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# Synthesis of O-prenylated and O-geranylated derivatives of 5-benzylidene2,4-thiazolidinediones and evaluation of their free radical scavenging activity as well as effect on some phase II antioxidant/detoxifying enzymes

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**Abstract**—A series of 5-arylidene-2,4-thiazolidinediones and its geranyloxy or prenyloxy derivative were synthesized and studied for their radical scavenging activity using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. Their comparable scavenging activities were expressed as $IC_{50}$ value. Compounds **2c**, **2d**, **4d**, and **6a** showed appreciable radical scavenging activities. The vanillin based thiazolidinedione compound **2c** displayed highest activity comparable to that of α-tocopherol. But in vivo, compound **6a** showed better results in inducing phase II detoxifying/antioxidative enzyme.


Thiazolidinediones (TZDs) have been the subject of extensive researches because of their deep involvement in the regulation of different physiological processes. Thiazolidinedione derivatives have been shown to possess potent immunostimulatory property, antiarthritic activity as well as oncostatic activity.[1] TZDs such as troglitazone, pioglitazone, and rosiglitazone are potent reducer of plasma glucose level in vivo. Besides their anti-diabetic potency, these TZDs have been shown to exert anti-inflammatory effects on vascular cells.[2] TZDs were also found to inhibit the production of inflammatory cytokines and the expression of inducible nitric oxide syntheses in monocytes/macrophages.[3,4] It has been shown that TZDs suppress the growth of several cancer cell lines including colon, breast, and prostate in vivo and in vitro.[5–7] TZDs were also found to inhibit angiogenesis.[8] Some thiazolidinedione derivatives also showed $Cu^{2+}$ mediated lipid-peroxidation inhibitory activity[9] and were found to inhibit serum ALT, AST as well as γ-GTP levels significantly during treatment in patients with type 2 diabetes[10]. TZDs are also potential cancer chemopreventive agents against colon, breast, tongue, and gastric carcinogenesis.[8]

The naturally occurring prenyl alcohol geraniol has got the potential to suppress the growth of tumor cells, both in vitro [11–15] and in vivo,[16] and that of chemically induced tumors[17,18]. O-protecting geraniol exhibited better antitumor activity compared to free alcohol.[19] On the other hand, addition of geraniol to ferulic acid resulted the geranyloxy ferulic acid which was found to be more potent than the ferulic acid.[20] Also Auraptene, a geranyl ether derivative of 7-hydroxyl coumarin, was shown to be more effective in inhibiting mouse skin tumor development than the parent hydroxyl coumarin.[21]

Free radicals are being formed during normal cellular metabolism and they are known to contribute to healthy functions in human health and development when they are not excessive. Formation of free radicals is not limited to normal cellular process but also occurs upon exposure to certain chemicals (polycyclic aromatic hydrocarbon, cadmium, lead, etc.), radiation, cigarette smoke, and high fat diet. Exposure of a healthy cell to free radical is known to damage structures and consequently interfere with functions of enzymes and critical macromolecule. Mammalian cells possess elaborate

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defense mechanism to detoxify free radicals. A balance between formation of free radicals and their detoxification is essential for normal cellular function. When such a balance is disrupted as a result of excessive generation of damaging species or low levels of antioxidants, a cell enters a state of oxidative stress and is damaged. If the damage persists the cell will enter a state of genetic instability that can lead to chronic diseases including cancer.[22]

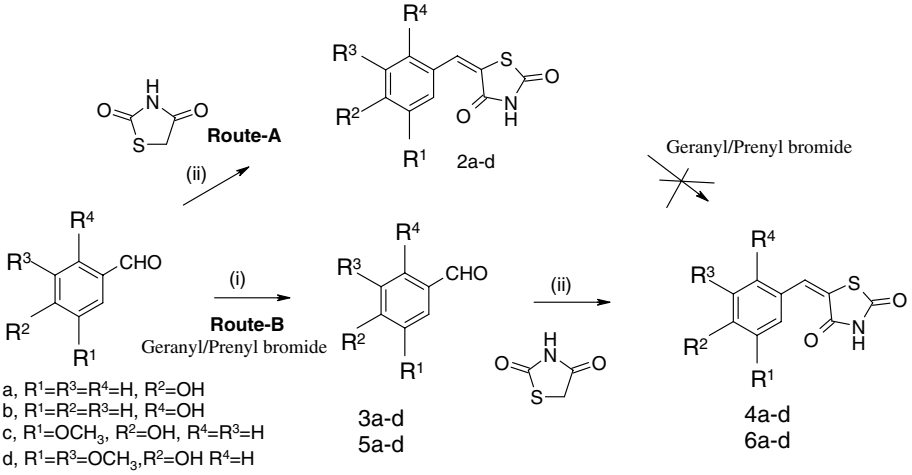
In this report, we describe the synthesis of several 5-arylidene-2,4-thiazolidinedione derivatives with geranyloxy or prenyloxy substituent on the 5-arylidene moiety of 5-arylidene-2,4-thiazolidinediones. We also report the evaluation of their radical scavenging activities using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and also the effect of the two most active compounds **2c** and **4d** (in DPPH assay) on some phase II antioxidative and detoxifying enzyme (glutathione-*S*-transferase, superoxide dismutase, and catalase), as well as on lipid-peroxidation level screened in vivo in Swiss albino mice. The effect of these compounds on ALT, AST, and urea level has also been reported here.

The thiazolidinedione derivatives (**2a**–**d**) were prepared as shown in Scheme 1. The Knoevenagel condensation between active methylene group of 2,4-thiazolidinedione and hydroxy benzaldehyde (**1a**–**d**) in presence of catalytic amount of piperidine (Route A) furnished the 5-arylidene-2,4-thiazolidinediones (**2a**–**d**) as yellow colored solid in 80–85% yield. Compounds (**2a**–**d**) on treatment with either prenyl bromide or geranyl bromide in presence of $K_2CO_3$ or even NaH did not produce compounds (**4a**–**d**) or (**6a**–**d**),[29] each time the starting material was recovered back. We presume that the apparent inactivity of the phenolic group was due to the stabilization of the phenolate anion which is attributed to the extended conjugation of the aryl moiety with the thiazolidinedione ring. Compounds (**4a**–**d**) and (**6a**–**d**) were finally prepared following route B. Hydroxy benzaldehydes (**1a**–**d**) were first converted to the corresponding prenyloxy (**3a**–**d**) or geranyloxy derivative (**5a**–**d**) by treating with either prenyl bromide or geranyl bromide in presence of anhydrous $K_2CO_3$ and 10% tetrabutyl ammonium hydrogen sulfate in acetone at room temperature. The products were obtained as oil and purified through column chromatography. Compounds (**3a**–**d**) and (**5a**–**d**) were then converted to (**4a**–**d**) and (**6a**–**d**), respectively, by condensation with 2,4-thiazolidinedione in benzene in presence of piperidine with azeotropic removal of water. Compounds (**2a**–**d**), (**4a**–**d**), and (**6a**–**d**) were purified by column chromatography and obtained in good yields (70–85%).

$^1H$, $^{13}C$, and EIMS were used to confirm the structure and purity of all listed compounds (**2a**–**d**, **4a**–**d**, and **6a**–**d**). Characteristically, a single 5-methylidene proton was observed in the range of δ 7.72–7.97 as a singlet and NH proton was observed in the range of δ12.5–13.5 as a broad signal in $CDCl_3$ or DMSO-$d_6$ solution, both observations were consistent with previously reported data in the literature.[23] The absence of 5-$CH_2$ resonance of 2,4-thiazolidinedione confirmed the structure of the desired product (**2a**–**d**), (**4a**–**d**) and (**6a**–**d**). The geometry of all benzylidenethiazolidine-2,4-diones was assumed to be (*Z*)-isomer as observed in other instances.[24]

The scavenging effects of all of the synthesized compounds on the DPPH free radical were evaluated. Nowadays, antioxidants that exhibit DPPH radical scavenging activity are increasingly receiving attention.[9] They have been reported to have interesting anticancer, anti-aging, and anti-inflammatory activities. Accordingly, a study of the syntheses of novel 5-arylidene-2,4-thiazolidinedione derivatives with antioxidant activity would support the development of new drugs and improve the treatment of various diseases.

The model of scavenging of the stable DPPH radical is extensively used to evaluate radical scavenging activities in less time than other methods. Compound reacts with DPPH, which is a nitrogen centered radical with a characteristic absorption at 517 nm, and convert it to stable diamagnetic molecule 1,1-diphenyl-picryl hydrazine, due to its hydrogen donating ability at a very rapid rate.[25]

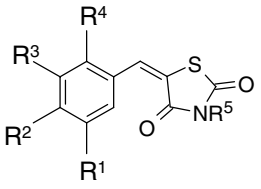



**Scheme 1.** Reagents and condition: (i) Tetrabutyl ammonium hydrogen sulfate, potassium carbonate, Acetone, rt.

When this electron becomes paired off, the absorption decreases stoichiometrically with respect to the number of electrons taken up. Such a change in the absorbance produced in this reaction has been widely applied to test the capacity of numerous molecules to act as free radical scavengers.[9]

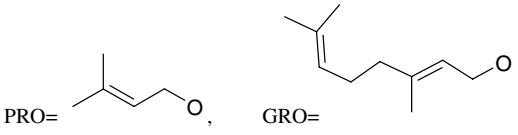
The entire synthesized compounds scavenged DPPH radical significantly in a concentration-dependent manner. Their comparable scavenging activities were expressed in $IC_{50}$ (concentration required for 50% inhibition of 0.1 mM DPPH concentration) value. α-Tocopherol was used as the positive standard. The radical scavenging activities of the synthesized compounds are summarized in Table 1. Compounds **2c**, **2d**, **4d**, and **6a** showed appreciable radical scavenging activity. The activity showed by the vaniline based compound **2c** was comparable to that of α-tocopherol. The strong activity showed by **2c** and also by **2d** was perhaps due to the presence of the free OH group in the aryl moiety of 5-arylidene-2,4-thiazolidinediones, which can donate hydrogen atoms. After donating a hydrogen atom, compounds exist in its radical form, and the electron conjugation effect in the structure stabilizes the radical which favors the reaction to occur. That the presence of free hydroxyl group in the aryl moiety is one of the factors in determining the DPPH scavenging activity of the compound is also described by Tominaga et al.[26] where protection of the free hydroxyl group drastically reduced the DPPH scavenging activity. The difference in activity amongst compounds **2a**–**d** was due to the difference in the stability of the oxygen centered radical formed in these compounds. The radical centered on oxygen (compounds **2a**–**d**) is stabilized by extended conjugation which formed para quinonoid structure for **2a**, **2c**, and **2d**, and ortho quinonoid structure for **2b**. As the para quinonoid structure has more stabilization than the ortho quinonoid structure, compound **2b** was found to be the least active compound amongst **2a**–**d**. The presence of the electron donating $OCH_3$ group at the ortho position enhanced the stabilization of the resulting oxygen centered radical as the number of conjugating structure is more than that without the $OCH_3$ group. As a result compounds **2c** and **2d** were more active than **2a**. Amongst **2c** and **2d** the presence of an extra methoxy group in **2d** slightly reduced the stability of the radical formed due to cross conjugation, hence **2c** was found to be the most active compound. The presence of unsaturated double bond as well as presence of NH group which can donate hydrogen atom in thiazolidinedione moiety may also contribute to the radical scavenging activity of these compounds as evidenced from the results showed by compounds **4d** and **6a** where free OH group is not available. The NH group does have the radical scavenging property as the N-protected compound (7), prepared for some other purpose, showed practically no DPPH scavenging activity as shown in Figure 1. The difference of activity of **4a**–**d** may be due to the stability of the nitrogen centered radical. The presence of methoxy group in the aromatic ring enhanced the stability of the nitrogen centered radical due to electron conjugation effect and this effect is more when there are two methoxy groups in the aromatic ring in compound **4d** (synergistic effect) compared to compound **4c** which

**Table 1.** Inhibition of DPPH radical by synthesized compound




| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $IC_{50}$ (μM) |
|---|---|---|---|---|---|---|
| α-Tocopherol | | | | | | 2.3 |
| **2a** | H | OH | H | H | H | 11.97 |
| **2b** | H | H | H | OH | H | 23.49 |
| **2c** | $OCH_3$ | OH | H | H | H | 2.49 |
| **2d** | $OCH_3$ | OH | $OCH_3$ | H | H | 2.85 |
| **4a** | H | PRO | H | H | H | >50 |
| **4b** | H | H | H | PRO | H | 43.3 |
| **4c** | $OCH_3$ | PRO | H | H | H | 17.89 |
| **4d** | $OCH_3$ | PRO | $OCH_3$ | H | H | 4.08 |
| **6a** | H | GRO | H | H | H | 9.8 |
| **6b** | H | H | H | GRO | H | 11.97 |
| **6c** | $OCH_3$ | GRO | H | H | H | 17.57 |
| **6d** | $OCH_3$ | GRO | $OCH_3$ | H | H | 32.13 |
| **7** | H | GRO | H | H | $(CH_2)_5Br$ | Very high |

$IC_{50}$: concentration required for 50% reduction of 0.1 mM DPPH radical.



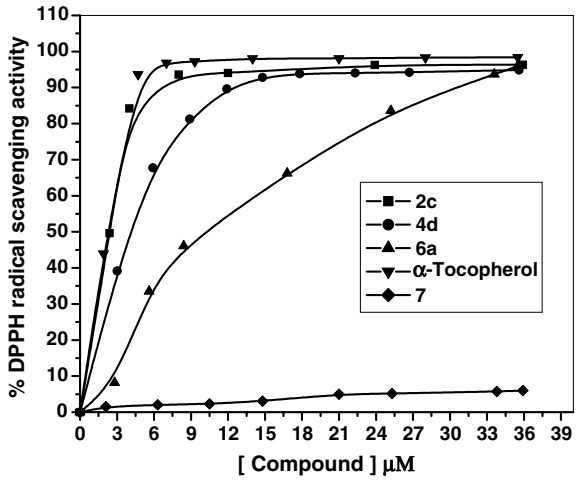



**Figure 1.** Graphical representation of % DPPH radical scavenging activity of compounds **2c**, **4d**, **6a**, **7**, and α-tocopherol.

has one methoxy group in the aromatic ring. Compounds **4a** and **4b** which do not have any methoxy group showed less activity. The better activity of **4b** as compared to **4a** may be due to the 1,7-sigmatropic shift[30] of the prenyl group attached to the aromatic oxygen atom to the carbonyl oxy atom of the thiazolidine ring, which is possible, resulting more stable phenoxy radical. The difference in activity amongst compounds **6a**–**d** may be in part due to the steric interaction between the bulky geranyl group and the proximate methoxy group in compounds **6c** and **6d** which disturbed the planarity of the molecule as a result the stability of the nitrogen centered radical through conjugation is also disturbed. In case of compound **6a** which does not have any proximate methoxy group, such steric interaction is minimum providing better stability of the nitrogen centered radical by extended conjugation resulting in para quinonoid structure which has more stabilization than the ortho quinonoid structure formed for compound **6b**. As a result compound **6a** was found more active than **6b** and also the most active amongst **6a**–**d**.

The effect of the thiazolidinedione derivatives **2c**, **4d**, and **6a** on different phase II/detoxifying enzymes as well as on serum ALT, AST, and urea level in Swiss albino mice was evaluated and the results are summarized in Tables 2 and 3.

The compounds (**2c**, **4d**, and **6a**) were found to be effective in enhancing the host antioxidant defense system

**Table 3.** Modulation of hepatoprotecting activity by compounds **2c**, **4d**, & **6a** in normal Swiss albino mice liver

| Compound | ALT (U/I) | AST(U/I) | Urea (mg/dl) |
|---|---|---|---|
| Normal | 12.7 ± 1.3 | 42.47 ± 1.6 | 18.48 ± 0.65 |
| **2c** | 4.8 ± 1.5* | 38.1 ± 2.3* | 13.83 ± 0.53** |
| **4d** | 7.3 ± 1.2** | 37.99 ± 1.6* | 16.53 ± 1.2* |
| **6a** | 6.32 ± 1.22* | 32.88 ± 3.3* | 14.69 ± 2.1* |

Results are expressed as means ± SD. $n = 6$ animals per group.
* Significantly different from normal control group at $p < 0.01$.

such as superoxide dismutase (SOD), catalase (CAT), glutathione-*S*-transferase (GST), and reduced Glutathione (GSH), and at the same time lowering the serum ALT and AST level at the preliminary screening dose of 3 mg/kg in normal Swiss albino mice given orally for 20 days as compared to the control animals. The hepatic lipid-peroxidation level (LPO) remained unchanged.

The vulnerability of the liver to chemical injury is due to its anatomical proximity to the blood supply and digestive tract as to its ability to biotransform and concentrate xenobiotics.[27] Serum ALT and AST are two marker enzymes which indicate the extent of liver injury. In the literature it was observed that thiazolidinedione derivative compounds were effective to inhibit serum ALT, AST level significantly.[10] In the present experiment, the thiazolidinedione compounds **2c**, **4d**, and **6a** decreased serum ALT and AST activities, characterizing hepatoprotective effect of the compounds lowering release of these enzymes to plasma in mice.

In addition, these three compounds caused decrease in serum urea levels and did not change creatine level suggesting no renal toxicity. A number of reports showed that enhanced serum urea and creatine levels are indicative of renal injury.[28]

Substitution of the phenolic hydrogen by the Prenyl/Geranyl group though lowered the radical scavenging activity to some extent still it has the potential to upregulate host antioxidant defense system in a significant manner. Geranyloxy derivative of thiazolidinedione (**6a**) showed better effect compared to prenyloxy derivative (**4d**) as an antioxidant by enhancing detoxifying enzyme as well as lowering lipid peroxidation level. In conclusion, these synthesized compounds are found to be highly promising to be used as antioxidants against oxidative stress related diseases with special reference to cancer.

**Table 2.** Modulation of Phase II detoxifying enzymes (GST, SOD, CAT, and GSH) and lipid peroxidation by compounds **2c**, **4d**, and **6a** in normal Swiss albino mice liver

| Compound | LPO (nmTBARS/mg protein) | GST (nmol CDNB-GSH $min^{-1}mg^{-1}$) | GSH (nmol GSH/mg protein) | SOD (unit of inhibition/mg protein) | CAT (units/mg protein) |
|---|---|---|---|---|---|
| Normal | 0.15 ± 0.01 | 113.86 ± 9.12 | 101.17 ± 11.84 | 57.4 ± 3.4 | 12.26 ± 0.37 |
| **2c** | 0.143 ± 0.01* | 220.8 ± 3.96* | 184.09 ± 18.4* | 65.45 ± 3.7* | 16.85 ± 1.2* |
| **4d** | 0.158 ± 0.011* | 140.54 ± 11* | 238.22 ± 22.3* | 67.07 ± 6.6* | 23.97 ± 2.25* |
| **6a** | 0.148 ± 0.013* | 160.33 ± 12* | 245.32 ± 11.3* | 70.15 ± 12.3* | 22.32 ± 1.2* |

Results are expressed as means ± SD. $n = 6$ animals per group.
* Significantly different from normal control group at $p < 0.01$.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.12.040.

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29. Preparation of 5-[4-(3,7-dimethyl-octa-2,6-dienyloxy)-benzylidene]-thiazolidine-2,4-dione: (**6a**) Geranyl bromide (1.064 ml, 4.9 mmol) in 4 ml acetone was added dropwise to a mixture containing 4-hydroxybenzaldehyde (300 mg, 2.45 mmol), potassium carbonate (677.3 mg), and tetrabutylammonium hydrogen sulfate (30 mg) in 6 ml dry acetone at room temperature under anhydrous condition. After stirring at room temp. for 24 h, acetone was removed in vacuo and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 4% aqueous NaOH sol (3× 10 ml) then with water and finally dried over $CaCl_2$, $CHCl_3$ was removed in vacuo to leave an oil which was purified by column chromatography over silica gel (60–120 mesh) with $CHCl_3$–petroleum ether (3:1,v/v) to give the compound **5a** (150 mg, 51.6%).
A mixture of **5a** (150 mg, 0.588 mmol), 2,4-thiazolidinedione (82.7 mg, 0.706 mmol), and catalytic amount of pyperidine (20 μl) in 15 ml benzene was stirred at refluxing temperature for 24 h in dean-stark apparatus. The reaction mixture was cooled at room temperature and the solid separated filtered. The crude product was purified through column chromatography over silica gel (60–120 mesh) with Petroleum ether–diethyl ether (5:2, v/v) to give the title compound (**6a**) as yellow color solid. It was then crystallised from diethyl ether–petether (60–80 °C) to get an analytical sample (90 mg, 67.17%). Yield: 67.17%, mp: 120–121 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.6 (3H, s), $\delta$ 1.67 (3H, s), $\delta$ 1.75 (3H, s), $\delta$ 2.1 (4H, s), $\delta$ 4.6 (2H, d, 6.5 Hz), $\delta$ 5.1 (1H, s), $\delta$ 5.47 (1H, t, 6.3 Hz), $\delta$ 6.99 (2H, d, 8.7 Hz), $\delta$ 7.44 (2H, d, 8.7 Hz), $\delta$ 7.83 (1H, s), $\delta$ 9.08 (1H, s). $^{13}$C (75 M Hz, $CDCl_3$): 167.87, 167.5, 161.02, 141.99, 134.52, 132.56, 125.37, 123.61, 118.68, 115.47, 65.14, 39.48, 26.18, 25.64, 17.66, and 16.68. EIMS: *m*/*z*, 357 ($M^+$), 221 ($M^+-C_{10}H_{15}$), 150 ($M^+-C_{10}H_{15}$, CONHCO). IR (KBr) $\nu_{max}$ cm$^{-1}$: 2976.0, 1743.5, 1687.6, 1583.4, 1512.1. Anal. Found C, 67.12; H, 6.54, N, 3.88. Calcd for $C_{20}H_{23}NO_3S$: C: 67.2, H: 6.49, N: 3.92.

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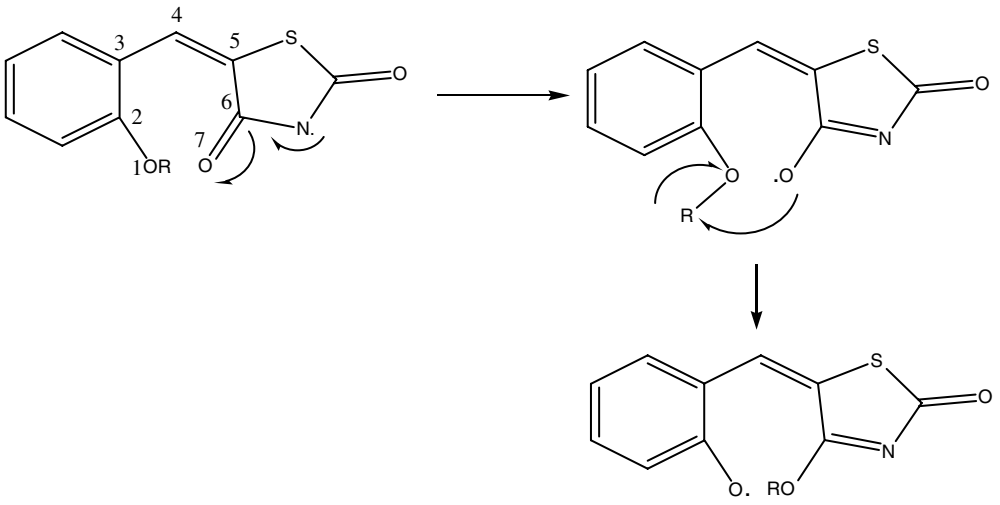


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