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IDENTIFICATION, SYNTHESIS AND PHOTO-PROTECTION EVALUATION OF ARYLTHIAZOLE DERIVATIVES AS A NOVEL SERIES OF SUNSCREENS

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Abstract – A novel series of arylthiazole derivatives have been designed, synthesized and evaluated in preventing keratinocytes cell (HaCaT) from UVB exposure induced cellar damage. The structure-activity relationship (SAR) was discussed. More importantly, compound **5a** significantly protected the dorsal skin of BALB/c-nu mice against UVB-induced decrustation *in vivo*. The *in vitro* and *in vivo* data for these arylthiazole derivatives suggest further studies for their potential use as photo-protection agents as well as sunscreen candidates.

Excessive exposure to ultraviolet radiation (UV) is believed to induce various skin diseases such as sunburn, photo-aging and photo-immunosuppression.[1-3] Moreover, skin oncology research has demonstrated that acute or chronic UV exposure is responsible for photo-carcinogenesis as one of the key factors in the process of skin cancer.[4-6] Commercial sunscreens have been used since 1928 as one of the most effective and prevalent methods of photo-protection, which have still played a major role in decreasing UV radiation and skin cancer occurrence until today.[7] Among UV light, UVB (290-320 nm) is a predominant and most harmful component, which was regarded as main reasons for the most severe damages.[8, 9] As a result, more concern should be taken to develop sunscreen products capable of

preventing UVB exposure. Up to date, FDA has approved a series of UVB organic sunscreen filters, which include aminobenzoates, cinnamates, salicylates, octocrylene and ensulizole.[10] However, several striking weaknesses such as photoallergic reaction or estrogen-like side effects restrict the popularity of these sunscreens.[11] In addition, a limited number of sunscreen products can't meet our growing demand. Thus discovering and developing more effective and safer sunscreens that minimize damage from UVB radiation is still a crucial goal of our research.

In this study, a series of arylthiazole derivatives were identified as a novel class of sunscreens for their potent protective activity against UVB-induced damage. By screening our chemical library with high structural diversity which was derived from ChemBridge company as well as set up in our laboratory, we found compound **1** (Figure 1), an arylthiazole derivative exerted commendable ability to protect keratinocytes cell from UVB-induced damage. Arylthiazole derivatives were reported to show various biological activities such as antitumor,[12] anti-tubercular,[13] anti-virulence,[14] accelerating neuronal differentiation.[15] But whether these arylthiazole compounds showed the function of reversing or blocking UVB-induced damage or not still remained unclear. Therefore, a series of novel arylthiazole derivatives based on compound **1** were designed, synthesized and their activity were assessed for their photo-protection effects. The most potent compound **5a** was validated through cell viability assay *in vitro* and skin damage experiment *in vivo*. Compound **5a** effectively protected UVB-induced skin damage of nude mice, suggesting it was a novel potential photo-protection agent or a promising sunscreen candidate.

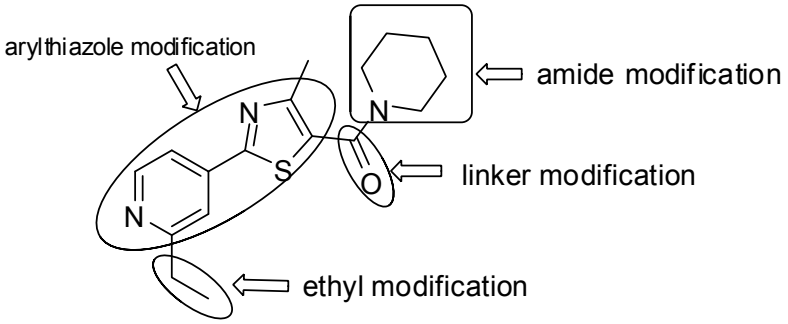
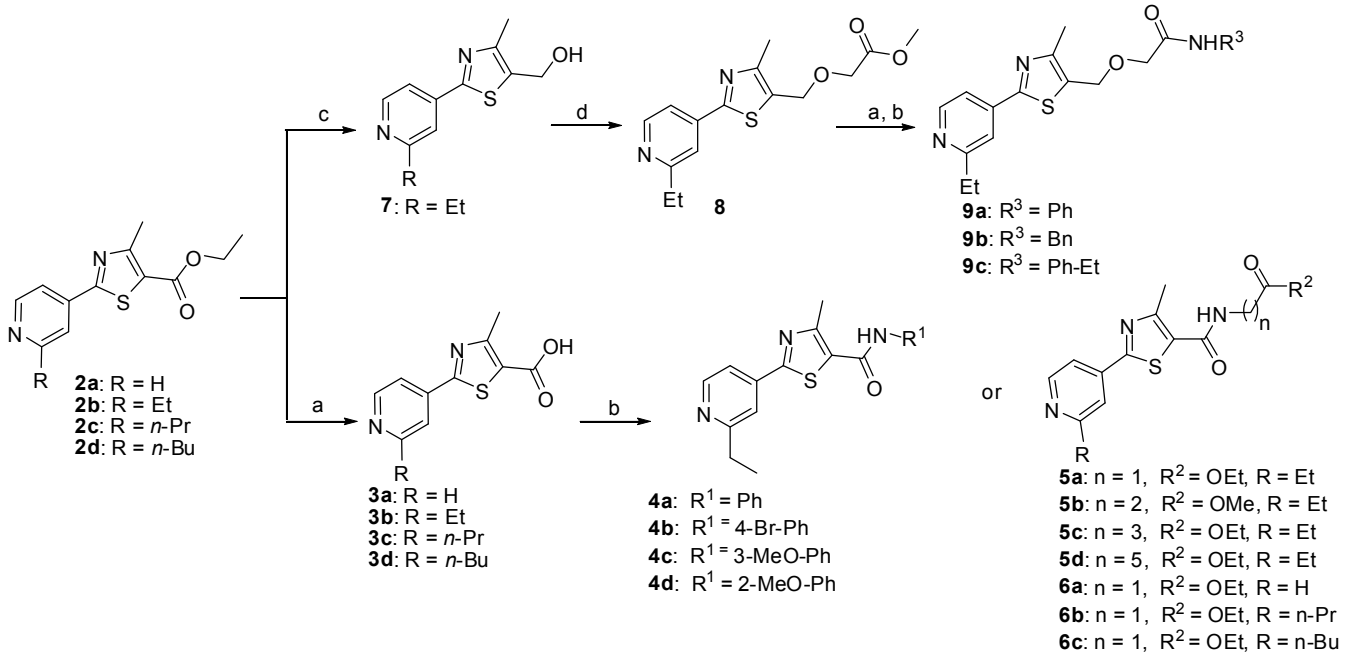


Figure 1. The chemical structure of compound **1** and possible modification strategies

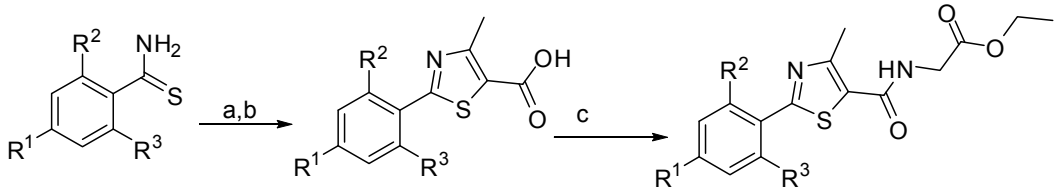
Synthesis of 2-(4-pyridinyl)thiazole derivatives (4a−d, 5a−d, 6a−c, 8, 9a−c). Compounds **4a**−**d**, **5a**−**d**, **6a**−**c**, **8** and **9a**−**c** were prepared using the methods outlined in Scheme 1. Compounds **2a**−**d**[16] were hydrolyzed to corresponding acids **3a**−**d**, compound **3b** was further coupled with arylamines in the presence of EDC·HCl and HOBt to provide compounds **4a**−**d**. Coupling of acid **3b** with a variety of amino acid esters gave compounds **5a**−**d**, while **6a**−**c** were afforded based on **3a** and **3c**−**d** coupled with glycine ethyl ester hydrochloride. In addition, compound **2b** can also be reduced under lithium aluminium

hydride to give compound **7** in a high yield, which was then reacted with methyl bromoacetate in the presence of sodium hydride at ambient temperature to generate intermediate **8**, which was hydrolyzed and then coupled with various amines to afford compounds **9a**−**c**.



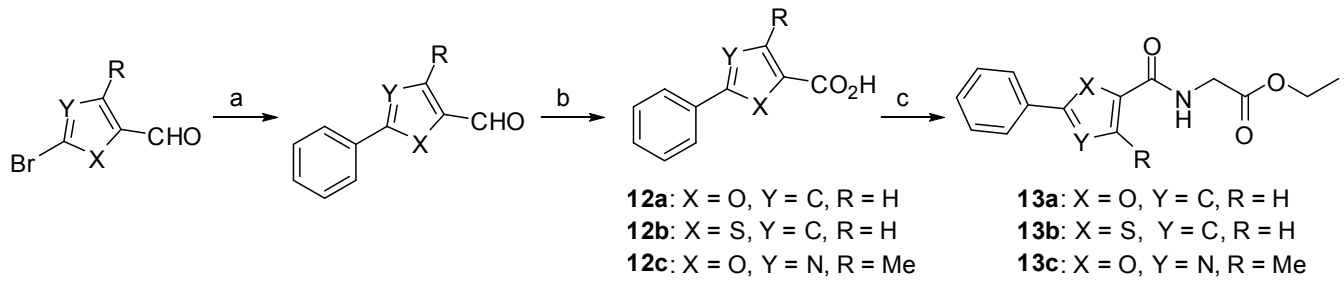
Scheme 1. Reagents and conditions: (a) $LiOH·H_2O$, MeOH, H_2O; (b) amines, EDC·HCl, HOBt, anhydrous DMF; (c) $LiAlH_4$, Et_2O; (d) NaH (60%), methyl 2-bromoacetate, anhydrous DMF.

Synthesis of 2-phenylthiazole derivatives (11a−f). To synthesize compounds **11a**−**f**, a series of commercial or prepared substituted thiobenzamides were selected to react with ethyl 2-bromo-3-oxobutanoate to afford corresponding esters,[16] which were then hydrolyzed by lithium hydroxide monohydrate to obtain compound **10a**−**f**, then coupled with glycine ethyl ester hydrochloride under EDC·HCl and HOBt conditions to give target compounds **11a**−**f** in a satisfactory yield.



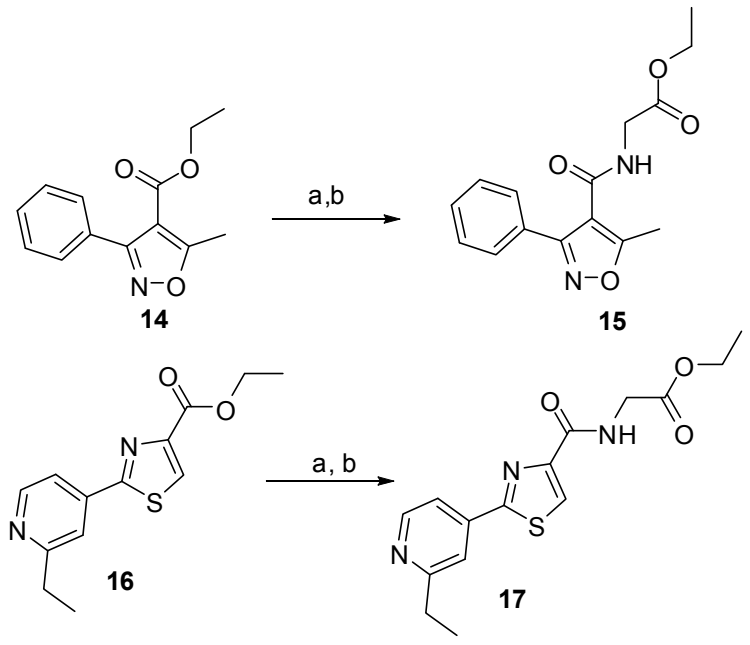
Scheme 2. Reagents and conditions: (a) 2-bromo-3-oxobutanoate, anhydrous EtOH, reflux, 2 h; (b) $LiOH·H_2O$, MeOH, H_2O; (c) EDC·HCl, HOBt, anhydrous DMF.

Synthesis of compound 13a-c. Intermediates **12a**−**c** were prepared using standard palladium-catalyzed cross-coupling reaction followed by oxidation with selenium dioxide.[17,18] Compounds **12a**−**c** were subsequently coupled with glycine ethyl ester hydrochloride to give target compounds **13a**−**c**, as shown in Scheme 3.



Scheme 3. Reagents and conditions: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3; (b) SeO_2, THF, reflux; (c) EDC·HCl, HOBt, anhydrous DMF.

Synthesis of compound 15 and 17. Compounds **15** and **17** were afforded through intermediates **14**[19] and **16**,[20] which were hydrolyzed, and then coupled with glycine ethyl ester hydrochloride to give compounds **15** and **17**.



Scheme 4. (a) $LiOH·H_2O$, MeOH, H_2O; (b) EDC·HCl, HOBt, anhydrous DMF.

Structure-activity relationship of arylthiazole derivatives

To investigate the photo-protection activities of these arylthiazole derivatives, polydatin[15] and BP-3

(2-hydroxy-4-methoxy-benzophenone)[16] which showed photo-protection and sunscreen activities were selected as positive controls. For demonstration of structure-activity relationships, a series of compounds containing arylthiazole skeleton derived from compound **1** were evaluated for their photo-protective effects against 30 mJ/cm^2 of UVB exposure which was appropriate to induce about 50% HaCaT cell death. The strategic modification was shown in Figure 1. Firstly, piperidinyl group of compound **1** was replaced by alkyl or alkenyl amines with the retention of 2-(2-ethylpyrdinyl)thiazole scaffold. Unfortunately the result indicated that protective effects of these compounds were significantly lost (data not shown). Secondly, substitutive anilines with different electron-donating or electron-withdrawing properties were selected to afford compounds **4a-d** based on coupling with the 2-(2-ethylpyrdinyl)thiazole scaffold of the hit compound **1**. Examination of the assay result, compound **4c** with introduction of 3-methoxyphenyl group showed mild protection against UVB exposure as compound **1**, though the protection effect was weaker than positive controls polydatin and BP-3 (Figure 3). These results suggested that more diverse substitution would be explored to increase activities. Subsequently a variety of chainlike amino acid esters with different length were chosen to couple with 2-(2-ethylpyrdinyl)thiazole carboxylic acid **3b** because amino acid ligands usually contributed to potent protection against UVB induced damage.[17] Interestingly, the length of chain between amino and terminal carboxyl group of amino acid demonstrated extremely influences toward protective activity. When n = 1, compound **5a** provided best protective effect among them (**5a**−**d**) and superior to positive controls polydatin and **BP-3** in the same concentration, while the potency was decreased when increasing chain length (**5a** >**5b** >**5c** >**5d**). Thus compound **5a** was chosen for subsequent optimizations (Figures 1, 2).

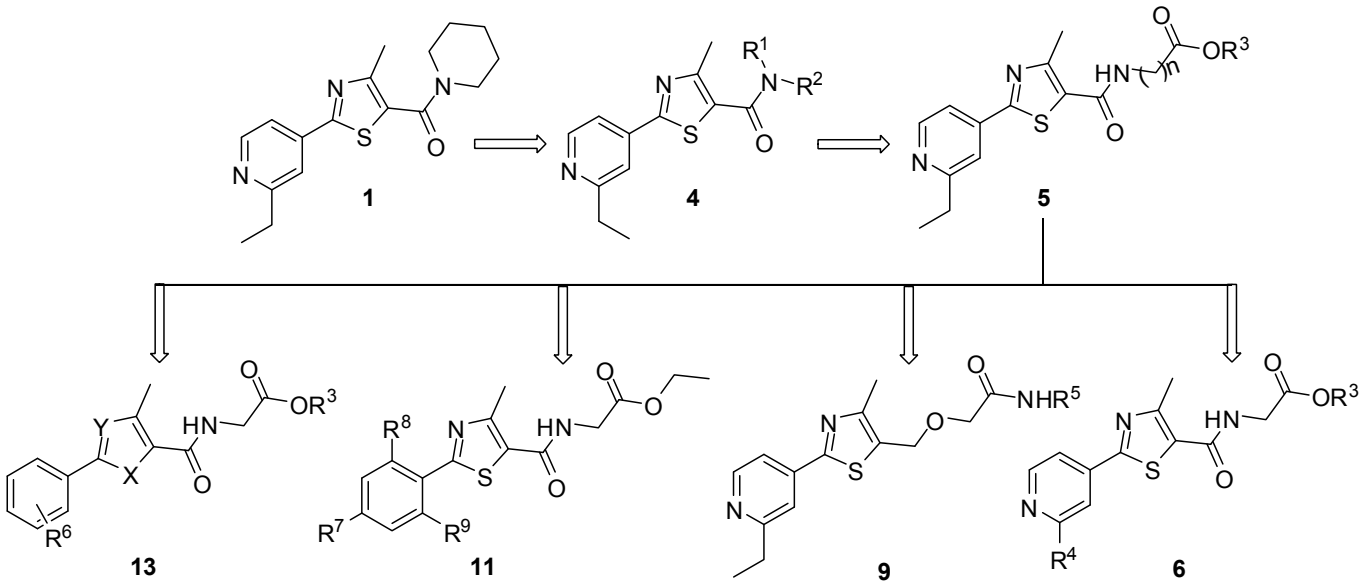


Figure 2. Representative derivatives based on hit compound **1** optimization

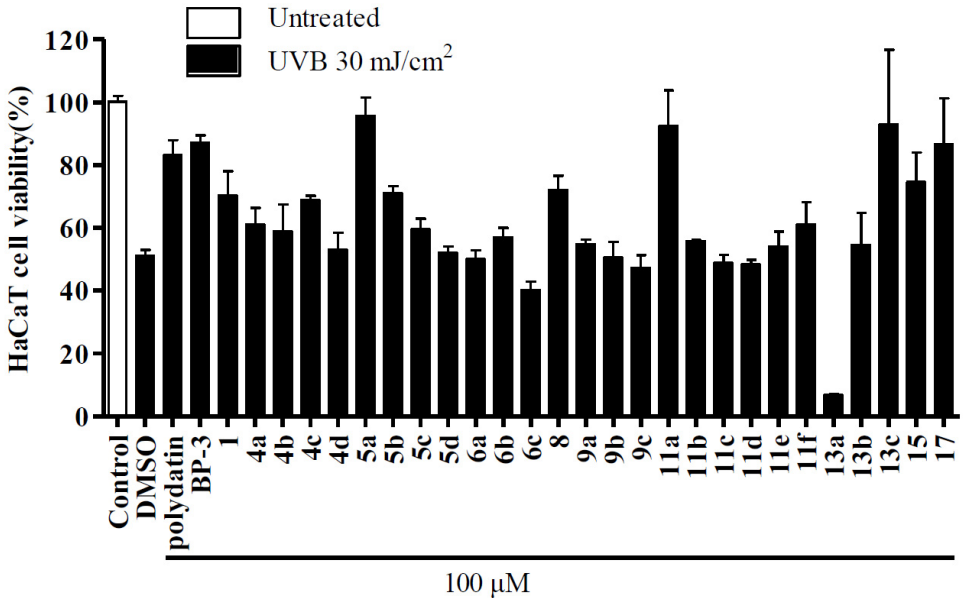


Figure 3. The screening results of target compounds via cell viability assay: control group was without UVB and others with UVB irradiation (30 mJ/cm^2), polydatin and BP-3 were used as positive controls.

The following chemical modifications of compound **5a** were divided into four parts. As listed in Figure 2 and Figure 3, the first part was that the substitution in pyridinyl group, alkyl substitutions (**6b**−**c**) in this position as well as hydrogen atom (**6a**) were explored, which showed that a suitable small alkyl group was crucial for maintaining the activity. For example, when the position was not substituted (**6a**), the activity was decreased compared to **5a**, while if the substitution was a large group such as butyl group (**6c**), it showed toxicity against the HaCat cell instead of protection. Our interest was then turned over other parts of compound **5a**. Next, when the linker amide of **5a** was investigated for changing to ether **8** with similar length, the activity was not increased, and replacement of ester with amide moiety in the terminal of compound **8** was also proven to decrease the activities of those compounds (**9a**−**c**). Further pyridinyl group was substituted by other biomimetic aryl groups such as substituted phenyl ring (**11a**−**f**), which resulted in the discovery of **11a** with almost equal activity to compound **5a**, while other substituted phenyl ring either with electron-donating or electron-withdrawing groups showed no increase in activity. These results suggested that pyridinyl group was not the necessary moiety, and other aromatic groups might lead to the bioactive compounds. Thus pyridinylthiazole group was further replaced by other heteroaromatic groups such as phenylfuran (**13a**), phenylthiophene (**13b**), phenyloxazole (**13c**), phenylisoxazole (**15**) and phenylthiazole (**17**). The result showed these changes were tolerant, since most of them showed good photo-protection against UVB exposure except **13a**, which showed severe cytotoxicity against HaCaT cell (Figure 3). In conclusion, the introduction of amino acid moiety to the arylthiazole skeleton and the existence of amide other than ether as a linker group were necessary for

retaining photo-protection activities of these compounds. Replacement of thiazole with oxazole moiety that possessed similar electron configuration was tolerant, whose activity was in line with compound **5a**. With good potency against UVB induced damage, compounds **5a**, **11a**, **15** and **17** were selected for comprehensive comparison. Among these candidates, compound **5a** was found to show lower cytotoxicity, better photo-protection effect against UV radiation, and more favourable physical characters especially water solubility, and was subsequently chosen for further evaluation *in vitro* and *in vivo*.

In order to detect the toxicity of compound **5a** against HaCaT cell, a viability test experiment was carried out and the result suggested that inferior to 500 μM, compound **5a** had very weak effects on the viability of HaCaT cell, and the viability of HaCaT cell was maintained more than 75% (Figure 4A). Irradiation with 30 mJ/cm^2 of UVB resulted in half of cell death compared with the non-irradiated group while treatment with compound **5a** reduced HaCaT cell death induced by UVB-irradiation in a dose-dependent manner and the proportions of cell death were 35.0 ± 7.0%, 23.7 ± 6.2% and 8.1 ± 6.8% at 25, 50, 100 μM of **5a**, respectively, compared with the non-irradiated group. Those results showed that the photo-protection activity of compound **5a** was directly correlated with its treatment dose suggesting its potential use as a sunscreen (Figure 4B). Furthermore, more cell death was observed after UVB irradiation compared with the non-irradiated groups and compound **5a** dose-dependently reduced HaCaT cell death by photograph (Figure 4C). To further investigate the mechanisms of compound **5a**, the free radical scavenging capacity and UV absorption spectra of compound **5a** were assessed. We found that compound **5a** did not have radical scavenging activity but potently absorbed the UVB radiation at wavelength 200-400 nm (Figure S2 and Figure S3). Moreover, we compared the photo-protective effect of compound **5a** with a widely known UV absorber BP-3 (2-hydroxy-4-methoxy-benzophenone).[16] As shown in Figure S1C, both **5a** and BP-3 have the photo-protective effect on HaCaT cells and there is no significant difference between them at the indicated concentrations. Taken together, our results indicated that **5a** is an effective sunscreen candidate.

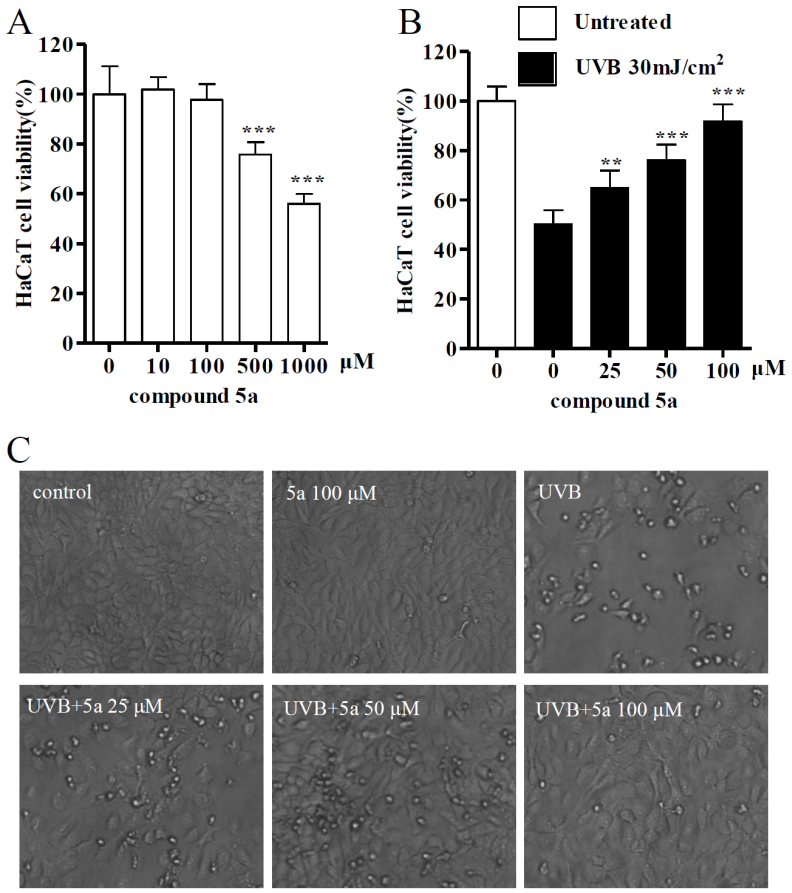


Figure 4. (A) Cell viability was assessed after treatment with various concentrations (0 μM, 10 μM, 100 μM, 500 μM, 1000 μM) of compound **5a** for 24 h. (B) Compound **5a** protected HaCaT cells from UVB-induced cell death in dose-dependent manner. (C) Pictures of UVB-irradiated HaCaT cells which were pretreated with or without indicated concentrations of compound **5a** were taken at 10 h.

Compound 5a protects BALB/c-nu mice against UVB-induced desquamation and epidermis thickness

Compound **5a** was next investigated its protective effect from UVB induced skin damages in BALB/c-nu mice. For *in vivo* studies, the ointment containing **5a** (1.0 mM) was applied on the right side of BALB/c-nu mice dorsal skin once every 12 h while the left side as a control was treated with ointment without compound **5a**. One hour later, the animals were irradiated with Bio-Sun system at wavelength 312 nm for UVB (360 mJ/cm^2) irradiation once a day for 7 days. The results were listed in Figure 5A and Figure 5B. Figure 5A clearly demonstrated that 360 mJ/cm^2 UVB irradiation resulted in severe desquamation whereas treatment with 1.0 mM **5a** attenuated those skin damages induced by UVB irradiation. As shown in Figure 5B, the epidermis thickness of nude mice dorsal skin was incrassate after UVB exposure and the average thickness of epidermis of UVB-irradiated mice was 86.8 ± 8.4 μm which was decreased to 37.5 ± 3.7 μm after treatment with 1.0 mM **5a** twice a day. Altogether, these data suggested that compound **5a** effectively protect against UVB-induced skin damage *in vivo*.

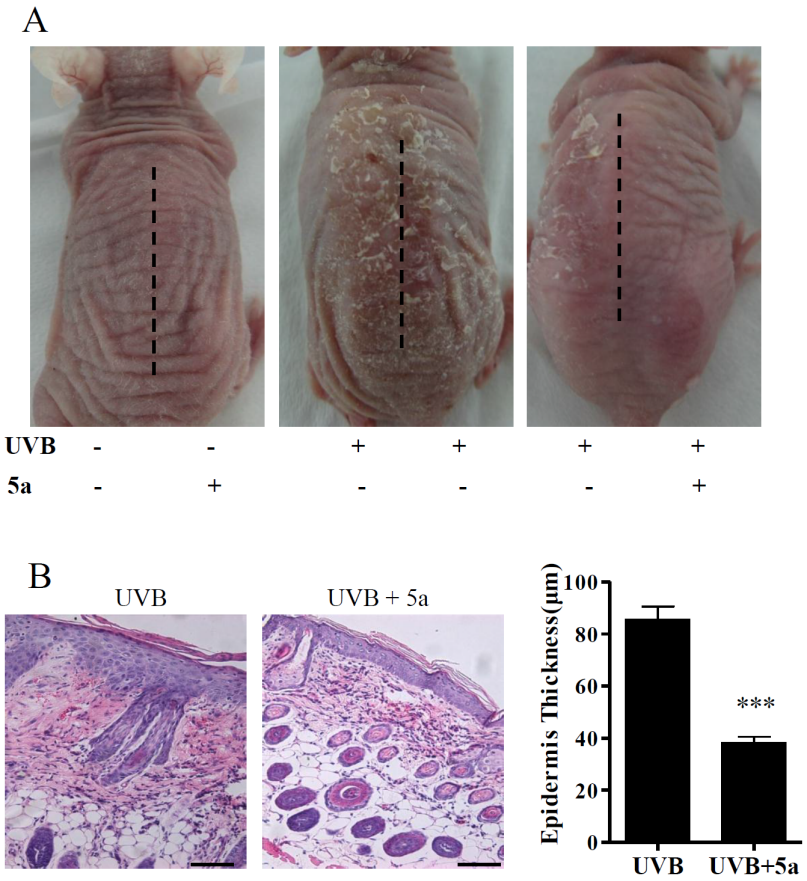


Figure 5. (A) BALB/c-nu mice skin were treated with only ointment on left dorsal skin and ointment containing 10 mg/mL compound **5a** on right dorsal skin, and were exposed to UVB. After 7 days, animals' images were shot. (B) The normal and UVB irradiated mice skin which was coated with or without compound **5a** were stained with hematoxylin-eosin and beside was a statistic panel.

CONCLUSION

In this study, a novel class of arylthiazole derivatives were designed and synthesized and then their effect on UVB-induced cellular damage were evaluated by measuring cell viability. The relationship between their structure and photo-protection activity was concluded. The photo-protection activity of potent compound **5a** was studied at BALB/c-nu mice model. Both *in vivo* and *in vitro* experiments suggested that compound **5a** had an excellent photo-protective activity on UVB-induced damage. Further studies to identify the detail mechanism of photo-protective activity of compound **5a** are in process.

EXPERIMENTAL

All of the reagent and solvents used in synthesis experiments were purchased from Sigma-Aldrich and TCI Co. Ltd, and when necessary, were purified and dried by standard methods before use.

The ^{1}H NMR Spectra were recorded with a Bruker Avance 300 MHz spectrometer instruments, using TMS as an internal standard. Chemical shifts are expressed in parts per million (ppm). Mass spectra were

obtained in ESI mode via Shimadzu LCMS spectrometer. TLC and preparative thin-layer chromatography were performed on silica gel GF/UV 254, and the chromatography were performed on silica gel (200-300 mesh) visualized under UV light at 254 nm and 365 nm. Unless otherwise a special note, the progress of reaction was detected by TLC and protected under nitrogen. High-resolution mass data of **5a**, **8**, **11a**, **13c**, **15** and **17** were obtained on a Micromass Q-Tof UltimaTM spectrometer.

***N*-(Ethoxycarbonylmethyl)-2-(2-ethyl-4-pyridinyl)-4-methyl-5-thiazolecarboxamide (5a).** The title compound was prepared according to **4a** except using glycine ethyl ester hydrochloride instead of aniline. Yield: 44%: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, *J* = 5.1 Hz, 1H), 7.67 (s, 1H), 7.57 (d, *J* = 5.1 Hz, 1H), 6.71 (br s, 1H), 3.73–3.68 (m, 5H), 2.90 (q, *J* = 7.2 Hz, 2H), 2.75 (s, 3H), 2.70 (t, *J* = 5.7 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.90, 165.42, 165.11, 161.56, 156.92, 150.39, 140.11, 127.22, 118.88, 118.06, 62.15, 42.17, 31.62, 17.67, 14.35, 13.98. ESI-HRMS Calculated for $[C_{16}H_{19}N_3O_3S + H]^+$: 334.1225, found: 334.1227.

Methyl 2-((2-(2-ethyl-4-pyridinyl)-4-methyl-5-thiazolyl)methoxy)acetate (8). To a solution of compound 7 (1.22 g, 5.2 mmol) in 10 mL of DMF was added sodium hydride (60%, 312 mg, 7.8 mmol) at 0 °C with stirring for 10 min, then methyl 2-bromoacetate (0.73 mL, 7.8 mmol) was added in at the same temperature. The resultant mixture was sirring at room temperature for 2 h. The reaction was quenched with ice water and extracted with EtOAc. The organic layer was washed with water and brine in twice and then dried with anhydrous Na_2SO_4. After concentrated by a rotary evaporator, the products was purified by silica gel column chromatography (petroleum ether/EtOAc = 1/1) to give compound **8** (908 mg, 57% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, *J* = 5.1 Hz, 1H), 7.66 (s, 1H), 7.55 (d, *J* = 5.1 Hz, 1H), 4.81 (s, 2H), 4.16 (s, 2H), 3.79 (s, 3H), 2.88 (q, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ESI-HRMS Calculated for $[C_{15}H_{18}N_2O_3S + H\ ]^+$: 307.1116, found: 307.1096.

***N*-(Ethoxycarbonylmethyl)-2-phenyl-4-methyl-5-thiazolecarboxamide (11a).** The title compound was prepared according to **5a** except using compound **10a** instead of **3b**. Yield 63%: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94–7.92 (m, 2H), 7.46–7.44 (m, 3H), 6.39 (br s, 1H), 4.27 (q, *J* = 6.9 Hz, 2H), 4.21 (d, *J* = 4.8 Hz, 2H), 2.77 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.01, 167.98, 161.99, 156.82, 133.08, 131.09, 129.28, 127.00, 125.44, 62.08, 42.15, 17.74, 14.37. ESI-HRMS Calculated for $[C_{15}H_{16}N_2O_3S + Na]^+$: 327.0779, found: 327.0777.

***N*-(Ethoxycarbonylmethyl)-2-phenyl-4-methyl-5-oxazolecarboxamide (13c).** The title compound was prepared according to **5a** except using compound **12c** instead of **3b**. Yield 63%: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08–8.05 (m, 2H), 7.49–7.47 (m, 3 H), 6.81 (br s, 1H), 4.28 (q, *J* = 6.9 Hz, 2H), 4.22 (d, *J* = 4.8 Hz, 2H), 2.56 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.02, 160.66, 158.49, 144.92, 138.87, 131.60, 129.15, 127.17, 126.60, 62.02, 41.12, 14.38, 13.31. ESI-HRMS

Calculated for $[C_{15}H_{16}N_2O_4 + Na]^+$: 311.1008, found: 311.1003.

***N*-(Ethoxycarbonylmethyl)-3-phenyl-5-methyl-4-isooxazolecarboxamide (15)**. The title compound was prepared according to **5a** except using 5-methyl-3-phenyl-4-isoxazolecarboxylic acid instead of **3b**. Yield 44%: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.63 (m, 2H), 7.54–7.52 (m, 3H), 5.95 (br s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.03 (d, *J* = 5.4 Hz, 2H), 2.74 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.78, 169.41, 161.81, 160.47, 130.72, 129.39, 129.30, 128.16, 110.70, 61.76, 41.52, 14.32, 13.28. ESI-HRMS Calculated for $[C_{15}H_{16}N_2O_4 + Na]^+$: 311.1008, found: 311.0997.

***N*-(Ethoxycarbonylmethyl)-2-phenyl-4-thiazolecarboxamide (17).** The title compound was prepared according to **5a** except using 2-(2-ethyl-4-pyridinyl) thiazole-4-carboxylic acid instead of **3b**. Yield 27%: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 15.3 Hz,), 7.73–7.68 (m, 1H), 7.61–7.56 (m, 2H), 7.05 (d, *J* = 15.3 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.00 (d, *J* = 2.0 Hz, 2H), 3.33 (s, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.88, 166.14, 165.17, 161.01, 150.93, 150.45, 140.00, 124.98, 118.92, 118.04, 61.89, 41.52, 31.68, 14.39, 14.07. ESI-HRMS Calculated for $[C_{15}H_{17}N_3O_3S + H]^+$: 320.1069, found: 320.1072.

ACKNOWLEDGEMENTS

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