Synthesis and Biological Properties of New Stilbene Derivatives of Resveratrol as New Selective Aryl Hydrocarbon Modulators

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We developed new stilbene derivatives of resveratrol (*E*)-1-(4′-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethene) selective for AhR and devoid of affinity for ER. Among the 24 stilbenes synthesized, all display a higher affinity than resveratrol for AhR. (*E*)-1-(4′-Trifluoromethylphenyl)-2-(3,5-ditrifluoromethylphenyl)ethene (**4e**), (*E*)-1-(4′-methoxyphenyl)-2-(3,5-dichlorophenyl)ethene (**4j**), and (*E*)-1-(4′-chlorophenyl)-2-(3,5-dichlorophenyl)ethene (**4b**) are selective, high-affinity AhR antagonists with, respective, K_is of 2.1, 1.4, and 1.2 nM. (*E*)-1-(4′-Trifluoromethylphenyl)-2-(3,5-dichlorophenyl)ethene (**4i**) displays a K_i of 0.2 nM and is a selective and high-affinity agonist on AhR.

Introduction

The aryl hydrocarbon receptor (AhR), also known as the Dioxin (TCDD, 2,3,7,8-tetrachlorodibenzoparadioxin) receptor, is an intracellular, ligand-dependent, basic helix−loop−helix/PAS (per-arnt-sim) transcription factor. AhR binds cis-acting dioxin-responsive elements (DRE) and modulates the expression of various genes in a wide range of tissues and species.[1,2] AhR agonists such as TCDD, benzo[*a*]pyrene (BaP), and 7,12-dimethylbenzenthracene (DMBA) are environmental toxicants suspected to be responsible of numerous pathologies in humans such as cancers, immunosuppression, atherosclerosis, osteoporosis, skin disorders, and reproductive failures. These xenobiotics induce the transcription of phase I cytochrome genes (CYP1A, 1A2, 1B1), phase II detoxifying enzyme genes (glutathione-*S*-transferase, microsomal epoxide hydrolase), as well as numerous human and viral genes related to important pathologies.[3,4] Among AhR agonists, BaP (a constituent of tobacco smoke and exhaust fumes) is a potent carcinogen in several mammalian species including humans. The AhR-dependent activation of CYP1 1A1 is responsible for its own oxidation into highly mutagenic and carcinogenic species such as 7,8-diol-epoxide-BaP.[5] Two main lines of evidence highlight the importance of the AhR in the mediation of the carcinogenicity of arylhydrocarbons: (1) BaP is not carcinogenic in mice lacking AhR;[6] (2) mice expressing constitutively active AhR spontaneously develope cancers.[7,8] Thus, development of AhR antagonists represents a challenge for the development of prophylactic as well as curative drugs for major diseases involving AhR activation. As the three-dimensional molecular structure of AhR has not been reported yet, details of the specificity of the recognition of AhR by its cognate ligands have been assessed indirectly. Structure−activity relationship analysis was performed on numerous halogenated aromatic hydrocarbons (HAH) and polycyclic aromatic hydrocarbons (PAH) and suggested that the ligand binding site of AhR binds planar ligands with a maximal dimension of 14 Å × 12 Å × 5 Å.[10] It has been proposed that HAH interaction with AhR involves mainly steric-,[10,11] electrostatic-, and dispersion-type interactions.[10,12−14] Besides environmental toxicants, physiological oxysterol, such as 7-ketocholesterol, and phytochemicals, such as flavonoids and resveratrol, have been identified as AhR mixed agonist/antagonists.[15−21] This offers opportunities to develop high-affinity and selective AhR antagonists based on their chemical structure.

Resveratrol ((*E*)-1-(4′-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethene) is a phytoalexine with multiple potencies in various pathologies from osteoporosis to chemoprevention against environmental contaminants.[4,22] These properties have been related to its antioxidant potency,[23] estrogenic potency,[24] and antagonistic activity against the arylhydrocarbon receptor (AhR).[16] The antioxidant properties of resveratrol have been related to its polyphenolic nature, especially to the presence of hydroxyl groups.[25,26] Phenolic groups are also known as an important structural determinant for estrogen receptor (ER) binding.[9,27,28] We investigated the chemical modification of resveratrol in order to obtain specific antagonists of dioxins with a higher affinity for AhR but devoid of affinity for ER. We performed isosteric modifications of resveratrol, keeping the stilbene backbone of resveratrol in order to design high-affinity and specific antagonists for the AhR and replacing the hydroxyl by various functional groups including chlorine atoms. Compound binding capacities were measured on ER and AhR, their agonist/antagonist properties were estimated, and their toxicity on established cell lines was evaluated.

Results and Discussion

Chemistry. Wittig reactions were carried out according to the procedure described by Bellucci et al.[29]

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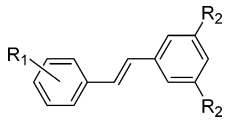
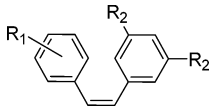
Table 1. Receptor Binding and Biological Activity of *trans*-Stilbene Derivatives



			AhR		ER	
compounds	R_1	R_2	K_i,[a] nM	activity[b]	K_i,[c] nM	activity[d]
resveratrol	4′-OH	OH	169 ± 5.2	antagonist	785 ± 4.1	agonist
4a	4′-OMe	OMe	7.7 ± 0.2	antagonist	261 ± 3.2	agonist
4b	4′-Cl	Cl	1.2 ± 0.4	antagonist	>100 000	
4c	4′-OMe	F	9.2 ± 1.7	antagonist	>100 000	
4d	4′-F	F	3.8 ± 2.2	antagonist	>100 000	
4e	4′-CF_3	CF_3	2.1 ± 0.8	antagonist	>100 000	
4f	4′-F	OMe	3.1 ± 0.8	antagonist	>100 000	
4g	4′-OEt	OMe	5 ± 1.8	antagonist	380.8 ± 2.2	agonist
4h	4′-OBu	OMe	20 ± 1.4	antagonist	>100 000	
4i	4′-CF_3	Cl	0.2 ± 0.4	agonist	>100 000	
4j	4′-OMe	Cl	1.4 ± 0.7	antagonist	>100 000	
4k	3′-CF_3	Cl	6.8 ± 1.4	antagonist	>100 000	
4l	3′-OMe	Cl	5.7 ± 1.1	antagonist	>100 000	

[a] Cytosols from rabbit liver were incubated with 0.2 nM [^{3}H]-TCDD and 12 concentrations of unlabeled test ligands ranging from 0.1 nM to 1 μM as described by Savouret et al.[20] IC_{50} values were determined using the iterative curve-fitting program GraphPad Prism (version 4.0). IC_{50} values were converted into the apparent K_i using the Cheng−Prussoff equation and K_d values of 0.01 nM. [b] Agonist denotes a compound that stimulate the transcription of TCDD-responsive chloramphenicol acetyl transferase (CAT) in the 47DRE cell line,[16] whereas an antagonist denotes a compound capable of suppressing at least 50% of TCDD stimulation of TCDD-responsive CAT achieved with 5 nM TCDD. [c] Cytosols from MCF-7 cells expressed exclusively the Erα isoform[31] were incubated with 2 nM [^{3}H]-estradiol and eight concentrations of unlabeled test ligands ranging from 10 nM to 10 μM.[32] IC_{50} and K_i were calculated as described above with K_d values of 0.1 nM. [d] Agonist denotes a compound that stimulates the transcription of estrogen-responsive luciferase (LUC) on MELN cell line,[33] whereas an antagonist denotes a compound capable of suppressing at least 50% of estradiol stimulation of ERE-responsive LUC achieved with 1 nM estradiol.

Table 2. Receptor Binding and Biological Activity of *cis*-Stilbene Derivatives



			AhR		ER	
compounds	R_1	R_2	K_i,[a] nM	activity[a]	K_i,[a] nM	activity[a]
5a	4′-OMe	OMe	75 ± 3.2	antagonist	132 ± 2.8	agonist
5b	4′-Cl	Cl	13 ± 2.4	antagonist	>100 000	
5c	4′-OMe	F	22 ± 1.8	antagonist	>100 000	
5d	4′-F	F	63 ± 3.1	antagonist	>100 000	
5e	4′-CF_3	CF_3	60 ± 3.2	antagonist	>100 000	
5f	4′-F	OMe	96 ± 3.4	antagonist	>100 000	
5g	4′-OEt	OMe	65 ± 3.1	antagonist	136 ± 1.9	agonist
5h	4′-OBu	OMe	43 ± 2.8	antagonist	>100 000	
5i	4′-CF_3	Cl	14 ± 1.8	antagonist	>100 000	
5j	4′-OMe	Cl	12 ± 2.2	antagonist	>100 000	
5k	3′-CF_3	Cl	19 ± 1.7	antagonist	>100 000	
5l	3′-OMe	Cl	24 ± 1.6	antagonist	>100 000	

[e] K_i and transcriptional modulation were determined as described in the caption of Table 1.

Phosphonium chloride with aryl aldehyde, potassium hydroxide, and 18-crown-6 followed by organic extraction and purification by RP HPLC gave the corresponding *trans*-stilbenes **4a**−**l** and *cis*-stilbenes **5a**−**l**. Cis or trans geometries of these compounds were confirmed by their coupling constants for the olefinic protons of about 12 Hz for cis isomers and 16.0−16.5 Hz for trans isomers. The structure and purity of the compounds were confirmed by CI-MS, ^{1}H NMR, and elemental analysis. The stereochemical stability of the compounds was checked by HPLC and showed no isomerization of compounds during the time of the experiments or up to 1 year when conserved in ethanolic solution at −20 °C in the dark.

Binding Affinities for the AhR and for the ER. Table 1 shows the properties of 12 *trans*-stilbenes **4a**−**l,** while Table 2 shows the corresponding *cis*-stilbenes **5a**−**l**. In the cis series almost all compounds showed a higher affinity than resveratrol for AhR. The trichloro derivative **5b** had a 12.4-fold higher affinity, and the 4′-trifluoromethyl-3,5-dichlorostilbene derivative (**5i**) displayed a 10.9-fold increase in affinity for AHR. In the 4′-methoxy series 3,5-difluoro and 3,5-dichloro derivatives (**5c** and **5j**) had, respectively, a 7.2- and 13-fold increase in affinity for AhR with regard to resveratrol. The 4′-fluoro-3,5-dimethoxy derivative **5f** displayed a 1.3-fold lower affinity for AhR than resveratrol. Compounds of the trans (*E*) series were the most potent compared to their cis (*Z*) isomers, suggesting that AhR preferentially recognized *trans*-stilbenes. Replacement of the hydroxyl groups of resveratrol with various functional groups produced dramatic effects on affinity.

Replacement of resveratrol hydroxyls by the same substituent produced compounds with the following order of affinity: OH (resveratrol) ≪ OMe (**4a**) < F (**4d**) < CF_3 (**4e**) < Cl (**4b**). 3,5-Dimethoxy stilbene compounds **4f** and **4g** displayed almost the same affinity for AhR, showing that these substituents were both important for binding to AhR, but 4′-fluoro compound **4f** was selective for AhR over ER. 4′-BuO derivative **4h** is the compound of the 3,5-dimethoxy series with the lowest affinity. (*E*)-1-(4′-Chlorophenyl)-2-(3,5-dichlorophenyl)-ethene (**4b**) exhibited a K_i of 1.25 ± 0.4 nM for AhR and no affinity for ER, confirming that replacement of hydroxyl with chloride abolished binding on ER and increased dramatically the affinity for AhR. (*E*)-1-(4′-Trifluoromethylphenyl)-2-(3,5-dichloromethylphenyl)-ethene (**4i**) and (*E*)-1-(4′-methoxyphenyl)-2-(3,5-dichlorophenyl)ethene (**4j**) bound selectively to AhR with respective K_i of 1.44 ± 0.7 and 0.21 ± 0.4 nM and without detectable affinity for ER. The presence of Cl, MeO, or CF_3 in the 4′ position and of Cl in the 3 and 5 positions of the stilbene backbone produced a high affinity and selective ligand for AhR. Compounds **4k** and **4l** are the regioisomers of compounds **4i** and **4j**, bearing their substituent in the meta position regarding the ethylene bond. They displayed, respectively, a 32- and 4-fold lower affinity than their para-substituted isomers. This suggests that the para position for these substituents was more favorable for their interaction with the receptor. All the tested compounds were within the range of the estimated cavity volume defined as 14 Å × 12 Å × 5 Å for the AhR. Substitution of the three hydroxyl groups with methoxy groups or halogens in the *Z* or *E* geometry induced an overall increase in affinity for AhR, although these modifications had less incidence in the cis series than in the trans series. Trisubstituted methoxy derivatives are interesting compounds in these series because they induce a 21-fold increase in affinity for AhR and a 14-fold increase in affinity for the ER. Replacement of the oxygen-bearing substituents with halogens abolished affinities for ER, which was consistent with the previously published structure−affinity relationship for the diethylstilbestrol series.[28] Several generalizations can be drawn from these observations. The loss of affinity toward ER for compounds **4b**−**f**, **4h**−**l**, **5b**−**f,** and **5h**−**l** shows that trisubstitution with a hydroxyl or methoxy group is required for binding to the ER but not to the AhR. Replacement of hydroxyl or methoxy groups by a halogen or a trifluoromethyl group induced a complete loss of affinity for ER.

AhR- and ER-Mediated Transactivation. Cis and trans isomers were tested for TCDD antagonistic activity in our stable cell line (47DRE) bearing the DRE-TK-CAT reporter construct. Results for the trans series are reported in Table 1, and the effect of selected compounds is exemplified in Figure 1A. Dioxin stimulated CAT transcription, while resveratrol completely abolished it at 10 μM, consistent with published data.[16] Compound **4a** produced an effect similar to that of resveratrol. Compounds **4b** and **4j** were the most potent AhR antagonists in this series, being 10-fold more efficient than resveratrol and compound **4a**. Curiously, compound **4i**, showing the highest affinity for AhR, behaved as an agonist. Figure 1B shows the ER-mediated activity of the compounds. 17β-Estradiol and

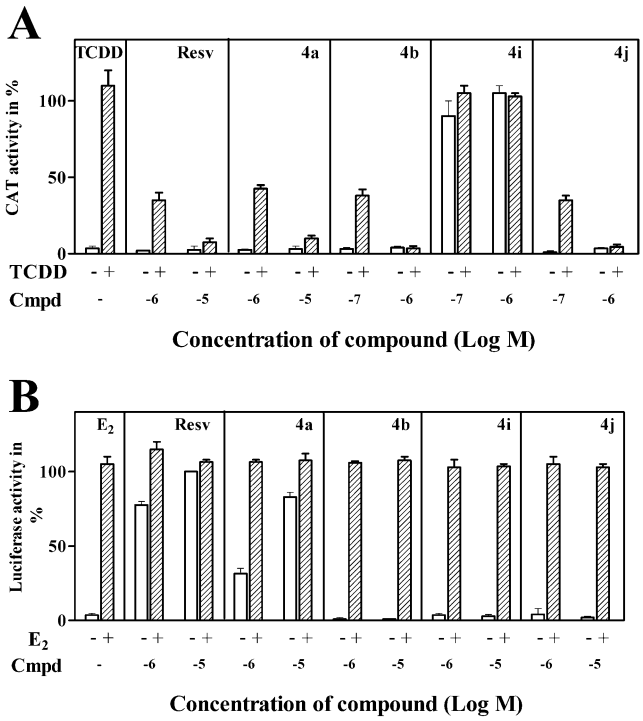


Figure 1. (A) Transcriptional modulation by AhR was performed on the 47DRE reporter cell line as described in Casper et al.[16] Cells were treated 48 h with solvant vehicle or various concentrations of compounds (white bars) or in the presence of 5 nM dioxin (striated bars) and analyzed for CAT expression. (B) Transcriptional modulation by ER was measured on the MELN reporter cell line as described in Doisneau-Sixou et al.[33] Cells were incubated for 8 h in the presence of solvant vehicle or various concentrations of compounds alone (white bars) or in the presence of 1 nM 17β-estradiol (striated bars) and analyzed for luciferase activity.

resveratrol both stimulated transcription of the luciferase reporter. As expected, compound **4a**, which displayed affinity for ER, was a potent agonist on ER. Compounds **4b**, **4i,** and **4j**, devoid of measurable affinity for ER, did not show any effect on ER-driven transcription. Consequently, compounds **4b**, **4i,** and **4j** are selective AhR modulators with regard to ER. The removal of phenolic or anilic groups in these compounds suppressed their antioxidant properties. All cis compounds were antagonistic at 1 and 10 μM with no detectable agonistic activity. Their potency was comparable to that of resveratrol.

Measurements of Cytotoxicity. Low toxicity is a prerequisite for the possible prophylactic use of such selective aryl hydrocarbon receptor inhibitors. Cytotoxicity was evaluated on various human tumoral cell lines such as A549 (human lung carcinoma), MCF-7, and T47D (human breast cancers). Resveratrol and its halogenated homologues were not toxic up to a 10 μM concentration (not shown). Methoxy-stilbenes such as trimethoxylated derivatives **4a** and **5b** and 3,5-methoxy derivatives **4g** and **5g** induced cytotoxicity at doses lower than 100 nM, which is consistent with previously published data.[30] 3,5-Methoxy derivatives (**4f**, **5f**, **4h**, **5h**) showed cytotoxicity at concentrations higher than 10 μM.

Conclusions

We describe here the synthesis of 24 new stilbene derivatives, isosters of *cis*- and *trans*-resveratrol. Trans

derivatives displayed the highest affinity for the AhR over cis derivatives. Replacement of 3-OH, 5-OH with chlorine coupled with replacement of 4′-OH with chlorine (**4b**) or a methoxy group (**4j**) yielded selective TCDD antagonists with high affinity for the AhR (135- and 117-fold higher than resveratrol, respectively). In sharp contrast, replacement of 3- and 5-OH groups by chlorine and replacement of the 4′-OH with a trifluoromethyl group (**4i**) yielded a potent agonist with high affinity (805-fold higher than resveratrol). None of these compounds showed any detectable affinity for the ER. This latter property should eliminate estrogen-related risks, such as the increased risk of breast and genital cancers. Moreover, antagonist compounds **4b** and **4j** may present an interest as "nonhormonal bone protective therapy" by preventing AhR-dependent interleukin-1β expression at the level of bone tissue. These compounds are not toxic on cell culture up to 10 μM. Compounds **4b** and **4j** constitute new leads for the development of pure antagonists of the AhR receptor. They will be useful to further investigate the role of AhR both at the physiological level and in pathologies involving the regulatory functions of this receptor.

Experimental Section

TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) was a gift from Dr S. Safe (College Station, Texas A&M University, TX). 2,3,7,8-Tetrachloro-1,6-3*H*-dibenzo-*p*-dioxin, 28 Ci/mmol, was purchased from Terrachem (Lenexa, KS). Dioxin stock solutions were dissolved in dimethyl sulfoxide and handled under a fume hood. TCDD stock was subsequently diluted in ethanol for use in experiments. Steroids were purchased from Steraloids (Wilton, NH). All other chemicals were purchased from Sigma Chemicals.

General Procedure for the Preparation of (*Z*)- and (*E*)-Stilbenes. Phosphonium salt (1 mmol) was dissolved in dichloromethane(1 mL). Aryl aldehyde (1 mmol), 18-crown-6 (0.1 mmol), and potassium hydroxide (3 mmol) were added to the solution. The reaction mixture was stirred at room temperature and periodically monitored by TLC (toluene or hexane) until complete consumption of the aldehyde. The mixture was diluted with dichloromethane and filtered. The organic layer was washed with water, dried over $MgSO_4$, and evaporated under vacuum. Purification by RP HPLC (Ultrasep ES 100 RP 18, 250 × 8 mm, 6.0 μm; methanol:water, 80:20 or 85:15; flow rate 1 mL/min) afforded pure product.

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Supporting Information Available: Experimental details and elemental analysis for **4a**−**l** and **5a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Nebert, D. W.; Roe, A. L.; Dieter, M. Z.; Solis, W. A.; Yang, Y.; et al. Role of the aromatic hydrocarbon receptor and [Ah] gene battery in the oxidative stress response, cell cycle control, and apoptosis. *Biochem. Pharmacol.* **2000**, *59*, 65−85.
(2) Denison, M. S.; Nagy, S. R. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 309−334.
(3) Mimura, J.; Fujii-Kuriyama, Y. Functional role of AhR in the expression of toxic effects by TCDD. *Biochim. Biophys. Acta* **2003**, *1619*, 263−268.
(4) Savouret, J. F.; Berdeaux, A.; Casper, R. F. The aryl hydrocarbon receptor and its xenobiotic ligands: a fundamental trigger for cardiovascular diseases. *Nutr. Metab. Cardiovasc. Dis.* **2003**, *13*, 104−113.
(5) Nebert, D. W.; Dalton, T. P.; Okey, A. B.; Gonzalez, F. J. Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. *J. Biol. Chem.* **2004**, *279*, 23847−23850.
(6) Shimizu, Y.; Nakatsuru, Y.; Ichinose, M.; Takahashi, Y.; Kume, H.; et al. Benzo[*a*]pyrene carcinogenicity is lost in mice lacking the aryl hydrocarbon receptor. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 779−782.
(7) Andersson, P.; McGuire, J.; Rubio, C.; Gradin, K.; Whitelaw, M. L.; et al. A constitutively active dioxin/aryl hydrocarbon receptor induces stomach tumors. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 9990−9995.
(8) Moennikes, O.; Loeppen, S.; Buchmann, A.; Andersson, P.; Ittrich, C.; et al. A constitutively active dioxin/aryl hydrocarbon receptor promotes hepatocarcinogenesis in mice. *Cancer Res.* **2004**, *64*, 4707−4710.
(9) Sadler, B. R.; Cho, S. J.; Ishaq, K. S.; Chae, K.; Korach, K. S. Three-dimensional quantitative structure−activity relationship study of nonsteroidal estrogen receptor ligands using the comparative molecular field analysis/cross-validated r2-guided region selection approach. *J. Med. Chem.* **1998**, *41*, 2261−2267.
(10) Waller, C. L.; McKinney, J. D. Three-dimensional quantitative structure−activity relationships of dioxins and dioxin-like compounds: model validation and Ah receptor characterization. *Chem. Res. Toxicol.* **1995**, *8*, 847−858.
(11) Gasiewicz, T. A.; Kende, A. S.; Rucci, G.; Whitney, B.; Willey, J. J. Analysis of structural requirements for Ah receptor antagonist activity: ellipticines, flavones, and related compounds. *Biochem. Pharmacol.* **1996**, *52*, 1787−1803.
(12) Fraschini, E.; Bonati, L.; Pitea, D. Molecular polarizability as a tool for understanding the binding properties of polychlorinates dibenzo-*p*-dioxins: definition of a reliable computational procedure. *J. Phys. Chem.* **1996**, *100*, 10564−10569.
(13) Beger, R. D.; Wilkes, J. G. Models of polychlorinated dibenzodioxins, dibenzofurans, and biphenyls binding affinity to the aryl hydrocarbon receptor developed using (13)c NMR data. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1322−1329.
(14) Mhin, B. J.; Lee, J. E.; Choi, W. Understanding the congener-specific toxicity in polychlorinated dibenzo-*p*-dioxins: chlorination pattern and molecular quadrupole moment. *J. Am. Chem. Soc.* **2002**, *124*, 144−148.
(15) Ciolino, H. P.; Wang, T. T.; Yeh, G. C. Diosmin and diosmetin are agonists of the aryl hydrocarbon receptor that differentially affect cytochrome P450 1A1 activity. *Cancer Res.* **1998**, *58*, 2754−2760.
(16) Casper, R. F.; Quesne, M.; Rogers, I. M.; Shirota, T.; Jolivet, A.; et al. Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity. *Mol. Pharmacol.* **1999**, *56*, 784−790.
(17) Ciolino, H. P.; Daschner, P. J.; Yeh, G. C. Dietary flavonols quercetin and kaempferol are ligands of the aryl hydrocarbon receptor that affect CYP1A1 transcription differentially. *Biochem. J.* **1999**, *340* (Pt 3), 715−722.
(18) Ashida, H.; Fukuda, I.; Yamashita, T.; Kanazawa, K. Flavones and flavonols at dietary levels inhibit a transformation of aryl hydrocarbon receptor induced by dioxin. *FEBS Lett.* **2000**, *476*, 213−217.
(19) Quadri, S. A.; Qadri, A. N.; Hahn, M. E.; Mann, K. K.; Sherr, D. H. The bioflavonoid galangin blocks aryl hydrocarbon receptor activation and polycyclic aromatic hydrocarbon-induced pre-B cell apoptosis. *Mol. Pharmacol.* **2000**, *58*, 515−525.
(20) Savouret, J. F.; Antenos, M.; Quesne, M.; Xu, J.; Milgrom, E.; et al. 7-ketocholesterol is an endogenous modulator for the arylhydrocarbon receptor. *J. Biol. Chem.* **2001**, *276*, 3054−3059.
(21) Zhang, S.; Qin, C.; Safe, S. H. Flavonoids as aryl hydrocarbon receptor agonists/antagonists: effects of structure and cell context. *Environ. Health Perspect.* **2003**, *111*, 1877−1882.
(22) Cal, C.; Garban, H.; Jazirehi, A.; Yeh, C.; Mizutani, Y.; et al. Resveratrol and cancer: chemoprevention, apoptosis, and chemoimmunosensitizing activities. *Curr. Med. Chem. Anti-Cancer Agents* **2003**, *3*, 77−93.
(23) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **1997**, *275*, 218−220.
(24) Gehm, B. D.; McAndrews, J. M.; Chien, P. Y.; Jameson, J. L. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14138−14143.

(25) Wright, J. S.; Johnson, E. R.; Dilabio, G. A. Predicting the activity of phenolic antioxidants: theorical method, analysis of substituent effects, application to major families of antioxidants. *J. Am. Chem. Soc.* **2001**, *123*, 1173−1183.
(26) Stivala, L. A.; Savio, M.; Carafoli, F.; Perucca, P.; Bianchi, L.; et al. Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. *J. Biol. Chem.* **2001**, *276*, 22586−22594.
(27) Ekena, K.; Katzenellenbogen, J. A.; Katzenellenbogen, B. S. Determinants of ligand specificity of estrogen receptor-alpha: estrogen versus androgen discrimination. *J. Biol. Chem.* **1998**, *273*, 693−699.
(28) Gao, H.; Katzenellenbogen, J.; Garg, R.; Hansch, C. Comparative QSAR analysis of estrogen receptor ligands. *Chem. Rev.* **1999**, *99*, 723−744.
(29) Bellucci, G.; Chiappe, C.; Lo Moro, G. Crown Ether Catalyzed Stereospecific Synthesis of *Z*- and *E*-Stilbenes by Wittig Reaction in a Solid−Liquid Two-Phases System. *Tetrahedron Lett.* **1996**, *37*, 4225−4228.
(30) Cushman, M.; Nagarathnam, D.; Gopal, D.; He, H. M.; Lin, C. M.; et al. Synthesis and evaluation of analogues of (*Z*)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene as potential cytotoxic and antimitotic agents. *J. Med. Chem.* **1992**, *35*, 2293−2306.
(31) Sun, J.; Huang, Y. R.; Harrington, W. R.; Sheng, S.; Katzenellenbogen, J. A.; et al. Antagonists selective for estrogen receptor alpha. *Endocrinology* **2002**, *143*, 941−947.
(32) Poirot, M.; De Medina, P.; Delarue, F.; Perie, J. J.; Klaebe, A.; et al. Synthesis, binding and structure-affinity studies of new ligands for the microsomal anti-estrogen binding site (AEBS). *Bioorg. Med. Chem.* **2000**, *8*, 2007−2016.
(33) Doisneau-Sixou, S. F.; Cestac, P.; Chouini, S.; Carroll, J. S.; Hamilton, A. D.; et al. Contrasting effects of prenyltransferase inhibitors on estrogen-dependent cell cycle progression and estrogen receptor-mediated transcriptional activity in MCF-7 cells. *Endocrinology* **2003**, *144*, 989−998.

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