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Synthesis and antioxidant activities of some novel fluorinated spiro[oxindole-thiazolidine] fused with sulfur and phosphorus heterocycles

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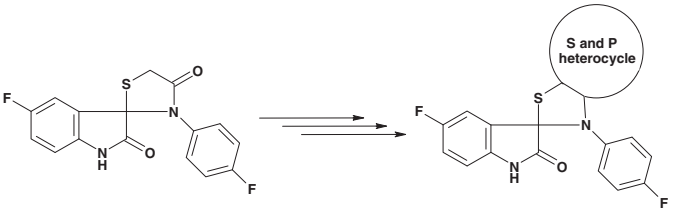
Facile routes were achieved for the synthesis of novel fluorinated spiro[oxindole-thiazolidinone] fused with some sulfur and phosphorus heterocycles starting from 5-fluoro-3′-(4-fluorophenyl)-4′*H*-spiro[indole-3,2′-thiazolidine]-2,4′(1*H*)-dione (**1**) *via* its reaction with trifluoroacetamide, 2-chloro-6-fluorobenzaldehyde and hydrazine hydrate followed by treatment with some suitable sulfur and phosphorus reagents. The antioxidant activities of the synthesized compounds were also evaluated.



Keywords: spiro[oxindole-thiazolidine]; fluorine; sulfur and phosphorus heterocycles; antioxidant activities

1. Introduction

The spiro[oxindole-thiazolidinone] system is a structural unit presented in many pharmacologically important synthetic and natural compounds.[1] These compounds have biological antiproliferative,[2] antitumor,[3] antimicrobial,[4] anti-inflammatory,[5] antihistamic [6] and anticonvulsant activities.[7] Incorporation of fluorine atoms in different heterocycles is known to affect the course of the reaction besides influencing the biological activities.[8–10] In addition, sulfur- and phosphorus-containing heterocyclic compounds play an important role in organic chemistry due to diversity of their chemical transformations and broad spectrum of biological activities.[11–17] We hope that coupling of some sulfur and phosphorus heterocycles with the fluorinated spiro[oxindole-thiazolidine] system in one molecular frame may lead to better biological properties. Consequently, in continuation of our research devoted to preparation of new bioactive

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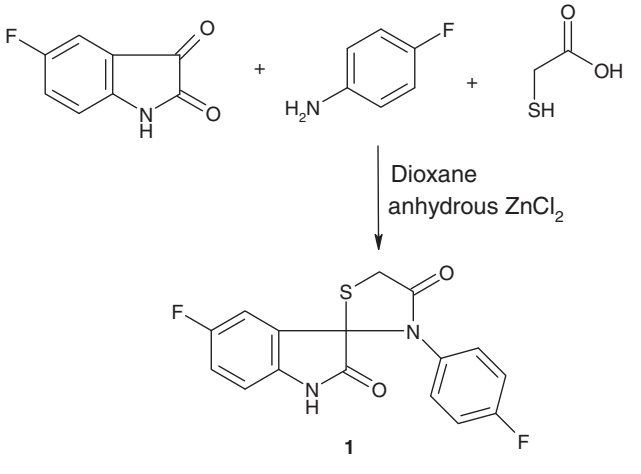
sulfur and phosphorus compounds,[18–20] we report here the synthesis of some novel fluorinated spiro[oxindole-thiazolidine] fused with a selection of sulfur and phosphorus heterocycles. The antioxidant properties of the synthesized compounds were also evaluated.

2. Results and discussion

2.1. *Chemistry*

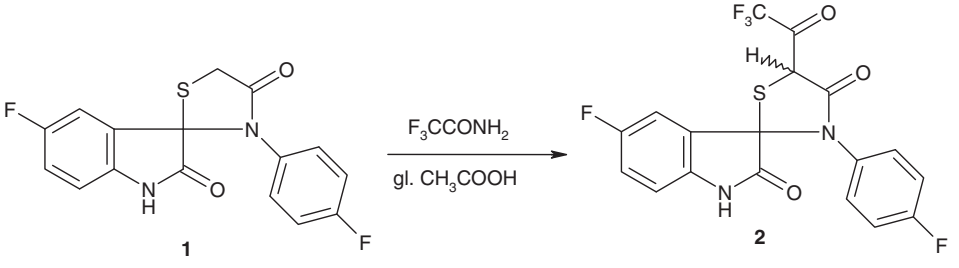
The most convenient method for the synthesis of 2,3-disubstituted-4-thiazolidinones is the one-pot three-component reaction of a primary amine, an oxo-compound and a thiolic agent.[21–23] Thus, 5-fluoro-3′-(4-fluorophenyl)-4′*H*-spiro[indole-3,2′-thiazolidine]-2,4′(1*H*)-dione (**1**) was obtained *via* reaction of 4-fluoroaniline, 5-fluoroisatin and thioglycolic acid in dry dioxane in the presence of anhydrous zinc chloride (Scheme 1).[23] The IR spectrum of compound **1** showed the characteristic absorption bands 3277 (NH), 1728 (C=$O_{oxindole}$) and 1682 (C=$O_{thiazolidinone}$) cm^{-1}. Also, its ^{1}H-NMR spectrum revealed the characteristic methylene protons as two doublets at δ 3.85 and 4.29 ppm with a coupling constant of 15 Hz. Furthermore, the specific carbon atoms CH_2, C-*spiro*, C=$O_{thiazolidinone}$ and C=$O_{oxindole}$ were observed at δ 32.7, 70.3, 172.4 and 176.5 ppm, respectively, in its ^{13}C-NMR spectrum. The molecular ion of compound **1** was also observed at m/z 332 (42%) in its mass spectrum.



Scheme 1. The reaction of 5-fluoroisatin, 4-fluoroaniline and thioglycolic acid in the presence of anhydrous zinc chloride.

Compound **1** turned out to be a fairly reactive compound to generate **2**, **5** and **8** *via* its condensation with trifluoroacetamide, 2-chloro-6-fluorobenzaldehyde and hydrazine hydrate, respectively. Thus, treatment of compound **1** with trifluoroacetamide in the presence of glacial acetic acid afforded beige crystals of 5-fluoro-3′-(4-fluorophenyl)-5′-(trifluoroacetyl)-spiro[indole-3,2′-thiazolidine]-2,4′(1*H*)-dione (**2**) (Scheme 2). The structure of compound **2** was confirmed by both spectral and elemental analysis. Its IR spectrum indicated the presence of three carbonyl groups at 1748 (C=$O_{trifluoroacetyl}$), 1717 (C=$O_{oxindole}$) and 1650 (C=$O_{thiazolidinone}$) cm^{-1}. Also, the ^{1}H-NMR spectrum of compound **2** showed a characteristic singlet at δ 4.68 ppm, which was assigned to

the proton at C–5 of the thiazolidinone moiety. The carbon atoms of trifluoroacetyl group were observed at δ 113.6 (CF_3) and 172.6 (C=O) ppm in the ^{13}C-NMR spectrum of compound **2**. Moreover, its mass spectrum showed the molecular ion peak at m/z 428 (62%) that agrees with the proposed formula.

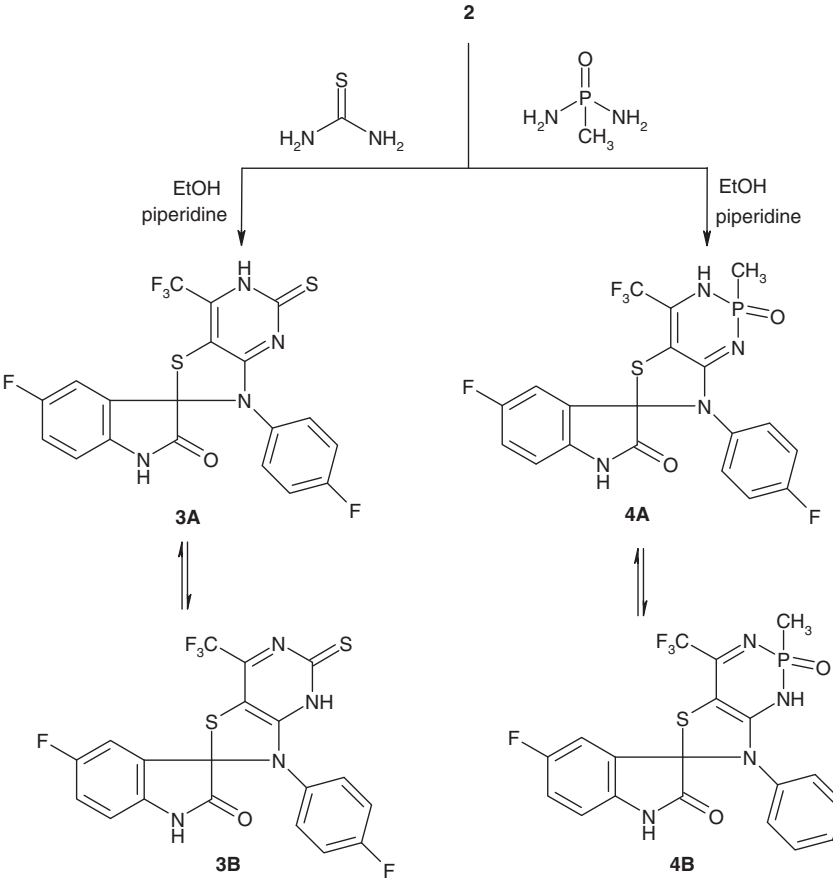


Scheme 2. Trifluoroacetylation of compound **1** with trifluoroacetamide in glacial acetic acid.

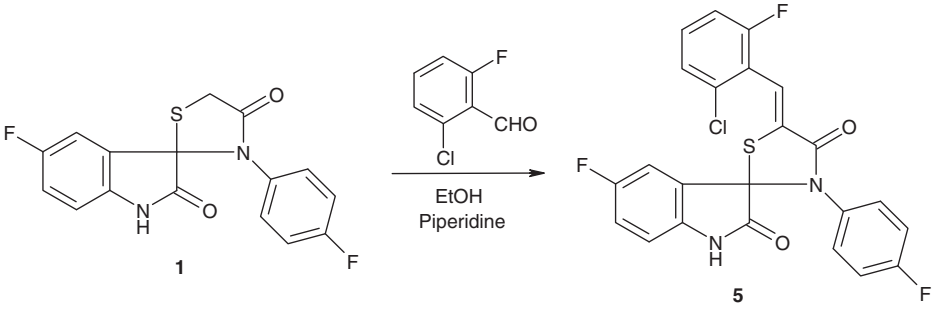
When the trifluoroacetyl derivative **2** was treated with thiourea and methyl phosphoric diamide, in refluxing absolute ethanol containing few drops of piperidine as a catalyst, 5-fluoro-3′-(4-fluorophenyl)-5′-thioxo-7′-(trifluoromethyl)-spiro{indole-3,2′-thiazolo[4′,5′-*d*] pyrimidin}-2-one (**3**) and 5-fluoro-7′-(4-fluorophenyl)-4′-(trifluoromethyl)-2′-methyl-2′-oxido-1′,2′-dihydro-spiro{indole-3,6′-thiazolo[4′,5′-*d*][1,3,2]diazaphosphinin}-2-one (**4**) were obtained, respectively, in moderate yields (Scheme 3). The IR and ^{13}C-NMR spectra of compounds **3** and **4** indicated the disappearance of the carbonyl groups of the thiazolidinone and trifluoroacetyl moieties of compound **2**. Furthermore, their ^{1}H-NMR spectra exhibited two singlets for the NH protons of the pyrimidinethione and diazaphosphorine rings which suggest existence of the two products in tautomeric forms **A** and **B** due to amino-imino tautomerism (Scheme 3).

Recently, α,β-unsaturated ketones have been reported as reactive chemical precursors for the synthesis of bioactive heterocycles.[24,25] Thus, compound **1** was allowed to condense with 2-chloro-6-fluorobenzaledyde in absolute ethanol with few drops of piperidine as catalyst to afford a product identified as 5′-(2-chloro-6-fluorobenzylidene)-5-fluoro-3′-(4-fluorophenyl)-4′*H*- spiro[indole-3,2′-thiazolidine]-2,4′-(1*H*)-dione (**5**) (Scheme 4). The structure of compound **5** was established on the basis of ^{1}H- and ^{13}C-NMR spectral data that confirmed disappearance of the methylene group of compound **1** (see Section 4).

Compound **5** appears to be a logical starting material for synthesis of the target heterocycles *via* its reaction with some sulfur and phosphorus nucleophiles. Thus, reaction of compound **5** with thioglycolic acid in dry dioxane containing anhydrous potassium carbonate furnished 6′-(2-chloro-6-fluorophenyl)-5-fluoro-3′-(4-fluorophenyl)-2′,3′-dihydro-spiro{indole-3,2′-thieno[3,4-d]thiazol}-2-one (**6**) in good yield (Scheme 5). A plausible mechanism involved an initial Michael-type addition of the thiol group of thioglycolic acid to the activated double bond in compound **5**, followed by cyclocondensation between the active methylene and the carbonyl group to give the nonisolable intermediate **B**. Decarboxylation and aromatization of the intermediate **B** produced the final product **6** (Scheme 5). The chemical structure of compound **6** was deduced from the absence of thiazolidinone carbonyl or hydroxyl groups in its IR and ^{13}C-NMR spectra that confirms the decarboxylation process. Also, its ^{1}H-NMR spectrum displayed a characteristic singlet at δ 6.20 ppm due to the C_2–H proton of the thiophene moiety. Moreover, the molecular ion peak of compound **6** was recorded at m/z 500 (M^+, 7%) in its mass spectrum, which agreed with the suggested structure.

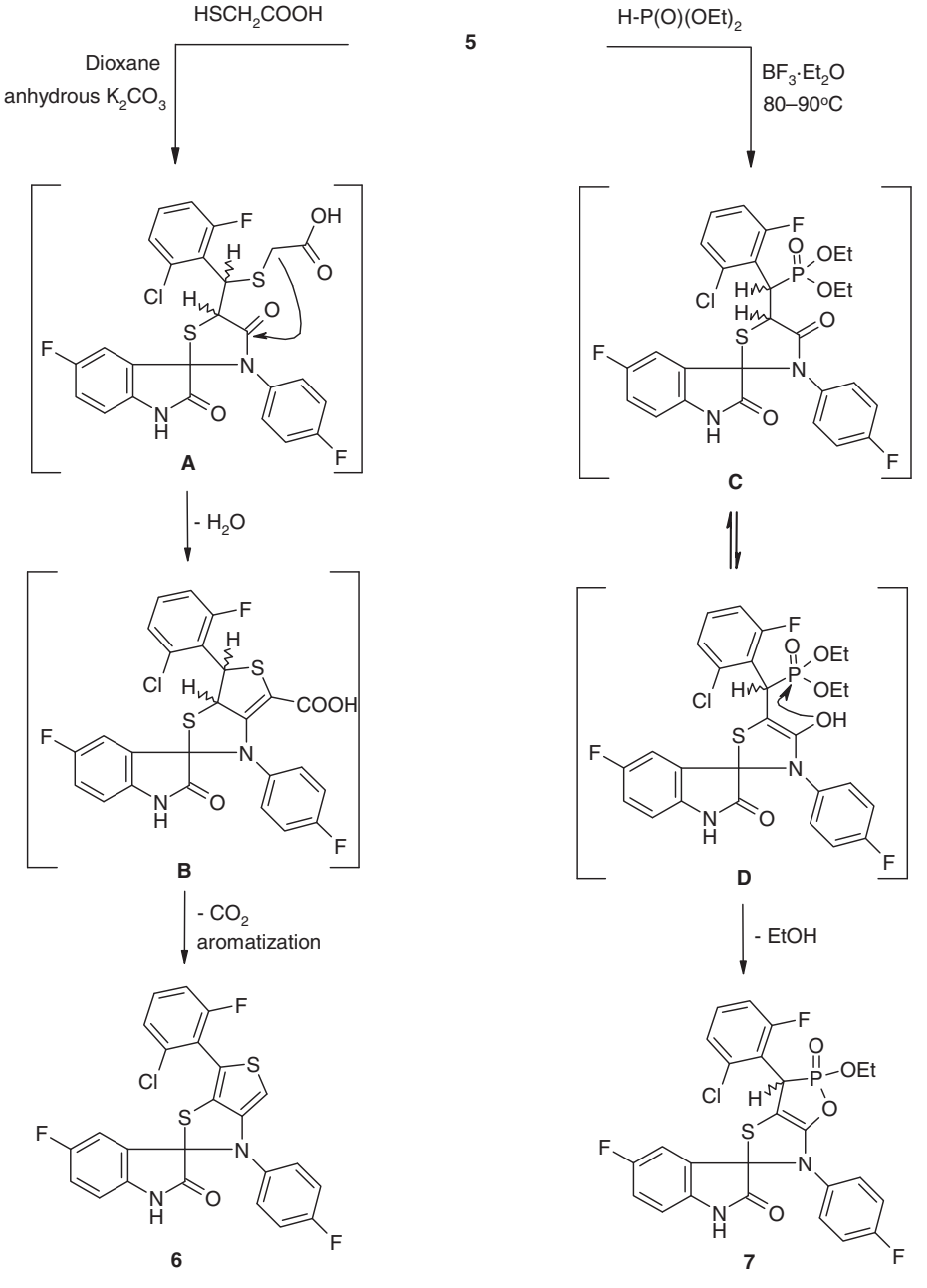


Scheme 3. The reaction of compound **2** with thiourea and methyl phosphoric diamide.



Scheme 4. Condensation reaction of compound **1** with 2-chloro-6-fluorobenzaldehyde.

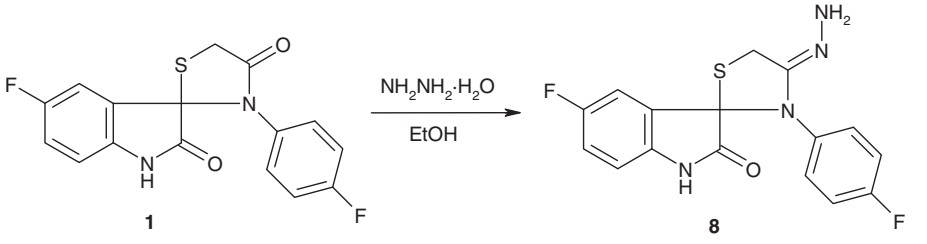
Consequently, it has been found that the one-pot reaction of the compound **5** with diethyl phosphite in the presence of $BF_3{\cdot}Et_2O$ at 80–90°C for 16 h afforded 3′-(2-chloro-6-fluorophenyl)-2′-ethoxy-5-fluoro-6′-(4-fluorophenyl)-2′-oxido-spiro{indole-3,5′-[1,2]oxaphospholo[5,4-d]thiazol}-2-one (**7**) (Scheme 5). The proposed mechanism involved an initial Michael-type addition of the phosphorus atom of diethyl phosphite to the activated double bond in compound **5** to give the non-isolable phosphonate **C**, which underwent cyclization by elimination of ethanol to give the product



Scheme 5. The reaction of compound **5** with thioglycolic acid and diethyl phosphite.

7 (Scheme 5).[26] The ^{1}H-NMR spectrum of compound **7** displayed a doublet at δ 5.18 ppm ($J = 22.2$ Hz) assignable to proton C_3–H of the oxaphosphole ring, while the ethoxy protons appeared as a triplet and quartet at δ 1.20 and 3.85 ppm ($J = 7.2$ Hz), respectively. Its ^{13}C-NMR spectrum revealed characteristic peaks at δ 16.8 (CH_3), 62.3 (CH_2), 42.6 (C_3–$H_{oxaphosphole}$) and 165.2 (C_5–$H_{oxaphosphole}$) ppm. Also, its IR spectrum confirmed the disappearance of the carbonyl group of compound **5**, which supports the cyclized state.

Reaction of compound **1** with hydrazine hydrate in refluxing absolute ethanol produced the corresponding hydrazone **8** in high yield (Scheme 6). The structure of compound **8** was established on the basis of its elemental analysis, IR, ^{1}H-NMR and mass spectral data (see Section 4).



Scheme 6. Condensation reaction of compound **1** with hydrazine hydrate.

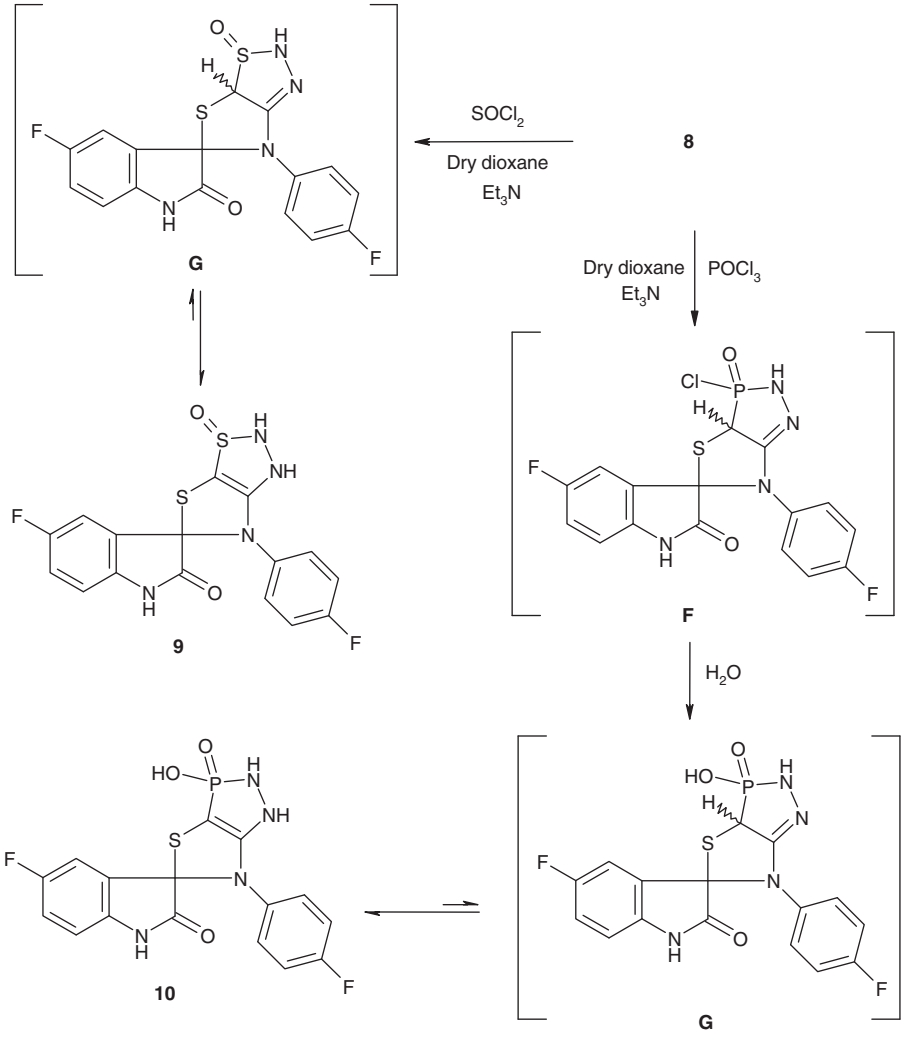
It is known that hydrazones could be used as a precursor for the synthesis of a variety of bioactive heterocyclic systems.[27,28] Thus, treatment of the hydrazone **8** with thionyl chloride and phosphorus oxychloride in dry dioxane containing triethylamine as a catalyst produced the corresponding thiazolothiadiazole **9** and thiazolodiazaphosphole **10** derivatives, respectively, in moderate yields (Scheme 7). The chemical structures of **9** and **10** were established on the basis of spectral data. Their IR spectra showed the presence of NHNH groups in the 3145–3354 cm^{-1} region, while their ^{1}H-NMR spectra revealed broad singlets at δ 5.09 and 6.29 ppm, respectively, assignable to NHNH protons. In addition, a broad singlet at δ 8.45 ppm due to the HO–P=O group in compound **10** was observed. The ^{13}C-NMR spectra of compounds **9** and **10** were also supportive of the proposed structures exhibiting characteristic signals at δ 98.0 (C–$5_{thiadiazole}$) and 158.3 (C–$4_{thiadiazole}$) for compound **9** and at δ 90.0 (C–$4_{diazaphosphole}$) and 155.0 (C–$5_{diazaphosphole}$) ppm for compound **10**. The ^{1}H- and ^{13}C-NMR spectra of **9** and **10** confirmed localization of the protons on the nitrogen atoms and not on the carbon atoms of the thiadiazole and diazaphosphole rings.

2.2. *Antioxidant activity*

All the synthesized compounds were tested for antioxidant activity by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method.[29,30] The results of scavenging the stable DPPH radical are tabulated in Table 1 and illustrated in Figure 1, where it is documented that at 150, 300 and 450 $\mu mol\,L^{-1}$ of the synthesized compounds under study scavenged between 49% and 78% of the DPPH radicals. This increase in the % DPPH inhibition is caused by the reaction between the compounds under study with DPPH radicals. Hence, DPPH radical is an important substrate to evaluate the antioxidant activity.[31] The results suggested that compounds **1**, **2**, **5**, **6**, **8** and **9** showed moderate activities in the range of 49–60% at different concentrations, while compounds **7** and **10** showed very good activities in range of 63–71%. Furthermore, compounds **3** and **4** proved to exhibit potent antioxidative activities in range of 70–78%. The presence of trifluoromethyl group and oxindole moiety incorporated with thiazolopyrimidinethione or thiazolodiazaphosphorine enhanced the antioxidant activity.

3. Conclusion

Facile routes were achieved to synthesize novel fluorinated spiro[oxindole-thiazolidinone] fused with some sulfur and phosphorus heterocycles in two steps starting from 5-fluoro-3′-(4-fluorophenyl)-4′*H*-spiro[indole-3,2′-thiazolidine]-2,4′-(1*H*)-dione (**1**). Some of the novel



Scheme 7. The reaction of compound **8** with thionyl chloride and phosphorus oxychloride.

products recorded good antioxidant properties. We hope that this approach may be value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

4. Experimental

4.1. *General remarks*

Melting points of the products were determined on Stuart SMP3. A Perkins Elmer model RXI-FT-IR system 55529 was used for recording the IR spectra of the prepared compounds. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker 600 MHz spectrometer operating at 600 and 150 MHz, respectively. The chemical shifts in NMR spectra are reported in ppm with respect to the references and were stated relative to tetramethylsilane. Mass spectra were recorded on a Gas Chromatographic DI analysis Shimadzu instrument Q-2010 Plus at 70 eV. Elemental micro-analyses were performed with Perkin-Elmer 2400II at the Chemical War Department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography.

Table 1. DPPH radical scavenging activities (%) of the synthesized compounds **1**–**10** at 150, 300 and 450 μmol L^{-1}.

	DPPH % inhibition antioxidant ± SD		
Compd no.	150 (μmol L^{-1})	300 (μmol L^{-1})	450 (μmol L^{-1})
1	54.12 ± 0.13	56.54 ± 0.12	58.95 ± 0.13
2	51.59 ± 0.12	53.78 ± 0.18	56.47 ± 0.12
3	70.35 ± 0.12	74.55 ± 0.18	77.45 ± 0.12
4	72.67 ± 0.18	75.01 ± 0.18	77.78 ± 0.12
5	52.83 ± 0.06	54.12 ± 0.18	58.32 ± 0.18
6	53.92 ± 0.06	55.87 ± 0.06	58.02 ± 0.06
7	62.68 ± 0.18	65.37 ± 0.06	68.12 ± 0.06
8	49.23 ± 0.06	51.29 ± 0.38	56.75 ± 0.06
9	55.30 ± 0.06	57.34 ± 0.38	59.71 ± 0.38
10	65.54 ± 0.18	68.20 ± 0.06	70.65 ± 0.18
Ascorbic acid	43.00	50.70	55.20

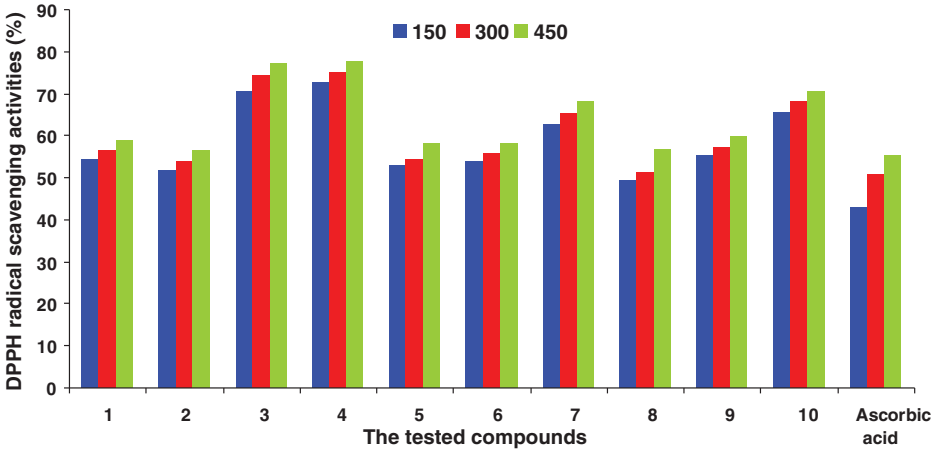


Figure 1. The DPPH radical scavenging activity (%) for the tested compounds.

4.2. *5-Fluoro-3′-(4-fluorophenyl)-4′H-spiro[indole-3,2′-thiazolidine]-2,4′(1H)-dione (1)*

A mixture of 4-fluoroaniline (2.5 mmol, 0.28 g) and 5-fluoroisatin (2.5 mmol, 0.41) was heated in dry dioxane (15 ml) under reflux for 30 min, followed by the addition of a solution of thioglycolic acid (3 mmol, 0.20 ml) in dry dioxane (5 ml) and 1.0 g freshly fused zinc chloride. The reaction mixture was heated under reflux for additional 20 h. The mixture was cooled then neutralized with aqueous $NaHCO_3$ (10%, 20 ml). The formed solid was filtered off, washed with water three times and crystallized from ethanol to give yellow crystals in 72% yield; mp 184–186°C [Lit. [23] 182°C]. IR (KBr) (ν_{max}, cm^{-1}): 3277 (NH), 1728 ($C{=}O_{oxindole}$), 1682 ($C{=}O_{thiazolidinone}$), 1618 (C=C), 1219 (C–F). ^{1}H-NMR (DMSO, δ ppm): 3.85, 4.29 (dd, 2H, J = 15 Hz, CH_2 AB system), 6.76 (d, 1H, J = 7.2 Hz, Ar–H), 6.90–7.07 (m, 4H, Ar–H), 7.19 (t, 1H, J = 7.8 Hz, Ar–H), 7.40 (d, 1H, J = 7.8 Hz, Ar–H), 10.34 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 32.7, 70.3, 111.1, 116.2, 117.9, 122.9, 124.6, 130.2, 137.8, 141.8, 161.1, 162.7, 172.4, 176.5. MS (m/z, I%): 332 (M^+, 42%). Anal. Calcd for $C_{16}H_{10}F_2N_2O_2S$ (332.33): C, 57.83; H, 3.03; N, 8.43; S, 9.65. Found: C, 57.59%; H, 2.87%; N, 8.10%; S, 9.32%.

4.3. *5-Fluoro-3′-(4-fluorophenyl)-5′-(trifluoroacetyl)-spiro[indole-3,2′-thiazolidine]-2,4′(1H)-dione (2)*

A mixture of 5-fluoro-3′-(4-fluorophenyl)-4′*H*-spiro[indole-3,2′-thiazolidine] -2,4′(1*H*)-dione (**1**) (2.5 mmol, 0.83 g) and trifluoroacetamide (2.5 mmol, 0.28 g) in the presence of few drops of glacial acetic acid was fused at 120°C for 1 h. The cooled reaction mixture was poured onto 50 g of crushed ice. The formed solid was filtered off, washed with water three times then crystallized from aqueous ethanol to give beige crystals; 68% yield; mp 112–114°C. IR (KBr) (ν_{max}, cm^{-1}): 3247 (NH), 1748 (C=$O_{trifluoroacetyl}$), 1717 (C=$O_{oxindole}$), 1650 (C=$O_{thiazolidinone}$), 1620 (C=C), 1230 (C–F). ^{1}H-NMR (DMSO, δ ppm): 4.68 (s, 1H, CH), 6.76 (d, 1H, $J = 7.8$ Hz, Ar–H), 6.90–6.97 (m, 2H, Ar–H), 7.00–7.08 (m, 2H, Ar–H), 7.19 (t, 1H, $J = 7.2$ Hz, Ar–H), 7.41 (d, 1H, $J = 7.2$ Hz, Ar–H), 10.31 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 66.9, 70.3, 111.0, 113.6, 116.2, 117.8, 122.9, 124.6, 130.2, 137.8, 141.8, 161.0, 162.7, 172.3, 172.6, 176.5. MS (*m*/*z*, I%): 428 (M^+, 62%). Anal. Calcd for $C_{18}H_9F_5N_2O_3S$ (428.34): C, 50.47; H, 2.12; N, 6.54; S, 7.49. Found: C, 50.09%; H, 2.00%; N, 6.19%; S, 7.12%.

4.4. *5-Fluoro-3′-(4-fluorophenyl)-5′-thioxo-7′-(trifluoromethyl)-spiro{indole-3,2′-thiazolo[4′,5′-d]pyrimidin}-2-one (3)*

A mixture of compound **2** (1 mmol, 0.43 g) and thiourea (1 mmol, 0.08 g) in absolute ethanol (15 ml) containing few drops of piperidine was heated under reflux for 10 h. After cooling, the formed solid was filtered off and crystallized from ethanol to give yellow crystals; 56% yield; mp 226–228°C. IR (KBr) (ν_{max}, cm^{-1}): 3289 (NH), 1761 (C=$O_{oxindole}$), 1219 (C–F), 1155 (C=S). ^{1}H-NMR (DMSO, δ ppm): 6.91 (t, 1H, $J = 8.4$ Hz, Ar–H), 6.99–7.11 (m, 4H, Ar–H), 7.70–7.76 (m, 2H, Ar–H), 10.33 (s, 1H, $NH_{oxindole}$), 10.65, 10.77 (ss, 1H, $NH_{pyrimidine}$). ^{13}C-NMR (DMSO, δ ppm): 70.3, 111.5, 112.2, 115.5, 117.2, 118.6, 122.1, 125.9, 133.0, 136.5, 138.0, 156.7, 161.1, 162.7, 169.3, 174.9, 190.3. MS (*m*/*z*, I%): 468 (M^+, 13%). Anal. Calcd for $C_{19}H_9F_5N_4OS_2$ (468.43): C, 48.72; H, 1.94; N, 11.96; S, 13.69. Found: C, 48.39%; H, 1.63%; N, 11.69%; S, 13.40%.

4.5. *5-Fluoro-7′-(4-fluorophenyl)-4′-(trifluoromethyl)-2′-methyl-2′-oxido-1′,2′-dihydro-spiro{indole-3,6′-thiazolo[4′,5′-d][1,3,2]diazaphosphinin}-2-one (4)*

A mixture of compound **2** (1 mmol, 0.43 g) and methyl phosphoric diamide (1 mmol, 0.1 g) in absolute ethanol (15 ml) containing few drops of piperidine was heated under reflux for 10 h. After cooling, the formed solids were filtered off and crystallized from ethanol to brown crystals; 61% yield; mp 196–198°C. IR (KBr) (ν_{max}, cm^{-1}): 3266 (NH), 1738 (C=$O_{oxindole}$), 1212 (C–F), 1180 (P=O). ^{1}H-NMR (DMSO, δ ppm): 2.14 (d, 3H, $J = 8.4$ Hz, P–CH_3), 6.79–6.89 (m, 3H, Ar–H), 6.97 (t, 1H, $J = 8.4$ Hz, Ar–H), 7.13 (dd, 1H, $J = 8.4$ and 2.4 Hz, Ar–H), 7.53–7.58 (m, 2H, Ar–H), 9.47, 10.66 (ss, 1H, $NH_{diazaphosphorine}$), 10.14 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 29.6, 69.8, 110.0, 110.8, 112.1, 113.3, 115.0, 121.4, 123.7, 134.9, 137.0, 139.5, 157.9, 159.4, 163.8, 168.9, 176.9. MS (*m*/*z*, I%): 486 (M^+, 21%). Anal. Calcd for $C_{19}H_{12}F_5N_4O_2PS$ (486.36): C, 46.92; H, 2.49; N, 11.52; S, 6.59. Found: C, 46.68%; H, 2.11%; N, 11.19%; S, 6.23%.

4.6. *5′-(2-Chloro-6-fluorobenzylidene)-5-fluoro-3′-(4-fluorophenyl)-4′H-spiro[indole-3,2′-thiazolidine]-2,4′-(1H)-dione (5)*

A mixture of compound **1** (2.5 mmol, 0.83 g) and 2-chloro-6-fluorobenzaldehyde (2.5 mmol, 0.39 g) in absolute ethanol (20 ml) containing few drops of piperidine was heated under reflux for 10 h. After cooling, the formed solid was filtered off and crystallized from ethanol to give beige

crystals; 73% yield; mp 148–150°C. IR (KBr) (ν_{max}, cm^{-1}): 3359 (NH), 1719 (C=$O_{oxindole}$), 1653 (C=$O_{thiazolidinone}$), 1605 (C=C), 1215 (C–F). ^{1}H-NMR (DMSO, δ ppm): 6.74–6.76 (m, 2H, Ar–H), 6.91–6.98 (m, 4H, Ar–H), 7.05–7.07 (m, 3H, Ar–H), 7.16 (dd, 1H, J = 7.8 and 3.0 Hz, Ar–H), 7.53 (s, 1H, CH=C), 10.40 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 70.3, 112.0, 113.5, 113.7, 116.3, 117.9, 120.0, 122.0, 126.2, 127.3, 128.0, 130.2, 131.7, 135.0, 137.8, 142.0, 159.6, 161.1, 162.8, 172.4, 176.5. MS (m/z, I%): 473 (M^+, 76%). Anal. Calcd for $C_{23}H_{12}ClF_3N_2O_2S$ (472.88): C, 58.42; H, 2.56; N, 5.92; S, 6.78. Found: C, 58.09%; H, 2.34%; N, 5.73%; S, 6.53%.

4.7. *6′-(2-Chloro-6-fluorophenyl)-5-fluoro-3′-(4-fluorophenyl)-2′,3′-dihydro-spiro {indole-3,2′-thieno[3,4-d]thiazol}-2-one (6)*

A mixture of chalcone **5** (1 mmol, 0.47 g) and thioglycolic acid (3 mmol, 0.2 ml) in dry dioxane (15 ml) in the presence of anhydrous potassium carbonate (1 g) was refluxed for 8 h. After cooling, the resulting precipitate was filtered off, washed with water several times and crystallized from ethanol to give pale yellow crystals in 78% yield; mp 222–224°C. IR (KBr) (ν_{max}, cm^{-1}): 3231 (NH), 1731 (C=$O_{oxindole}$), 1605 (C=C), 1217 (C–F). ^{1}H-NMR (DMSO, δ ppm): 6.20 (s, 1H, C_2–$H_{thiophene}$), 6.74–6.76 (m, 2H, Ar–H), 6.91–6.98 (m, 4H, Ar–H), 7.05–7.08 (m, 3H, Ar–H), 7.17 (dd, 1H, J = 7.8 and 2.4 Hz, Ar–H), 10.44 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 70.3, 111.1, 114.0, 116.1, 116.2, 117.9, 121.0, 122.0, 123.0, 124.6, 126.2, 127.0, 130.3, 131.1, 131.9, 133.0, 134.0, 138.0, 158.0, 161.0, 162.7, 176.9. MS (m/z, I%): 501 (M^+, 7%). Anal. Calcd for $C_{24}H_{12}ClF_3N_2OS_2$ (500.95): C, 57.54; H, 2.41; N, 5.59; S, 12.80. Found: C, 57.19%; H, 2.21%; N, 5.21%; S, 12.52%.

4.8. *3′-(2-Chloro-6-fluorophenyl)-2′-ethoxy-5-fluoro-6′-(4-fluorophenyl)-2′-oxido-spiro{indole-3,5′-[1,2]oxaphospholo [5,4-d]thiazol}-2-one (7)*

A mixture of chalcone **5** (1 mmol, 0.47 g) and diethyl phosphite (1.5 ml) in the presence of boron trifluoride etherate (0.2 ml) was heated on water bath for 16 h. The excess of diethyl phosphite was removed under reduced pressure. The formed precipitate was filtered off and crystallized from ethanol to give pale brown crystals in 79% yield; mp 110–112°C. IR (KBr) (ν_{max}, cm^{-1}): 3246 (NH), 1731 (C=$O_{oxindole}$), 1619 (C=C), 1216 (C–F), 1189 (P=O). ^{1}H-NMR (DMSO, δ ppm): 1.20 (t, 3H, J = 7.2 Hz, CH_3), 3.85 (q, 2H, J = 7.2 Hz, CH_2), 5.18 (d, 1H, J = 22.2 Hz, CH–P), 6.76 (d, 2H, J = 7.8 Hz, Ar–H), 6.91–6.95 (m, 3H, Ar–H), 7.00–7.07 (m, 3H, Ar–H), 7.19 (t, 1H, J = 7.8 Hz, Ar–H), 7.40 (d, 1H, J = 7.8 H, Ar–H), 10.32 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 16.8, 42.6 (d, J = 150.4 Hz, CH–P), 62.3, 70.3, 111.1, 115.0, 116.0, 116.2, 122.9, 124.6, 126.0, 127.0, 128.0, 130.2, 131.2, 131.9, 135.0, 141.8, 160.0, 161.0, 162.7, 165.2, 172.6. MS (m/z, I%): 565 (M^+, 10%). Anal. Calcd for $C_{25}H_{17}ClF_3N_2O_4PS$ (564.91): C, 53.16; H, 3.03; N, 4.96; S, 5.66. Found: C, 52.93%; H, 2.84%; N, 4.71%; S, 5.29%.

4.9. *5-Fluoro-3′-(4-fluorophenyl)-4′-hydrazinylidene-spiro[indole-3,2′-thiazolidin]-2(1H)-one (8)*

A mixture of compound **1** (2.5 mmol, 0.83 g) and hydrazine hydrate (4 mmol, 0.2 ml) in absolute ethanol (15 mL) was heated under reflux for 10 h. After cooling, the formed solid was filtered off and crystallized from DMF–EtOH to give white crystals; 85% yield; mp 226–227°C. IR (KBr) (ν_{max}, cm^{-1}): 3246 (NH), 1731 (C=$O_{oxindole}$), 1636 (C=N), 1216 (C–F). ^{1}H-NMR (DMSO, δ ppm): 3.83, 4.33 (dd, 2H, J = 15 Hz, CH_2 AB system), 5.37 (br, 2H, NH_2), 6.76 (d, 1H, J = 7.2 Hz, Ar–H), 6.92–7.05 (m, 4H, Ar–H), 7.20–7.41 (m, 2H, Ar–H), 10.02 (s, 1H, $NH_{oxindole}$).

MS (m/z, I%): 346 (M^+, 4%). Anal. Calcd for $C_{16}H_{12}F_2N_4OS$ (346.36): C, 55.48; H, 3.49; N, 16.18; S, 9.26. Found: C, 55.12%; H, 3.13%; N, 15.80%; S, 8.98%.

4.10. *5-Fluoro-4′-(4-fluorophenyl)-1′-oxido-2′, 3′, 4′,5′-tetrahydro-spiro{indole-3,5′-thiazolo[4,5-d][1,2,3]thiadiazol}-2-one (9)*

A mixture of hydrazone **8** (0.57 g, 1.66 mmol) in dry dioxane (15 ml) containing triethylamine (4 mmol, 0.4 ml) was kept with constant magnetic stirring, maintaining the temperature below 0°C. A solution of thionyl chloride (2 mmol, 0.15 ml) in dry dioxane (10 ml) was added to the above mixture with constant magnetic stirring, maintaining the temperature below 0°C. After the complete addition, the temperature was allowed to rise to room temperature for 2 h. The mixture was heated under reflux for a further 3 h. After cooling, the mixture was poured into ice. The resulting product **9** was isolated using an extraction isolation technique and recrystallized from ethanol as brown crystals; 60% yield; mp 170–172°C. IR (KBr) (ν_{max}, cm^{-1}): 3354, 3145 (NHNH), 1736 (C=$O_{oxindole}$), 1587 (C=C), 1210 (C–F), 1080 (S=O). ^{1}H-NMR (DMSO, δ ppm): 5.09 (br, 2H, NHNH), 7.04 (t, 2H, J = 8.4 Hz, Ar–H), 7.16 (t, 2H, J = 8.4 Hz, Ar–H), 7.73 (t, 2H, J = 7.2 Hz, Ar–H), 8.01 (t, 1H, J = 7.2 Hz, Ar–H), 9.71 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 66.9, 98.0, 110.0, 115.1, 115.3, 122.5, 125.0, 130.2, 134.9, 140.0, 158.3, 159.9, 163.8, 172.6. MS (m/z, I%): 392 (M^+, 3%). Anal. Calcd for $C_{16}H_{10}F_2N_4O_2S_2$ (392.41): C, 48.97; H, 2.57; N, 14.28; S, 16.34. Found: C, 48.61%; H, 2.13%; N, 13.91%; S, 16.09%.

4.11. *5-Fluoro-6′-(4-fluorophenyl)-3′-hydroxy-2′,3′,5′,6′-tetrahydro-1H-spiro{indole-3,5′-thiazolo[5,4-d][1,2,3]diazaphosphol}-2-one (10)*

A mixture of hydrazone **8** (0.57 g, 1.66 mmol) in dry dioxane (15 ml) containing triethylamine (4 mmol, 0.4 ml) was kept with constant magnetic stirring, maintaining the temperature below 0°C. A solution of phosphorus oxychloride (2 mmol, 0.19 ml) in dry dioxane (10 ml) was added to the above mixture with constant magnetic stirring, maintaining the temperature below 0°C. After the complete addition, the temperature was allowed to rise to room temperature for 2 h. The mixture was heated under reflux for a further 3 h. After cooling, the mixture was poured into ice. The resulting product **9** was isolated using an extraction isolation technique and recrystallized from ethanol as beige crystals; 58% yield; mp 230–232°C. IR (KBr) (ν_{max}, cm^{-1}): 3247 (br, OH, NH), 1729 (C=$O_{oxindole}$), 1619 (C=C), 1217 (br, C–F and P=O). ^{1}H-NMR (DMSO, δ ppm): 6.29 (br, 2H, NHNH), 6.85 (d, 2H, J = 7.8 Hz, Ar–H), 6.97 (t, 2H, J = 7.2 Hz, Ar–H), 7.13 (t, 2H, J = 7.8 Hz, Ar–H), 7.41 (d, 1H, J = 7.2 Hz, Ar–H), 8.45 (br, 1H, OH), 9.74 (s, 1H, $NH_{oxindole}$). ^{13}C-NMR (DMSO, δ ppm): 67.9, 90.0, 110.2, 115.2, 118.3, 121.8, 127.4, 135.0, 138.9, 140.0, 155.0, 160.0, 162.0, 172.5. MS (m/z, I%): 408 (M^+, 45%). Anal. Calcd for $C_{16}H_{11}F_2N_4O_3PS$ (408.33): C, 47.06; H, 2.72; N, 13.72; S, 7.85. Found: C, 46.87%; H, 2.43%; N, 13.49%; S, 7.56%.

4.12. *Antioxidant activity*

The nitrogen-centered stable free radical DPPH has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at λ 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties. The solutions of test compounds (150, 300 and

450 μmol L^{-1}) were added to DPPH (100 μM) in DMSO/ethanol. The tubes were kept at an ambient temperature for 20 min and the absorbance was measured at λ 517 nm.[29,30] The difference between the test and the control experiments was taken and expressed as the percent scavenging of the DPPH radical using the following formula % inhibition = (AB - AA/AB) × 100, where AB is the absorption of blank and AA the absorption of the tested compound. The radical scavenging activity of ascorbic acid was also measured and compared with that of the different synthesized compounds.

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