60 (d, J=2.4 Hz, 1H), 7.64 (d, J=2.4 Hz, 1H), 7.66 (d, J=2.4 Hz, 1H), 7.72 (d, J=2.8 Hz, 1H), 7.81 (d, J=2 Hz, 1H), 8.96 (s, 1H, N=CH, azomethine, 12.91 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 168.59 (C=O), 159.10 (N=C), 143.40, 145.80, 136.79, 135.34, 133.68, 122.41, 121.30, 120.41, 119.01, 115.78, 111.94, 109.93 (aromatic carbons), 29.20 (N-CH_3). Anal. Calcd for $C_{15}H_{11}N_2O_2SBr$: (%): C, 49.60; H, 3.05; N, 7.71; S, 8.83. Found: C, 49.33; H, 2.94; N, 7.44; S, 8.43.

6-(5-Chloro-2-hydroxybenzylideneamino)benzo[d]thiazol-2(3H)-one (**5g**)
Yellow powder; m.p.: 278-279°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 6.99 (d, J= 8.8 Hz, 1H), 7.17 (d, J= 8.8 Hz, 1H), 7.37 (dd, J= 10.4 Hz, J= 2 Hz, 1H), 7.42 (dd, J= 11.6 Hz, J= 2.8 Hz, 1H), 7.71 (d, J= 2.8 Hz, 1H), 7.73 (d, J= 2.4 Hz, 1H), 8.94 (s, 1H, N=CH, azomethine), 12.00 (s, 1H, N-H) , 12.93 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 169.91 (C=O), 160.55 (N=C), 158.69, 142.87, 135.60, 132.52, 130.72, 124.53, 122.55, 120.68, 120.49, 118.57, 115.59, 112.05 (aromatic carbons). Anal. Calcd for $C_{14}H_9N_2O_2SCl$: (%): C, 55.17; H, 2.98; N, 9.19; S, 10.52. Found: C, 54.81; H, 2.83; N, 8.82; S, 10.24.

3-Methyl-6-(5-chloro-2-hydroxybenzylideneamino)benzo[d]thiazol-2(3H)-one (**5h**)
Yellow powder; m.p.: 218-219°C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 3.44 (s, 3H, N-CH_3), 6.99 (d, J= 8.8 Hz, 1H), 7.40 (m, 2H), 7.48 (dd, J= 10.8 Hz, J= 2.4 Hz, 1H), 7.72 (d, J= 2.8 Hz, 1H), 7.81 (d, J= 2 Hz, 1H), 8.97 (s, 1H, N=CH, azomethine), 12.89 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 168.59 (C=O), 160.80

(N=C), 158.70, 143.41, 136.80, 132.58, 130.71, 122.58, 122.41, 120.69, 120.42, 118.58, 115.76, 111.94 (aromatic carbons), 28.19 (N-CH_3). Anal. Calcd for $C_{15}H_{11}N_2O_2SCl$: (%): C, 56.52; H, 3.48; N, 8.79; S, 10.06. Found: C, 56.39; H, 3.38; N, 8.32; S, 9.96.

Measurement of Free Radical-Scavenging Action

Free radical scavenging activity of the synthesized compounds against stable free radical 2,2-diphenyl-2-picrylhydrazylhydrate (DPPH, Sigma-Aldrich Chemie, Steinheim, Germany) was determined spectrophotometrically and estimated as previously described with some modifications [42]. When DPPH reacts with antioxidant compounds, which can donate hydrogen, it is reduced. Following the reduction, its deep violet color in methanol bleached to yellow, showing a significant absorption decrease at 517 nm. Then 500 µL of various concentrations (5, 10, 30, 50 and 100 µM) of the compounds (**5a-5h**) dissolved in methanol were added to 500 µL of methanol solution of DPPH (0.6 mM). After a 30 min incubation period at room temperature, the absorbance was read against a blank at 517 nm. Ascorbic acid (vitamin C) and butylated hydroxytoluene (BTH) were used as the reference compounds. All tests and analyses were done in three replicates and the results were averaged.

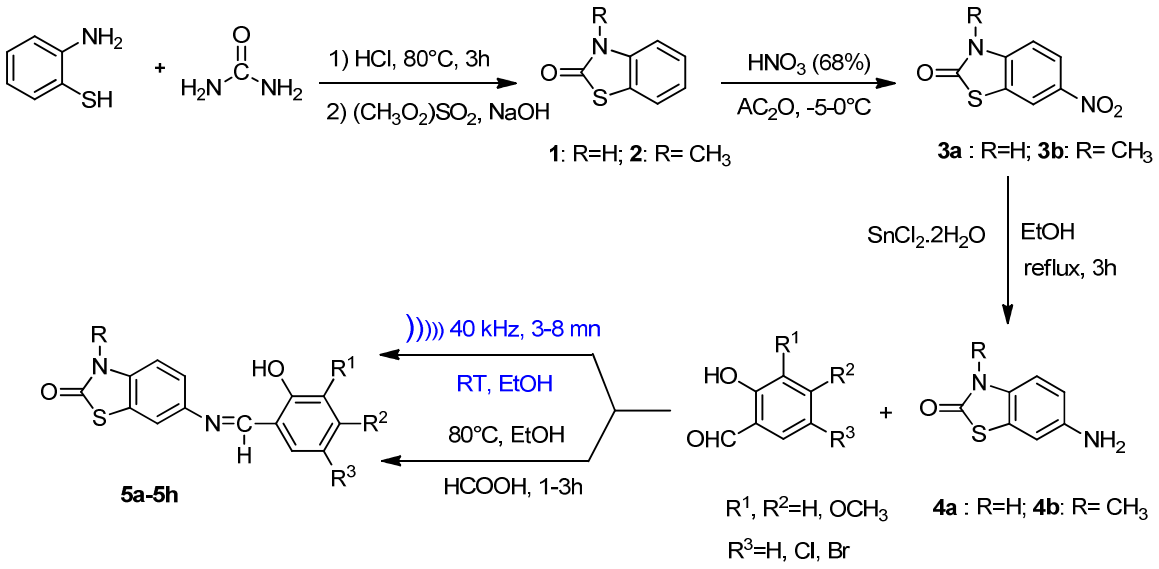
The free radical scavenging activity of each solution was then calculated as percent inhibition (%RSC) according to the following equation:

$$\%RSC = 100 * \frac{(A_{blank} - A_{sample})}{A_{blank}}$$

Where A_{blank} is the absorbance of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound.

The antioxidant activities of various concentrations of the compounds (**5a-5h**) were expressed as IC_{50}, defined as the concentration of the test material required to cause a 50% decrease in initial DPPH concentration.

RESULTS AND DISCUSSION



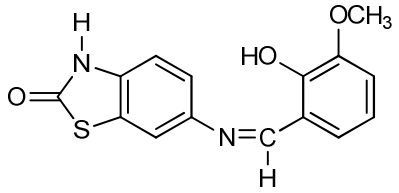
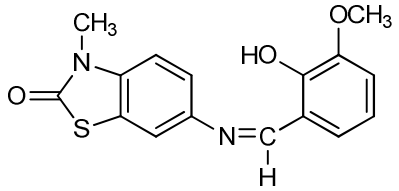
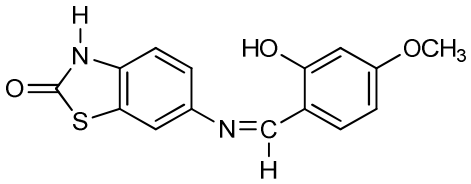
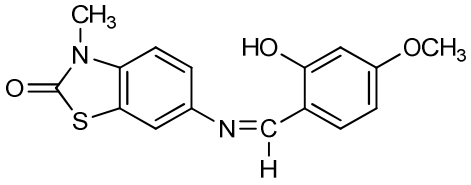
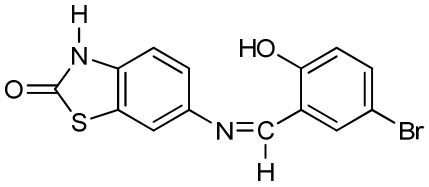
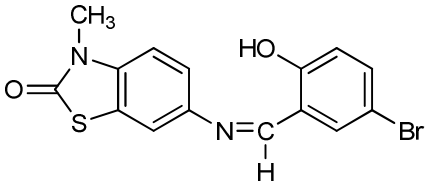
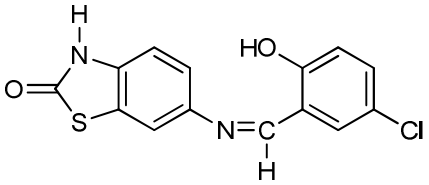
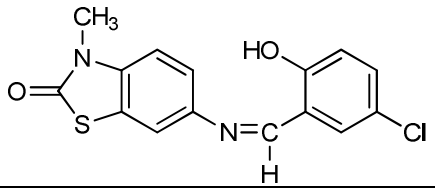
Scheme 1 Synthesis of compounds 5a-5h

Chemistry

In this present work, new Schiff bases derived from 2(3H)-benzothiazolone have been successfully synthesized, by the condensation of 6-amino-2(3H)-benzothiazolone derivatives with substituted salicylaldehyde under reflux conditions. The synthetic route used for the preparation of the novel Schiff base ligands **5a-5h** have been realized as shown in scheme 1. 2(3H)-benzothiazolones **4a** and **4b** bearing an amino group in 6-position were used as starting materials to prepare the target compounds. Syntheses of the title compounds were started by obtaining 2(3H)-benzothiazolone **1** from 2-aminothiophenol by reaction with urea under heat, that was N-methylated using dimethylsulfate in basic medium, leading to the formation of the corresponding 3-methylbenzothiazolone derivative **2**. Nitration of the aromatic ring of **1** and **2** with nitric acid in acetic anhydride produced the 6-nitro-benzothiazolone and 3-methyl-6-nitro-benzothiazolone derivatives **3a** and **3b** respectively. Reduction of the nitro group of the intermediates **3a** and **3b** was carried under standard conditions, using tin chloride dihydrate ($SnCl_2$. $2H_2O$) in

ethanol to give the corresponding 6-aminobenzothiazolone substrates **4a** and **4b**, respectively (Scheme 1). Finally, the new target compounds **5a**-**5h** were obtained with yields ranging from 67% to 87%, when synthesized by conventional method in ethanol at reflux in presence of catalytic amount of acetic acid. The reaction was completed in (91-98%) of yield within 3-8 minutes when ultrasound irradiation was used to the synthesis of these desired Schiff base compounds, under catalyst-free condition, by condensation of the appropriate salicylaldehyde with the corresponding appropriate 6-aminobenzothiazolone substrates **4a** and **4b**, as illustrated in Table 1 (Scheme 1).

Table 1 Comparison between reaction times and yields for conventional and ultrasonic irradiation methods

Entry	Structure	Conventional		Ultrasound	
		Time (h)	Yield (%)	Time (min)	Yield (%)
5a		1	87	8	97
5b		1	74	6	95
5c		2	67	7	94
5d		1	81	5	96
5e		1	78	3	95
5f		1	80	4	96
5g		2	70	3	96
5h		1	81	4	98

Antioxidant Activity

The antioxidant activity of the newly synthesized ligands **5a–5h** was investigated and evaluated for their free radical scavenging activity using the stable DPPH (2,2-diphenyl-2-picrylhydrazylhydrate) radical. The IC_{50} was calculated for each compound with ascorbic acid and BHT as standard compounds and are summarized in Table 2. The synthesized compounds **5a**–**5h** showed activity in the range of 32.55-118.10 μM (Table 2). Compound **5e** (IC_{50} = 32.55 μM) showed highest activity, more active than the standard BHT (IC_{50} = 36.81μM).

Ascorbic acid, a phenolic antioxidant used as a standard compound showed stronger antioxidant activity (IC_{50} value of 13.12 μM) than that of any the other synthesized compounds.

Table 2 DPPH radical scavenging and IC_{50} (μM) of Schiff bases 5a-5h and reference compounds ascorbic acid and BHT

	%RSC					
Compound	5 μM	10 μM	30 μM	50 μM	100 μM	IC_{50}
5a	12.67	27.16	47.14	55.39	69.65	54.35
5b	4.69	17.70	28.33	42.56	57.62	81.23
5c	5.94	15.58	24.02	46.15	65.64	69.18
5d	6.20	8.74	24.29	37.49	54.37	84.92
5e	33.71	41.04	57.54	62.92	74.65	32.55
5f	10.48	20.35	42.37	56.29	62.54	65.15
5g	2.23	20.16	27.84	38.59	53.72	87.70
5h	2.80	10.36	20.12	26.93	42.56	118.10
Ascorbic acid	20.72	51.83	68.36	79.87	95.61	13.12
BHT	22.22	31.85	40.05	72.72	82.66	36.81

Acknowledgements

This work was supported by Algerian Ministry of Higher Education and Scientific Research. Authors are highly thankful to Pr. G. Kirsch, for carrying out spectral ^{1}H-NMR and ^{13}C-NMR and microanalysis for compounds.

CONCLUSION

In conclusion, some novel Schiff base ligands derived from 6-amino-2(3H)-benzothiazolones and substituted 2-hydroxybenzaldehyde (**5a-5h**) have been successfully synthesized and characterized on the basis of their analytical and spectroscopic properties, and evaluated them for their in vitro antioxidant activity by DPPH method. The IC_{50} value was determined for every compound. From results of DPPH assay, it has been found that the compound **5e** showed promising antioxidant activity compared to the synthetic antioxidant BHT. The above results suggested that the rational design of benzothiazolone based Schiff base derivatives could have great importance as novel antioxidant agents, and contributing to the development of novel effective compounds with potential antioxidative activity for prevention, reduction of risk factors and treatment of disease associated with oxidative stress related degenerative diseases. Further studies on the corresponding action mechanisms of these compounds are under investigation.

REFERENCES

[1] C. A. Rice-Evans, N. J. Miller, P. G. Bolwell, P. M. Bramley, J. B. Pridham, *Free Radic. Res.*, **1995**, 22, 375.
[2] S. Burda, W. Oleszek, *J. Agric. Food. Chem*., **2001**, 49, 2774.
[3] M. Antolovich, P. D. Prenzler, E. Patsalides, S. McDonald, K. Robards, *Analyst*, **2002**, 127, 183.
[4] G. Bartosz, *Comments on Toxicology*, **2003**, 9, 5.
[5] S. Chung, P. P. Dzeja, R. S. Faustino, C. Perez-Terzic, A. Behfar, A. Terzic, *Nat. Clin. Pract. Cardiovasc. Med.*, **2007**, 4, 60.
[6] B. Halliwell, J. M. C. Gutteridge, Free radicals in biology and medicine, Oxford University Press: Oxford, **1999.**
[7] B. N. Ames, M. K. Shigenaga, T. M. Hagen, *Proc. Natl. Acad. Sci. USA*, **1993**, 90, 7915.
[8] A. A. Eurton, S. Fairhurst, *Crit. Rev. Toxicol.*, **1987**, 18, 27.
[9] H. L. Wang, Z. Y. Yang, B. D. Wang, *Transition Met. Chem*., **2006**, 31, 470.
[10] P. R. Devi, S. K. Kumari, C. Kokilavani, *Indian J. Clin. Biochem*., **2007**, 22, 143.
[11] B. A. Freeman, J. D. Crapo, *Lab Invest*., **1982**, 47, 412.
[12] S. O. Oyedemi, G. Bradley, A. J. Afolayan, *Afr. J. Pharm. Pharmacol*., **2010**, 4, 70.
[13] O. Polterat, *Curr. Org. Chem.*, **1997**, 1, 415.
[14] N. J. Long, *Angew. Chem. Int. Ed. Engl*., **1995**, 34, 21.
[15] P. Espinet, M. A. Esteruelas, L. A. Ore, J. L. Sarrano, E. Sola, *Coord. Chem. Rev.*, **1992**, 117, 215.
[16] H. Y. Li, Z. Yang, B. Wang, *Transition Met. Chem*., **2006**, 31, 598.
[17] D. Sriram, P. Yogeeswari, N. S. Myneedu, V. Saraswat, *Bioorg. Med. Chem. Lett*., **2006**, 16, 2127.
[18] X. U. Dongfang, M. A. Shuzhi, D. U. Guangying, H. E. Qizhuang, S. U. N. Dazhi, *J. Rare Earths*, **2008**, 26, 643.

[19] L. Araya, J. Vargas, J. Costamagna, *Transition Met. Chem.*, **1986**, 11, 312.
[20] O. Petrov, M. Gerova, K. Petrova, Y. Ivanova, *J. Heterocyclic Chem*., **2009**, 46, 44.
[21] A. H. Abdelazeem, S. I. Khan, S. W. White, K. J. Sufka, C. R. McCurdy, *Bioorg. Med. Chem*., **2015**, 23, 3248.
[22] Y. Dundar, B. Çakir, E. Kupeli, M. F. Şahin, *Turkish J. Pharm. Sci*., **2006**, 3, 51.
[23] S. Ünlü, T. Onkol, Y. Dundar, B. Okcelik, E. Kupeli, E. Yesilada, N. Noyanalpan, M. F. Sahin *Arch. Pharm. Pharm. Med. Chem*., **2003**, 336, 353.
[24] O. Petrov, A. Antonova, V. Kalcheva, L. Daleva, *Med. Chem. Res*., **1995**, 5, 442.
[25] I. Yekini, F. Hammoudi, F. Martin-Nizard, S. Yous, N. Lebegue, P. Berthelot, P. Carato, *Bioorg. Med. Chem*., **2009**, 17, 7823.
[26] S. H. Ferreira, B. Lorenzetti, M. Devissaguet, D. Lesiuer, Y. Tsouderos, *Br. J. Pharmacol*., **1995**, 114, 303.
[27] B. S. Bhatkhande, M. V. Adhikari, S. D. Samant, *Ultrason Sonochem*., **2002**, 9, 31.
[28] G. V. Ambulgekar, S. D. Samant, A. B. Pandit, *Ultrason Sonochem*., **2005**, 12, 85.
[29] G. Cravotto, G. Palmisano, S. Tollari, G. M. Nano, A. Penoni, *Ultrason Sonochem*., **2005**, 12, 9.
[30] F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron*, **2005**, 61, 11771.
[31] S. Tangestaninejad, M. Moghadam, V. Mirkhani, H. Kargar, *Ultrason Sonochem*., **2006**, 13, 32.
[32] G. Cravotto, M. Beggiato, A. Penoni, G. Palmisano, S. Tollari, J. M. Leveque, W. Bonrath, *Tetrahedron Lett*., **2005**, 46, 2267.
[33] S. Moon, L. Duchin, J. V. Cooney, *Tetrahedron Lett.*, **1979**, 20, 3917.
[34] J. L. Luche, C. Einhorn, J. Einhorn, J. V. Sinisterra-Gago, *Tetrahedron Lett*., **1990**, 31, 4125.
[35] T. Lepoint, F. Mullie, *Ultrason Sonochem*., **1994**, 1, 13.
[36] J. J. D'Amico, R. W. Fuhrhop, F. G. Bollinger, W. E. Dahl, *J. Heterocycl. Chem*., **1986**, 23, 641.
[37] Y. Li, C. Li, K. Jin, .S. Sun, X. Zhou, *Acta Chimica Sinica*, **2012**, 70, 151.
[38] H. Zinner, W. Nimmich, *J. Pract. Chem*., **1961**, 14, 139.
[39] T. H. Fife, J. E. C. Hatchins, M. S. Wang, *J. Am. Chem. Soc.*, **1975**, 97, 5878.
[40] J. J. D'Amico, F. G. Bollinger, J. J. Freeman, J. *Heterocycl. Chem*., **1988**, 25, 1503.
[41] N. Suzuki, S. Kodoya, R. Donmori, *Chem. Pharm. Bull*., **1976**, 24, 1050.
[42] L. L. Mensor, F. S. Menezes, G. G. Leitão, A. S. Reis, T. C. dos Santos, C. S. Coube, S. G. Leitão, *Phytother. Res.*, **2001**, 15,127.