Activation of Anti-oxidant Nrf2 Signaling by Substituted *trans* Stilbenes

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Abstract- Nrf2, which is a member of the cap'n'collar family of transcription factors, is a major regulator of phase II detoxification and anti-oxidant genes as well as anti-inflammatory and neuroprotective genes. The importance of inflammation and oxidative stress in many chronic diseases supports the concept that activation of anti-oxidant Nrf2 signaling may have therapeutic potential. A number of Nrf2 activators have entered into clinical trials. Nrf2 exists in the cytosol in complex with its binding partner Keap1, which is a thiol-rich redox-sensing protein. In response to oxidative and other stress, select cysteine residues of Keap1 are modified, which weakens the interaction between Nrf2 and Keap1 and allows Nrf2 to enter the nucleus. Numerous Nrf2-activating chemicals, including a number of natural products, are electrophiles that modify Keap1, often by Michael addition, leading to activation of Nrf2. One concern with the design of Nrf2 activators that are electrophilic covalent modifiers of Keap1 is the issue of selectivity. In the present study, substituted *trans* stilbenes were identified as activators of Nrf2. These activators of Nrf2 are not highly electrophilic and therefore are unlikely to activate Nrf2 through covalent modification of Keap1. Dose-response studies demonstrated that a range of substituents on either ring of the *trans* stilbenes, especially fluorine and methoxy substituents, influenced not only the sensitivity to activation, reflected in EC₅₀ values, but also the extent of activation, which suggests that multiple mechanisms are involved in the activation of Nrf2. The stilbene backbone appears to be a privileged scaffold for development of a new class of Nrf2 activators.

1. Introduction

Inflammation and oxidative stress are associated with most chronic diseases, including neurodegenerative and neuropsychiatric diseases. In Alzheimer's disease (AD), for example, focal activation of microglia, the resident brain macrophage, which is a source of pro-inflammatory signals and oxidative stress, is seen consistently in the vicinity of plaques, both in pathological samples from AD patients and in animal models.¹⁻⁵ A normal response to oxidative stress is activation of a number of anti-oxidant genes to counteract the development of oxidative stress. The promoters for these anti-oxidant genes commonly have an anti-oxidant response element (ARE) where transcription factor Nuclear factor erythroid 2 related factor 2 (Nrf2) can bind to induce gene expression.

Nrf2, which is a member of the cap'n'collar family of transcription factors, is a major regulator of phase II detoxification and anti-oxidant genes as well as anti-inflammatory and neuroprotective genes.⁶⁻¹⁴ In unstressed cells, Nrf2 is retained in the cytosol through formation of a complex between Nrf2, Kelch-like ECH associated protein 1 (Keap1), and Cul3, which is an adaptor to link Nrf2 to an E3 ubiquitin ligase complex. Nrf2 is continuously synthesized and then degraded by ubiquitination and proteosomal degradation, which limits the cytosolic concentration of Nrf2. In response to oxidative and other stress, select cysteine residues of Keap1 are modified, which weakens the interaction between Nrf2 and Keap1. This allows newly synthesized Nrf2 to accumulate and translocate to the nucleus where it interacts with small Maf proteins and subsequently binds to promoters with ARE sequences. Nrf2 can also be released from Keap1 by covalent modification of Keap1 by electrophiles.

Nrf2 is widespread in the CNS and is recognized as an important regulator of brain inflammation. In animal models with Nrf2 deficiency, neurodegeneration is observed, especially in areas with high oxidative metabolism.^{7,15} In animal models of stroke and traumatic brain injury, Nrf2 deficiency leads to more intense inflammation and more severe injury.^{16,17} In humans, Nrf2 declines with age and may contribute to age as a risk factor for neurological disease. Activation of Nrf2 in astrocytes can protect neurons from oxidative stress.¹⁸ The impaired translocation of Nrf2 to the nucleus in neurons from AD subjects¹⁹ suggests that defects in Nrf2 activation may play a major role in the development of oxidative damage in AD brains.

Recently we reported that the natural product resveratrol, which is a *trans* stilbene, and a synthetic *trans* stilbene ((E)-2-fluoro-4'-methoxystilbene, designated **LD55**) were effective at reducing both brain inflammation and plaque accumulation in a transgenic animal model of AD.²⁰ **LD55** was selected based upon its ability to inhibit activation of the pro-inflammatory transcription factor NF- κ B in a reporter cell-based assay and on its ability to inhibit expression of pro-inflammatory signals in a microglia cell line in response to LPS.²¹ Resveratrol also inhibits the activation of NF- κ B.²² In the present study, we demonstrate that **LD55** also shares

with resveratrol the ability to activate Nrf2, and we describe the activities of a series of *trans* stilbenes that were compared to resveratrol and **LD55** for their abilities to promote activation of Nrf2 in reporter assays. The natural product isothiocyanate sulforaphane, which is a well-established activator of Nrf2,²³ was used as a positive control.

2. Materials and methods

Scheme 1

2.1. Synthesis of substituted *trans* stilbenes

The synthesis of 56 substituted *trans* (E)-stilbenes (Table 1) was accomplished using Horner-Wadsworth-Emmons (HWE) olefination chemistry.²⁴ The starred compounds in Table 1 are new to the literature, and their synthesis is described in Scheme 1.²⁵ Synthesis of the other compounds in Table 1 was accomplished using a method reported previously.²¹ HWE chemistry was used to avoid formation of a mixture of E and Z isomers and formation of triphenylphosphine oxide, which complicates the purification process.

The required phosphonate ester starting materials were prepared in high yields by the classical solvent free Michaelis-Arbuzov reaction of substituted benzyl chlorides or bromides with triethylphosphite at 130°C.²⁶ Removal of excess triethylphosphite and chloroethane or bromoethane product was carried out by vacuum distillation. Further purification using a short silica gel column and eluting with ethyl acetate/hexane provided pure phosphonate esters as oils.²⁷

Reaction of the appropriately substituted diethyl benzylphosphonate ester with a corresponding freshly distilled substituted benzaldehyde in dry tetrahydrofuran using sodium hydride as the base (Scheme 1) afforded the 20 new substituted stilbenes (Table 1) exclusively in the E conformation. There was no detectable Z isomer, and the *trans* geometry of the substituted stilbenes was confirmed by the coupling constants of approximately 16.5 Hz for the olefinic protons in the proton NMR spectra. The reaction conditions allowed for a straightforward workup since the diethylphosphoric acid byproducts are water-soluble and were easily removed by extraction. Purification of the benzaldehydes and phosphonate esters was found to be critical for obtaining good yields and pure products.

Table 1

3. Results and discussion

3.1. Activation of Nrf2 by resveratrol, LD55 and sulforaphane

Resveratrol, **LD55** and sulforaphane were compared in an Nrf2-ARE reporter-HepG2 stable cell line, which was designed for use as a luciferase reporter-based assay for activators of Nrf2. The ability of both resveratrol and **LD55** to activate Nrf2 signaling extends the known activities of these two *trans* stilbenes to include both anti-inflammatory activities as inhibitors of the pro-inflammatory NF- κ B signaling pathway as well as anti-oxidative stress activities as activators of Nrf2. It is noteworthy that the extent of activation of Nrf2 differs for these three activators (Table 2). **LD55** was 5-fold better than resveratrol in the extent of Nrf2 activation. Concentrations that produced 50% activation (EC_{50}) were obtained from dose-response curves. Resveratrol and **LD55** show low EC_{50} values (5.4 μ M), comparable to sulforaphane (1.2 μ M) (Table 2). The fact that these activators of Nrf2 can vary both in their EC_{50} values and in the extent of activation requires that both of these factors be considered in evaluation of the activities of Nrf2 activators.

3.2. Activation of Nrf2 by monofluoro *trans* stilbenes

A library of substituted *trans* stilbenes was screened to identify activators of Nrf2. With few exceptions, such as resveratrol, only compounds with fluorine or methoxy substituents showed significant activity. From this screen, a group of 56 substituted *trans* stilbenes was identified as activators of Nrf2. A series of monofluoro *trans* stilbenes was compared with resveratrol and **LD55**. The series was screened at 15 μ M concentrations of the compounds, a concentration that did not produce any solubility problems and was sufficiently higher than the EC_{50} values to allow a comparison of the differing extents of activation (Table 2). All of these monofluoro *trans* stilbenes were activators of Nrf2, although the extent of activation varied almost 20-fold. Many of the compounds were better Nrf2 activators than sulforaphane and were much better than resveratrol. The EC_{50} values for these monofluoro *trans* stilbenes ranged from 0.7 μ M (*trans* stilbene **2**) to 12.4 μ M (*trans* stilbene **4**). Comparison of *trans* stilbenes **2**, **3** and **4**, all of which contain a single fluorine substituent on one of the aromatic rings and no substituent on the other ring, suggests that fluorine substitution in the ortho position, as in **LD55**, is preferred. However, this is not consistently observed. Comparison of **LD55** with **5** and **6**, all of which contain a para methoxy substituent, shows little effect of altering the position of the fluorine on EC_{50} values which ranged from 4.2 to 8.9 μ M (Table 2). Likewise, altering the positions of both the fluorine and methoxy substituents as in **LD55**, **5**, **6**, **10-13**, all of which are isomers, has a modest effect with EC_{50} values ranging from 2.3 to 8.9 μ M. The extent of activation, however, differs markedly. For example, isomer **10** is activated almost 10-fold more than isomer **6** (Table 2).

Replacing the methoxy substituent with a methyl substituent (**7**, **8** and **9**) lowers EC₅₀ to low or even sub-micromolar values.

Table 2

3.3. Activation of Nrf2 by polyfluoro *trans* stilbenes

A series of polyfluoro *trans* stilbenes was compared with resveratrol and **LD55**. EC₅₀ values ranged from 0.3 to >15 μ M (Table 3) and extent of activation varied about 5-fold, with all of these stilbenes better than resveratrol with respect to fold activation. As with the monofluoro *trans* stilbenes, the location of the fluorine substituents markedly affected EC₅₀ values and fold activations, but not in readily predictable patterns. For example, EC₅₀ for the difluoro *trans* stilbene **33** is sub-micromolar (0.65 μ M) while EC₅₀ for its isomer **25** is >15 μ M. Likewise, the EC₅₀ for the trifluoro *trans* stilbene **34** is sub-micromolar (0.3 μ M) while EC₅₀ for its isomer **24** is >15 μ M. Multiple trifluoro isomers (**34**, **35**, **38**) exhibited sub-micromolar EC₅₀ values. Isomer **34** was the most effective activator when expressed as fold activation divided by EC₅₀. The conclusion from the data in Tables 2 and 3 is that all of these fluorine substituted *trans* stilbenes demonstrate measurable activity as activators of Nrf2.

Table 3

3.4. Activation of Nrf2 by nonfluoro *trans* stilbenes

A series of substituted *trans* stilbenes, most of which contained methoxy groups at one or more positions, demonstrated activity as activators of Nrf2, as shown in Table 4. EC₅₀ values ranged from 0.8 μ M (*trans* stilbene **56**) to >15 μ M. All of these *trans* stilbenes were as good as or better than sulforaphane with respect to fold activation and were much better than resveratrol. Compounds **51** and **54** demonstrated the highest fold activations of all of the *trans* stilbenes, 69 and 65.5 fold, respectively. The results from this study support the conclusion that the stilbene scaffold is a useful structure upon which to explore chemical space to develop activators of Nrf2, especially those that include fluorine and methoxy functional groups as in **LD55**.

Table 3

The importance of inflammation and oxidative stress in many chronic diseases supports the concept that activation of anti-oxidant Nrf2 signaling may have therapeutic potential. Cells have developed complex adaptive responses to oxidative stress to maintain redox homeostasis and to reduce oxidative stress.⁴⁵ Stress activation of Nrf2 may be the result of exposure to xenobiotics, including many natural products.⁴⁶ Many of these Nrf2 activators are electrophiles. One of the

major mechanisms of Nrf2 activation is through covalent modification of select cysteine sulfhydryl residues in Keap1. Numerous Nrf2-activating chemicals, including natural products such as sulforaphane, are electrophiles that modify Keap1, often by Michael addition.⁴⁷⁻⁴⁹ Cysteine residues 273, 288 and 151 appear to be especially important targets, as determined by site-directed mutagenesis. Resveratrol and other natural product phenols activate Nrf2 after oxidation to electrophilic quinones that contain Michael acceptor functionalities.⁴⁹ Moreover, some natural product phenols including resveratrol can activate Nrf2 by additional mechanism, such as increasing the level of Nrf2 mRNA.⁴⁹

A number of Nrf2 activators have entered into clinical trials. Bardoxolone methyl, an oleanolic acid-derived synthetic triterpene, is a potent Nrf2 activator that was evaluated for its ability to slow progression to end-stage renal disease in patients with type 2 diabetes and stage 4 chronic kidney disease. Bardoxolone methyl is able to modify Keap1 as a Michael acceptor. The clinical trial was terminated in phase III owing to an increase in heart failure.⁵⁰ Dimethyl fumarate, a simple derivative of the metabolic intermediate fumaric acid, has recently been FDA-approved for the treatment of relapsing-remitting multiple sclerosis.⁵¹ Dimethyl fumarate is active as the monomethyl derivative formed by the action of non-specific esterases. Monomethyl fumarate modifies Keap1 through electrophilic addition. For both bardoxolone methyl and dimethyl fumarate, however, mechanisms in addition to modification of Keap1 may play a role in activation of Nrf2.

One concern with the design of Nrf2 activators that are electrophilic covalent modifiers of Keap1 is the issue of selectivity. Bardoxolone methyl, for example, has been shown to react with multiple targets.⁵² To address this concern, a number of recent studies have focused on development of non-electrophilic activators of Nrf2,⁵³ aided by the availability of the crystal structures of the BTB domain of Keap1, which contains residue cysteine151 that is the target for covalent modification by bardoxolone methyl,⁵⁴ the Kelch domain of Keap1⁵⁵ and the Keap1-Nrf2 interface.⁵⁶ Peptide inhibitors of the Keap1-Nrf2 protein-protein interaction have been described^{57,58} as well as a variety of small molecules that inhibit the Keap1-Nrf2 interaction.⁵⁹⁻⁶²

There are additional mechanisms for activation of Nrf2. Epigenetic modifications of CpG methylation status of Nrf2 by the anti-cancer drug 3,3'-diindolylmethane resulted in enhanced expression of Nrf2 and of Nrf2-target genes in cell-based studies.⁶³ This was suggested as an explanation for the chemopreventive activity of this drug. The promoter of the gene encoding Nrf2 contains XRE sequences, which can recruit the aromatic hydrocarbon receptor AhR; this allows the Nrf2 gene to be activated by polycyclic aromatic hydrocarbons.⁶⁴ The promoter of the Nrf2 gene also contains ARE-like sequences, which allows Nrf2 to regulate its own expression.⁶⁵ The Nrf2 promoter also contains an NF- κ B binding site, which allows activation of Nrf2 by pro-inflammatory stimuli.⁶⁶

The autophagy cargo receptor and signaling adaptor protein p62 contains a binding site for Keap1. The attraction of Keap1 to this site is further regulated by phosphorylation by mTORC1, which leads to autophagosome –mediated destruction of Keap1 and activation of Nrf2.^{67,68} This is one example of proteins other than Nrf2 that interact specifically with Keap1, which indicates a broad role for Keap1 and a complex set of mechanisms that impact Nrf2 levels.⁶⁹ There are, therefore, numerous targets for potential activators of Nrf2.

In the present study, we identified numerous substituted *trans* stilbenes as activators of Nrf2, especially *trans* stilbenes with fluorine and/or methoxy ring substituents. The double bond in the *trans* stilbene scaffold is generally a low-reactivity center which would be unlikely to modify Keap1 by electrophilic addition. It remains to be determined which site(s) is the target for activation of Nrf2 by substituted *trans* stilbenes. Likewise, it remains to be determined how different *trans* stilbenes produce markedly different fold activations, which likely involves multiple mechanisms.

4. Conclusions

Substituted *trans* stilbenes represent promising compounds for the development of potential drugs that target oxidative stress in chronic diseases, through activation of the anti-oxidant Nrf2 signaling pathway.

5. Experimental

5.1. Reporter Assay:

A Nrf2-ARE reporter-HepG2 stable cell line (BPS Bioscience, San Diego, CA) is grown in a humidified atmosphere at 37°C in 5% CO₂/95% air. The cells are maintained in MEM medium with Earles balanced salts and L-glutamine supplemented with 10% fetal bovine serum (FBS), 1 mM sodium pyruvate, 1% non-essential amino acids, 100 units/ml penicillin, 100 µg/ml streptomycin, and 400 µg/ml Geneticin. One day prior to treatment, the Nrf2-ARE cells are plated into 24-well cell culture plates at approximately 30% confluency in the above media without Geneticin. The following day, fresh media with or without substituted *trans* stilbene or sulforaphane is applied to the cells. DMSO concentrations are kept at 0.1%. The cells are again placed in a humidified atmosphere at 37°C in 5% CO₂/95% air for 5 hours. Plate wells are gently washed with phosphate buffered saline (PBS) pH 7.4 and lysed with 1x passive lysis buffer (Promega, Madison, WI, USA). The subsequent lysates are analyzed with the Luciferase Assay System (Promega) utilizing a GloMax 20/20 luminometer (Promega, Sunnyvale, CA, USA). The firefly luciferase relative light units are normalized to protein (mg/ml) with BCATM Protein Assay Kit protein (Pierce, Rockford, IL, USA)

5.2. Synthesis:

Reagents were purchased from commercial sources (Aldrich, Acros). Tetrahydrofuran was distilled from lithium aluminum hydride. Thin layer chromatography was carried out on silica gel 60F254 plates. All compounds were shown to be > 98% pure by ^1H NMR and/or ^{13}C NMR unless otherwise noted. Column chromatographic separations were performed by using EM type 60 silica gel (230-400 mesh). Melting points were taken on a Thomas-Hoover Uni-Melt capillary melting point apparatus and reported uncorrected. Unless otherwise noted, ^1H spectra were recorded by using CDCl_3 solutions at 300 MHz; ^{13}C NMR spectra were recorded in CDCl_3 at 75 MHz; ^{19}F were recorded in CDCl_3 at 282 MHz. Chemical shifts are reported in ppm relative to CDCl_3 at 7.24 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR and the external standard hexafluorobenzene for ^{19}F NMR at -164.9 ppm. Peak assignments were made with the aid of DEPT spectra. ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet), coupling constant (J in Hz) and integration. High resolution mass spectra (HRMS) were obtained at the UNM Mass Spectrometry Facility, Albuquerque, New Mexico.

General Procedure for Synthesis of Phosphonate Esters

Benzyl chloride or benzyl bromide derivatives (1eq) were added to triethylphosphite (1.5 eq) and heated to 130°C for 20 h. After cooling, the resulting crude product was distilled in vacuo to remove excess triethylphosphite and ethyl chloride or ethyl bromide. Purification by filtration through a pad of silica gel (70% ethyl acetate/30% hexanes) gave the phosphonate ester products as colorless oils.

General Procedure for Synthesis of Stilbenes

The appropriately substituted phosphonate ester (10 mmol) was dissolved in dry tetrahydrofuran (20 ml) and stirred at 0-5°C. Sodium hydride (25 mmol) was added to the solution slowly and after thirty minutes the appropriate freshly distilled aldehyde (10 mmol) in tetrahydrofuran (30 ml) was added dropwise. The mixture was allowed to stir at room temperature overnight. In order to increase the yield, compounds 35, 37 and 40 were heated under reflux for 3-4 hours. The mixture was cooled and quenched with ice water (10 ml) and poured onto ice. Dilute hydrochloric acid (1M) was added until acidic and the solution was extracted with ethyl acetate (4 x 50 ml). The combined organic layers were washed with saturated salt and dried over magnesium sulfate. Filtration and evaporation of the ethyl acetate afforded crude stilbene products as oils or solids. The solids were crystallized from 95% ethanol to afford crystalline stilbenes. The oils were chromatographed on silica gel using methylene chloride to give pure products.

(*E*)-1-Fluoro-2-(2-methoxystyryl)benzene **10**: 98% yield, white crystals; mp 34-35 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.66 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.62 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.54 (d, *J* = 16.6 Hz, 1H), 7.27 (d, *J* = 16.6 Hz, 1H), 7.22 (m, 2H), 7.13 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.05 (dt, *J* = 8.0, 1.3 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 160.5 (d, *J* = 247.7 Hz), 157.2 (s), 129.2 (s), 128.6 (d, *J* = 8.4 Hz), 127.0 (d, *J* = 3.4 Hz), 126.7 (s), 126.5 (s), 126.0 (d, *J* = 12.1 Hz), 125.7 (d, *J* = 3.6 Hz), 124.2 (d, *J* = 3.1 Hz), 121.1 (d, *J* = 4.0 Hz), 120.9 (s), 115.5 (d, *J* = 22.2 Hz), 110.8 (s), 55.7 (s). ¹⁹F (CDCl₃, 282 MHz): δ -116.9 (s, 1F). HRMS (EI) calcd for C₁₅H₁₃FO [M]⁺: 228.0950; found, 228.0950.

(*E*)-1-(3-Fluorostyryl)-2,3-dimethoxybenzene **16**: 98% yield, oil; ¹H NMR (CDCl₃, 300 MHz): δ 7.45 (d, *J* = 16.5 Hz, 1H), 7.27 (m, 3H), 7.23 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.08 (d, *J* = 16.5 Hz, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.96 (m, 1H), 6.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 163.2 (d, *J* = 245.1 Hz), 153.3 (s), 147.3 (s), 140.1 (d, *J* = 7.6 Hz), 131.0 (s), 130.1 (d, *J* = 8.4 Hz), 128.7 (s), 124.3 (s), 124.2 (s), 122.6 (s), 117.9 (s), 114.4 (d, *J* = 21.5 Hz), 112.9 (d, *J* = 21.8 Hz), 111.8 (s), 61.2 (s), 56.0 (s). ¹⁹F (CDCl₃, 282 MHz): δ -111.9 (s, 1F). HRMS (EI) calcd for C₁₆H₁₅FO₂ [M]⁺: 258.1056; found, 258.1058.

(*E*)-1-(4-Fluorostyryl)-2,3-dimethoxybenzene **17**: 87% yield, white crystals; mp 50-51 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.50 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.36 (d, *J* = 16.5 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 16.4 Hz, 1H), 7.04 (m, 3H), 6.83 (d, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 162.4 (d, *J* = 247.1 Hz), 153.2 (s), 147.0 (s), 133.9 (d, 2.9 Hz), 131.4 (s), 128.7 (s), 128.2 (d, *J* = 7.9 Hz), 124.2 (s), 122.8 (s), 117.8 (s), 115.6 (d, *J* = 21.6 Hz), 111.5 (s), 61.1 (s), 55.8 (s). ¹⁹F (CDCl₃, 282 MHz): δ -112.7 (s, 1F). HRMS (EI) calcd for C₁₆H₁₅FO₂ [M]⁺: 258.1056; found, 258.1060.

(*E*)-2-(4-Fluorostyryl)-1,4-dimethoxybenzene **18**: 74% yield, white crystals; mp 58-59 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.49 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.37 (d, *J* = 16.4 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 7.05 (d, *J* = 16.4 Hz, 1H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.80 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 162.3 (d, *J* = 247.0 Hz), 153.8 (s), 151.4 (s), 134.0 (d, 3.1 Hz), 128.1 (s), 128.0 (d, *J* = 7.7 Hz), 123.1 (s), 115.6 (d, *J* = 21.6 Hz), 113.7 (s), 112.2 (s), 111.7 (s), 56.2 (s), 55.7 (s). ¹⁹F (CDCl₃, 282 MHz): δ -112.9 (s, 1F). HRMS (EI) calcd for C₁₆H₁₅FO₂ [M]⁺: 258.1056; found, 258.1057.

(*E*)-1,2-Difluoro-4-(4-methylstyryl)benzene **22**: 97% yield, white crystals; mp 90-92 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.29 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.13 (m, 2H), 6.99 (d, *J* = 16.4 Hz, 1H), 6.92 (d, *J* = 16.4 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 151.7 (dd, *J* = 69.7, 13.3 Hz), 148.5 (dd, *J* = 70.7, 13.3 Hz), 138.0 (s), 134.9 (t, *J* = 5.0 Hz), 133.9 (s), 129.7 (s), 129.5 (s), 126.5 (s), 125.5 (s), 122.6 (dd, *J* = 6.1, 2.9 Hz), 117.3 (d, *J* =

17.5 Hz), 114.5 (d, $J = 17.6$ Hz), 21.3 (s). ^{19}F (CDCl_3 , 282 MHz): δ -136.3 (d, $J = 20.9$ Hz, 1F), -137.7 (d, $J = 20.9$ Hz, 1F). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2$ $[\text{M}]^+$: 230.0907; found, 230.0911.

(E)-1,4-Difluoro-2-(4-methoxystyryl)benzene **23**: 60% yield, pale yellow crystals; mp 109-110 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.46 (d, $J = 8.6$ Hz, 2H), 7.25 (m, 1H), 7.06 (s, 2H), 6.98 (m, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.86 (m, 1H), 3.81 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 159.8 (s), 159.2 (d, $J = 200.2$ Hz), 156.0 (d, $J = 201.6$ Hz), 131.5 (d, $J = 3.9$ Hz), 129.5 (s), 128.1 (s), 127.0 (dd, $J = 14.5, 8.2$ Hz), 117.6 (s), 116.7 (dd, $J = 25.4, 8.7$ Hz), 114.5 (dd, $J = 24.5, 9.0$ Hz), 114.2 (s), 112.4 (dd, $J = 24.6, 3.8$ Hz), 55.3 (s). ^{19}F (CDCl_3 , 282 MHz): δ -117.7 (d, $J = 17.2$ Hz, 1F), -122.9 (d, $J = 17.2$ Hz, 1F). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}$ $[\text{M}]^+$: 246.0856; found, 246.0852.

(E)-1,2-Difluoro-4-(2-fluorostyryl)benzene **24**: 82% yield, white crystals; mp 85-86 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.56 (dt, $J = 7.7, 1.6$ Hz, 1H), 7.33 (dt, $J = 7.7, 1.8$ Hz, 1H), 7.23 (m, 2H), 7.17 (d, $J = 16.4$ Hz, 1H), 7.10 (m, 3H), 7.05 (d, $J = 16.3$ Hz, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 160.7 (d, $J = 247.9$ Hz), 152.1 (dd, $J = 44.2, 12.0$ Hz), 148.8 (dd, $J = 46.6, 12.0$ Hz), 134.7 (t, $J = 6.2$ Hz), 129.4 (d, $J = 8.4$ Hz), 128.9 (s), 127.3 (d, $J = 3.2$ Hz), 124.7 (d, $J = 11.9$ Hz), 124.4 (d, $J = 2.7$ Hz), 123.1 (dd, $J = 5.3, 3.0$ Hz), 122.3 (s), 117.6 (d, $J = 17.5$ Hz), 116.1 (d, $J = 22.1$ Hz), 115.0 (d, $J = 17.6$ Hz). ^{19}F (CDCl_3 , 282 MHz): δ -116.0 (s, 1F), -136.0 (d, $J = 20.8$ Hz, 1F), -136.8 (d, $J = 21.1$ Hz, 1F). HRMS (EI) calcd for $\text{C}_{14}\text{H}_9\text{F}_3$ $[\text{M}]^+$: 234.0656; found, 234.0652.

(E)-1,2-Difluoro-4-(4-methoxystyryl)benzene **26**: 66% yield, white crystals; mp 73-74 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.41 (d, $J = 8.6$ Hz, 2H), 7.27 (m, 1H), 7.11 (m, 2H), 6.94 (d, $J = 16.5$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 2H), 6.83 (d, $J = 16.5$ Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 159.8 (s), 151.8 (dd, $J = 79.6, 12.7$ Hz), 148.6 (dd, $J = 81.0, 13.2$ Hz), 135.2 (t, $J = 4.9$ Hz), 129.6 (d, $J = 13.0$ Hz), 129.5 (s), 128.0 (s), 124.5 (s), 122.5 (dd, $J = 5.4, 2.8$ Hz), 117.5 (d, $J = 17.4$ Hz), 114.5 (d, $J = 16.0$ Hz), 114.4 (s), 55.5 (s). ^{19}F (CDCl_3 , 282 MHz): δ -136.4 (d, $J = 20.9$ Hz, 1F), -138.1 (d, $J = 20.8$ Hz, 1F). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}$ $[\text{M}]^+$: 246.0856; found, 246.0860.

(E)-1,4-Difluoro-2-(2-fluorostyryl)benzene **29**: 88% yield, white crystals; mp 79-81 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.60 (dt, $J = 7.7, 1.6$ Hz, 1H), 7.27 (s, 2H), 7.26 (m, 2H), 7.13 (dd, $J = 7.6, 1.1$ Hz, 1H), 7.08 (m, 1H), 7.00 (m, 1H), 6.90 (m, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 160.6 (d, $J = 250.4$ Hz), 159.3 (d, $J = 185.2$ Hz), 156.1 (d, $J = 189.0$ Hz), 129.6 (d, $J = 8.5$ Hz), 127.2 (d, $J = 2.9$ Hz), 126.5 (dd, $J = 14.4, 7.9$ Hz), 124.6 (d, $J = 12.0$ Hz), 124.3 (d, $J = 3.3$ Hz), 124.1 (s), 122.0 (s), 116.8 (dd, $J = 25.3, 8.9$ Hz), 115.9 (d, $J = 22.2$ Hz), 115.5 (dd, $J = 24.5, 8.8$ Hz), 112.8 (dd, $J = 24.7, 3.5$). ^{19}F (CDCl_3 , 282 MHz): δ -115.9 (s, 1F), -117.3 (d, $J = 17.2$ Hz, 1F), -122.4 (d, $J = 17.2$ Hz, 1F). HRMS (EI) calcd for $\text{C}_{14}\text{H}_9\text{F}_3$ $[\text{M}]^+$: 234.0656; found, 234.0654.

(*E*)-1,2-Difluoro-4-(3-fluorostyryl)benzene **30**: 95% yield, white crystals; mp 48-49 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.30 (m, 2H), 7.16 (m, 4H), 6.98 (m, 1H), 6.96 (d, *J* = 16.5 Hz, 1H), 6.90 (d, *J* = 16.5 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 163.2 (d, *J* = 245.6 Hz), 152.0 (dd, *J* = 42.1, 11.1 Hz), 148.7 (dd, *J* = 44.7, 11.1 Hz), 139.1, (d, *J* = 7.8 Hz), 134.2 (t, *J* = 5.9 Hz), 130.2 (d, *J* = 8.4 Hz), 128.5 (s), 127.8 (s), 122.9 (dd, *J* = 6.2, 3.6 Hz), 122.6 (d, *J* = 2.3 Hz), 117.5 (d, *J* = 17.5 Hz), 114.9 (d, *J* = 5.3 Hz), 114.7 (s), 112.8 (d, *J* = 21.9 Hz). ¹⁹F (CDCl₃, 282 MHz): δ -111.4 (s, 1F), -135.8 (d, *J* = 20.9 Hz, 1F), -136.5 (d, *J* = 20.8 Hz, 1F). HRMS (EI) calcd for C₁₄H₉F₃ [M]⁺: 234.0656; found, 234.0660.

(*E*)-1,4-Difluoro-2-(3-fluorostyryl)benzene **34**: 89% yield, white crystals; mp 73-74 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.27 (m, 4H), 7.18 (d, *J* = 16.5 Hz, 1H), 7.06 (d, *J* = 16.6 Hz, 1H), 7.01 (m, 2H), 6.91 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 163.2 (d, *J* = 245.7 Hz), 159.3 (d, *J* = 179.4 Hz), 156.0 (d, *J* = 183.7 Hz), 139.0 (d, *J* = 7.7 Hz), 130.8 (s), 130.2 (d, *J* = 8.3 Hz), 126.1 (m), 122.8 (d, *J* = 2.0 Hz), 121.2 (s), 116.9 (dd, *J* = 25.3, 8.8 Hz), 115.5 (dd, *J* = 24.5, 8.7 Hz), 115.1 (d, *J* = 21.6 Hz), 113.1 (d, *J* = 21.9 Hz), 112.8 (dd, *J* = 24.6, 3.8 Hz). ¹⁹F (CDCl₃, 282 MHz): δ -111.5 (s, 1F), -117.3 (d, *J* = 17.2 Hz, 1F), -122.0 (d, *J* = 17.2 Hz, 1F). HRMS (EI) calcd for C₁₄H₉F₃ [M]⁺: 234.0656; found, 234.0659.

(*E*)-2,4-Difluoro-1-(3-fluorostyryl)benzene **35**: 67% yield, white crystals; mp 60-61 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.50 (dd, *J* = 15.0, 8.3 Hz, 1H), 7.23 (m, 3H), 7.16 (d, *J* = 16.5 Hz, 1H), 7.04 (d, *J* = 16.5 Hz, 1H), 6.88 (m, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 163.2 (d, *J* = 245.5 Hz), 163.1 (dd, *J* = 143.9, 12.3 Hz), 159.8 (dd, *J* = 146.1, 12.2), 139.5 (d, *J* = 7.6 Hz), 130.2 (d, *J* = 8.4 Hz), 129.4 (s), 128.0 (dd, *J* = 9.4, 5.0 Hz), 122.5 (d, *J* = 2.2 Hz), 121.3 (s), 121.1 (d, *J* = 3.5 Hz), 114.8 (d, *J* = 21.4 Hz), 112.9 (d, *J* = 21.9 Hz), 11.7 (dd, *J* = 22.0, 3.7 Hz), 104.2 (t, *J* = 25.8 Hz). ¹⁹F (CDCl₃, 282 MHz): δ -108.6 (d, *J* = 6.1 Hz, 1F), -111.6 (s, 1F), -111.7 (d, *J* = 6.3 Hz, 1F). HRMS (EI) calcd for C₁₄H₉F₃ [M]⁺: 234.0656; found, 234.0658.

(*E*)-2,4-Difluoro-1-(2-fluorostyryl)benzene **36**: 70% yield, white crystals; mp 84-85 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.60 (t, *J* = 8.8 Hz, 1H), 7.58 (t, *J* = 8.7 Hz, 1H), 7.25 (s, 2H), 7.22 (m, 1H), 7.13 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dt, *J* = 9.5, 1.3 Hz, 1H), 6.83 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 162.6 (dd, *J* = 250.5, 13.9 Hz), 162.3 (t, *J* = 5.1 Hz), 158.9 (t, *J* = 10.2 Hz), 129.3 (d, *J* = 8.4 Hz), 128.1 (dd, *J* = 9.5, 5.2 Hz), 127.2 (d, *J* = 3.1 Hz), 125.1 (d, *J* = 11.9 Hz), 124.4 (d, *J* = 3.2 Hz), 122.9 (s), 122.2 (s), 121.7 (dd, *J* = 11.7, 3.6 Hz), 116.0 (d, *J* = 22.2 Hz), 111.8 (dd, *J* = 21.6, 3.5 Hz), 104.3 (t, *J* = 25.7 Hz). ¹⁹F (CDCl₃, 282 MHz): δ -108.8 (s, 1F), -112.2 (d, *J* = 5.6 Hz, 1F), -116.4 (s, 1F). HRMS (EI) calcd for C₁₄H₉F₃ [M]⁺: 234.0656; found, 234.0658.

(*E*)-2,4-Difluoro-1-(4-methylstyryl)benzene **37**: 32% yield, white crystals; mp 72-73 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.55 (dd, *J* = 15.0, 8.4 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 16.5 Hz, 1H), 7.07 (d, *J* = 16.5 Hz, 1H), 6.85 (m, 2H), 2.35 (s, 3H). ¹³C

NMR (CDCl₃, 75 MHz): δ 162.9 (dd, J = 131.0, 12.1 Hz), 159.5 (dd, J = 133.5, 12.0 Hz), 137.9 (s), 134.3 (s), 130.5 (s), 129.5 (s), 127.7 (dd, J = 9.2, 5.4 Hz), 126.5 (s), 121.8 (dd, J = 12.5, 3.8 Hz), 118.9 (s), 111.5 (dd, J = 21.5, 2.8 Hz), 104.1 (t, J = 25.7 Hz), 21.4 (s). ¹⁹F (CDCl₃, 282 MHz): δ -109.7 (d, J = 5.3 Hz, 1F), -112.4 (d, J = 4.4 Hz, 1F). HRMS (EI) calcd for C₁₅H₁₂F₂ [M]⁺: 230.0907; found, 230.0912.

(*E*)-1,4-Difluoro-2-(4-fluorostyryl)benzene **40**: 50% yield, buff crystals; mp 76-77 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.48 (dd, J = 8.5, 5.5 Hz, 2H), 7.25 (m, 1H), 7.09 (s, 2H), 7.00 (m, 3H), 6.90 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 162.8 (d, J = 248.3 Hz), 159.2 (d, J = 190.6 Hz), 156.0 (d, J = 192.8 Hz), 132.9 (d, J = 3.0 Hz), 130.7 (d, J = 4.3 Hz), 128.3 (d, J = 8.0 Hz), 126.5 (m), 119.7 (s), 116.8 (dd, J = 25.3, 8.9 Hz), 115.7 (d, J = 21.8 Hz), 115.1 (dd, J = 24.6, 8.9 Hz), 112.7 (dd, J = 24.7, 3.0 Hz). ¹⁹F (CDCl₃, 282 MHz): δ -111.5 (s, 1F), -117.4 (d, J = 17.0 Hz, 1F), -122.5 (d, J = 16.9 Hz, 1F). HRMS (EI) calcd for C₁₄H₉F₃ [M]⁺: 234.0656; found, 234.0659.

(*E*)-1,2-Dimethoxy-3-(4-methylstyryl)benzene **48**: 92% yield, white crystals; mp 38-40 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.43 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 16.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 16.6 Hz, 1H), 7.02 (t, J = 8.2 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 3.83 (s, 6H), 2.34 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 153.1, 146.8, 137.5, 134.9, 131.7, 129.8, 129.3, 126.6, 124.1, 121.9, 117.8, 111.1, 61.0, 55.7, 21.2. HRMS (EI) calcd for C₁₇H₁₈O₃ [M]⁺: 270.1256; found, 270.1258.

(*E*)-1-Methoxy-2-(3-methoxystyryl)benzene **49**: 86% yield, white crystals; mp 49-50 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.55 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 16.5 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.9 Hz, 1H), 7.06 (d, J = 16.6 Hz, 1H), 7.05 (s, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.76 (dd, J = 8.0, 1.9 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.8, 156.9, 139.4, 129.5, 128.9, 128.7, 126.4, 126.2, 123.8, 120.7, 119.3, 113.0, 111.7, 110.9, 55.4, 55.1. HRMS (EI) calcd for C₁₆H₁₆O₂ [M]⁺: 240.1150; found, 240.1156.

(*E*)-1,4-Dimethoxy-2-(3-methoxystyryl)benzene **50**: 96% yield, white crystals; mp 48-49 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.44 (d, J = 16.4 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.10 (m, 3H), 7.05 (d, J = 16.4 Hz, 1H), 6.78 (m, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.9, 153.8, 151.5, 139.3, 129.5, 129.2, 127.1, 123.6, 119.4, 113.8, 113.2, 112.3, 111.8, 111.7, 56.2, 55.7, 55.2. HRMS (EI) calcd for C₁₇H₁₈O₃ [M]⁺: 270.1256; found, 270.1258.

(*E*)-1,2-Dimethoxy-3-(4-(trifluoromethyl)styryl)benzene **54**: 84% yield, white crystals; mp 67-69 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.62 (d, J = 9.3 Hz, 2H), 7.59 (d, J = 9.7 Hz, 2H), 7.54 (d, J = 16.7 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 16.6 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 153.1, 147.3,

141.2, 130.9, 128.3, 126.7, 125.6, 125.5, 124.2, 118.0, 112.0, 61.3, 56.0. ^{19}F (CDCl_3 , 282 MHz): δ -60.9 (s, 3F). HRMS (EI) calcd for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{O}_2$ $[\text{M}]^+$: 308.3002; found, 308.3000.

(E)-1-(4-Isopropylstyryl)-2,3-dimethoxybenzene **55**: 96% yield, oil; ^1H NMR (CDCl_3 , 300 MHz): δ 7.35 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 16.5 Hz, 1H), 7.24 (dd, J = 6.3, 1.6 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 16.5 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.84 (dd, J = 8.1, 1.2 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.94 (sept, J = 6.9 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 153.1, 148.5, 146.8, 135.3, 131.8, 129.8, 126.7, 126.6, 124.1, 122.0, 117.8, 111.1, 61.0, 55.7, 33.9, 23.9. HRMS (EI) calcd for $\text{C}_{19}\text{H}_{22}\text{O}_2$ $[\text{M}]^+$: 282.1620; found, 282.1618.

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Table 1
Structures of (E)-Stilbenes^a

Product	R ₁	R ₂	Reference ^b	Product	R ₁	R ₂	Reference ^b
1	4-OCH ₃	2-F	21	29*	2-F	2,5-diF	-
2	-	2-F	21	30*	3-F	3,4-diF	-
3	-	3-F	21	31	2-F	2,6-diF	35
4	-	4-F	21	32	3-F	3-F	31
5	4-OCH ₃	3-F	21	33	3-F	4-F	36
6	4-OCH ₃	4-F	21	34*	3-F	2,5-diF	-
7	4-CH ₃	4-F	28	35*	3-F	2,4-diF	-
8	4-CH ₃	3-F	28	36*	2-F	2,4-diF	-
9	4-CH ₃	2-F	28	37*	4-CH ₃	2,4-diF	-
10*	2-F	2-OCH ₃	-	38	4-F	2,4-diF	39
11	3-OCH ₃	2-F	29	39	4-F	3,4-diF	39
12	3-OCH ₃	4-F	30	40*	4-F	2,5-diF	-
13	3-OCH ₃	3-F	31	41	-	2,3-diOCH ₃	21
14	3-F	3,4-diOCH ₃	32	42	-	2-OCH ₃	21
15	4-F	3,4-diOCH ₃	33	43	4-OCH ₃	2,4-diOCH ₃	21
16*	3-F	2,3-diOCH ₃	-	44	4-OCH ₃	2-Cl	21
17*	4-F	2,3-diOCH ₃	-	45	4-OCH ₃	3-OH	34
18*	4-F	2,5-diOCH ₃	-	46	4-OCH ₃	3-OCH ₃ , 4-OH	40
19	4-Cl	2-F	29	47	4-CH ₃	3-CF ₃	31
20	4-OH	2-F	34	48*	2,3-OCH ₃	4-CH ₃	-
21	-	2,6-diF	35	49*	3-OCH ₃	2-OCH ₃	-
22*	4-CH ₃	3,4-diF	-	50*	3-OCH ₃	2,5-diOCH ₃	-
23*	4-OCH ₃	2,5-diF	-	51	4-OCH ₃	3-NO ₂	41
24*	2-F	3,4-diF	-	52	-	3-NO ₂	42
25	2-F	3-F	36	53	4-CH ₃	3-NO ₂	43
26*	4-OCH ₃	3,4-diF	-	54*	2,3-diOCH ₃	4-CF ₃	-
27	2-F	2-F	37	55*	2,3-diOCH ₃	4-CH(CH ₃) ₂	-
28	4-F	2-F	38	56	2,4-diOCH ₃	2,5-diOCH ₃	44

^a data for starred compounds is reported in the experimental section

^b melting points and NMR data of known compounds are in agreement with the literature data

Table 2. Activation of Nrf2 by monofluoro *trans* stilbenes

Number	Structure	EC ₅₀ (μM)	Fold activation
Sulforaphane		1.2 ± 0.08	12.4 ± 0.3
Resveratrol		5.4 ± 0.5	3.2 ± 0.2
1 (LD55)		5.4 ± 0.3	14.9 ± 1.2
2		0.7 ± 0.1	10.7 ± 0.6
3		3.1 ± 0.4	4.9 ± 2.3
4		12.4 ± 0.5	4.8 ± 0.3
5		8.9 ± 0.9	3.6 ± 0.2
6		4.2 ± 0.4	1.7 ± 0.1
7		1.3 ± 0.2	1.1 ± 0.2
8		0.8 ± 0.08	4.7 ± 0.03
9		1.4 ± 0.2	10.1 ± 0.5
10		3.1 ± 0.2	18.4 ± 0.6
11		3.8 ± 0.2	14.4 ± 0.4
12		6.0 ± 0.5	4.4 ± 0.8
13		2.3 ± 0.5	15.1 ± 0.8
14		9.5 ± 0.7	5.9 ± 0.7
15		2.6 ± 0.5	1.6 ± 0.02
16		1.9 ± 0.1	19.4 ± 0.5
17		2.9 ± 0.1	16.9 ± 0.5
18		5.1 ± 0.5	10.7 ± 0.5

19		1.6 ± 0.2	5.3 ± 0.05
20		11.4 ± 1.6	13.4 ± 1.3

Table 3. Activation of Nrf2 by polyfluoro *trans* stilbenes

Number	Structure	EC ₅₀ (μM)	Fold activation
21		6.9 ± 0.1	11.4 ± 0.4
22		2.6 ± 0.18	10.2 ± 0.2
23		3.2 ± 0.5	17.0 ± 0.9
24		>15	11.5 ± 2.0 ^a
25		>15	8.5 ± 0.2 ^a
26		>15	4.6 ± 0.6 ^a
27		4.3 ± 0.4	13.9 ± 0.9
28		3.6 ± 0.3	12.7 ± 0.4
29		5.9 ± 0.2	22.3 ± 0.5
30		5.0 ± 0.1	12.2 ± 0.8
31		1.4 ± 0.5	21.2 ± 2.0
32		1.0 ± 0.12	7.0 ± 0.7
33		0.65 ± 0.12	4.5 ± 0.4
34		0.3 ± 0.02	10.7 ± 1.0
35		0.45 ± 0.01	8.2 ± 0.2
36		9.6 ± 0.14	5.0 ± 0.8
37		2.0 ± 0.07	13.5 ± 0.2
38		0.9 ± 0.08	16.8 ± 1.8
39		>15	7.0 ± 0.5 ^a
40		2.9 ± 0.59	11.2 ± 0.1

a. Fold activation at 15 μM

Table 4. Activation of Nrf2 by nonfluoro *trans* stilbenes

Number	Structure	EC ₅₀ (μM)	Fold activation
41		4.7 ± 0.7	25.4 ± 0.1
42		4.4 ± 0.1	23.1 ± 0.6
43		4.6 ± 0.4	15.6 ± 2.0
44		3.1 ± 0.2	17.8 ± 0.7
45		>15	28.1 ± 0.1 ^a
46		3.7 ± 0.5	27.7 ± 1.1
47		1.5 ± 0.5	19.2 ± 1.1
48		1.1 ± 0.2	16.1 ± 2.3
49		4.4 ± 0.2	29.2 ± 1.2
50		>15	15.7 ± 3.2 ^a
51		3.3 ± 0.4	69.0 ± 1.6
52		3.0 ± 0.4	18.6 ± 0.5
53		3.7 ± 0.2	11.9 ± 2.1
54		2.2 ± 0.1	65.5 ± 2.5
55		2.7 ± 0.3	33.9 ± 0.7
56		0.8 ± 0.03	12.9 ± 1.2

a. Fold activation at 15 μM