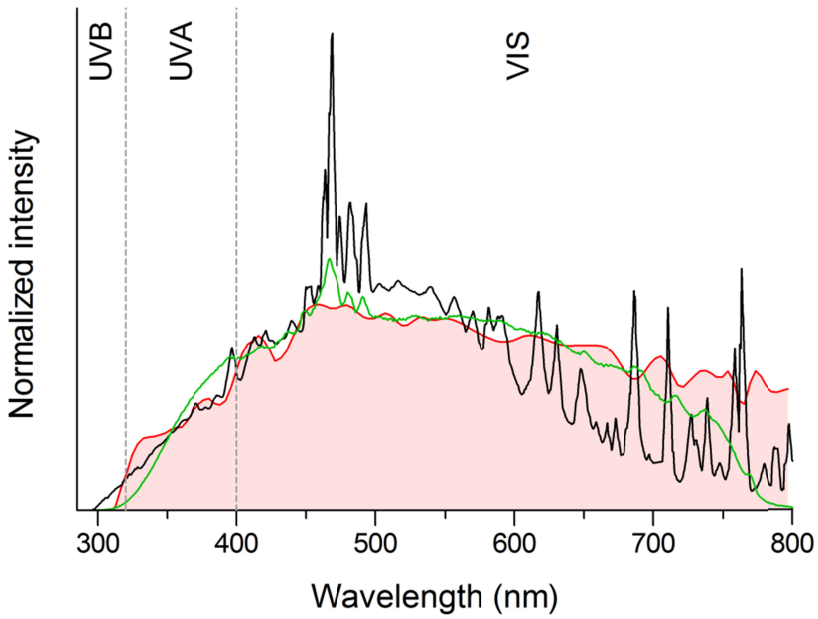


Fig. 1 Spectral patterns of simulated sunlight in Atlas Suntest CPS series, Seric SXL-2500V2, and standard daylight (CIE85/1989). Black line, simulated sunlight emitted from Atlas Suntest CPS series; green line, from Seric SXL-2500V2; and red line, standard daylight (CIE85/1989).

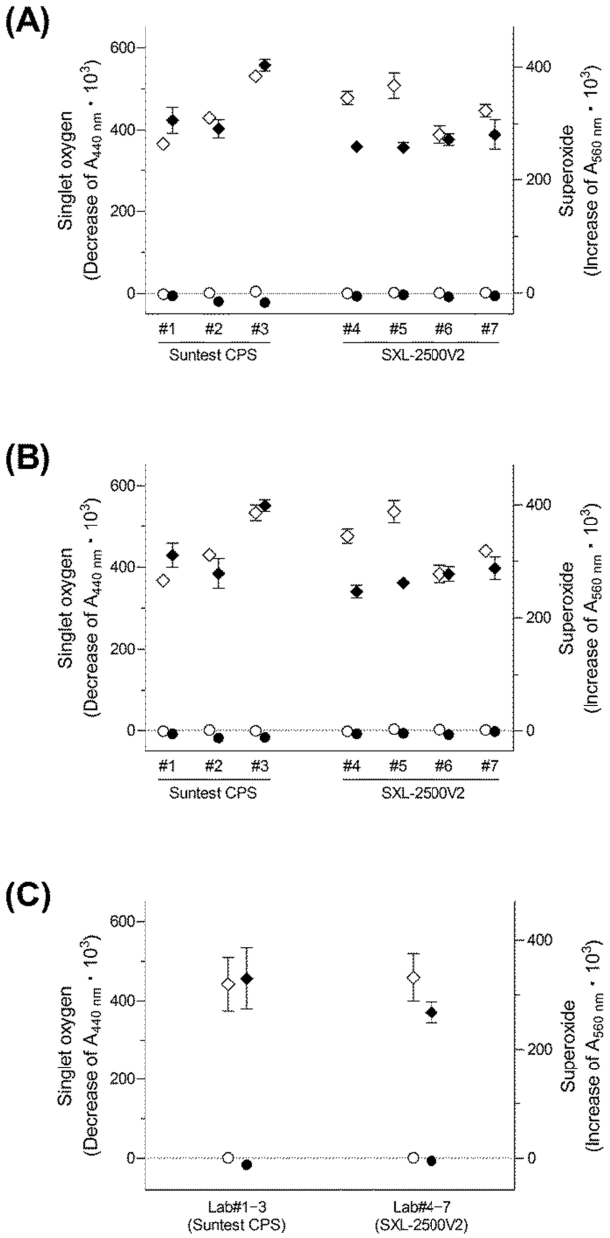


Fig. 2 Intra- and inter-laboratory reproducibility on ROS measurement in 2 different solar simulators. (A) Intra-laboratory reproducibility (intra-day), (B) intra-laboratory reproducibility (inter-day), and (C) inter-laboratory reproducibility. The ROS assay on quinine (**1**) and sulisobenzone (**2**) at a concentration of 200 μM was conducted in 7 laboratories employing the Atlas Suntest CPS series (ca. 2.0 mW/cm^2, Lab#1–3) or Seric SXL-2500V2 (ca. 3.0–5.0 mW/cm^2, Lab#4–7). ◇, singlet oxygen for quinine (**1**); ◆, superoxide; ○, singlet oxygen for sulisobenzone (**2**); and ●, superoxide. Data represent mean±SD of three repeated experiments for intra-day (n=9) precision and three repeated experiments for inter-day precision (days 1, 2, and 3; n=9).

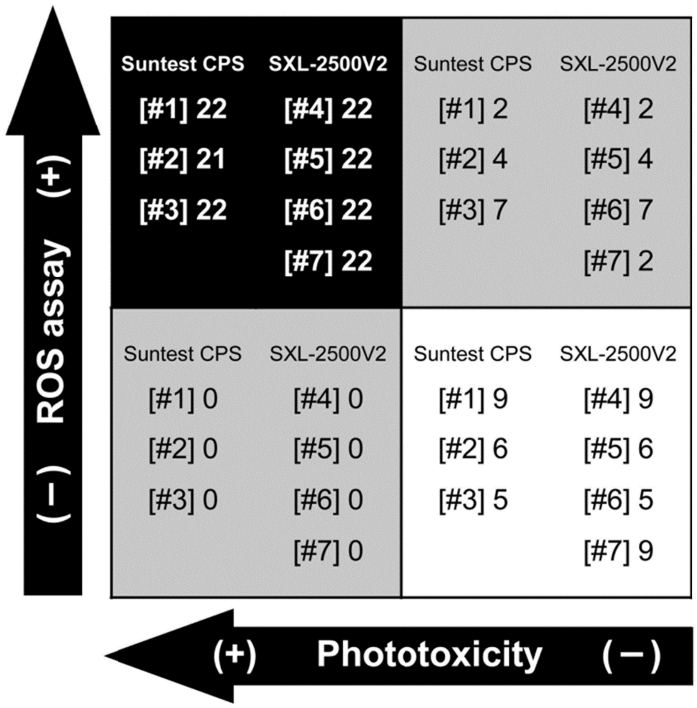
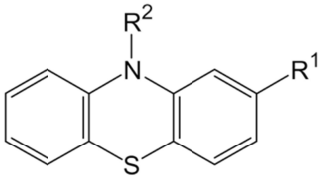


Fig. 3 Positive and negative predictivity of the ROS assay in Lab#1–7.



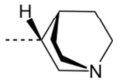
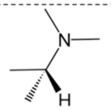
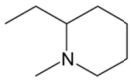
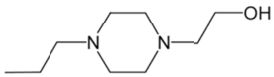
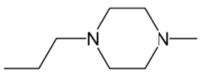
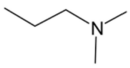
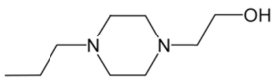
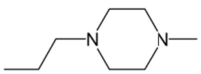
PTZs	CAS No.	Clog *P* [a]	R^1	R^2
Non-halogenated group				
Mequitazine (MQ)	88598-74-7	4.91	−H	
Promethazine HCl (PM)	58-33-3	4.60	−H	
Thioridazine HCl (TD)	130-61-0	6.20	$-SCH_3$	
Fluorinated group				
Fluphenazine 2HCl (FP)	146-56-5	4.32	$-CF_3$	
Trifluoperazine 2HCl (TF)	440-17-5	4.89	$-CF_3$	
Chlorinated group				
Chlorpromazine HCl (CP)	69-09-0	5.50	−Cl	
Perphenazine (PP)	58-39-9	4.01	−Cl	
Prochlorperazine dimaleate (PC)	84-02-6	4.58	−Cl	

Fig. 4 Chemical structures of PTZs. [a], Calculated on ChemBioDraw Ultra 13.0 software.

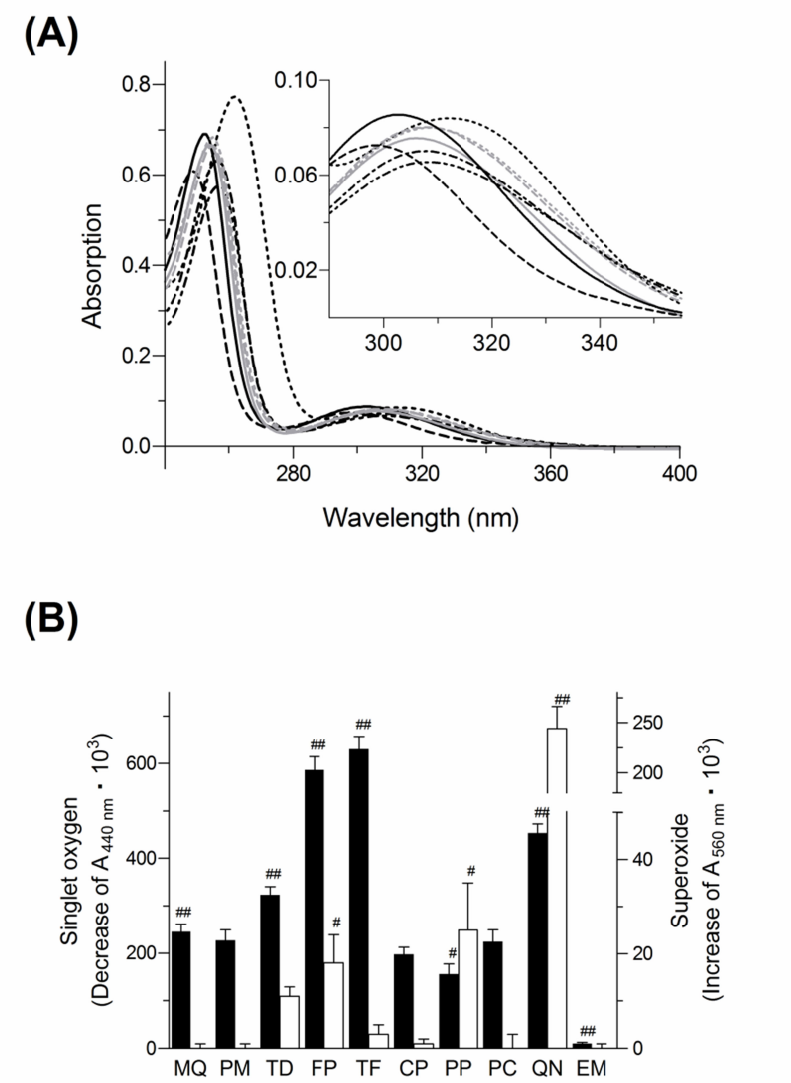


Fig. 5 Photochemical properties of PTZs. (A) UV spectral patterns of PTZs (20 μM) in 20 mM NaPB (pH7.4). Solid line, MQ; broken line, PM; dotted line, TD; dashed-dotted line, FP; dashed-two dotted line, TF; gray solid line, CP; gray broken line, PP; and gray dotted line, PC. (B) Generation of singlet oxygen (filled bars) and superoxide (open bars) from PTZs (200 μM) exposed to simulated sunlight (2.0 mW/cm^2). QN, quinine as positive control; and EM, erythromycin as negative control. Data represent mean±SD of 3 experiments. $^{\#}$, $P<0.05$ and $^{\#\#}$, $P<0.01$ with respect to CP in each ROS determination.

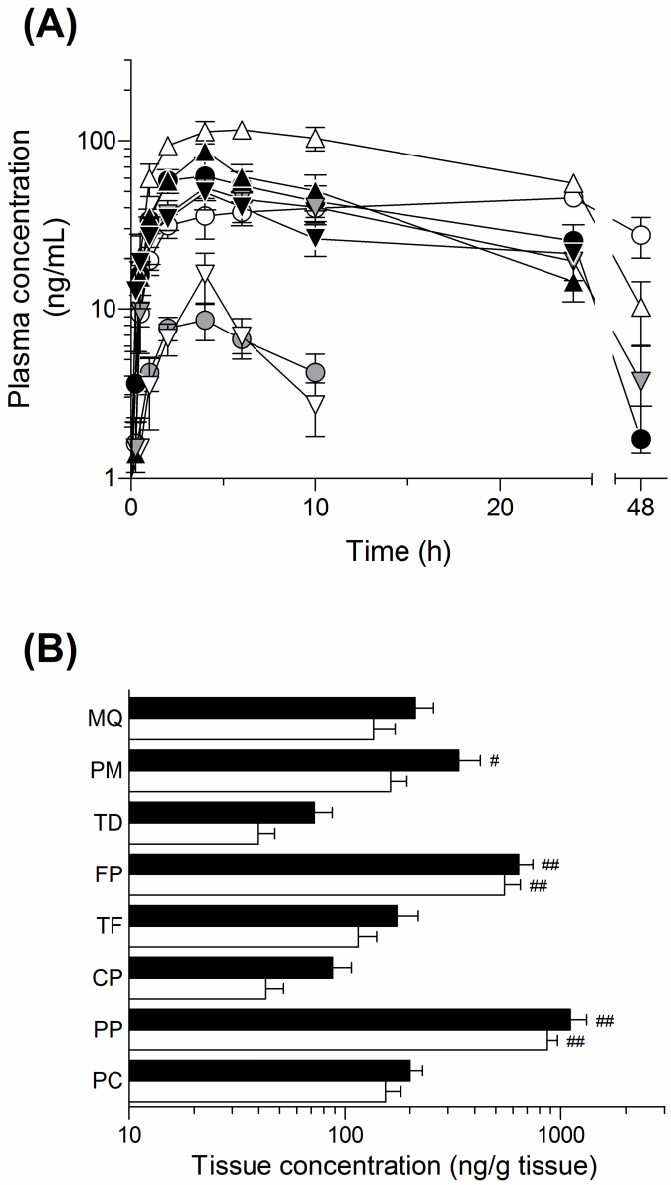


Fig. 6 Pharmacokinetic characteristics of PTZs in rats. (A) Plasma concentrations of PTZs in rats after oral cassette-dosing of 8 PTZs (5 mg/kg, each). ○, MQ; ●, PM; ●, TD; △, FP; ▲, TF; ▽, CP; ▼, PP; and ▼, PC. Data represent mean±SEM of 4 experiments. (B) Deposition of PTZs in skin (filled bars) and eyes (open bars) at 4.5 h after oral cassette-dosing of 8 PTZs (5 mg/kg each). Data represent mean±SEM of 4 experiments. $^{\#}$, $P<0.05$ and $^{\#\#}$, $P<0.01$ with respect to TD.

Table 1 Pharmacokinetic parameters of PTZs after oral cassette-dosing

	C_{max} (ng/mL)	T_{max} (h)	k_{el} (h^{-1})	$AUC_{0-\infty}$ (ng•h/mL)
MQ	52.3±3.6	17.0±4.0	0.033±0.019	5,395±473
PM	9.8±1.5	3.0±0.6	0.13±0.046	301±36
TD	66.1±14.8	4.0±0.8	0.044±0.026	1,604±308
FP	119.8±12.3	4.0±0.8	0.030±0.013	4,310±304
TF	75.6±13.4	4.0±0.8	0.088±0.026	1,415±191
CP	13.5±4.6	3.3±0.8	0.39±0.13	109±30
PP	53.4±3.2	4.5±0.5	0.045±0.012	1,325±170
PC	52.7±8.5	3.3±0.8	0.054±0.034	985±292

Cmax, maximum concentration; Tmax, time to maximum concentration; kel, apparent elimination rate constant; and AUC0-∞, area under the curve of blood concentration vs. time from t=0 to t=∞ after administration. Values are expressed as mean±SEM of 4 experiments.

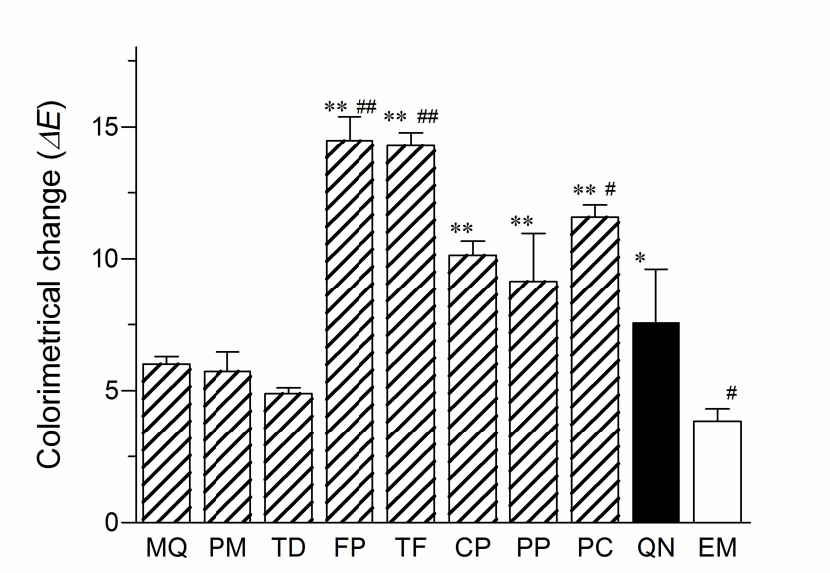


Fig. 7 Colorimetrical evaluation of PTZ-induced phototoxic skin response. Differences in skin color (ΔE) between irradiated and non-irradiated rats treated with each drug (100 mg/kg, *p.o.*) were calculated on the basis of L^*, a^*, and b^* values. QN, quinine as positive control; and EM, erythromycin as negative control. Data represent mean±SEM of 4 experiments. *, $P<0.05$ and **, $P<0.01$ with respect to EM-treated group; $^{\#}$, $P<0.05$ and $^{\#\#}$, $P<0.01$ with respect to QN-treated group.

Table 2 Summary of outcomes from photosafety testing on PTZs

	Obtained data/prediction
Experimental data	
Photoreactivity (UV, ROS)	**FP** ≒ **TF** ≫ TD > MQ ≒ PM ≒ CP ≒ PC > PP
Skin/ocular distribution	PP ≫ **FP** > PM > MQ ≒ PC ≒ **TF** > CP ≒ TD
In vivo phototoxicity	**FP** ≒ **TF** > PC > PP ≒ CP ≫ MQ ≒ PM ≒ TD
Matrix-decision	**FP** > PP > **TF** > PC > MQ ≒ PM ≒ TD > CP
Conclusion	**Fluorinated PTZs** > Chlorinated > Non-halogenated

White cells, non-halogenated PTZs; gray cells, chlorinated PTZs; and black cells, fluorinated PTZs.

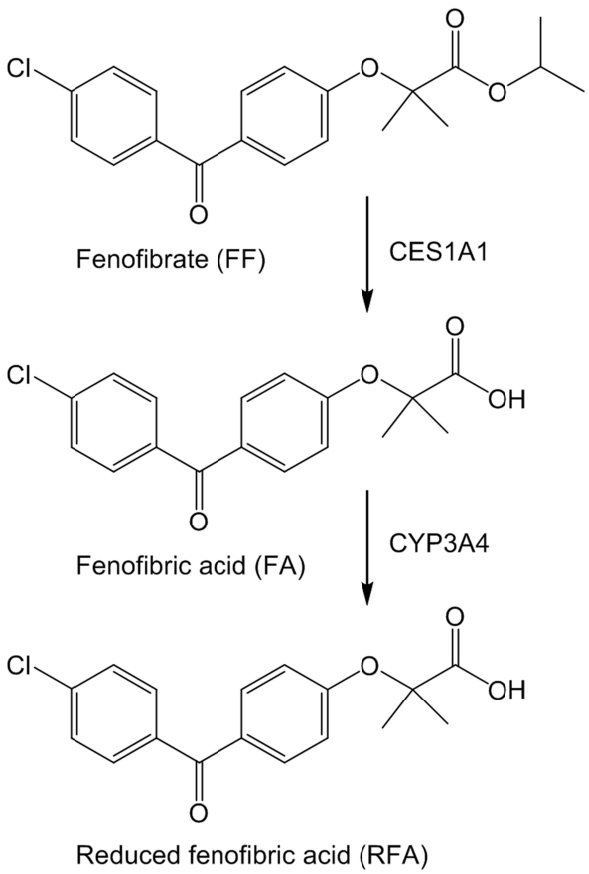


Fig. 8 Chemical structures of each test compound and metabolic pathways

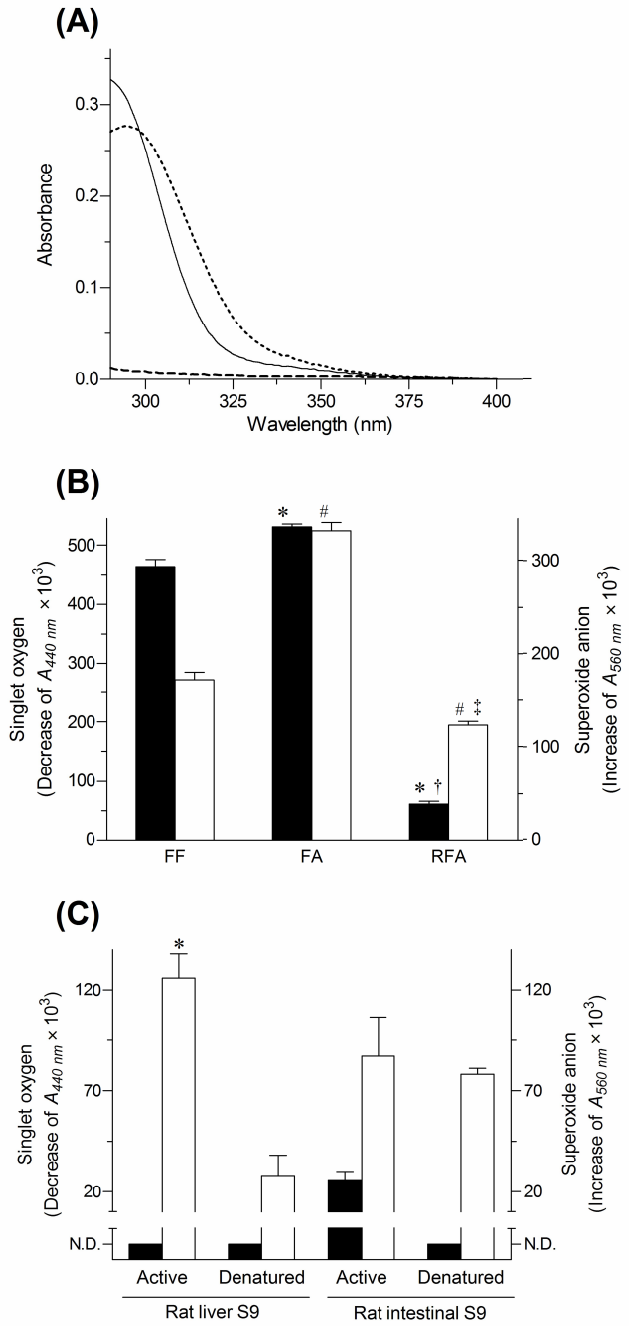


Fig. 9 Photochemical properties of FF, FA and RFA. UV-absorption spectra of test compounds (20 μM) in ethanol (A). *Solid line*, FF; *dashed line*, RFA; *dotted line*, FA. Generation of ROS from FF, FA and RFA (B) and from FF after incubation with active and denatured rat *hepatic/*intestinal S9 fractions (C). *Filled columns*, generation of singlet oxygen; *Open columns*, generation of superoxide. $^{*}P<0.05$, vs singlet oxygen of FF; $^{\dagger}P<0.05$, vs singlet oxygen of FA; $^{\#}P<0.05$, vs superoxide of FF; $^{\ddagger}P<0.05$, vs superoxide of FA (B). $^{*}P<0.05$, vs superoxide in denatured rat hepatic S9 fractions (C). Data represent the mean±SD (n=3).

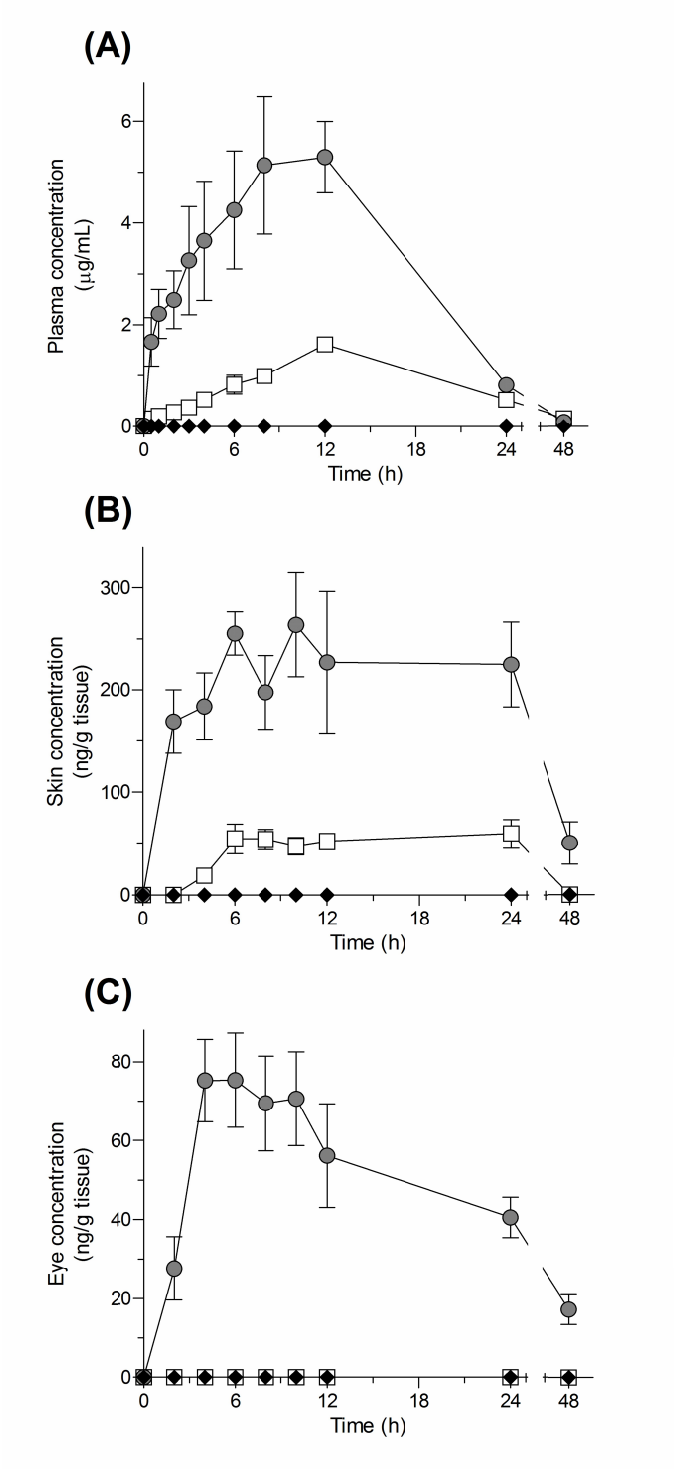


Fig. 10 Concentration-time profiles of FF, FA and RFA in plasma (A), skin (B) and eyes (C) after oral administration of FF (5 mg/kg, *p.o.*) in rats. *Filled diamonds*, FF; *gray circles*, FA; *open squares*, RFA. Each value represent the mean±SEM (*n*=7–4).

Table 3 PK parameters in plasma, skin and eyes after oral administration of FF in rats

		$t_{1/2}$ (h)	C_{max} (μg/mL) or C_{max} (ng/g tissue)	T_{max} (h)	$AUC_{0-\infty}$ (h·μg/mL) or $AUC_{0-\infty}$ (h·μg/g tissue)	$MRT_{0-\infty}$ (h)
FF	Plasma	N.A.	N.A.	N.A.	N.A.	N.A.
	Skin	N.A.	N.A.	N.A.	N.A.	N.A.
	Eye	N.A.	N.A.	N.A.	N.A.	N.A.
FA	Plasma	6.4±0.40	6.3±1.1	9.7±1.1	97±14	13±0.70
	Skin	11±1.5	340±17	13±3.9	8.5±1.3	20±2.1
	Eye	22±6.9	100±5.5	6.0±1.4	2.6±0.33	34±10
RFA	Plasma	12±1.0	1.6±0.10	12±0.0	33±3.2	21±1.5
	Skin	17±3.3	80±6.7	16±4.7	2.0±0.60	30±4.2
	Eye	N.A.	N.A.	N.A.	N.A.	N.A.

Each value represents the mean±SEM for 4–7 rats. N.A., not available due to concentrations below the limit of detedction.

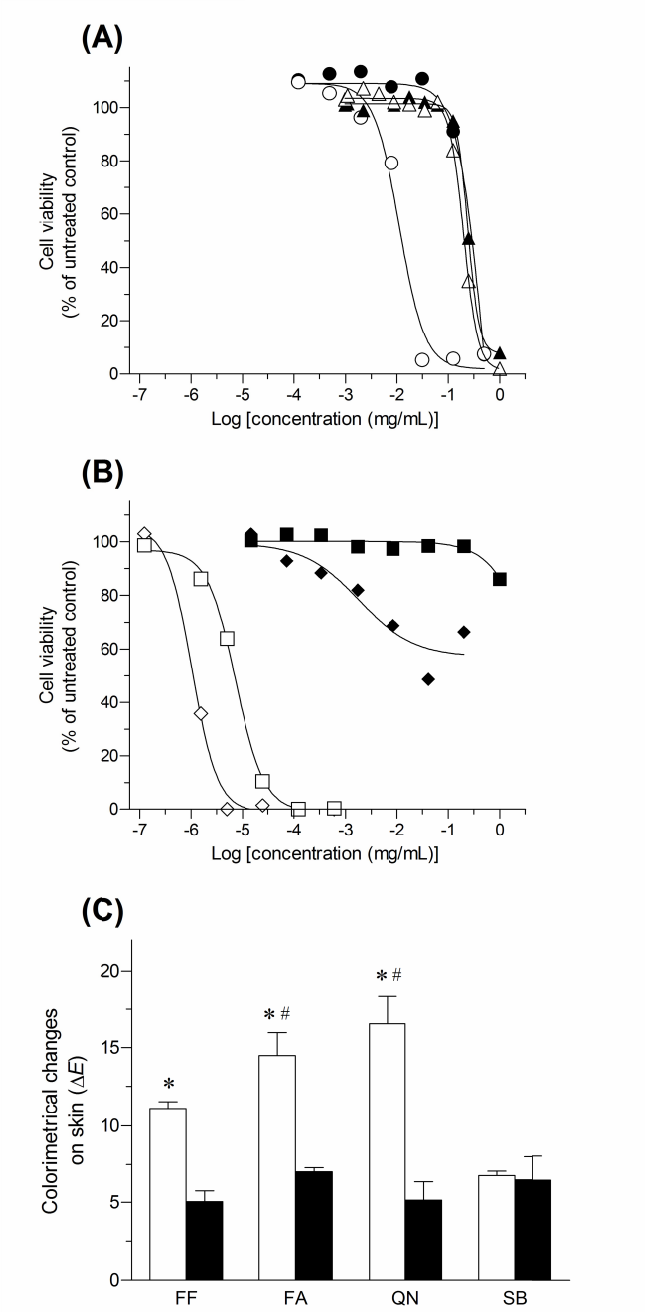


Fig. 11 *In vitro*/*in vivo* phototoxicity of compounds. Photodynamic cytotoxicity of QN: positive control and SB: negative control (A), FF and FA (B) in 3T3 NRU PT, and colorimetrical evaluation of phototoxic skin responses in rats treated with FF, FA, quinine (QN) and sulisobenzone (SB) (C). *Open symbols* and *open columns*, UVA-irradiated groups; *filled symbols* and *filled columns*, non-irradiated groups. Each value represents the mean of duplicate measurements (A, and B) and the mean±SEM of 4 experiments (C). $^{*}P<0.05$ with respect to the non-irradiated group of each compound; $^{\#}P<0.05$ with respect to UV-irradiated groups of SB.

Table 4 Decision matrix

		FF	FA	RFA
Photochemical properties				
UV absorbance λ_{max}/ε ($M^{-1}cm^{-1}$)		**290 nm/17×10^3**	**295 nm/14×10^3**	290 nm/0.85×10^3
ROS assay	$^1O_2$ ($\Delta A_{440\ nm}$)	**463**	**531**	61
	O_2^- ($\Delta A_{560\ nm}$)	171	**332**	123
Distribution to UV exposing tissues				
$t_{1/2}$ (h)	Skin	N.A.	11	**17**
	Eyes	N.A.	**22**	N.A.
C_{max}	Skin	N.A.	**340**	80
(ng/g tissue)	Eyes	N.A.	100	N.A.
$AUC_{0-\infty}$	Skin	N.A.	**8.5**	2.0
(h•μg/g tissue)	Eyes	N.A.	2.6	N.A.

Each crucial factor was divided into three levels. Black, gray and white cells represent high, moderate and low levels, respectively. N.A., not available due to concentrations below the limit of detection.