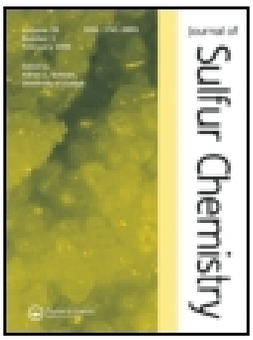

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Synthesis and evaluation of biological activities of 4-cyclopropyl-5-(2-fluorophenyl) arylhydrazono-2,3-dihydrothiazoles as potent antioxidant agents

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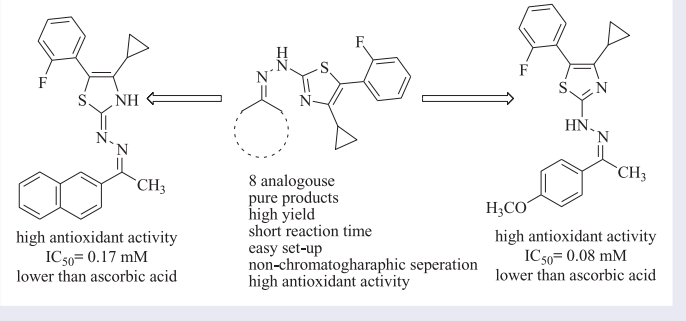
ABSTRACT

A new series of 4-cyclopropyl-5-(2-fluorophenyl)arylhydrazono-2,3-dihydrothiazole derivatives was synthesized via the reaction of prepared thiosemicarbazones with 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone in the presence of Et_3N as a catalyst through a semi Hantzsch cyclization. The optimized reaction conditions for this one-pot reaction were achieved. The products were obtained in short reaction times, high yields and high purities. Antioxidant activity of products was evaluated using DPPH (2,2-diphenyl-2-picryl-hydrazyl) and ABTS 2,2-azinobis(3-ethylbenzothiazoline-sulfonate) assays. Products showed higher antioxidant activity using the ABTS method. Compounds **5c** and **5g** showed lower IC_{50} values compared with ascorbic acid as a standard. Compounds **5a–5h** possessed moderate to high antioxidant activity by both methods. Also, antibacterial activity of **5a–5h** was evaluated against gram-positive and gram-negative bacterial strains. None of the compounds inhibited *A. hydrophila*, while they had moderate to low inhibitory activity against other tested bacterial strains.



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Introduction

Sulfur-containing heterocyles have been under investigation for a long time because of their interesting and diverse biological properties. Also, sulfur is an important element that is incorporated into proteins and some biomolecules.[1] Thiazoles as sulfur-containing compounds possessed various applications in medicine. Thiazole moiety is found in thiamine (vitamin B_1). Also, some important drugs such as penicillin, sulfathiazole, ritonavir, abafungin, bleomycine, and tiazofurin have thiazole moiety as their integral part. Thiazoles have attracted considerable attention due to their wide biological activities such as antitrypanosomal,[2] anti-inflammatory,[3,4] antihypertensive,[5] anti-allergic,[6] antibacterial,[7] anti-schizophrenia,[8] anti-HIV,[9] analgesic,[10] and anti-viral.[11] Moreover, hydrazinyl thiazole derivatives exhibited interesting biological activities including antioxidant,[12,13] antibacterial,[14] anti-malarial,[15] antitumor,[16] and antifungal.[17] Also, hydrazinyl thiazole derivative of isatin has been used as a naked eye chemosensor for fluoride anion detection.[18] Recently, various biological activities, *e.g.* antibacterial, antifungal, antioxidant, cytotoxicity and DNA cleavage of complexes derived from thiazoles have been studied.[19,20]

Compounds bearing fluorine atom have shown interesting biological activities.[21,22] According to the literature, the presence of fluorine atom can increase the potential of biological activities, *e.g.* fluorinated Schiff bases derived from 1,2,4-triazoles showed potent antiproliferative activity,[23] and fluorine atom enhanced insecticidal activity of 2-(3-(2,6-dichloro-4-(3,3-dichloroallyloxy)phenoxy)propoxy)-5-(trifluoromethyl) benzo[*d*]oxazole.[24]

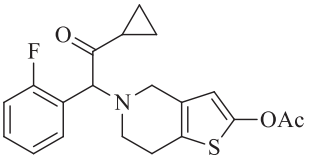
Sunlight, ultraviolet light, ionizing radiation, chemical reactions, and metabolic processes can produce free radical species. Free radical species can react and oxidize DNA, lipids, and proteins, and nucleic acids in living systems and result in degenerative disease and health problems. Antioxidants are a class of compounds which trap free radicals, so can reduce the risk for chronic diseases such as cancer and heart disease.[25]

As a part of our current studies in synthesis of thiazolyl-pyrazoline derivatives,[26] *bis*-thiazoles,[27] thiazolyl-pyridazinones,[28] and 1,4-dihydropyridines bearing thiazole moiety and possessing high antioxidant activity [29] here, we reported synthesis of new hydrazinyl thiazoles and evaluation of their antioxidant and antibacterial activities.

Results and discussion

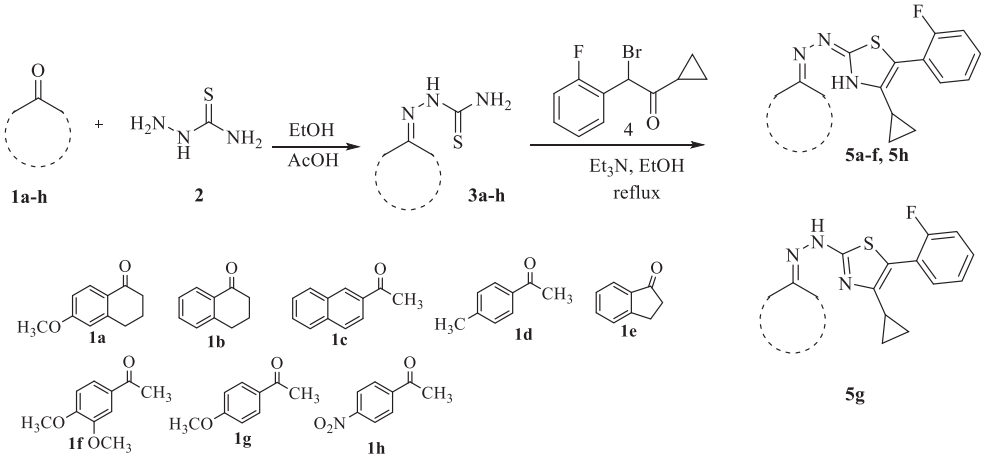
Chemistry

α-Halocarbonyl compounds are convenient and widely used building blocks for various types of heterocyclization and for the Hantzsch's thiazole synthesis.[30] 2-Bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (α-halocarbonyl compound) is a key moiety in prasugrel as a platelet inhibitor drug, which is more efficient than ticlopidine and clopidogrel [31] (Figure 1). Recently, it has been used in the synthesis of thiazol-2-imine derivatives [32] so this prompted us to investigate synthesis of new thiazoles using 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone. Even though, the carbonyl group 4 is condensed to a carbon of thiazole ring, but the cyclopropyl and 2-fluorophenyl moieties still presented in the skeleton of target products 5 (Scheme 1).



prasugrel

Figure 1. Structure of prasugrel.



Scheme 1. Synthesis of 4-cyclopropyl-5-(2-fluorophenyl)arylhydrazono-2,3-dihydrothiazole derivatives **5a–5g.**

In this study, new 4-cyclopropyl-5-(2-fluorophenyl)arylhydrazono-2,3-dihydrothiazole derivatives **5a–5h** were synthesized through the reaction of carbonyl compounds **1a–1h**, thiosemicarbazide **2**, and 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone **4**. Thiosemicarbazone derivatives **3a–3h** were prepared through the condensation of carbonyl compounds **1a–1h** and thiosemicarbazide **2** in the presence of a few drops of AcOH in EtOH. Then, cyclization of thiosemicarbazones **3a–3h** with 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone **4** under optimized reaction conditions led to the corresponding products **5a–5h** (Scheme 1).

With the aim to obtain the optimal reaction conditions, preparation of **5a** was selected as a model reaction. Results are summarized in Table 1. The effects of different basic catalysts, amounts of catalyst, and solvents were studied. According to the results, the reaction proceeded slowly in low yield in the absence of catalyst (entry 1), while product **5a** was obtained in a higher yield and shorter reaction time in the presence of Et_3N (entry 2). Increasing the amount of catalyst showed no substantial improvement in the yield (entry 5), while the yield was decreased by reducing the amount of catalyst to 10% (entry 4). Moreover, the effects of other polar solvents such as DMF, methanol (MeOH) and CH_3CN on the yield and time of the reaction were studied (entry 6–11). Thus, compound **5a** was obtained from the reaction of thiosemicarbazone **3a** and **4** in the presence of Et_3N (20 mol%) in high yield (95%) and short reaction time (30 min) in EtOH as the solvent under

Table 1. Optimization of reaction condition for synthesis of **5a**.

Entry	catalyst	Solvent	Condition	Time (min)	Yield%
1	–	EtOH	r.t.	240	53
2	Et_3N (20 mol%)	EtOH	r.t.	120	85
3	Et_3N (20 mol%)	EtOH	Reflux	30	95
4	Et_3N (10 mol%)	EtOH	Reflux	45	88
5	Et_3N (40 mol%)	EtOH	Reflux	30	94
6	Et_3N (20 mol%)	DMF	Reflux	30	91
7	Et_3N (20 mol%)	MeOH	Reflux	40	82
8	Et_3N (20 mol%)	CH_3CN	Reflux	50	85
9	DBU (20 mol%)	EtOH	Reflux	40	80
10	piperidine (20 mol%)	EtOH	Reflux	45	82
11	NaOAc (20 mol%)	EtOH	Reflux	90	76

reflux conditions. The formation of product **5a** was indicated by a reaction color change from yellow to dark orange within 5 min, however completion of the reaction took place within 30 min.

The scope of this method was explored for the synthesis of new 4-cyclopropyl-5-(2-fluorophenyl)arylhydrazono-2,3-dihydrothiazoles **5a–5h** with different carbonyl compounds **1a–1h** under the optimized reaction conditions. The results showed that this procedure is reliable, simple setup, reproducible, high yield, economic and products purified without chromatographic methods. All products were fully characterized by IR, ^{1}H NMR and ^{13}C NMR spectra. The physicochemical properties of synthesized compounds are presented and summarized in Table 2.

IR spectra of products **5a–5h** showed characteristic absorption bands at 3320–3200, 1620–1600 and 1070–1050 cm^{-1} due to N–H, C=N and C–F bonds, respectively. ^{1}H NMR spectra of products were in accordance with expected number, chemical shifts and coupling constants. Aromatic protons appeared at 8.28–6.66 ppm. Also, aliphatic proton of cyclopropyl moiety (H_c) and methylene protons appeared as multiples at 1.99–1.86 and 1.20–0.88 ppm, respectively. In addition, N–H can be endo- or exo-cyclic. However, according to the literature [33] a signal at 14.50–11.45 ppm is related to exocyclic N–H. So, we can propose an exo-cyclic N–H for compound **5g** according to a down field signal at 12 ppm and an endo-cyclic N–H for other compounds.

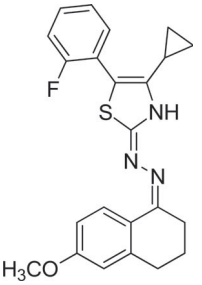
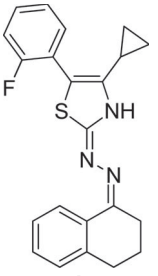
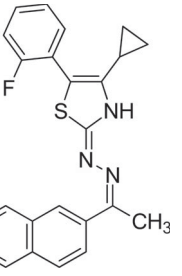
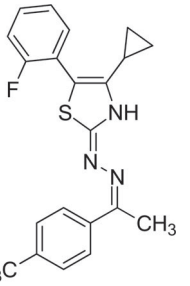
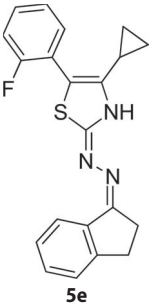
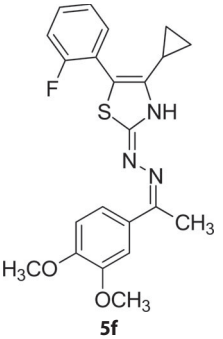
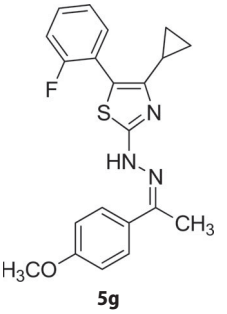
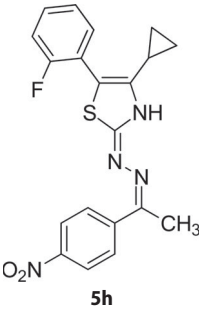
^{13}C NMR spectra of compounds **5a–5h** corresponded to the expected number and types of carbons. Aromatic and olefinic carbons appeared at 168.6–108.4 ppm and aliphatic carbons appeared at their expected chemical shifts at 55.9–7.8 ppm. ^{13}C NMR spectra of products represented C–F couplings clearly. Fluorine atom has split all carbons of the phenyl ring. All chemical shifts and coupling constants of important carbon atoms are summarized in Table 3.

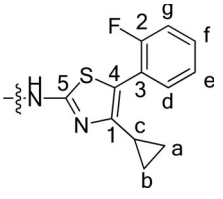
Biology

Antioxidant activity

All products were screened for their *in vitro* antioxidant activity. DPPH (2,2-diphenyl-2-picrylhydrazyl) radical and ABTS 2,2-azinobis(3-ethylbenzothiazoline-sulfonate) radical cation are widely used, rapid, simple, and inexpensive methods to evaluate antioxidant ability of compounds. In this research, the antioxidant activity of compounds was evaluated using colorimetric DPPH and ABTS methods. When a compound acts as an antioxidant

Table 2. Data related to synthesized 4-cyclopropyl-5-(2-fluorophenyl)arylhydrazono-2,3-dihydrothiazoles.

				
Compound	**5a**	**5b**	**5c**	**5d**
Time (min)	30	30	20	35
Yield %	95	94	96	89
m.p. (°C)	114–118	120–123	195–198	89–92
				
Compound	**5e**	**5f**	**5g**	**5h**
Time (min)	20	40	35	30
Yield %	93	90	91	88
m.p. (°C)	182–186	153–157	85–87	166–170



it can scavenge free radicals and lead to a decrease in absorption band at 517 and 734 nm for DPPH and ABTS solutions, respectively. Moreover, potential antioxidant activity leads to a rapid decrease in absorbance. ABTS is also frequently used by the food industry and agricultural researchers to measure the antioxidant capacities of foods. ABTS is converted to its radical cation ($ABTS^{\bullet+}$) by the addition of sodium persulfate or potassium persulfate. $ABTS^{\bullet+}$ scavenging is considered as an electron transfer reaction.[34] ABTS radical cation is blue in color, when it reacts with an antioxidant compound the blue color changes to yellow or colorless. Also, the DPPH radical changes from purple to colorless in reaction with an antioxidant compound. $DPPH^{\cdot}$ scavenging may be through donation of a radical hydrogen atom ($H^{\bullet}$) to form a stable DPPH-H molecule.[35]

The antioxidant activities of compounds were screened at concentrations of 125–4000 μg/mL at 517 and 734 nm for DPPH and ABTS assays, respectively. Also, IC_{50}

Table 3. ^{13}C NMR spectroscopy data of significant carbon atoms of **5a–5h**.

Compound	5a	5b	5c	5d	5e	5f	5g	5h
C_1	140.8	139.1	139.9	139.9	139.4	146.3	140.0	143.3
C_2	159.9	159.9	159.9	159.9	159.9	159.9	159.9	159.9
	$^1J_{C,F} = 247$	$^1J_{C,F} = 247$	$^1J_{C,F} = 249$	$^1J_{C,F} = 248$	$^1J_{C,F} = 248$	$^1J_{C,F} = 247$	$^1J_{C,F} = 249$	$^1J_{C,F} = 247$
C_3	120.5	120.4	116.7	118.6	116.7	120.2	116.9	119.6
	$^2J_{C,F} = 16$	$^2J_{C,F} = 16$	$^2J_{C,F} = 15$	$^2J_{C,F} = 15$	$^2J_{C,F} = 14$	$^2J_{C,F} = 15$	$^2J_{C,F} = 15$	$^2J_{C,F} = 15$
C_4	112.9	113.2	112.3	112.5	111.7	112.9	112.0	113.9
C_5	168.3	168.3	168.1	168.6	167.3	168.1	167.9	167.3
C_6	150.2	150.4	155.6	157.7	149.8	148.9	155.2	149.7
$C_{a,b}$	11.1, 11.1	11.1, 11.1	9.3, 9.3	10.2, 10.2	9.2, 9.2	11.0, 11.0	9.3, 9.3	10.8, 10.8
C_c	7.8	7.8	8.3	7.9	8.3	7.8	8.3	7.9
C_d	132.3	132.3	131.7	–	131.6	132.3	131.7	132.2
	$^3J_{C,F} = 3$	$^3J_{C,F} = 3$	$^3J_{C,F} = 1$	–	$^3J_{C,F} = 2$	$^3J_{C,F} = 3$	$^3J_{C,F} = 2$	$^3J_{C,F} = 2$
C_e	124.1	124.4	124.8	124.4	123.3	124.1	124.7	124.2
	$^4J_{C,F} = 4$	$^4J_{C,F} = 4$	$^4J_{C,F} = 4$	$^4J_{C,F} = 4$	$^4J_{C,F} = 4$	$^4J_{C,F} = 3$	$^4J_{C,F} = 3$	$^4J_{C,F} = 4$
C_f	129.1	129.1	131.5	130.2	131.4	129.3	131.3	129.7
	$^3J_{C,F} = 8$	$^3J_{C,F} = 8$	$^3J_{C,F} = 8$	$^3J_{C,F} = 8$	$^3J_{C,F} = 9$	$^3J_{C,F} = 8$	$^3J_{C,F} = 8$	$^3J_{C,F} = 8$
C_g	116.0	116.0	116.5	116.2	116.5	116.0	116.4	116.1
	$^2J_{C,F} = 22$	$^2J_{C,F} = 22$	$^2J_{C,F} = 22$	$^2J_{C,F} = 21$	$^2J_{C,F} = 22$	$^2J_{C,F} = 21$	$^2J_{C,F} = 22$	$^2J_{C,F} = 22$

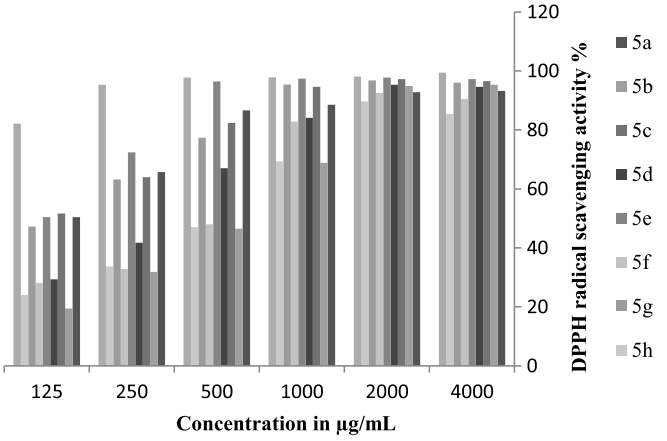


Figure 2. DPPH radical-scavenging activity.

values (the concentration of compounds to scavenge 50% of DPPH or ABTS) were calculated by plotting radical scavenging activity against concentration and obtaining a line equation. Ascorbic acid was used as a standard. The investigation of antioxidant activity revealed that all the newly synthesized compounds showed potent to moderate radical scavenging activity when compared with ascorbic acid as a standard. As it is depicted in Figures 2 and 3 radical scavenging activity of products **5a–5h** was dose dependent. In the DPPH assay, compounds **5a**, **5b**, **5e** and **5g** showed higher antioxidant activity at lower concentration (125–500 µg/mL) in comparison with others. While, at higher concentrations the antioxidant activity of all products was approximately equal. Moreover, compounds **5a** and **5e** showed a chigher antioxidant activity at low concentration (120 µg/mL) in the ABTS assay, while higher concentrations represented potent antioxidant activity.

In addition, IC_{50} values of products **5a–5h** were calculated (Figure 4). The IC_{50} values were in the range of 1.92–0.17 and 0.96–0.08 µM for DPPH and ABTS assays, respectively.

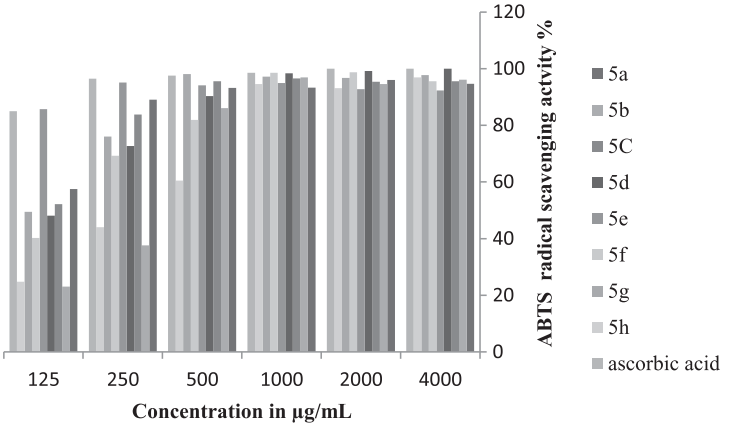


Figure 3. ABTS radical-scavenging activity.

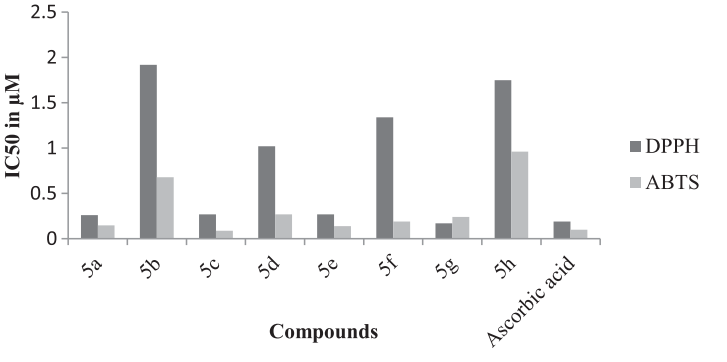
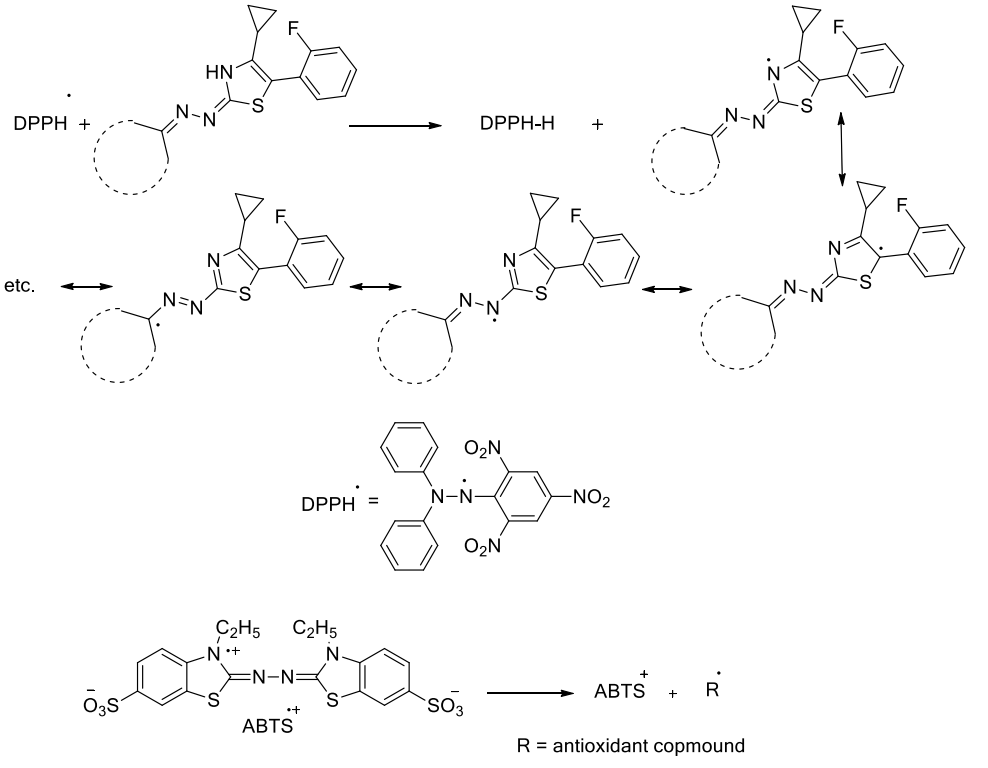


Figure 4. IC_{50} values of **5a–5h** using DPPH and ABTS assays.

As it is evident, the ABTS assay showed more potent antioxidant activity. It shows that compounds **5a–5h** can donate radical electron better than the hydrogen radical. Product **5g** was more active than ascorbic acid according to the DPPH assay, while compound **5c** represented better antioxidant activity when compared with ascorbic acid in the ABTS assay. However, compounds **5a**, **5c**, **5e** and **5g** showed potent antioxidant activity. Other compounds showed moderate activity.

Thiazole moiety has an important role in antioxidant activity.[25,12] As it is depicted in Scheme 2 the endo- or exo- N–H readily can donate a hydrogen radical to the DPPH radical and generate a new radical species which can resonate through the thiazole ring and =C–N–N=C moieties. So, the new radical can be stable by resonance through this structure. Although the thiazole and =C–N–N=C moieties have an important role in antioxidant activity, however other parts of products can affect this activity as well. Probably, the high antioxidant activity of 5c can be due to the fused aromatic rings which can stabilize the free radical by resonance through a longer system. Low antioxidant activity of **5h** is due to the presence of an electron-withdrawing group NO_2, which resulted in destabilization of radicals (Scheme 2).[36]



Scheme 2. Proposed mechanism for antioxidant activity of compounds **5a–5h.**

Antibacterial activity

The new synthesized compounds **5a–5h** were screened for their *in vitro* antibacterial activity against Gram-positive and Gram-negative bacterial strains including: *Staphylococcus aureus* (*S. aureus*), *Micrococcus luteus* (*M. luteus*), *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*Ps. aeruginosa*), *Bacillus subtilis* (*B. subtilis*), and *Aeromonas hydrophila* (*A. hydrophila*) using the well-diffusion method. Penicillin G and Gentamicin were used as positive controls. DMSO was used as a negative control and showed no activity against mentioned bacterial strains. The antibacterial activity of products **5a–5h** was screened at a concentration of 1000 µg/mL in DMSO. The experiments were performed in triplicate. The results are presented as mean ± standard deviation in millimeter.

According to Table 4 all of the compounds were inactive against *A. hydrophila*, while all of the compounds showed antibacterial activity against *Ps. aeruginosa.* Moreover, **5a** and **5f** showed low antibacterial activity against *S. aureus*; however, most of the compounds possessed antibacterial activity against *E. coli* and *B. subtilis.* Furthermore, **5e** showed the highest antibacterial activity against *B. subtilis* (14.3 ± 0.57) among all of the compounds. Also, **5f** and **5b** possessed higher antibacterial activity against *M. luteus* (10.6 ± 0.57) and *E. coli* (11.6 ± 1.15), respectively. Moreover, compounds **5a** and **5c** showed similar activity (10.3 ± 0.57) against *Ps. aeruginosa*. In addition, the antibacterial activity of compounds **5a–5h** was not comparable to standard drugs.

Table 4. Antibacterial assay of **5a–5h.** Results are presented as mean ± SD in mm.

Compound	*E. coli*	*A. hydrophila*	*Ps. aeruginosa*	*M. luteus*	*S. aureus*	*B. subtilis*
5a	9.3 ± 0.57	–	10.3 ± 0.57	–	8.6 ± 0.57	9.3 ± 0.57
5b	11.6 ± 1.15	–	8.3 ± 0.57	8.6 ± 0.57	–	11.3 ± 0.57
5c	7.6 ± 0.57	–	10.3 ± 0.57	8.3 ± 0.57	–	8.6 ± 0.57
5d	9.3 ± 0.57	–	9.3 ± 0.57	7.3 ± 0.57	–	10.3 ± 0.57
5e	–	–	9.3 ± 0.57	7.6 ± 0.57	–	14.3 ± 0.57
5f	–	–	9.3 ± 0.57	10.6 ± 0.57	9.6 ± 0.57	8.6 ± 0.57
5g	9.3 ± 0.57	–	9 ± 1.0	8.3 ± 0.57	–	10.3 ± 0.57
5h	8.6 ± 0.57	–	8.6 ± 0.57	7.6 ± 0.57	–	–
Penicillin G	45.0 ± 1.0	46.6± 1.52	24.0± 1.0	54.0± 1.0	23.0± 1.0	32.0± 1.0
Gentamicin	32.0 ± 1.0	41.3± 1.57	29.6± 0.57	46.0± 1.0	30.0± 1.0	35.3± 0.57

Conclusion

In conclusion we have reported an efficient, convenient and easy setup procedure for synthesis of new 4-cyclopropyl-5-(2-fluorophenyl)arylhydrazono-2,3-dihydrothiazole derivatives. The optimized procedure led to high yields and high purities products in short reaction time. The obtained data revealed that products namely **5a**, **5c**, **5e** and **5g** exhibited promising antioxidant activity. The important role of hydrazinyl-thiazole moiety of synthesized compounds in antioxidant activity was discussed. The antioxidant activity by the ABTS method was higher than the DPPH method; this presents potential electron donation capacity of products besides their hydrogen atom transfer capacity. Products showed moderate to low antibacterial activity.

Experimental

Materials and instruments

Starting materials containing ketones, thiosemicarbazide, and 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone were obtained from Fluka company (Switzerland) and Merck company (Germany), antioxidant reagents were supplied from Sigma company (Germany), and biological cultures were obtained from Merck company (Germany) and Quelab company (Canada). All chemicals were used without further purification. All reactions were monitored by TLC performed on silica gel plates (60 F_{254} Merck). IR spectra were recorded on a Shimadzu IR-470 spectrophotometer in anhydrous potassium bromide (KBr). ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker spectrometers using $CDCl_3$ as the solvent and chemical shifts are expressed relative to TMS. Coupling constants were expressed in hertz (Hz). Melting points were determined using a Mettler Fp5 apparatus and are uncorrected. Absorbance of antioxidant assays was recorded on the Unico 2100 spectrophotometer. Elemental analyses were made by a Carlo–Erba EA1110 CNNO-S analyzer.

General procedure for synthesis of 5a–5h

Thiosemicarbazide **2** (2 mmol, 0.18 g) was added to a solution of carbonyl compound **1a–1h** (2 mmol) in 10 mL EtOH as the solvent in the presence of a few drops of AcOH and refluxed for 2 h. The mixture was cooled down and the resulting precipitate was filtered off and dried at room temperature. Resulted thiosemicarbazone **3a-h** (1 mmol) was dissolved in EtOH (5 mL) and 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone **4** (1 mmol) was

added to the mixture. The solution was refluxed in the presence of Et_3N (20% mole) for appropriate time. The progress of the reaction was monitored by TLC (*n*-hexane:EtOAc 7:2). After completion of the reaction, pH was controlled and the mixture was neutralized with saturated Na_2CO_3 solution. The solids was filtered off and dried at room temperature. The products obtained from EtOH:H_2O recrystallization.

4-Cyclopropy-5-(2-fluorophenyl)-2-((6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)hydrazono)-2,3-dihydrothiazole **5a**

Brown solid, yield: 95%, m.p. 114–118°C, IR (KBr, cm^{-1}) ν: 3320 (stretch N–H), 2930, 2820 (stretch C–H ali.), 1620 (stretch C=N), 1540, 1490 (stretch C=C), 1320 (stretch C–N), 1240, 1010 (stretch C–O), 1060 (stretch C–F), 890, 840, 810, 750 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.07 (d, J = 8.8 Hz, 1H, H_n), 7.55 (dt, J = 7.1, 1.6 Hz, 1H, H_g), 7.38–7.32 (m, 1H, H_e), 7.24–7.17 (m, 2H, H_d, H_f), 6.82 (dd, J = 8.8, 2.4 Hz, 1H, H_m), 6.66 (d, J = 2.0 Hz, 1H, H_k), 3.84 (s, 3H, H_l), 2.78 (t, J = 6.0 Hz, 2H, H_h), 2.60 (t, J = 6.4 Hz, 2H, H_j), 2.00 (q, 2H, H_i), 1.94–1.87 (m, 1H, H_c), 1.00–0.91 (m, 4H, H_a, $H_{a'}$, $H_{b,}$ $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.3 (C_5), 160.1, 159.9 ($^1J_{C,F}$ = 247 Hz, C_2), 150.2 (C_6), 146.4, 140.8 (C_1), 132.3 ($^3J_{C,F}$ = 3 Hz, C_d), 129.1 ($^3J_{C,F}$ = 8 Hz, C_f), 126.4, 125.0, 124.1 ($^4J_{C,F}$ = 4 Hz, C_e), 120.5 ($^2J_{C,F}$ = 16 Hz, C_3), 116.0 ($^2J_{C,F}$ = 22 Hz, C_g), 113.2, 112.9 (C_4), 112.5, 55.3, 29.7 (C_j), 25.2 (C_i), 21.6 (C_h), 11.1 (C_b or C_a),11.1 (C_a or C_b), 7.8 (C_c) ppm. Anal. calcd. for $C_{23}H_{22}FN_3OS$: C, 67.75; H, 5.49; N, 10.36. Found: C, 67.80; H, 5.45; N, 10.30%.

4-Cyclopropy-2-((3,4-dihydronaphthalen-1(2H)-ylidene)hydrazono)-5-(2-fluorophenyl)-2,3-dihydrothiazole **5b**

Light orange solid, yield: 94%, m.p. 120–123°C, IR (KBr, cm^{-1}) ν: 3310 (stretch N–H), 2930 (stretch C–H ali.), 1610 (stretch C=N), 1540, 1480 (stretch C=C), 1280 (stretch C–N), 1060 (stretch C–F), 760, 750, 730 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15–8.12 (m, 1H, H_n), 7.99 (br, s, 1H, NH), 7.57 (t, J = 7.6 Hz, 1H, H_g), 7.37–7.09 (m, 6H, H_d,H_e, H_f, H_k, H_l, H_m), 2.80 (t, J = 5.8 Hz, 2H, H_j), 2.59 (t, J = 6.6 Hz, 2H, H_h), 2.00 (q, 2H, H_i), 1.95–1.88 (m, 1H, H_c), 1.00–0.88 (m, 4H, H_a, $H_{a'}$, $H_{b,}$ $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.3 (C_5), 159.9 ($^1J_{C,F}$ = 247 Hz, C_2), 150.4 (C_6), 146.2, 139.1 (C_1), 132.3 ($^3J_{C,F}$ = 3 Hz, C_d), 132.1, 129.1 ($^3J_{C,F}$ = 8 Hz, C_f), 128.8, 128.4, 126.3, 124.6, 124.1 ($^4J_{C,F}$ = 4 Hz, C_e), 120.4 ($^2J_{C,F}$ = 16 Hz, C_3), 116.0 ($^2J_{C,F}$ = 22 Hz, C_g), 113.2 (C_4), 55.3, 29.4 (C_j), 25.2 (C_i), 21.5 (C_h), 11.1 (C_b or C_a),11.1 (C_a or C_b), 7.8 (C_c) ppm. Anal. calcd. for $C_{22}H_{20}FN_3S$: C, 70.02; H, 5.36; N, 11.10. Found: C, 69.98; H, 5.33; N, 11.14%.

4-Cyclopropy-5-(2-fluorophenyl)-2-((1-(naphthalen-2-yl)ethylidene)hydrazono)-2,3-dihydrothiazole **5c**

Yellow solid, yield: 96%, m.p. 195–198°C, IR (KBr, cm^{-1}) ν: 3030 (stretch C–H ar.), 1600 (stretch C=N), 1540, 1490 (stretch C=C), 1340 (stretch C–N), 1070 (stretch C–F), 820, 810, 750 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.17 (s, 1H, H_o), 8.03 (dd, J = 8.8, 1.6 Hz, 1H, H_i), 7.94–7.92 (m, 1H, H_j), 7.89–7.85 (m, 2H, H_n, H_k), 7.59–7.47 (m, 4H, H_g, H_m, H_l, NH), 7.33–7.24 (m, 3H, H_d, H_e, H_f), 2.69 (s, 3H, H_h, CH_3), 1.99–1.93 (m, 1H, H_c), 1.20–1.11 (m, 4H, H_a, $H_{a'}$, $H_{b,}$ $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1 (C_5), 159.9 ($^1J_{C,F}$ = 249 Hz, C_2), 155.6 (C_6), 139.9 (C_1), 134.2, 133.3, 132.9, 131.7 ($^3J_{C,F}$ = 1 Hz, C_d), 131.5 ($^3J_{C,F}$ = 8 Hz, C_f), 128.8, 128.3, 127.7, 127.5, 127.4, 126.7, 124.8 ($^4J_{C,F}$ = 4 Hz, C_e),

123.2, 116.7 ($^2J_{C,F}$ = 15 Hz, C_3), 116.5 ($^2J_{C,F}$ = 22 Hz, C_g), 112.3 (C_4), 15.7 (CH3), 9.3 (C_b or C_a), 9.3 (C_a or C_b), 8.3 (C_c) ppm. Anal. calcd. for $C_{24}H_{20}FN_3S$: C, 71.82; H, 5.04; N, 10.49. Found: C, 71.78; H, 5.01; N, 10.45%.

*4-Cyclopropy-5-(2-fluorophenyl)-2-((1-(p-tolyl)ethylidene)hydrazono)-2,3-dihydrothiazole **5d***

Brown solid, yield: 89%, m.p. 89–92°C, IR (KBr, cm^{-1}) ν: 3080 (stretch C–H ar.), 2910 (stretch C–H ali.), 1600 (stretch C=N), 1560, 1540, 1510, 1480 (stretch C=C), 1300 (stretch C–N), 1060 (stretch C–F), 810, 750 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (d, J = 8.4 Hz, 1H, H_i), 7.53 (dt, J = 7.6, 1.6 Hz, 1H, H_g), 7.42–7.36 (m, 1H, H_e), 7.27–7.13 (m, 5H, H_d, H_f, H_j, NH), 2.40 (s, 3H, H_h or H_k), 2.38 (s, 3H, H_k or H_h), 1.96–1.88 (m, 1H, H_c), 1.07–0.94 (m, 4H, H_a, $H_{a'}$, H_b, $H_{b'}$)ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6 (C_5), 159.9 ($^1J_{C,F}$ = 248 Hz, C_2), 157.7 (C_6), 140.4, 139.9 (C_1), 130.2 ($^3J_{C,F}$ = 8 Hz, C_f), 129.2, 129.2, 128.9, 126.9, 124.4 ($^4J_{C,F}$ = 4 Hz, C_e), 118.6 ($^2J_{C,F}$ = 15 Hz, C_3), 116.2 ($^2J_{C,F}$ = 21 Hz, C_g), 112.5 (C_4), 21.3 (CH_3–C_k), 14.5 (CH_3–C_h), 10.2 (C_a, C_b), 7.9 (C_c) ppm. Anal. calcd. for $C_{21}H_{20}FN_3S$: C, 68.98; H, 5.55; N, 10.48. Found: C, 69.03; H, 5,50; N, 10.52%.

*4-Cyclopropy-2-((2,3-dihydro-1H-inden-1-ylidene)hydrazono)-5-(2-fluorophenyl)-2,3-dihydrothiazole **5e***

Light yellow solid, yield: 93%, m.p. 182–186°C, IR (KBr, cm^{-1}) ν: 3050 (stretch C–H ar.), 2910 (stretch C–H ali.), 1610 (stretch C=N), 1340 (stretch C–N), 1055 (stretch C–F), 810, 750 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.78 (d, J = 7.6 Hz, 1H, H_m), 7.54 (dt, J = 7.4, 1.4 Hz, 1H, H_g), 7.51–7.44 (m, 2H, H_k, H_l), 7.39 (d, J = 7.6 Hz, 1H, H_j), 7.36–7.23 (m, 4H, H_d, H_e, H_f, NH), 3.24–3.21 (m, 2H, H_i), 3.15–3.12 (m, 2H, H_h), 1.97–1.91 (m, 1H, H_c), 1.13–1.09 (m, 4H, H_a, $H_{a'}$, H_b, $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.3 (C_5), 165.7, 159.9 ($^1J_{C,F}$ = 248 Hz, C_2), 149.8 (C_6), 139.4 (C_1), 135.9, 132.0, 131.6 ($^3J_{C,F}$ = 2 Hz, C_d), 131.4 ($^3J_{C,F}$ = 9 Hz, C_f), 127.3, 125.8, 123.3 ($^4J_{C,F}$ = 4 Hz, C_e), 122.3, 116.7 ($^2J_{C,F}$ = 14 Hz, C_3), 116.5 ($^2J_{C,F}$ = 22 Hz, C_g), 111.7 (C_4), 29.3 (C_i), 28.3 (C_h), 9.2 (C_b or C_a), 9.2 (C_a or C_b), 8.3 (C_c) ppm. Anal. calcd. for $C_{21}H_{18}FN_3S$: C, 69.43; H, 5.03; N, 11.58. Found: C, 69.39; H, 5.01; N, 11.54%.

*4-Cyclopropy-2-((1-(3,4-dimethoxyphenyl)ethylidene)hydrazono)-5-(2-fluorophenyl)-2,3-dihydrothiazole **5f***

Brown solid, yield: 90%, m.p. 153–157°C, IR (KBr, cm^{-1}) ν: 3250 (stretch N–H), 3090 (stretch C–H ar.), 2950, 2830 (stretch C–H ali.), 1610 (stretch C=N), 1550, 1510 (stretch C=C), 1330 (stretch C–N), 1240, 1020 (stretch C–O), 1060 (stretch C–F), 880, 860, 750 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (dt, J = 7.5, 1.8 Hz, 1H, H_g), 7.50 (d, J = 2 Hz, 1H, H_i), 7.41–7.31 (m, 1H, H_e), 7.25–7.17 (m, 3H, H_d, H_f, H_m), 6.87 (d, J = 8.4 Hz, 1H, H_l), 3.96 (s, 3H, H_j or H_k), 3.93 (s, 3H, H_k or H_j), 2.26 (s, 3H, H_h, CH_3), 1.91–1.86 (m, 1H, H_c), 1.00–0.89 (m, 4H, H_a, $H_{a'}$, H_b, $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1 (C_5), 159.9 ($^1J_{C,F}$ = 247 Hz, C_2), 150.2, 149.9, 148.9 (C_6), 146.3 (C_1), 132.3 ($^3J_{C,F}$ = 3 Hz, C_d), 130.4, 129.3 ($^3J_{C,F}$ = 8 Hz, C_f), 124.1 ($^4J_{C,F}$ = 3 Hz, C_e), 120.2 ($^2J_{C,F}$ = 15 Hz, C_3), 119.1, 116.0 ($^2J_{C,F}$ = 21 Hz, C_g), 112.9 (C_4), 110.3, 108.4, 55.9 (C_j or C_k), 55.8 (C_k or C_j), 12.9 (C_h), 11.0 (C_b or C_a), 11.0 (C_a or C_b), 7.8 (C_c) ppm. Anal. calcd. for $C_{22}H_{22}FN_3O_2S$: C, 64.25; H, 3.42; N, 10.24. Found: C, 64.20; H, 5.38; N, 10.19%.

4-Cyclopropy-5-(2-fluorophenyl)-2-(2-(1-(4-methoxyphenyl)ethylidene) hydrazinyl)thiazole 5g

Brown solid, yield: 91%, m.p. 85–87°C, IR (KBr, cm^{-1}) ν: 3200 (stretch N–H), 2920, 2820 (stretch C–H ali.), 1620 (stretch C=N), 1590, 1560, 1520, 1480 (stretch C=C), 1300 (stretch C–N), 1260, 1020 (stretch C–O), 1070 (stretch C–F), 850, 840, 810, 755 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.0 (s, br, 1H, NH), 7.75 (d, J = 9.2 Hz, 2H, H_i), 7.52 (dt, J = 7.6, 1.6 Hz, 1H, H_g), 7.49–7.44 (m, 1H, H_e), 7.31–7.21 (m, 2H, H_d, H_f), 6.93 (d, J = 8.8 Hz, H_j), 3.86 (s, 3H, H_k, OCH_3), 2.25 (s, 3H, H_h, CH_3), 1.96–1.90 (m, 1H, H_c), 1.16–1.07 (m, 4H, H_a, $H_{a'}$, $H_{b,}$ $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.9 (C_5), 161.6, 159.9 ($^1J_{C,F}$ = 249 Hz, C_2), 155.2 (C_6), 140.0 (C_1), 131.7 ($^3J_{C,F}$ = 2 Hz, C_d), 131.3 ($^3J_{C,F}$ = 8 Hz, C_f), 128.5, 128.2 (C_i), 124.7 ($^4J_{C,F}$ = 3 Hz, C_e), 116.9 ($^2J_{C,F}$ = 15 Hz, C_3), 116.4 ($^2J_{C,F}$ = 22 Hz, C_g), 113.9 (C_j), 112.0 (C_4), 55.4 (C_k), 15.6 (C_h), 9.3 (C_b or C_a), 9.3 (C_a or C_b), 8.3 (C_c) ppm. Anal. calcd. for $C_{21}H_{20}FN_3OS$: C, 66.15; H, 5.30; N, 11.05. Found: C, 66.10; H, 5.25; N, 10.98%.

4-Cyclopropy-5-(2-fluorophenyl)-(2-((1-(4-nitrophenyl)ethylidene)hydrazono)-2,3-dihydrothiazole 5h

Light red solid, yield: 88%, m.p. 166–170°C, IR (KBr, cm^{-1}) ν: 3000 (stretch C–H ar.), 1615 (stretch C=N), 1590, 1480 (stretch C=C), 1510, 1340 (stretch NO_2), 1050 (stretch C–F), 860, 810, 750, 740 (OOP. C–H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.28 (d, J = 6.8 Hz, 2H, H_j), 7.96 (d, J = 8.8 Hz, 2H, H_i), 7.55 (dt, J = 7.6, 1.6 Hz, 1H, H_g), 7.47–7.43 (m, 1H, H_e), 7.30–7.22 (m, 2H, H_d, H_f), 6.5–4 (br, s, 1H, NH), 2.45 (s, 3H, H_h, CH_3), 1.95–1.91 (m, 1H, H_c), 1.04–1.00 (m, 4H, H_a, $H_{a'}$, $H_{b,}$ $H_{b'}$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.3 (C_5), 159.9 ($^1J_{C,F}$ = 247 Hz, C_2), 149.7 (C_6), 147.7, 144.0, 143.3 (C_1), 132.2 ($^3J_{C,F}$ = 2 Hz, C_d), 129.7 ($^3J_{C,F}$ = 8 Hz, C_f), 126.5 (C_i), 124.2 ($^4J_{C,F}$ = 4 Hz, C_e), 123.7 (C_j), 119.6 ($^2J_{C,F}$ = 15 Hz, C_3), 116.1 ($^2J_{C,F}$ = 22 Hz, C_g), 113.9 (C_4), 13.0 (C_h), 10.8 (C_b or C_a), 10.8 (C_a or C_b), 7.9 (C_c) ppm. Anal. calcd. for $C_{20}H_{17}FN_4O_2S$: C, 60.63; H, 4.30; N, 14.16. Found: C, 60.61; H, 4.35; N, 14.12%.

Biology

DPPH radical-scavenging activity assay

DPPH radical-scavenging activity of compounds was evaluated according to the literature.[29] Appropriate amount of DPPH was dissolved in MeOH to give a concentration of 6.25×10^{-5} M. A series of sample solution at concentrations of 4000, 2000, 1000, 500, 250, 125 µg/mL in MeOH was prepared by two-fold serial dilution. To 0.1 mL of each sample solution was added 3.9 mL of fresh DPPH solution and was shaken vigorously. Samples were kept in darkness for 30 min then their absorbance was measured at 517 nm. MeOH was used as a blank. Radical-scavenging activity was calculated as follows:

$$\text{Radical scavengng activity \%} = \left(\frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}}\right) \times 100,$$

where A_{control} is the absorbance of negative control (3.9 mL DPPH + 0.1 mL MeOH) and A_{sample} the absorbance of the test compounds.

ABTS assay

The ABTS assay of compounds was evaluated according to the literature.[37] A solution of ABTS (7.4 mM) in MeOH and a solution of potassium persulfate ($K_2S_2O_8$) (2.6 mM) as an oxidizing agent in MeOH were mixed in equal volumes and allowed to react for 12 h in the dark at room temperature to produce the ABTS radical cation ($ABTS^{\bullet+}$) stock solution. Then, the resulted stock solution was diluted with MeOH to give an absorbance of 1.1 ± 0.02 at 734 nm. A series of sample solution at concentrations of 4000, 2000, 1000, 500, 250, 125 μg/mL in MeOH was prepared by two-fold serial dilution. Then, 150 μL of the sample solution was added to 3.0 mL of the $ABTS^{\bullet+}$ solution, this mixture was shaken and incubated in the dark for 2 h. Then, the absorbance of each solution was recorded at 734 nm. MeOH was used as a blank. Radical-scavenging activity was calculated by a similar formula of the DPPH radical-scavenging assay.

The IC_{50} values of each compound for DPPH and ABTS assays were calculated by plotting the inhibition percentage against concentration of the samples and the results were expressed in μM.

Antibacterial assay

The antibacterial activity of hydrazinyl-thiazoles **5a–5h** was evaluated biologically using the well-diffusion method against *S. aureus* (ATCC 29213), *M. luteus* (ATCC 4698), *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853), *B. subtilis* (DSM 6887), and *A. hydrophila* (ATCC 7966) supplied from the Iranian biological resource center, Tehran, Iran. First, nutrient agar and nutrient broth cultures were prepared according to manufactures' instructions and were incubated at 37°C. After incubation for the appropriate time, a suspension of 30 μL of each bacterium was added to the nutrient agar plates. Cups (5 mm in diameter) were cut in the agar using a sterilized glass tube. Each well received 30 μL of the test compounds at a concentration of 1000 μg/ml in DMSO. Then, plates were incubated at 37°C for 24 h, after this time the zone of inhibition was measured and values are expressed in millimeters (mm). The experiments were performed in triplicate. The results are reported as mean ± standard deviation of zone of inhibition in millimeter. Antibacterial activity of each hydrazinyl-thiazole was compared with penicillin G and gentamicin as standard drugs. DMSO was used as a negative control.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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