Supporting Information

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SI Materials and Methods

Materials. We obtained compounds and products from the following suppliers: 6-formylindolo[3,2-*b*]carbazole (FICZ) from Syntastic AB; H_2O_2, ellipticine, genistein, diosmin, α-naphtoflavone (αNF), cycloheximide, α-tocopherol, resorufin, 7-ethoxyresorufin, tryptophan (Trp), and fluorescamine from Sigma-Aldrich; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) from LGC Standards; ketoconazole from Toronto Research Chemicals Inc.; Ultraspec buffer from Nordic BioSite; RevertAid First Strand cDNA synthesis kit from Fermentas; SYBR Green Master Mix from Applied Biosystems; gene-specific primers for quantitative PCR (qPCR) from Invitrogen; human recombinant CYP1A1 Supersomes from BD Bioscience; and alamarBlue viability assay from Invitrogen. Trioxalen was provided by Desiree Edström Wiegleb (Karolinska University Hospital, Stockholm, Sweden) and 3′-methoxy-4′-nitroflavone was a kind gift from Michael S. Denison (University of California, Davis, CA). The immortalized human keratinocyte cell line HaCaT was kindly provided by N. E. Fusenig (Deutsches Krebsforschungszentrum, Heidelberg) and the AHR-silenced HaCaT cell variant by E. Fritsche (Leibniz-Institut für Umwelt-Medizinische Forschung, Düsseldorf, Germany). HEKa cells and all cell-culture reagents were procured from Invitrogen.

Treatment of Mice. Female C57BL/6J mice (Scanbur) (three in each group) were treated percutaneously on the back of the right ear with 10 ng FICZ dissolved in 5 μL dimethyl sulfoxide (DMSO)/acetone (1:1); control animals received the vehicle only. Treatment started at 07.00 h. At various time points after this administration, the animals were killed with CO_2, and their livers, adipose tissue (perirenal visceral fat), and right ears were dissected out and placed in liquid nitrogen. This experiment was conducted in accordance with the regulations for animal experimentation at Karolinska Institutet and was preapproved by the Ethical Committee on Animal Experimentation in Stockholm.

Cell Cultures and Media. HEKa cells were grown and treated in supplemented medium 154. For HaCaT cells, two other media were used: DMEM 21068 and custom-made DMEM 21068-like medium free from Trp but supplemented with recrystallized, purified Trp at the same concentration (78 μM) as in the commercial medium. This latter medium always was prepared shortly before use. HaCaT cells were cultured in DMEM supplemented with 10% (vol/vol) FBS, 2 mM glutamine, 1 mM sodium pyruvate, 100 μg streptomycin, 100 IU penicillin/mL, and 0.02 mM calcium chloride. For culturing of HaCaT cells in which the aryl hydrocarbon receptor (AHR) had been silenced or which had been transfected with the empty vector, 800 μg Geneticin/mL was added to the culture medium. Medium 154 was supplemented with 0.2% (vol/vol) bovine pituitary extract; 5 μg bovine insulin, 0.18 μg hydrocortisone, 5 μg bovine transferrin, 0.2 ng human epidermal growth factor, 10 μg gentamicin, and 0.25 μg amphotericin B per milliliter and with 0.04 mM calcium chloride. All culturing was performed at 37 °C under an atmosphere containing 5% CO_2. Before treatment, HaCaT and HEKa cells were grown for the different periods of time required to attain overconfluence in the routine cell medium supplemented with a higher concentration of calcium chloride (2 mM) to obtain differentiation.

Recrystallization of Trp. One gram of Trp was added to 250 mL absolute ethanol, and the solution was brought to boiling with stirring. More ethanol was added gradually until a saturated solution was obtained; the saturated solution was filtrated, slowly cooled, and left to crystallize at 4 °C. The crystals were collected and washed in absolute ethanol and were dried under vacuum. All procedures were carried out protected from light. Then 25 mg of the recrystallized Trp was dissolved in 50 mL water, concentrated on C18 SepPak cartridges (Waters), and a methanol eluate was analyzed by HPLC (fluorescence) for the presence of FICZ. FICZ in the recrystallized Trp was below the detection limit for this analytical setting (5 fmol).

Exposure of the Cell Cultures. With the exception of H_2O_2, which was dissolved in water, and α-tocopherol and trioxalen, which were dissolved in EtOH, all compounds to be tested were dissolved in DMSO and were added to the culture medium to give a final concentration of 0.1% (vol/vol) DMSO or EtOH. For UVB irradiation, UV lamps containing six (Philips TL20W/12RS sunlamps) or two (Philips PL, 36W, UV240 DT, IP20) UV tubes were used. All UVB irradiation of cells was performed in PBS supplemented with calcium and magnesium, and fresh medium was added immediately after irradiation.

Clearance of FICZ. To determine the clearance (i.e., metabolism) of FICZ by HaCaT cells, these cells were seeded onto 60-mm dishes and cultured as described above. At 0, 0.25, 0.5, 1.5, 3, 6, and 12 h, samples were taken by removing the medium, rapidly washing the cells with ice-cold PBS, and then harvesting the cells in distilled water. The cells then were sonicated on ice and stored at −20 °C until further analysis by HPLC.

Ethoxyresorufin Deethylarion Assay. The ethoxyresorufin deethylase (EROD) activity of isolated fractions containing human recombinant CYP1A1 (10 nM) was assayed by first preincubating with effector for 10 min followed by addition of ethoxyresorufin (1 μM) and NADPH (0.5 mM). To analyze CYP1A1-dependent EROD activity of intact living cells, HaCaT or HEKa cells were seeded onto 96-well plates and cultured as described above. At 1.5, 3, 6, 12, and 24 h (Fig. 2*B*); 1.5, 3, 6, 12, 24, and 48 h (Fig. 3*B* and 4 and Fig. S2); 1.5 and 3 h (Fig. S3); 1.5, 6, 24, and 48 h (Fig. S5); and 12, 24, and 48 h (Fig S6), the reaction was terminated by removing the medium and rinsing the cells with PBS. The EROD reaction then was initiated by addition of 2 μM 7-ethoxyresorufin in sodium phosphate buffer (50 mM, pH 8.0); then the cells were incubated at 37 °C for 15 min. In both cases formation of resorufin was quantified on a multiwell plate reader with the excitation/emission wavelengths of 535/590 nm; then this activity was expressed relative to the amount of protein present as determined by fluorescamine fluorescence (excitation/emission = 390/485 nm) or by using the DC protein assay kit (BioRad) in accordance with the manufacturer's protocol.

RT-qPCR. Total RNA isolated with Ultraspec (Biotecx) in accordance with the manufacturer's protocol was subjected to reverse transcription using the RevertAid First Strand cDNA synthesis kit and oligo $(dt)_{18}$ primers. Thereafter, SYBR Green Master Mix and gene-specific primers were used for qPCR. β-2-Microglobulin or β-actin was selected as the reference gene, and the results were analyzed with the mathematical model described by Pfaffl and colleagues (1).

Viability. Cell viability was assessed with the alamarBlue assay, which is based on the reduction of resazurin to resorufin by metabolically active cells.

Preparation of Whole-Cell Extracts and Immunoblotting. HaCaT cells were harvested in cell lysis buffer [25 mM Tris-phosphate (pH 7.8), 2 mM DTT, 2 mM 1,2-diaminocyclohexane-N,N,N′,N′,-tetraacetic acid, 10% (vol/vol) glycerol, 1% (vol/vol) Triton X-100) supplemented with protease inhibitor mixture (Roche). The proteins in this lysate were separated by 8.7% (wt/vol) SDS/PAGE, transferred onto a nitrocellulose membrane, and subjected to Western blotting with the following antibodies: rabbit anti-AHR (sc-5579) and anti-GAPDH (Santa Cruz Biotechnology) and HRP-conjugated anti-rabbit IgG (DakoCytomation). Finally, the immunoreactive proteins were visualized by enhanced chemiluminescence (Pierce/Thermo Fisher).

Chemical Analyses of Whole-Cell Lysates and Cell-Culture Media. The levels of FICZ in whole-cell lysates were analyzed using an in-line solid-phase extraction column coupled to a reverse-phase C18 column. In brief, the cell lysates were injected onto the extraction column, washed with water, and then separated on the analytical C18 column. FICZ was detected using excitation and emission wavelengths of 390 and 525 nm, respectively. With this system, ≥95% recovery was obtained, and the limit of detection for FICZ was 0.05 pmol. The cellular concentration of FICZ was related to protein content as determined by the Coomassie plus protein assay (Pierce), with BSA as the standard.

To avoid light-dependent formation of FICZ during extraction and analysis, all cell culture media were handled in the dark at all times, and the samples were stored in amber vials. Commercial DMEM was extracted at 4 °C using C18 SepPak cartridges (Waters) and subsequently was eluted with ethanol. This eluate then was mixed with an equal volume of water, followed by fractionation and analysis by HPLC (YL9100HPLC equipped with an Agilent 1200 fluorescence detector). Separation in this HPLC system was achieved using a reverse-phase C18 column [Alltech Alltima, 4.6 × 250 mm, particle size (dp) 5 μm; ScanTec] with a mobile phase consisting of water (A) and acetonitrile (B), both containing 1.5 mM formic acid. Initially, the solvent contained 50% B, with a linear increase to 80% B during a period of 20 min, at a flow rate of 0.8 mL/min.

The FICZ fraction isolated with this semipreparative liquid chromatograpy (LC) system was analyzed further using in-line concentration and enrichment on a precolumn (ReproSil DIBS-C4, 5 μm, 4.6 × 10 mm; Dr. Maisch GmbH), followed by elution onto a separation column (Acquity HSS T3 C18, 2.1 × 100 mm, dp 1.8 μm; Waters) connected to a quadrupole time-of-flight high-resolution mass spectrometer (QToF Premier; Waters). In this case the solvent was 100% A (5% acetonitrile in water), which was changed linearly to 50% B (5% water in acetonitrile) in 0.5 min, then changed linearly to 100% B in 2.5 min, and then held for 5 min. The flow rate was 0.150 mL/min for the first 0.5 min and 0.300 mL/min for the remaining 10.5 min (including the final 3-min reequilibration). The column temperature was maintained at 65 °C.

The precolumn was fitted to a six-port valve (Rheodyne) to which two LC pumps also were connected. The first pump (HP 1050; Hewlett Packard) was used to load the sample via a manual loop injector equipped with a 4-mL sample loop. The second LC pump, an Acquity ultra performance liquid chromatography system (Waters), was used for gradient elution of the sample, which involved back-flushing it from the precolumn onto the separation column.

The QToF MS was operated in the electrospray ionization negative-ion mode, with the TOF detector in the V-mode. The quadrupole was set to a wide-pass mode, and the collision energy alternated between 2 and 20 eV, using two full-scan MS functions. The duration of each scan was 0.2 s, and the interscan interval was 0.01 s. The mass ranges were 70–350 and 70–300 Thomson (Th) for functions 1 and 2, respectively.

The following settings were used: capillary voltage of 3.0 kV; sampling cone voltage of 35 V; extraction cone voltage of 2.9 V; source temperature of 100 °C, desolvation temperature of 350 °C; cone gas (nitrogen) flow rate of 50 L/h; and desolvation gas (nitrogen) flow rate of 700 L/h. Argon was used as the collision gas, at a flow rate of 0.5 mL/min, to produce a pressure of 3.5×10^{-3} mbar in the collision cell. External mass calibration was performed in the mass range (m/z) of 100–1,000 Th, using a series of cluster ions formed from 0.05 M NaOH and 0.5% formic acid dissolved in 2-propanol/H_2O (90:10). Sulfadimethoxine (m/z 309.0658) in methanol (0.1 ng/μL) was used as a lockspray solution. The lockspray was monitored once every 5 s (i.e., once after every 12 scans, on average).

1. Pfaffl MW (2001) A new mathematical model for relative quantification in real-time RT-PCR. *Nucleic Acids Res* 29(9):e45.

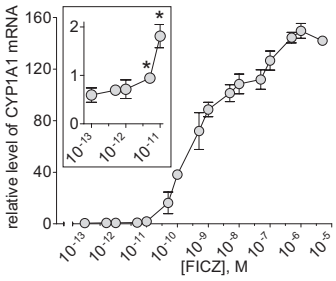

Fig. S1. FICZ is a potent inducer of CYP1A1 gene expression in vitro. The levels of CYP1A1 mRNA in HaCaT cells treated for 2 h with different concentrations of FICZ, ranging from 0.1 pM to 10 μM, was determined by qRT-PCR using the β-2-microglobulin housekeeping gene as an internal standard. The experiment was performed in triplicate. Error bars indicate SE, and asterisks denote significant differences (*$P < 0.05$) compared with DMSO-treated cells.

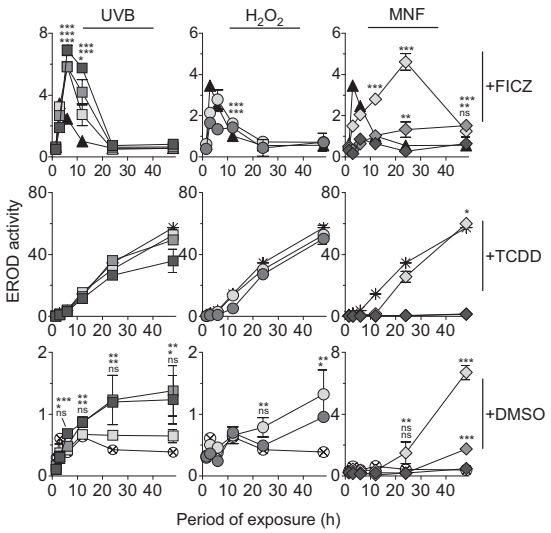

Fig. S2. UVB, H_2O_2, and 3′-methoxy-4′-nitroflavone (MNF) inhibit and induce CYP1A1 enzyme activity in HEKa cells. Cells were treated with 5 nM FICZ (black triangle) (*Top*), 5 nM TCDD (star) (*Middle*), or DMSO (crossed circle) (*Bottom*), either alone or in combination with 5 mJ/cm^2 (light gray square), 10 mJ/cm^2 (medium gray square), or 20 mJ/cm^2 (dark gray square) UVB, or with 0.2 mM (light gray circle) or 2 mM (medium gray circle) H_2O_2, or with 0.05 μM (light gray diamond), 0.5 μM (medium gray diamond), or to 2.5 μM (dark gray diamond) MNF. Treatments were terminated at the indicated time points, and EROD activity (pmol resorufin/mg protein) was measured. All cotreatments inhibited FICZ-dependent EROD activity at early time points ($P < 0.05$ to $P < 0.001$), and TCDD-dependent EROD activity was inhibited at all time points ($P < 0.05$ to $P < 0.001$) except for 0.05 μM MNF, which potentiated TCDD-dependent EROD activity at 48 h. Error bars indicate SE. Asterisks indicate statistically increased (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$) EROD activity caused by the different cotreatments together with FICZ, TCDD, and DMSO. ns, nonsignificant.

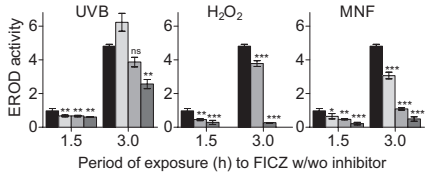

Fig. S3. Inhibitors of CYP1A1 cause an initial inhibition of FICZ-induced EROD activity. HaCaT cells were treated with 5 nM FICZ, either alone (black bar) or in combination with 5 mJ/cm^2 (light gray bar) 10 mJ/cm^2 (medium gray bar), or 20 mJ/cm^2 (dark gray bar) UVB (*Left*); or in combination with 0.2 mM (medium gray bar) or 2 mM (dark gray bar) H_2O_2; or in combination with 0.05 μM (light gray bar), 0.5 μM (medium gray bar), or 2.5 μM (dark gray bar) MNF. Treatments were terminated at the indicated time points, and EROD activity (pmol resorufin/mg protein) was measured. Error bars indicate SE. Asterisks denote significant differences (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$) between coexposed cells and cells exposed to FICZ alone. ns, nonsignificant.

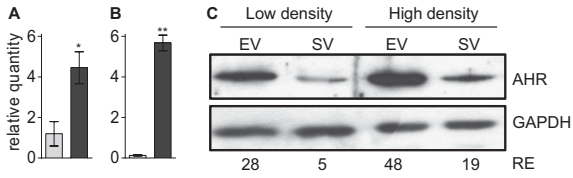

Fig. S4. Differentiated HaCaT cells express more AHR protein than do proliferating cells. Relative levels of the differentiation markers involucrin (*A*) and transglutaminase 1 (*B*) in cells grown at high (dark gray bars) or low (light gray bars) cell density were determined by qRT-PCR using the β-actin housekeeping gene as an internal standard. $n = 2$. Error bars indicate SD. *$P < 0.05$; **$P < 0.01$. (*C*) Western blot analysis of AHR levels in HaCaT cells grown at low or high density was determined in HaCaT cells stably expressing a lentiviral silencing vector (SV) with shRNA sequences for AHR and cells carrying an empty vector (EV). Relative expression (RE) was calculated based on signal intensity of the AHR compared with GAPDH, which was used as an internal standard.

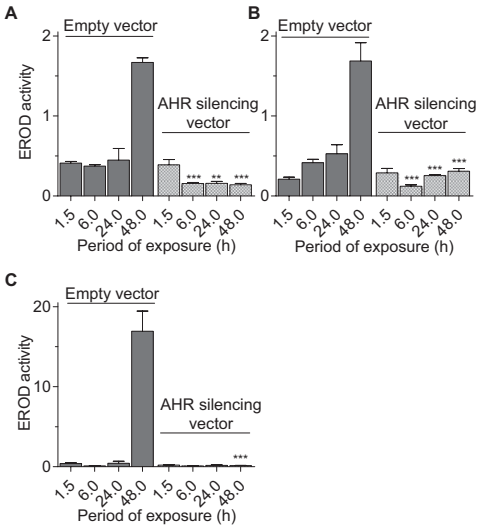

Fig. S5. Induction of CYP1A1 enzyme activity by UVB, H_2O_2, and MNF in cells cultured in commercial DMEM is AHR dependent. HaCaT cells containing empty vector or AHR silencing vector were treated with (*A*) 10 mJ/cm^{2}UVB, (*B*) 0.2 mM H_2O_2, or (*C*) 0.5 μM MNF. Treatments were terminated at the indicated time points, and EROD activity (pmol resorufin/mg protein) was measured. Error bars indicate SE. Asterisks denote significant differences (**$P < 0.01$; ***$P < 0.001$) between cells containing empty vector and cells containing AHR silencing vector.

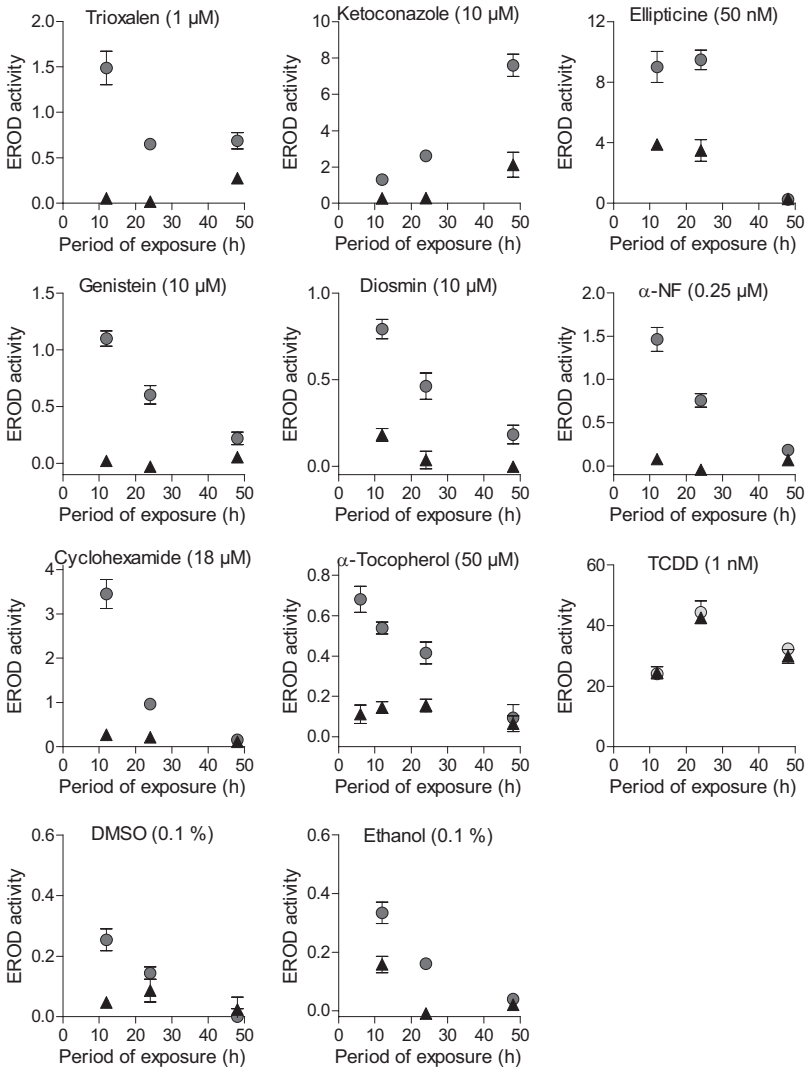

Fig. S6. Induction of CYP1A1 enzyme activity by different CYP1 inhibitors requires the presence of Trp derivatives in the culture medium. HaCaT cells were treated with nine different compounds, including TCDD as positive control, in commercial DMEM (gray circle) or in DMEM prepared with recrystallized Trp (black triangle). Treatments were terminated at the indicated time points, and EROD activity (pmol resorufin/mg protein) was measured. Error bars indicate SE.

Table S1. AHR-activating agents that also inhibit CYP1 enzymes

Class	Physical or chemical description	Compound name	References
Combustion products	Polycyclic aromatic hydrocarbons	Anthracene	(1, 2)
		Chrysene	(3, 4)
		Fluoranthene	(5, 6)
		Phenanthrene	(2, 7)
Clinical drugs	Antifertility drugs	3-(2-Ethyl phenyl)-5-(3-methoxy phenyl)-1H-1,2,4triazol (DL111)	(8)
	Anti-inflammatory drugs	Diclofenac	(9, 10)
		Leflunomide	(11, 12)
		Sulindac	(13)
	Antiparasitic drugs	Albendazole	(14, 15)
		Bitertanol	(16)
		Clotrimazole	(17, 18)
		Enilconazole	(19)
		Itraconazole	(20)
		Ketoconazole	(20)
		Medetomidine	(21)
		Miconazole	(22, 23)
		Oltipraz	(24, 25)
		Primaquine	(23, 26)
		Quinine	(27, 28)
	Beta-blockers	Metopropol	(11, 29)
		Propranolol	(9, 29)
		Timolol	(11, 29)
	Cytostatics, chemotherapeutic drugs	4-Aminophenyl, 2-(4-amino-3-methylphenyl) benzothiazole (DF 203)	(30)
		Anastrozole	(11, 31)
		Doxorubicin	(32, 33)
		Ellipticine	(34, 35)
		Flutamide	(36)
	Corticosteroids	Dexamethasone	(37, 38)
	Lipid-lowering agents	Ciprofibrate	(39, 40)
		Clofibrate	(41, 42)
		Fluvastatin	(43, 44)
	Psoriasis drugs	5-Methoxypsoralen	(45)
		8-Methoxypsoralen	(46, 47)
	Proton pump inhibitors	Omeprazole	(48, 49)
	Selective serotonin reuptake inhibitors	Fluoxetine	(11, 42)
		Fluvoxamine	(41, 50)
		Paroxetine	(41, 42)
		Sertraline	(11, 51)
Endogenous and natural substances	Arachidonic acid metabolites	Lipoxin A4	(52)
	Alkaloids	Berberine	(53),
		Caffeine	(54, 55)
		Cocaine	(56, 57)
		Evodiamine	(58, 59)
		Harman	(60, 61)
		Piperine	(62)
		Rutaecarpine	(58, 63)
		Δ^9-Tetrahydrocannabinol	(64)
	Organosulphur compounds	Diallyl sulfide	(65, 66)
		Diallyl disulfide	(67, 68)
		Diallyl trisulfide	(65, 68)
		Phenethyl isothiocyanate (PEITC)	(69, 70)
		Sulforaphane	(71, 72)
	Anthraquinones, chalcones, catechines, flavonoids, guaiacols and phenols	α-Naphthoflavone (αNF)	(73, 74)
		Apigenin	(50, 75)
		Baicalein	(76, 77)
		Biochanin A	(78)
		Chrysin	(77, 79)
		Daidzein	(77, 80)
		Diosmetin	(81)
		Diosmin	(70, 82)
		Ellagic acid	(83, 84)

Table S1. Cont.

Class	Physical or chemical description	Compound name	References
		Emodin	(77, 85)
		Epigallocatechin gallate (EGCG)	(86)
		Eugenol	(87, 88)
		Flavone	(89, 90)
		Galangin	(89, 91)
		Hesperetin	(92, 93)
		Hydroxychalcones	(94, 95)
		Isorhamnetin	(75, 96)
		Kaempferol	(75, 96)
		Luteolin	(75, 79)
		3′-Methoxy-4′-nitroflavone (MNF)	(97, 98)
		Phloretin	(99)
		Quercetin	(100, 101)
	Coumarins, furanocoumarins and terpenes	Angelicin	(102)
		Bergamottin	(102, 103)
		Isoimpinellin	(104)
		Limonene	(105)
	Curcuminoids	Curcumin	(106, 107)
	Heme metabolites	Hemin	(108, 109)
	Indoles	Diindolylmethane (DIM)	(69, 110)
		Indole-3-carbinol (I3C)	(110, 111)
		Melatonin	(11, 112)
		Tryptamine	(113)
	Methylenedioxyben-zenes	Isosafrole	(50, 114)
		Piperonyl butoxide	(115, 116)
		Safrole	(11, 117)
	Stilbenoids	Resveratrol	(23, 70)
	Vitamins and antioxidants	Lycopene	(118, 119)
		Menadione	(120, 121)
		Retinoic acid	(121, 122)
		α-Tocopherol	(120, 123)
		1-O-Hexyl-2,3,5-trimethylhydroquinone	(124)
		Propyl gallate	(125, 126)
		Tert-butylhydroquinone (tBHQ)	(68, 124)
		Tannic acid	(125, 126)
Dietary mutagens	Heterocyclic amines	2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)	(60)
		2-Amino-3-methyl-9H-pyrido[2,3-b]indole (MeA*alpha*C)	(60)
		3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)	(60)
Industrial compounds	Plastic monomers and additives	Bisphenol A (BPA)	(127, 128)
		Nonylphenol	(129, 130)
		Polybrominated diphenyl ethers (PBDE)	(131, 132)
		Toluene diisocyanate (TDI)	(133)
Metals		Cadmium	(134, 135)
		Chromium	(136, 137)
		Copper	(137, 138)
		Mercury	(137, 138)
Oxidants		Hyperoxia	(139, 140)
		Oxidized low-density lipoproteins (oxLDL)	(141, 142)
		Ozone	(143, 144)
Pesticides	Ureas	Diuron	(145, 146)
		N-Phenylthiourea (PTU)	(147, 148)
		Prochloraz	(149)
	Carbamates	Carbaryl	(150, 151)
	Organophosphates	Chlorpyrifos	(145, 152)
		Fenitrothion	(145, 153)
	Organochlorines	Endosulphan	(154, 155)
Specific inhibitors and blockers	Corticosteroid synthesis inhibitors	Metyrapone	(156)
	Carnitine palmitoyl-transferase-1 inhibitors	Etomoxir	(157)
	Cytochrome P4501 suicide inhibitors	1-Ethynylpyrene	(158)
		2-Phenylphenanthridinone	(159)
		SKF-525	(160, 161)
	Kinase inhibitors	Genistein	(67, 77)
		U0126	(162)
	5-Lipoxygenase inhibitors	Zileuton	(163, 164)

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Table S2. Viability of HaCaT cells exposed to inhibitors of CYP1A in commercial DMEM (Com) or in DMEM prepared with purified tryptophan (Pure)

	Viability*	
Compound (concentration)	Com	Pure
TCDD (1 nM)	101 ± 1.44	99.2 ± 4.12
Trioxalen (1 μM)	95.6 ± 1.99	94.2 ± 2.40
Ketoconazole (10 μM)	103 ± 2.85	100 ± 0.93
Ellipticine (0.05 μM)	92.3 ± 4.93	102 ± 1.84
Genistein (10 μM)	98.3 ± 1.74	99.9 ± 2.65
Diosmin (10 μM)	98.2 ± 3.62	101 ± 4.07
α-NF (0.25 μM)	103 ± 2.22	97.7 ± 1.88
Cycloheximide (18 μM)	88.0 ± 1.11	86.5 ± 2.06
α-Tocopherol (50 μM)	99.2 ± 1.69	100 ± 1.52
MNF (2.5 μM)	100 ± 3.03	104 ± 2.00
H_2O_2 (2 mM)	88.7 ± 4.37	94.2 ± 3.74
UVB (20 mJ/cm^2)	98.4 ± 3.46	100 ± 1.09

*Percent metabolically active cells as assessed with the Alamar Blue assay after 48 h of culturing; means ± SE of triplicate measurements from two independent cell cultures.