Challenges associated with the synthesis of unusual *o*-carboxamido stilbenes by the Heck protocol: Intriguing substituent effects, their toxicological and chemopreventive implications†

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The syntheses of fourteen unusual *o*-carboxamido stilbenes by the Heck protocol revealed surprising complexity related to intriguing substituent effects with mechanistic implications. The unexpected cytotoxic and chemopreventive properties also seem to be substituent dependent. For example, although stilbene **15d** (with a 4-methoxy substituent) showed cytotoxicity on HT29 colon cancer cells with an IC_{50} of 4.9 μM, the 3,4-dimethoxy derivative (**15c**) is inactive. It is interesting to observe that the 3,5-dimethoxy derivative (**15e**) showed remarkable chemopreventive activity in WRL-68 fetal hepatocytes, surpassing the gold standard, resveratrol. The resveratrol concentration needed to be 5 times higher than that of **15e** to produce comparable elevation of NQO1.

Introduction

In the fields of creative organic synthesis and medicinal chemistry, the aminostilbenes in general, and the *o*-amidostilbenes in particular, are beginning to attract the attention of the synthetic community.

Stilbene **1** (Fig. 1) prepared by the Stille protocol has been skilfully exploited by the Muñiz group in a novel $Pd(OAc)_2/PhI(OAc)_2$ promoted syntheses bisindolines (incorporating the diazabicyclo [3.3.0] octane skeleton.[1] By contrast, O'Shea[2] has, by means of some imaginative carbolithiation chemistry, transformed the stilbene **2** (prepared by the Suzuki–Miyaura coupling) to quinolines. We, by contrast, have discovered that treatment of the protected acetamido stilbene catecholic ether **3** with $FeCl_3$ gave rise *via* a radical cationic cascade to the indoline and the corresponding C(3)–C(3′) bisindoline.[3,4] By contrast treatment of the resorcinolic ether analogue **4** under the same conditions produced the unprecedented chloroindolostilbenes (incorporating two stereogenic axes).[5]

The intriguing properties of resveratrol **5** (Fig. 2) and questions relating to its mechanism of action *in vivo* have been the focus of intense research activity over the past ten years. Resveratrol, a phytoalexin, has a range of biological characteristics which, as previously stated, include antibacterial, antileukemic and antitumor properties.[6] It also shows chemopreventive behaviour which seems to be associated with its strong antioxidant and anti-inflammatory activities.[7] Resveratrol's low water solubility explains, at least in part, increasing interest in the synthesis and pharmacological evaluation of analogues.

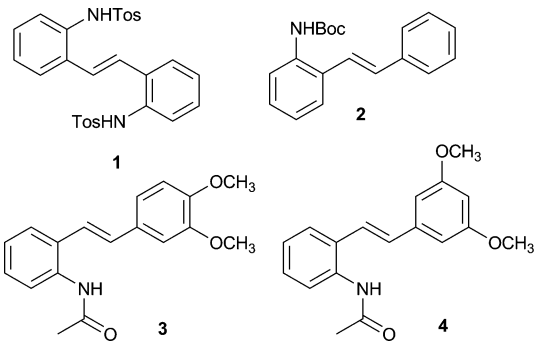

Fig. 1 Examples of *trans* stilbenes.

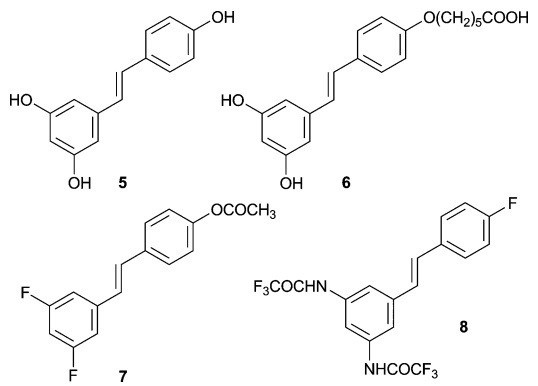

Fig. 2 Examples of biologically active *trans* stilbenes.

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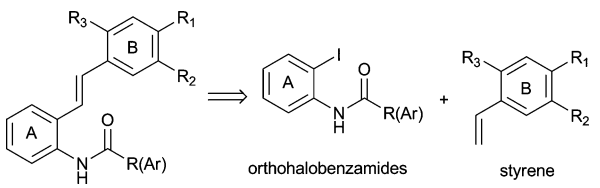
Thus we find that in a recent study,[8] the resveratrol aliphatic acid **6** inhibited cell apoptosis through TLR2 by the involvement of the AKt/GSK3β pathway. Moran *et al.*[9] have synthesized and evaluated fluorinated resveratrol derivatives incorporating nitro groups by the decarbonylative Heck and Wittig procedures. Reduction of the nitro group to the amino function and standard EDC coupling procedures provided aminostilbenes and the corresponding amino acid derivatives respectively. By such procedures, the fluoroacetoxystilbene **7** and the trifluoroacetylamino analogues **8** were prepared. Resveratrol **5** and the fluorinated acetate **7** were the most potent antiproliferative agents with IC_{50} values of 15 ± 3 μM and 10 ± 2 μM. This activity was obtained when these compounds were tested against the non-small lung cell carcinoma cell line DLKP. The (*E*)-3,5-di(trifluroacetylamino)-4′-fluorostilbene **8**, when tested in combination with epirubicin, showed the greatest antiproliferative effect. It was suggested that this synergy may indicate interaction with the multidrug resistant protein, P-glycoprotein (P-gp).[9]

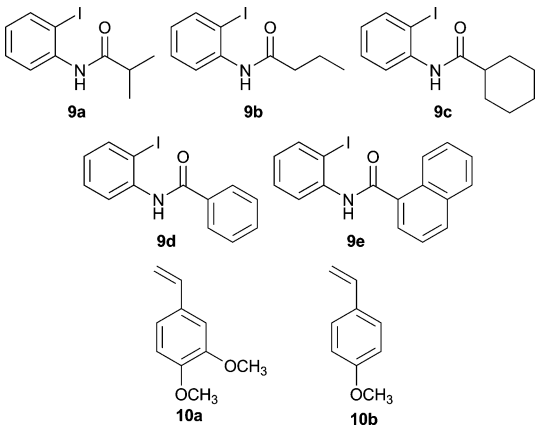
It seemed to us that the synthetic and pharmacological examination of the fourteen *trans*-aminostilbene carboxamides we have described in this report (having the carboxamide moiety at the *ortho* position) could very well fill a gap in the current literature. We were aware, as the reader would glean from our introductory comments, that other published methods for the syntheses of stilbenes including aminostilbenes could have been chosen as alternatives to the mechanistically complex Heck.[10] Nevertheless, imposing new steric and electronic demands on the proposed building blocks for our stilbene synthesis would have an impact on the efficacy of the reaction leading to the stilbenes described in this report and therefore compel us to examine the Heck's highly original mechanistic proposal from a different perspective. This, quite apart from the toxicological questions related to the stilbenes, is of some significance as it would provide an opportunity for us to re-evaluate our own preconceptions regarding the Heck mechanism, not least because this generally accepted mechanism has not been experimentally proven in all the steps.[11]

In our syntheses described herein, structural modifications in the amide moiety (R = methyl, isopropyl, benzyl, furyl, naphthyl), and in the B ring (Scheme 1; R_1 could even be aryl) should be illuminating. This is because variations in the yields of stilbenes resulting from the Heck procedure should enable us to reexamine the traditional Heck mechanism with a view to gaining new insights into this fascinating and important reaction. We believe these stilbene *o*-carboxamides are new chemical entities. In our experience, the structure of the stilbene profoundly affects radical-cationic properties. For this reason and other issues to be addressed later, careful comparative examination of the high resolution NMR spectra of our unusual stilbenes should provide much needed information that will hopefully guide future synthetic/mechanistic and toxicological studies.

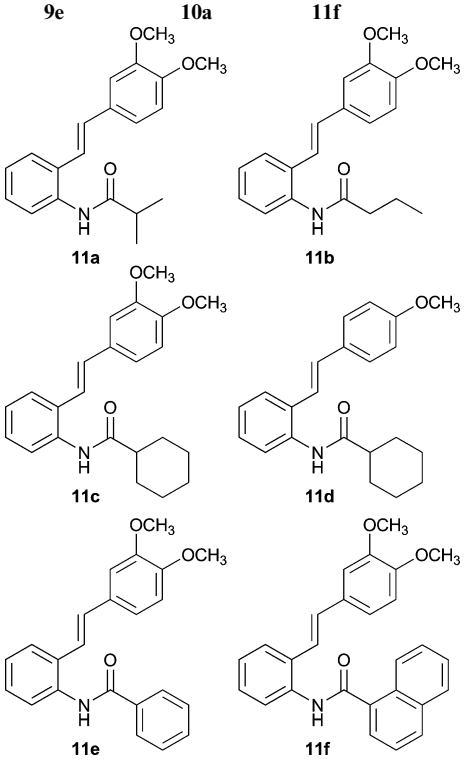


Scheme 1 Retrosynthetic analysis of our stilbene carboxamides.

Table 1 $Pd(OAc)_2$ catalyzed synthesis of stilbene derivatives[a]



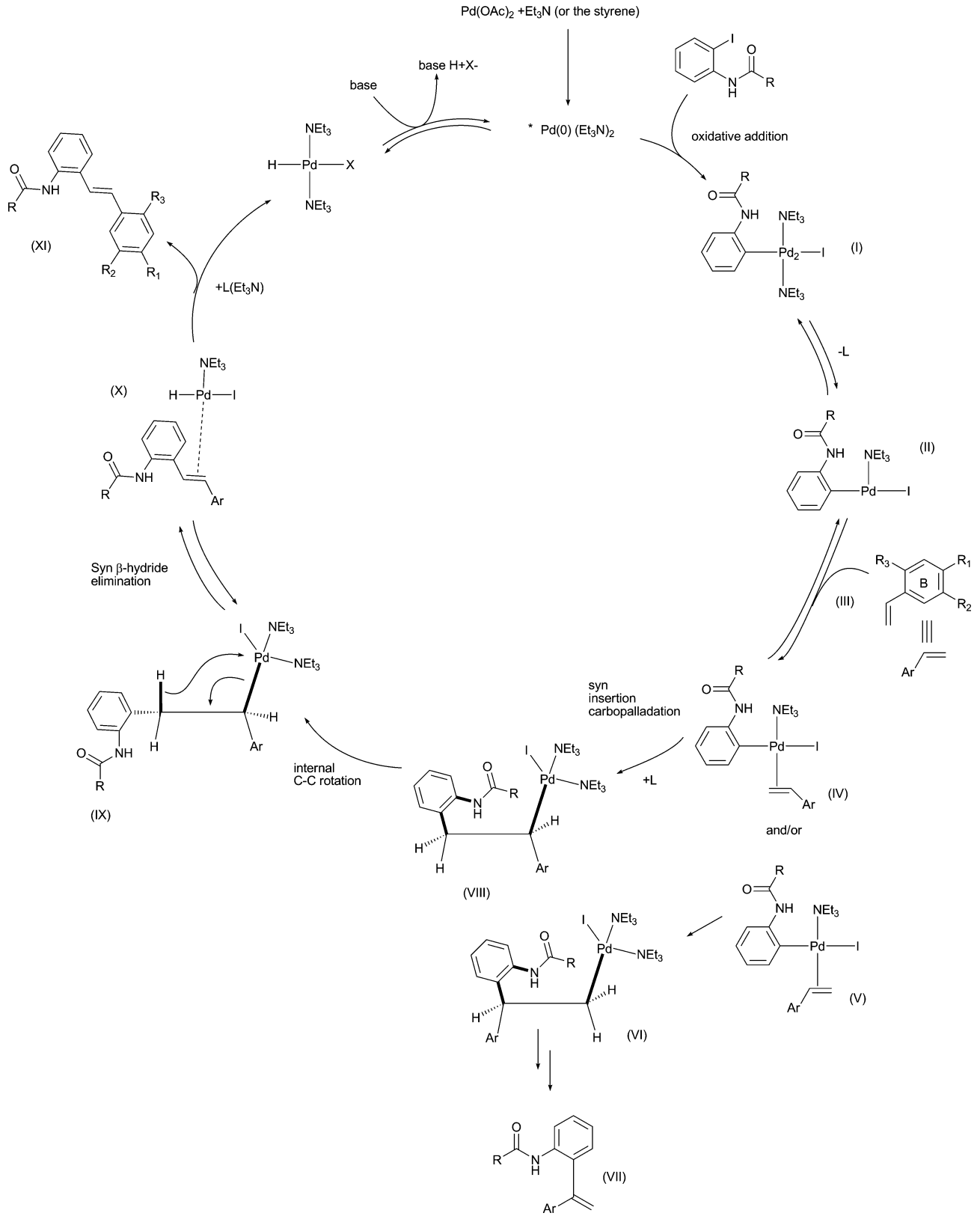
Entry	SM1	SM2	Product	Yield [%]
1	**9a**	**10a**	**11a**	21
2	**9b**	**10a**	**11b**	15
3	**9c**	**10a**	**11c**	31
4	**9c**	**10b**	**11d**	30
5	**9d**	**10a**	**11e**	18
6	**9e**	**10a**	**11f**	27



[a] All reactions were carried out using $Pd(OAc)_2$, Et_3N in DMF at 120 °C for 36 h.

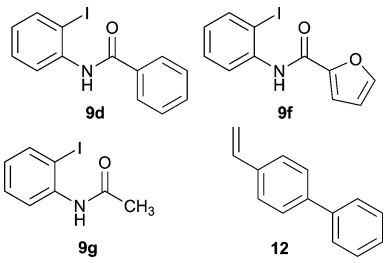
The questions to be addressed among others are:

1. Would the Heck construction (Scheme 2) tolerate structural modifications in the carboxamide moiety? The orthoamidostilbenes synthesized and presented in Tables 1, 2 and 3 show variations in steric bulk and electron-withdrawing tendencies as reflected in the NMR spectra (see electronic supplementary information†). The implications for palladacycle formation are discussed in the mechanistic section.

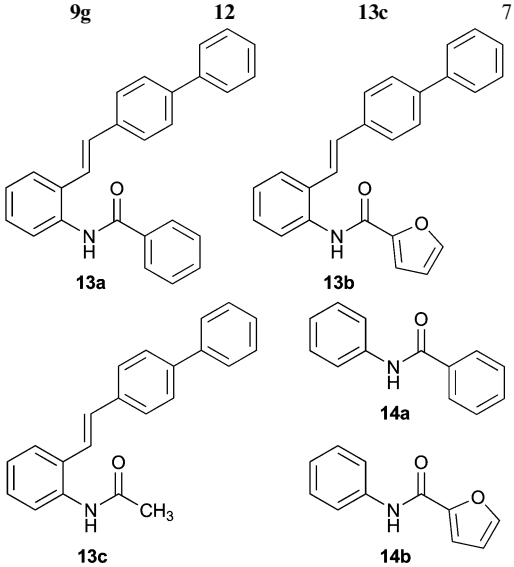


Scheme 2 Application of the traditional Heck mechanism to our stilbene (*Note that for the ionic mechanism, the active form of the catalyst would be $[Pd^0(OAc)(Et_3N)_2]^-$).

Table 2 $Pd(OAc)_2$ catalyzed synthesis of biphenyl stilbene derivatives[a]

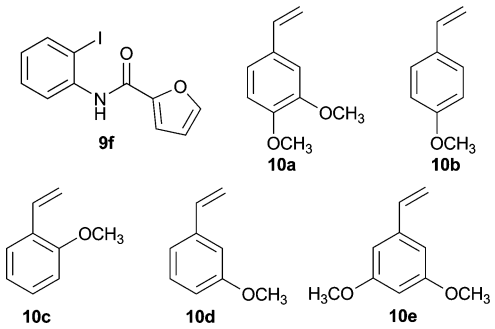


Entry	SM1	SM2	Product	Yield[%]
1	**9d**	**12**	**13a**	31
2	**9f**	**12**	**13b**	9
3	**9g**	**12**	**13c**	7

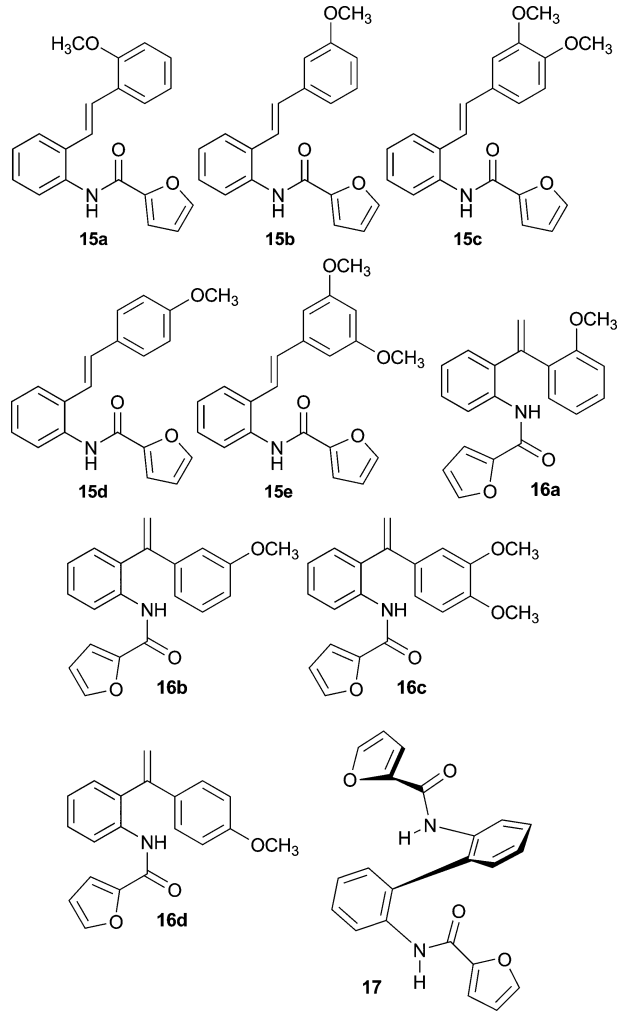


[a] All reactions were carried out using $Pd(OAc)_2$, Et_3N in DMF at 120 °C for 36h. Products **14a** and **14b** were isolated in minute quantities.

Table 3 $Pd(OAc)_2$ catalyzed synthesis of furancarboxamido stilbene derivatives[a]



Entry	Styrene	Major product	Yield [%]	Minor product[b]	Yield [%]
1	**10c**	**15a**	49	**16a**	8
2	**10d**	**15b**	33	**16b**	6
3	**10a**	**15c**	16	**16c**	4
4	**10b**	**15d**	36	**16d**	9
5	**10e**	**15e**	17	—	—



[a] All reactions were carried out using $Pd(OAc)_2$, Et_3N in DMF at 120 °C for 36 h. [b] Minor product **17**[14] was also isolated (average yield was 7%).

2. How would the carboxamide moiety influence the carbopalladation step IV to VIII (Scheme 2) involving electron rich styrenes (as opposed to electron deficient styrenes which are known to be superior coupling partners)?[12]

3. Would electronic and steric differences observed in the various stilbenes, and as indicated by variations in the chemical shift of the NH and olefinic moieties, profoundly affect both structure activity relationships and the oxidative radical cation chemistry?

In examining the traditional Heck reaction (Scheme 2) below as applied to our stilbenes, certain mechanistic questions naturally arise:

1. What is the real structure of intermediate II and if it is cyclic, how does this affect the *syn* insertion step IV to VIII?

2. Fourteen different stilbene carboxamides of generalized structure I (Scheme 2) have been prepared. Is oxidative addition leading to I the rate determining step in all these cases?

3. Following from (1), should E-2 elimination of HPdIL be considered (given the proximity of the electron withdrawing amide moiety) as competing with the more common *syn*-β-hydride elimination (IX, Scheme 2) possibly within a cyclic palladium complex ?

In this report we suggest tentative but thought-provoking answers to some of these questions. We duly embarked on the syntheses and spectroscopic examination described in the next section. Although some X-ray crystallographic details have been published, this is the first full description of the synthetic and

spectroscopic aspects of our study. Biological activities of our stilbenes in several cell lines originating from colon (HT29), liver (HepG2 and WRL-68) and blood (Jurkat and P388) are also described.

Results and discussion

The difficulties encountered in this study are both synthetic and chromatographic. The key C–C bond forming event is the Heck coupling exemplified by Scheme 1. All reaction products in Tables 1, 2, and 3 were subjected to chromatographic purification and all side products (as revealed by TLC) were isolated and characterized. The iodophenylamides (including *ortho*-halobenzamide **9d**)[13] were prepared by exposure of iodoaniline to the corresponding acyl chlorides in Et_3N prior to Heck coupling leading to the first series of stilbenes shown in Table 1.

Our second series of stilbenes were synthesized by coupling of the corresponding *N*-(2-iodophenyl)benzamide **9d**, furan carboxamide **9f** and acetamide **9g** to 4-vinyl biphenyl **12** (Table 2). Our third series (Table 3) are the furancarboxamido stilbenes prepared by Heck coupling of the *N*-(2-Iodophenyl)furancarboxamide **9f** with various substituted styrenes **10a–e**. The geminally functionalized olefins are minor products **16a–d**. Close examination of Tables 1 to 3 reveals certain entries that should be compared as these observations raise interesting mechanistic questions. In Table 1 (entries 3 and 4), notice that the substitution pattern in the styrene has little effect on the yield of the stilbene in contrast to Table 3 (entries 3 and 4), where a doubling in yield is observed as single methoxy substitution in the styrene **10b** replaces dimethoxy substitution in styrene **10a**. In the case of Table 2 (entries 1 and 3), a 22% drop in yield is observed when the benzene ring in **9d** is replaced by a furan ring in **9f**. A full spectroscopic discussion relating to these stilbenes can be found in the supporting information.†

Mechanistic considerations

Although a full mechanistic investigation is outside the scope of this work, we do hope that some of our tentative mechanistic hypotheses could form the basis for future studies. Some general observations relating to variations in yields in the Heck reaction and the effect of the styrene substitution pattern seem appropriate as these may have mechanistic implications. Some kind of "match/mismatch" principle with respect to styrene and iodophenylcarboxamide components must pertain (a phenomenon that has not previously been reported to the best of our knowledge in connection with the Heck reaction).

Within the furancarboxamido stilbene class (Table 3), molecules incorporating a single methoxy group in ring B were generated in yields higher than other compounds of this class with **15a** (having an *ortho* methoxy group in ring B), generated in the highest yield (49%).

It is interesting to note that the furancarboxamido stilbene incorporating the biphenyl **13b** (Table 2) was generated by our Heck procedure in the lowest yields (9%). Furthermore and in complete contrast, replacement of the furan in **9f** with the benzene ring in the iodophenyl amide **9d** (Table 2) which was then "Heck" coupled to the vinylbiphenyl **12** gave the corresponding stilbene **13a** in 31% yield.

It is perhaps significant that the Heck reaction of **9d** with 3,4-dimethoxystyrene **10a** (Table 1) produced the desired stilbene **11e** in 18% yield. With regard to the latter observation, the same Heck procedure is able to generate stilbenes **11c** and **11d** (Table 1) that incorporate bulky cyclohexylamides in ~30% yield irrespective of the presence of 3,4-dimethoxy or 4-methoxy substitution; a pattern that contrasts with furancarboxamido stilbene generation under the same Heck conditions as we previously discussed (see Table 3, entries 3 and 4). One might tentatively suggest that in the latter cases (the furancarboxamido stilbenes) produced by the coupling of 3,4 and 3,5-dimethoxy substituted styrenes respectively, the *syn* insertion into the carboxamide palladium chelate complex (see **27**, Scheme 7 below) is now the rate determining step and this step is sensitive to the styrene substitution pattern. Note the *syn* insertion step, IV to VIII, in Scheme 2.

Clearly there are a number of subtle steric and electronic effects to be evaluated in these reactions from a mechanistic standpoint and our careful consideration of these factors has influenced the particular attention that has been paid to the NMR spectra of the stilbene products. Two other points are worthy of attention.

Firstly, purification/chromatographic complexities should not be overlooked and are a factor, among others, to be taken into consideration where overall yields are concerned. This is particularly true of stilbenes that bear the biphenyl moiety as indicated in Table 2. We have therefore tried to resist the temptation to be dogmatic where mechanistic proposals are concerned.

Secondly, the *N*,*N*-biphenyl-2-carboxamide dimer **17** and the geminally substituted *ene* carboxamide **16a–d** are formed in amounts large enough for characterization only in the case of iodophenylamide **9f** incorporating the furan moiety. **16a–d** and **17** are of course generated in low yields 4–9% and 7% (average) respectively. A possible mechanism for the formation of **17** can be found in the supporting information.†

The Heck coupling is known to proceed with much greater efficiency with alkenes possessing electron-withdrawing groups.[15] The Heck coupling of electron rich styrenes such as ours was therefore always likely to be difficult. The presence of increasingly sterically demanding carboxamides would be expected to exacerbate these difficulties.

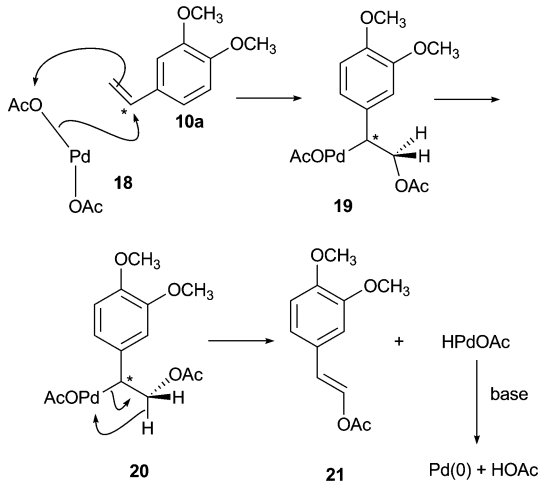
In the following sections, we will attempt (with all due caution) to comment on the mechanistic aspects with one eye on the traditional Heck mechanism (Scheme 2). We will revisit the question of the nature of structure II (Scheme 2), *i.e.* open or cyclic? We will consider alternative modes for the *syn* insertion, *i.e. exo* or *endo*; dehydropalladation (E-2 elimination) within a cyclic palladium complex and dehydropalladation (internal base).

Pd(II) to Pd(0)

The electron rich styrenes (*e.g.* 3,4-dimethoxystyrene **10a**) are capable of reducing Pd(II) to Pd(0) (see Scheme 3). Triethylamine is also an effective reductant for Pd(II).[16] *syn* Dehydropalladation converts **20** to **21** followed by regeneration of Pd(0).

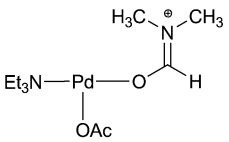
Oxidative addition by Pd(0)

In the course of the synthesis of, for example **15a** (Table 3, entry 1), it is reasonable to suppose that Pd(0) is in the form of **23**.



Scheme 3 Reduction of Pd(II) to Pd(0).

The intermediacy of the cationic complex **22** cannot be ruled out entirely.[16]



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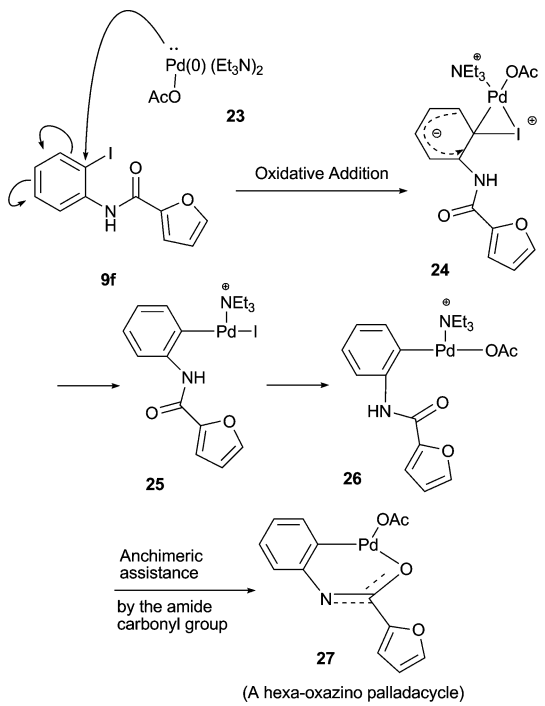
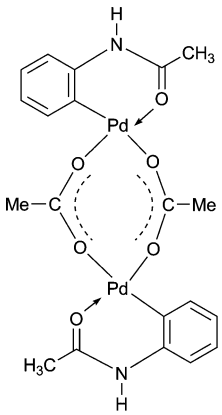
The following proposal (Scheme 4) for the oxidative addition step is reasonable in the light of the electron-withdrawing tendency of furancarboxamide group (compared to other groups).



Scheme 4 Proposed oxidative addition step (**9f** → **24**).[17]

If oxidative addition is accelerated by virtue of the presence of the furancarboxamide, it may help to explain the greater efficiency relatively speaking of stilbene formation from iodophenylcarboxamides (which are more electron withdrawing) – a property reflected in the NMR spectrum of the products **15a**, **15b** and **15d**. This is provided the styrene carries a single methoxy group. It is possible that the iodophenylcyclohexylamide follow a different course and formation of a complex analogous to **27** is prohibited (note the more shielded NH in the spectrum of **11c** and **11d**). On the other hand, the intramolecular complexation described above (see **27**) may well accelerate the oxidative addition step but at the expense of a decelerated alkene coupling (carbopalladation step – which is now the rate determining step). The observation that substituents (with heteroatoms) at the *ortho* position in an aromatic ring are capable of chelating to a Pd species (intramolecularly) is significant here.[15] Intramolecular chelation of an amide to a Pd species at the *ortho* position of a benzene ring has been proposed by Horino and Inoue[18] with relatively little mechanistic comment (Scheme 5). By contrast, we have studied a more diverse range of such carboxamides as Table 3 amply demonstrates. Numerous palladacycles, including **28**,[18] shown below are known to be catalytically active[19] in the Heck reaction.



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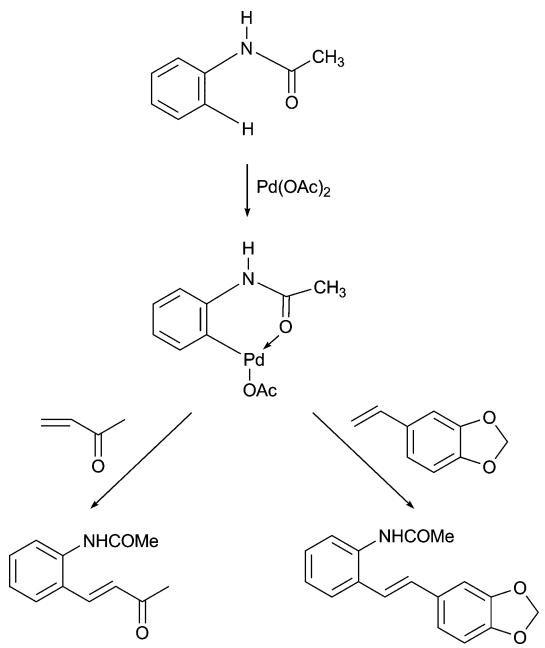
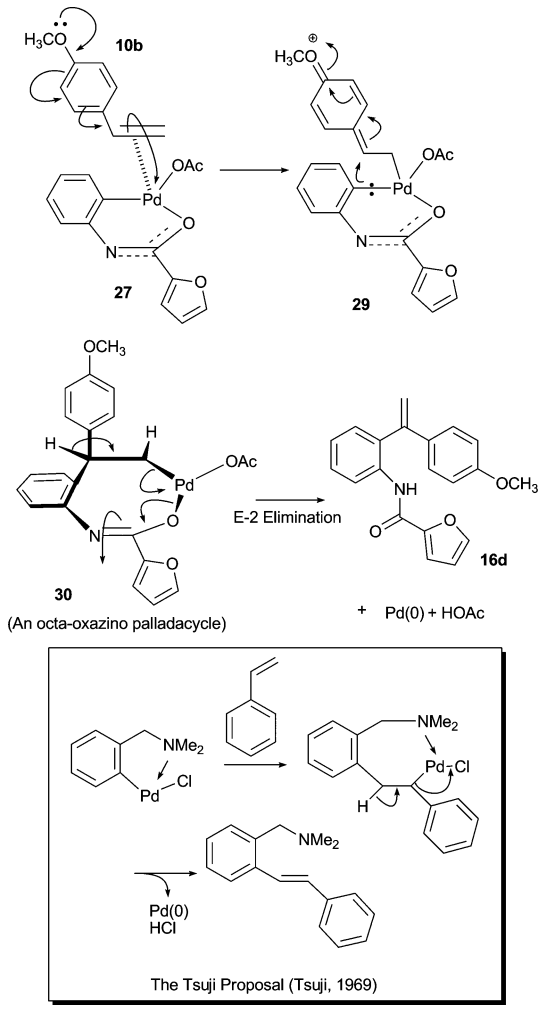


Scheme 5 $Pd(OAc)_2$ mediated construction of styrenes and stilbenes *via* an intramolecular amide/Pd complex leading to *ortho*-vinylation.[18]

Alkene *syn* insertion and the problem of dehydropalladation

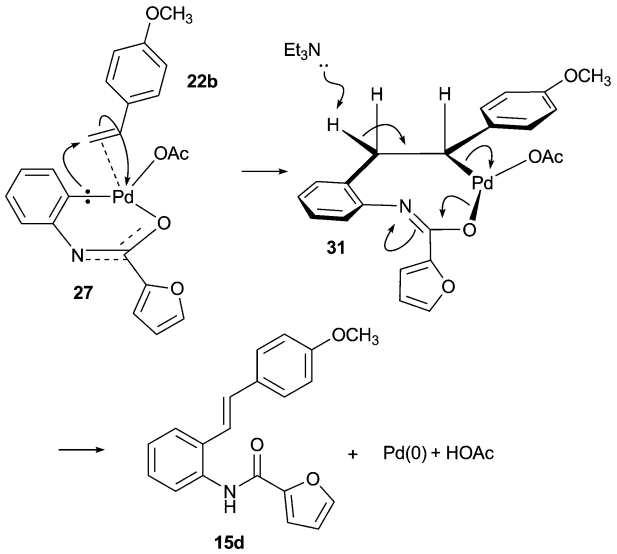
What are the options for a *syn* insertion mechanism? Two modes of addition can be envisaged. The aryl palladium carboxamide complex (or palladacycle) **27** can be attacked by the styrene in either the *endo* mode (Scheme 6) or the *exo* mode (Scheme 7). The E-2 elimination of Pd(0) and HOAc (see **30**, Scheme 6) is analogous to the loss of Pd(0) and HCl described by Tsuji[20] (see Scheme 6).



Scheme 6 *endo* Mode insertion of the styrene into the palladacycle **27** followed by E-2 elimination (**30** to **16d**).

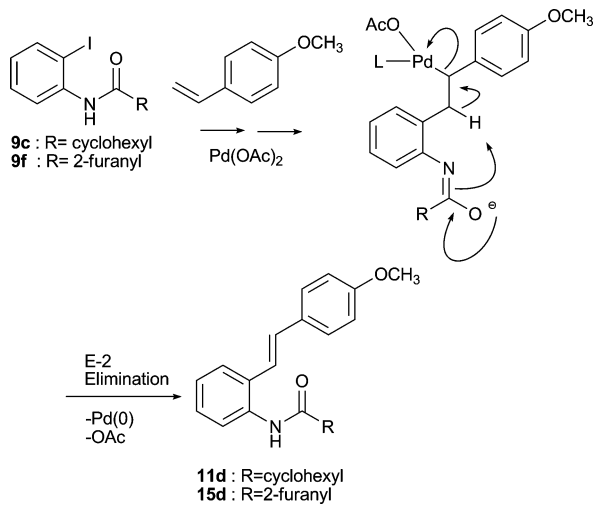
The tantalizing possibility of a based-induced E-2 elimination of PdH (**30**, Scheme 6 or **31**, Scheme 7) (in contrast to the more conventional β-hydride elimination) has been considered in careful review by Beletskaya[19] although in the special and restricted context of the arylation of disubstituted olefins with Hermann's palladacycle catalyst. Beletskaya felt this mechanistic option had a low probability. Whether this pathway, as depicted in the very different setting shown in our chemistry Scheme 7 (for example), is operating requires careful examination beyond the scope of our present studies.

At the present level of knowledge and with respect to the type of stilbenes we are examining, the based promoted *anti*-elimination of PdH (as depicted above) leading to the desired stilbene **15d**



Scheme 7 *exo* Mode insertion of the styrene into the palladacycle **27** followed by E-2 elimination of Pd^0.

(for example) remains, at least, a reasonable hypothesis (and may be in competition with the more conventional pathway). Another possibility is a non-palladacyclic E-2 elimination of PdH as illustrated (see Scheme 8). The "internal" base E-2 elimination does not involve the "internal" palladacycle. The amide moiety (aza-enolate) removes the C-8 proton thus promoting the elimination of HPdOAc. This mechanism might be the preferred path for those iodophenylcarboxamides with less electron withdrawing amides (where the furan ring has been replaced by, for example, cyclohexyl). The steric bulk of the cyclohexyl rings may render complexes analogous to **30** (Scheme 6) and **31** (Scheme 7) less stable than the furan analogues.



Scheme 8 The "internal base" E-2 elimination.

Biological evaluation of the stilbenes

The synthesized stilbenes were evaluated for biological activity in several cell lines originating from colon (HT29), liver (HepG2 and WRL-68) and blood (Jurkat and P388). However the pattern of cytotoxicity varied in these cell lines. The most potent from our

library of compounds was **15d** where the IC_{50}s were 2.2 μM and 4.9 μM in P388 and HT29 cells respectively (Table 4). This is a significant result as the cytotoxicity of *o*-amidostilbenes bearing a furan carboximido moiety had not previously been reported. This result also demonstrates the importance of a methoxy group specifically in the *para* position. However, no cytotoxicity was observed in HepG2 and Jurkat cells up to 100 μM for **15d**. In contrast, **15b** and **15c** showed cytotoxicity of 13.9 μM (HT29) and 48.7 μM (P388) respectively. In addition, **13a** showed a modest cytotoxicity in P388 cell with an IC_{50} of 79.9 μM.

Since some of our stilbenes were not cytotoxic in HepG2 and Jurkat cells, it is possible that these compounds may demonstrate chemopreventive activities including upregulation of detoxifying enzymes such as NAD(P)H: quinone oxidoreductase 1 (NQO1). In this respect, we assessed **15e** on WRL-68 fetal hepatocytes which can be induced to elevate the NQO1 expression. In order to determine the concentrations of **15e** for the NQO1 study, cytotoxicity tests were carried out at three concentrations, namely IC_{10}, IC_{25} and IC_{50} (Fig. 3 and 4).

Our study demonstrated a 2.4 fold increase of NQO1 activity in **15e** (IC_{10}) -treated WRL-68 cells. In contrast, resveratrol, a known chemopreventive stilbene showed similar elevation of NQO1 activity of around 2.6 fold *when cells were treated with 100 μM concentration which was five times higher than **15e***. This was in agreement with Hwang *et al.*[21] whereby the synthesized furan containing compound namely furan-2-yl-3-pyridin-2-yl-propenone has been demonstrated to elevate NQO1.

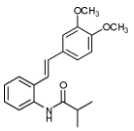
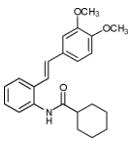
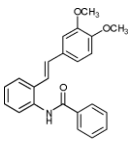
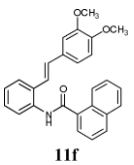
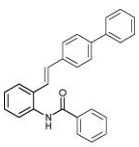
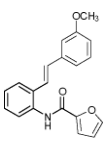
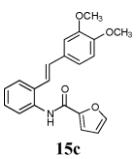
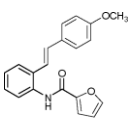
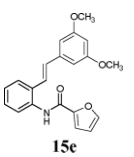
Experimental

Unless otherwise noted, materials were purchased from commercial suppliers and used without purification. THF was freshly distilled from calcium hydride. DMF was dried over molecular sieves 4 Å(Sigma–Aldrich) prior to use. Column chromatography was performed using Merck silica gel (0.040–0.063 mm). For thin layer chromatography, Merck TLC aluminium sheets (silica gel 60 F_{254}) were used; centrifugal chromatography, Merck silica gel 60 PF_{254} containing gypsum was used. Infrared spectra were recorded on a Perkin Elmer FTIR Spectrum RX-1 spectrometer at wavenumbers from 4000–400 cm^{-1}. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL JNM-LA 400 and JEOL ECA-400. Spectra are reported in units of ppm on the scale, relative to chloroform and the coupling constants are given in Hz. Ultra violet (UV) spectra were recorded from wavelength 190–400 nm, in methanol, on a Shimadzu UV-Visible Spectrophotometer 1650. Mass spectra were measured using Agilent 6530 Accurate-Mass Q-TOF LC/MS system. Melting points were determined with Mel-Temp II melting point apparatus. The HT29 experiments were run in Prof. Michael D. Threadgill's laboratory, HepG2, Jurkat and NQO1 experiments were run in Prof. Salmaan Inayat Hussain's laboratory and P388 experiments were run in Prof. Hiroshi Morita's laboratory.

General procedure[22a] for the preparation of compounds 9a–f

To a stirred, cooled (0–5 °C) solution of 2-iodoaniline (1 equiv) and Et_3N (1 equiv) in dry THF (20 ml) a solution of an appropriate acyl chloride (1 equiv) in dry THF (5 ml) was added dropwise. The ice bath was removed and the mixture was stirred vigorously

Table 4 Biological evaluation of selected stilbenes

Stilbene	IC_{50}/μM[a] HT29	HepG2	Jurkat	P388
 **11a**	>100	ND	ND	>100
 **11c**	>100	ND	ND	>100
 **11e**	>100	>100	>100	>100
 **11f**	>100	>100	>100	>100
 **13a**	ND	>100	>100	79.9
 **15b**	13.9	>100	>100	ND
 **15c**	>100	>100	>100	48.7
 **15d**	4.9	>100	>100	2.2
 **15e**	ND	>100	>100	>100

[a] ND = Not determined.

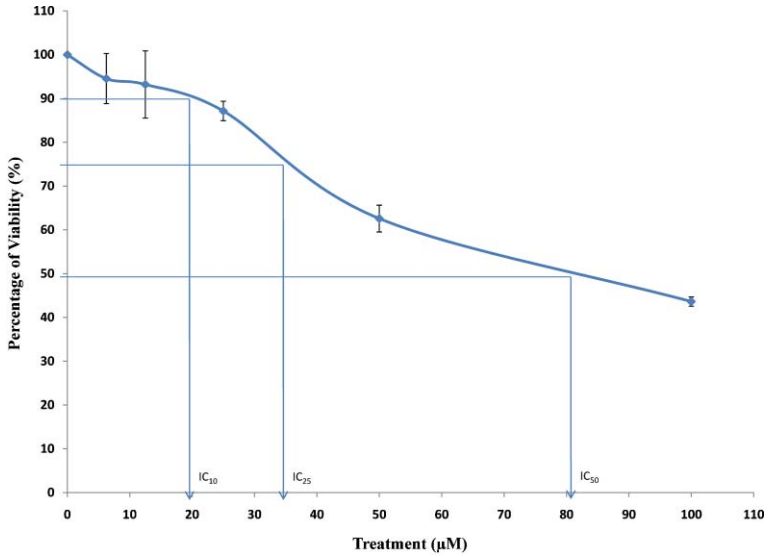


Fig. 3 Cytotoxicity of **15e** in WRL-68 fetal hepatocytes.

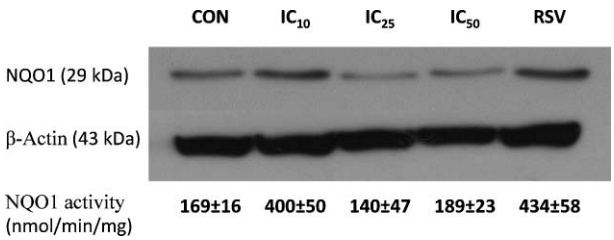


Fig. 4 NQO1 protein expression and activity in **15e** treated WRL-68 fetal hepatocytes. Legend: CON – Vehicle control; IC_{10} – Inhibition concentration 10% (21 μM); IC_{25} – Inhibition concentration 25% (36 μM); IC_{50} – Inhibition concentration 50% (81 μM); RSV – Resveratrol.

overnight at room temperature. The solid $Et_3N{\cdot}HCl$ was filtered off and washed with THF (3 × 5 ml). The resulting organic fractions were combined and THF was removed under reduced pressure to yield crude amides. Recrystallization from hexanes/chloroform and drying under vacuum afforded the desired product.

N-(2-Iodophenyl)isobutyramide (9a)

Off-white solid (5.46 g, 75%); mp 110–111 °C (lit.,[22a] 117–118 °C); δ_H(400 MHz; $CDCl_3$) 8.23 (d, J = 8.0 Hz, H-6, 1H), 7.75 (d, J = 8.1 Hz, H-3, 1H), 7.51 (br s, NH, 1H), 7.32 (t, J = 7.6 Hz, H-4, 1H), 6.82 (t, J = 7.3 Hz, H-5, 1H), 2.59 (septet, J = 7.0 Hz, H-8, CH, 1H), 1.30 (d, J = 6.8 Hz, H-9, H-10, 2 × CH_3, 6H); δ_C(100 MHz; $CDCl_3$) 175.3 (C-7), 138.8 (C-3), 138.2 (C-1), 129.4 (C-4), 125.9 (C-5), 122.0 (C-6), 90.2 (C-2), 37.1 (C-8, CH), 19.7 (C-9, C-10, CH_3).

N-(2-Iodophenyl)butyramide (9b)

Off-white solid (2.00 g, 69%); mp 81–83 °C (lit.,[22a] 83–84 °C); δ_H(400 MHz; $CDCl_3$) 8.22 (d, J = 7.8 Hz, H-6, 1H), 7.76 (dd, J = 8.0 Hz, 1.4 Hz, H-3, 1H), 7.43 (br s, NH, 1H), 7.33 (td, J = 8.0 Hz, 1.4 Hz, H-4, 1H), 6.82 (t, J = 7.8 Hz, H-5, 1H), 2.40 (d, J = 7.6 Hz, H-8, CH_2, 2H), 1.79 (sextet, J = 7.8 Hz, H-9, CH_2, 2H), 1.03 (t, J = 7.3 Hz, H-10, CH_3, 3H); δ_C(100 MHz; $CDCl_3$) 171.3 (C-7), 138.8 (C-6), 138.3 (C-1), 129.4 (C-3), 126.0 (C-4), 122.1 (C-5), 90.0 (C-2), 40.0 (C-8, CH_2), 19.2 (C-9, CH_2), 13.7 (C-10, CH_3).

N-(2-Iodophenyl) cyclohexanecarboxamide (9c)

Off-white solid (6.13 g, 74%); mp 134–136 °C (lit.,[22a] 139–140 °C); δ_H(400 MHz; $CDCl_3$) 8.24 (d, J = 8.2 Hz, H-6, 1H), 7.75 (dd, J = 8.2 Hz, 1.4 Hz, H-3, 1H), 7.51 (br s, NH, 1H), 7.32 (td, J = 7.4 Hz, 1.4 Hz, H-5, 1H), 6.82 (td, J = 7.8 Hz, 1.8 Hz, H-4, 1H), 2.30 (tt, J = 11.7 Hz, 3.4 Hz, H8, CH, 1H), 1.23–2.06 (m, H-9, H-10, H-11, H-12, H-13, CH_2, 10H); δ_C(100 MHz; $CDCl_3$) 174.4 (C-7), 138.8 (C-3), 138.3 (C-1), 129.3 (C-5), 125.9 (C-4), 122.1 (C-6), 90.2 (C-2), 46.7 (C-8, CH), 29.8 (C-9, C-13, CH_2), 25.8 (C-10, C-11, C-12, CH_2).

N-(2-Iodophenyl) benzamide (9d)

Yellowish solid (6.55 g, 81%); mp 135–137 °C (lit.,[13a] 133–134 °C); δ_H(400 MHz; $CDCl_3$) 8.46 (d, J = 8.3 Hz, H-6, 1H), 8.30 (br s, NH, 1H), 7.96–7.98 (m, H-9, H-13, 2H), 7.82 (dd, J = 7.9 Hz, 1.5 Hz, H-3, 1H), 7.51–7.61 (m, H-10, H-11, H-12, 3H), 7.41 (td, J = 7.8 Hz, 1.5 Hz, H-5, 1H), 6.89 (td, J = 7.7 Hz, 1.5 Hz, H-4, 1H); δ_C(100 MHz; $CDCl_3$) 165.4 (C-7), 138.9 (C-3), 138.4 (C-1), 134.6 (C-8), 132.3 (C-11), 129.5 (C-5), 129.0 (C-10, C-12), 127.3 (C-9, C-13), 126.2 (C-4), 121.9 (C-6), 90.3 (C-2).

N-(2-Iodophenyl)-1-naphthamide (9e)

To a stirred, cooled (0–5 °C) solution of 2-iodoaniline (1.06 g, 4.82 mmol) and Et_3N (3.20 ml, 22.96 mmol) in ethyl acetate (50 ml) was slowly added 1-naphthoyl chloride (0.70 ml, 4.66 mmol). The ice bath was removed and the mixture was stirred vigorously overnight at room temperature. The resulting suspension was filtered and the solid was washed with ether (3 × 15 ml) and $NaHCO_3$ aqueous saturated solution (3 × 15 ml) to yield the title compound as a yellow solid (757 mg, 42%); mp 158–160 °C (lit.,[22c] 160–161 °C); δ_H(400 MHz; $CDCl_3$) 8.48–8.52 (m, H-6, H-7′, 2H), 8.08 (br s, NH, 1H), 8.00 (d, J = 8.3 Hz, H-4′, 1H), 7.91 (d, J = 7.3 Hz, H-9′, 1H), 7.86 (d, J = 7.1 Hz, H-6′, 1H), 7.83 (dd,

J = 8.1 Hz, 1.5 Hz, H-3, 1H), 7.52–7.62 (m, H-5′, H-8′, H-10′, 3H), 7.44 (t, J = 7.7 Hz, H-5, 1H), 6.92 (td, J = 7.7 Hz, 1.4 Hz, H-4, 1H); δ_C(100 MHz; $CDCl_3$) 167.4 (C-7), 138.9 (C-3), 138.5 (C-1), 133.9 (C-2′/C-3′), 133.8 (C-2′/C-3′), 131.5 (C-4′), 130.2 (C-1′), 129.3 (C-5), 128.4 (C-9′), 127.4 (C′5′), 126.7 (C-10′), 126.3 (C-4), 125.4 (C-7′), 125.3 (C-6′), 124.8(C′8′), 122.2 (C-6), 90.4 (C-2).

N-(2-Iodophenyl) furan-2-carboxamide (9f)

Yellowish solid (5.49 g, 69%); mp 80–81 °C; ν_{max}(NaCl)/cm^{-1} 3364, 1683, 1582, 1526, 1430, 1304, 1162, 1010 and 750; λ_{max} (MeOH)/nm: 257, 231; δ_H(400 MHz; $CDCl_3$) 8.52 (br s, NH, 1H), 8.39 (dd, J = 8.7 Hz, 1.4 Hz, H-6, 1H), 7.80 (dd, J = 7.8 Hz, 1.4 Hz, H-3, 1H), 7.56 (d, J = 1.4 Hz, H-5′, 1H), 7.36 (td, J = 8.7 Hz, 1.4 Hz, H-5, 1H), 7.26 (d, J = 3.7 Hz, H-3′, 1H), 6.85 (td, J = 7.8 Hz, 1.4 Hz, H-4, 1H), 6.57 (dd, J = 3.6 Hz, 1.8 Hz, H-4′, 1H); δ_C(100 MHz; $CDCl_3$) 156.1(C-7), 147.7 (C-2′), 144.8 (C-5′), 139.0 (C-3), 138.0 (C-1), 129.4 (C-5), 126.1 (C-4), 121.7 (C-6), 115.8 (C-3′), 112.8 (C-4′), 89.9 (C-2); HRMS (+ESI) $[M+H]^+$: 313.9671, $C_{11}H_9INO_2$ requires 313.9672.

N-(2-Iodophenyl)acetamide (9g)

To a stirred, cooled (0–5 °C) solution of 2-iodoaniline (2.53 g, 11.57 mmol) in dry DMF (20 ml), sodium hydride (0.93 g, 23.14 mmol) and acetic anhydride (5.40 ml, 61.75 mmol) were added into the reaction flask. Then the ice bath was removed and the mixture was allowed to stir overnight at room temperature. Saturated ammonium chloride was added to the reaction mixture followed by extraction with ethyl acetate. The combined ethyl acetate extracts were then washed with distilled water to remove DMF. The solution was then filtered and dried over anhydrous sodium sulfate. The crude product, obtained after evaporation under reduced pressure, was purified by column chromatography to give the purified product as yellowish solid (1.82 g, 60%); mp 103–105 °C (lit.,[22a] 111–112 °C); δ_H(400 MHz; $CDCl_3$) 8.17 (d, J = 7.6 Hz, H-6, 1H), 7.75 (d, J = 7.8 Hz, H-3, 1H), 7.40 (br s, NH, 1H), 7.32 (t, J = 7.3 Hz, H-4, 1H), 6.82 (t, J = 7.4 Hz, H-5, 1H), 2.22 (s, CH_3, 3H); δ_C(100 MHz; $CDCl_3$) 168.1 (C-7), 138.8 (C-3), 138.2 (C-1), 129.2 (C-4), 126.0 (C-5), 122.1 (C-6), 90.0 (C-2), 24.8 (CH_3).

General procedure for the preparation of styrenes 10c–e and 12

To a suspension of methyltriphenylphosphonium iodide (1 equiv) in dry THF (25 ml), potassium *tert*-butoxide (1 equiv) was added in one portion. The mixture was stirred for 1 h under nitrogen at −70 to −80 °C. The appropriate aldehyde (1 equiv) was added to the solution. The ice bath was removed and the mixture was allowed to warm to room temperature. After consumption of starting material and product formation, the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 × 30 ml) and washed with distilled water (3 × 30 ml). The resulting organic extracts were combined and solvent was removed under reduced pressure to yield crude product. Purification by column chromatography afforded the desired product.

1-Methoxy-2-vinylbenzene (10c)

Colourless oil (2.83 g, 57%); δ_H(400 MHz; $CDCl_3$) 7.46 (dd, J = 7.8 Hz, 1.8 Hz, H-3, 1H), 7.23 (t, J = 7.8 Hz, H-5, 1H), 7.04 (dd, J = 17.8 Hz, 11.4 Hz, H-7, 1H), 6.93 (t, J = 7.3 Hz, H-4, 1H), 6.87 (d, J = 8.2 Hz, H-6, 1H), 5.73 (dd, J = 17.8 Hz, 1.4 Hz, H-8b, 1H), 5.25 (dd, J = 9.1 Hz, 1.4 Hz, H-8a, 1H), 3.84 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 156.9 (C-1), 131.9 (C-7), 129.0 (C-5), 126.9 (C-2), 126.7 (C-3), 120.8 (C-4), 114.6 (C-8), 111.0 (C-6), 55.6 (OCH_3).

1-Methoxy-3-vinylbenzene (10d)

Colourless oil (2.95 g, 60%); δ_H(400 MHz; $CDCl_3$) 7.26 (t, J = 8.0 Hz, H-5, 1H), 7.03 (t, J = 7.8 Hz, H-4, 1H), 6.98 (s, H-2, 1H), 6.83 (dd, J = 8.2 Hz, 2.8 Hz, H-6, 1H), 6.71 (dd, J = 17.8 Hz, 11.0 Hz, H-7, 1H), 5.77 (d, J = 17.8 Hz, H-8b, 1H), 5.27 (d, J = 11.0 Hz, H-8a, 1H), 3.83 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 159.9 (C-1), 139.1 (C-3), 136.9 (C-7), 129.6 (C-5), 119.1 (C-4), 114.2 (C-8, CH2), 113.5 (C-6), 111.6 (C-2), 55.3 (OCH_3).

1,3-Dimethoxy-5-vinylbenzene (10e)

Colourless oil (2.68 g, 54%); δ_H(400 MHz; $CDCl_3$) 6.66 (dd, J = 17.5 Hz, 10.7 Hz, H-2, 1H), 6.59 (d, J = 2.2 Hz, H-4, H-6, 2H), 6.41 (t, J = 2.3 Hz, H-7, 1H), 5.75 (dd, J = 17.6 Hz, 0.76 Hz, H-8b 1H), 5.26 (dd, J = 10.9 Hz, 0.72 Hz, H-8a, 1H), 3.80 (s, 2 × OCH_3, 6H); δ_C(100 MHz; $CDCl_3$) 160.8 (C-1, C-3), 139.5 (C-5), 136.8 (C-7), 114.2 (C-8, CH_2), 104.2 (C-4, C-6), 99.9 (C-2), 55.1 (2 × OCH_3).

4-Vinylbiphenyl (12)

White solid (0.54 g, 55%); mp 115–117 °C (lit.,[22b] 118–120 °C); δ_H(400 MHz; $CDCl_3$) 7.60 (d, J = 6.8 Hz, H-2, H-6, 2H), 7.57 (d, J = 8.2 Hz, H-2′, H-6′, 2H), 7.49 (d, J = 8.7 Hz, H-3′, H-5′, 2H), 7.44 (t, J = 7.5 Hz, H-3, H-5, 2H), 7.34 (t, J = 7.3 Hz, H-4′, 1H), 6.76 (dd, J = 17.8 Hz, 11.0 Hz, H-7, 1H), 5.80 (d, J = 17.8 Hz, H-8b, 1H), 5.28 (d, J = 11.0 Hz, H-8a, 1H); δ_C(100 MHz; $CDCl_3$) 140.9 (C-1′), 140.7 (C-1), 136.7 (C-4), 136.5 (C-7), 128.9 (C-3′, C-5′), 127.5 (C-4′), 127.4 (C-2′, C-6′), 127.1 (C-2, C-6), 126.8 (C-3, C-5), 114.0 (C-8, CH_2).

General procedure for the preparation of stilbenes 11a–f, 13a–c, and 15a–e

In a dry, two necked flask, the desired *N*-(2-iodophenyl)acylamide **9a–g** (1 equiv) was dissolved in dry DMF (20–25 ml) and stirred under nitrogen. The solution was heated at 120 °C and refluxed for a few minutes. Palladium(II) acetate (0.01 equiv) was added, followed by triethylamine (4–5 equiv). The desired styrene **10a–e** or **12** (1.1–1.6 equiv) was added to the reaction flask. The mixture was refluxed under nitrogen until consumption of **9a–g** (monitored by TLC) was complete. The reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate and washed with distilled water (3 × 30 ml). The resulting organic fractions were combined, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (hexane–ethyl acetate, 8 : 2 for **11a–f**, 9 : 1 for **13a–c**, 6 : 4 for **15a–e**) afforded the desired products. (Note: **10a** (CAS No.: 6380-23-0) and **10b** (CAS No.: 637-69-4) were purchased from Sigma–Aldrich and Merck respectively, and were used without further purification.)

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)phenyl)isobutyramide (11a)

Off-white solid (0.45 g, 27%); mp 166–168 °C; ν_{max}/cm^{-1} (NaCl): 3274, 1652, 1516, 1269, 1141, 1025, 961, 801, 752; λ_{max} (MeOH)/nm: 210, 236, 325; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.74 (d, J = 7.8 Hz, H-6′, 1H), 7.49 (d, J = 7.3 Hz, H-3′, 1H), 7.31 (br s, NH, 1H), 7.24 (t, J = 7.8 Hz, H-5′, 1H), 7.15 (t, J = 7.6 Hz, H-4′, 1H), 7.01 (d, J = 7.8 Hz, H-6, 1H), 7.00 (s, H-2, 1H), 6.97 (d, J = 16.4 Hz, H-8, 1H), 6.90 (d, J = 16.5 Hz, H-7, 1H), 6.85 (d, J = 8.7 Hz, H-5, 1H), 3.89 (s, 2 × OCH_3, 6H), 2.54–2.61 (m, H-8′, 1H), 1.27 (d, J = 6.9 Hz, H-9′, 6H); δ_C(100 MHz; $CDCl_3$) 175.6 (C-7′), 149.3 (C-4), 149.2 (C-3), 134.6 (C-1′), 132.1 (C-7), 130.9 (C-2′), 130.2 (C-1), 128.1 (C-5′), 126.8 (C-3′), 125.7 (C-4′), 124.5 (C-6′), 121.7 (C-8), 120.1 (C-6), 111.3 (C-5), 108.9 (C-2), 56.1 (OCH_3), 55.9 (OCH_3), 36.5 (CH, C-8′), 19.9 (2 × CH_3, C-9′).; HRMS (+ESI) $[M+H]^+$: 326.1759, $C_{20}H_{24}NO_3$ requires 326.1756.

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)phenyl)butyramide (11b)

Off-white solid (0.05 g, 15%); mp 139–140 °C; ν_{max}/cm^{-1} (NaCl): 3280, 2963, 1510, 1267, 1025, 759; λ_{max} (MeOH)/nm: 206, 323; δ_H(400 MHz; $CDCl_3$) 7.63 (d, J = 7.8 Hz, H-6′, 1H), 7.56 (br s, NH, 1H), 7.46 (d, J = 7.8 Hz, H-3′, 1H), 7.18 (t, J = 7.0 Hz, H-5′, 1H), 7.11 (t, J = 7.3 Hz, H-4′, 1H), 6.98 (d, J = 7.8 Hz, H-6, 1H), 6.97 (s, H-2, 1H), 6.95 (d, J = 15.6 Hz, H-8, 1H), 6.85 (d, J = 16.2 Hz, H-7, 1H), 6.81 (d, J = 8.2 Hz, H-5, 1H), 3.86 (s, OCH_3, 3H), 3.85 (s, OCH_3, 3H), 2.31 (t, J = 7.3 Hz, H-8′, CH_2, 2H), 1.69–1.75 (m, H-9′, CH_2, 2H), 0.97 (t, J = 7.3 Hz, H-10′, CH_3, 3H); δ_C(100 MHz; $CDCl_3$) 172.0 (C7′), 149.2 (C-4), 149.1 (C-3), 134.6 (C-1′), 131.6 (C-7), 131.1 (C-2′), 130.3 (C-1), 127.9 (C-5′), 126.5 (C-3′), 125.7 (C-4′), 124.9 (C-6′), 121.8 (C-8), 120.1 (C-6), 111.3 (C-5), 109.1 (C-2), 56.0 (OCH_3), 55.9 (OCH_3), 39.3 (CH_2, C-8′), 19.4 (CH_2, C-9′), 13.9 (CH_3, C-10′).; HRMS (+ESI) $[M+H]^+$: 326.1756, $C_{20}H_{24}NO_3$ requires 326.1751.

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)phenyl)cyclohexane carboxamide (11c)

White solid (0.07 g, 31%); mp 204–206 °C; ν_{max}/cm^{-1} (NaCl): 2930, 2853, 1682, 1515, 1449, 1269, 1137, 1026, 757; λ_{max} (MeOH)/nm: 217, 300; δ_H(400 MHz; $CDCl_3$) 7.77 (d, J = 8.2 Hz, H-6′, 1H), 7.50 (d, J = 7.3 Hz, H-3′, 1H), 7.25 (td, J = 8.0 Hz, 1.4 Hz, H-5′, 1H), 7.21 (br s, NH, 1H), 7.16 (d, J = 7.6 Hz, H-4, 1H), 7.03 (d, J = 7.3 Hz, H-6, 1H), 7.02 (s, H-2, 1H), 6.97 (d, J = 16.5 Hz, H-8, 1H), 6.91 (d, J = 16.5 Hz, H-7, 1H), 6.87 (d, J = 9.2 Hz, H-5, 1H), 3.91 (s, OCH_3, 3H), 3.90 (s, OCH_3, 3H), 2.31 (tt, J = 11.7 Hz, 3.4 Hz, H-8′, CH, 1H), 1.22–2.01 (m, H-9′(x2), H-10′(x2), H-11′,CH2, 10H); δ_C(100 MHz; $CDCl_3$) 174.5 (C-7′), 149.3 (C-4), 149.2 (C-3), 134.6 (C-1′), 132.2 (C-7), 130.8 (C2′), 130.2 (C-1), 128.1 (C-5′), 126.8 (C-3′), 125.6 (C-4′), 124.4 (C-6′), 121.7 (C-8), 120.1 (C-6), 111.3 (C-5), 108.9 (C-2), 56.1 (OCH_3), 55.9 (OCH_3), 46.3 (CH, C-8′), 29.9 (CH_2, C-9′(x2)), 25.8 (C-10′(x2), C-11′); HRMS (+ESI) $[M+H]^+$: 366.2069, $C_{23}H_{28}NO_3$ requires 366.2069.

(*E*)-*N*-(2-(4-Methoxystyryl)phenyl)cyclohexanecarboxamide (11d)

11d crystallized easily during work up. The white solid was filtered off *via* a Kirsch funnel and washed with a small amount of hexane, followed by diethyl ether. Yield 0.47 g (30%). mp 204–205 °C; ν_{max}/cm^{-1} (NaCl): 3271, 2930, 2848, 1648, 1513, 1250, 666; λ_{max} (MeOH)/nm: 283; δ_H(400 MHz; $CDCl_3$) 7.86 (d, J = 8.2 Hz, H-6′, 1H), 7.49 (d, J = 7.8 Hz, H-3, 1H), 7.43 (d, J = 9.2 Hz, H-2, H-6, 2H), 7.26 (td, J = 7.8 Hz, 1.4 Hz, H-5′, 1H), 7.17 (br s, NH, 1H), 7.15 (t, J = 7.3 Hz, H-4′, 1H), 6.99 (d, J = 16.4 Hz, H-8, 1H), 6.94 (d, J = 16.1 Hz, H-7, 1H), 6.92 (d, J = 8.7 Hz, H-3, H-5, 2H), 3.84 (s, OCH_3, 3H), 2.29 (tt, J = 11.9 Hz, 3.6 Hz, H-8′, CH, 1H), 1.23–2.02 (m, H-9′(x2), H-10′(x2), H- 11′, CH_2, 10H); δ_C(100 MHz; $CDCl_3$) 174.4 (C-7′), 159.8 (C-4), 134.7 (C-11′), 132.3 (C-7), 130.5 (C-2′), 129.9 (C-1), 128.1 (C-5′), 128.0 (C-2, C-6), 126.9 (C-3′), 125.3 (C-4′), 123.9 (C-6′), 121.3 (C-8), 114.3 (C-3, C-5), 55.5 (OCH_3), 46.4 (CH, C-8′), 29.9 (CH_2, C-9′(x2)), 25.8 (CH_2, C-10′(x2), C-11′); HRMS (+ESI) $[M+H]^+$: 336.1955, $C_{22}H_{26}NO_2$ requires 336.1958.

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)phenyl)benzamide (11e)

White solid (0.10 g, 18%); mp 169–171 °C; ν_{max}/cm^{-1} (NaCl): 3273, 3012, 1646, 1572, 1509, 1265, 749; λ_{max} (MeOH)/nm: 231, 324; δ_H(400 MHz; $CDCl_3$) 8.03 (br s, NH, 1H), 7.87 (d, J = 7.8 Hz, H-6′, H-9′, H-13′, 3H), 7.51– 7.55 (m, H-3′, H-11′, 2H), 7.44 (t, J = 7.3 Hz, H-10′, H-12′, 2H), 7.28 (t, J = 7.8 Hz, H-5′, 1H), 7.20 (t, J = 7.5 Hz, H-4′, 1H), 7.04 (d, J = 16.0 Hz, H-8, 1H), 6.98 (d, J = 9.2 Hz, H-6, 1H), 6.97 (s, H-2, 1H), 6.93 (d, J = 16.0 Hz, H-7, 1H), 6.82 (d, J = 8.2 Hz, H-5, 1H), 3.86 (s, OCH_3, 3H), 3.83 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 166.0 (C-7′), 149.4 (C-4), 149.2 (C-3), 134.8 (C-8′), 134.7 (C-1′), 132.5 (C-7), 132.0 (C-11′), 131.1 (C-2′), 130.2 (C-1), 128.9 (C-10′, C-12′), 128.2 (C-5′), 127.3 (C-9′, C-13′), 127.0 (C-3′), 125.9 (C-4′), 124.5 (C-6′), 121.7 (C-8), 120.1 (C-6), 111.3 (C-5), 109.1 (C-2), 56.0 (OCH_3), 55.9 (OCH_3); HRMS (+ESI) $[M+H]^+$: 360.1602, $C_{23}H_{22}NO_3$ requires 360.1594.

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)phenyl)-1-naphthamide (11f)

White solid (0.15 g, 27%); mp 175–177 °C; ν_{max}/cm^{-1} (NaCl): 3201, 1640, 1515, 1262, 1140, 1026, 730; λ_{max} (MeOH)/nm: 287, 320; δ_H(400 MHz; $CDCl_3$) 8.42 (dd, J = 5.9, 3.2 Hz, H-5″, 1H), 8.03 (d, J = 7.8 Hz, H-6′, 1H), 7.95 (d, J = 8.2 Hz, H-7″, 1H), 7.89 (dd, J = 5.4, 3.2 Hz, H-9″, 1H), 7.76 (d, J = 8.4 Hz, H-6″, 1H), 7.78 (br s, NH, 1H), 7.58 (d, J = 8.2 Hz, H-3′), 7.52–7.56 (m, H-4″, H-10″, 2H), 7.47 (t, J = 7.6 Hz, H-8′, 1H), 7.36 (t, J = 7.1 Hz, H-5′, 1H), 7.25 (t, J = 7.3 Hz, H-4′, 1H), 7.06 (d, J = 16.5 Hz, H-8, 1H), 6.93–6.99 (m, H-2, H-6, H-7, 3H), 6.79 (d, J = 8.7 Hz, H-5, 1H), 3.86 (s, OCH_3, 3H), 3.77 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 168.0 (C-7′), 149.3 (C-4), 149.1 (C-3), 134.6 (C-1′), 134.4 (C-1″), 133.9 (C-2″), 132.6 (C-7), 131.23 (C-7″), 131.17 (C-2′), 130.3 (C-3″), 130.0 (C-1), 128.6 (C-9″), 128.2 (C-5′), 127.4 (C-4″), 127.0 (C-3′), 126.7 (C-10″), 126.2 (C-4′), 125.4 (C-5″), 125.2 (C-6″), 124.9 (C-8″), 124.4 (C-6′), 121.4 (C-8), 120.2 (C-6), 111.2 (C-5), 109.0 (C-2), 56.0(OCH_3), 55.9 (OCH_3); HRMS (+ESI) $[M+H]^+$: 410.1750, $C_{27}H_{24}NO_3$ requires 410.1756.

(*E*)-*N*-(2-(2-(Biphenyl-4-yl)vinyl) phenyl)benzamide (13a)

White solid (0.06 g, 31%); mp 167–169 °C; ν_{max}/cm^{-1} (NaCl): 3271, 1648, 1517, 1487, 1302, 764; λ_{max} (MeOH)/nm: 319; δ_H(400 MHz; $CDCl_3$) 8.05 (br s, NH, 1H), 7.91 (d, J = 7.3 Hz, H-6′, H-9′, H-13′, 3H), 7.43–7.62 (m, H-2, H-2″, H-3, H-3″, H-6, H-6″, H-5, H-5″, H-4″, H-10′, H-11′, H-12′, 12H), 7.31–7.36 (m, H-3′, H-5′, 2H), 7.22–7.26 (m, H-8, H-4′, 2H), 7.06 (d, J = 16.5 Hz, H-7, 1H); δ_C(100 MHz; $CDCl_3$) 166.0 (C-7′), 140.9 (C-4), 140.6 (C-1″), 136.1 (C-4), 134.8 (C-1′), 134.7 (C-8′), 132.2 (C-7), 132.1

(C-11′), 131.0 (C-2′), 129.0 (C-3″, C-5″, C-10′, C-12′), 128.5 (C-3′), 127.6 (C-4″), 127.5 (C-2″, C-6″), 127.3 (C-9′, C-13′), 127.2 (C-2, C-6), 127.1 (C-12), 127.0 (C-3, C-5), 126.0 (C-4′), 124.7 (C-6′), 123.5 (C-8); HRMS (+ESI) $[M+H]^+$: 376.1691, $C_{27}H_{22}NO$ requires 376.1701.

(*E*)-*N*-(2-(2-(Biphenyl-4-yl)vinyl)phenyl)furan-2-carboxamide (13b)

Yellowish solid (0.04 g, 9%); mp 142–143 °C; ν_{max}/cm^{-1} (NaCl): 3283, 1671, 1585, 1521, 1487, 1452, 1304, 762; λ_{max} (MeOH)/nm: 204, 267, 323; δ_H(400 MHz; $CDCl_3$) 8.19 (br s, NH, 1H), 8.04 (d, J = 7.8 Hz, H-6′, 1H), 7.58–7.64 (m, H-2, H-2″, H-3, H-4″, H-5, H-6, H-6″, 7H), 7.52 (t, J = 0.92 Hz, H-3‴, 1H), 7.44–7.48 (m, H-3″, H-5″, 2H), 7.32–7.38 (m, H-3′, H-5′, 2H), 7.21–7.30 (m, H-8, H-4′, H-5‴, 3H), 7.10 (d, J = 16.5 Hz, H-7, 1H); δ_C(100 MHz; $CDCl_3$) 156.4 (C-7′), 148.0 (C-2‴), 144.5 (C- 5‴), 141.0 (C-1), 140.6 (C-1″), 136.1 (C-4), 134.2 (C-1′), 132.5 (C-7), 130.2 (C-2′), 129.0 (C-3″, C-5″), 128.6 (C-3′), 127.6 (C-4″), 127.5 (C-2″, C-6″), 127.3 (C-2, C-6, C-5′), 127.0 (C-3, C-5), 125.7 (C-4′), 123.7 (C-6′), 123.3 (C-8), 115.6 (C-3‴), 112.7 (C-4‴); HRMS (+ESI) $[M+Na]^+$: 388.1324, $C_{25}H_{19}NNaO_2$ requires 388.1308. X-ray crystallographic details for **13b** have been reported.[23]

(*E*)-*N*-(2-(2-(Biphenyl-4-yl)vinyl)phenyl)acetamide (13c)

White solid (0.04 g, 7%); mp 197–199 °C; ν_{max}/cm^{-1} (NaCl): 3271, 3030, 1668, 1522, 1488, 1450, 1298, 754, 697; λ_{max} (MeOH)/nm: 245, 296; δ_H(400 MHz; $CDCl_3$) 7.75 (d, J = 7.8 Hz, H-6′, 1H), 7.54–7.63 (m, H-2″, H-2, H-4″, H-6, H-6″, NH, 6H), 7.44–7.47 (m, H-3″, H-5″, 2H), 7.25–7.38 (m, H-3, H-5, H-3′, H-5′, 4H), 7.15–7.20 (m, H-8, H-4′, 2H), 7.01 (d, J = 16.5 Hz, H-7, 1H), 2.21 (s, CH_3, 3H); δ_C(100 MHz; $CDCl_3$) 168.8 (C-7′), 140.9 (C-1), 140.6 (C-1″), 136.1 (C-4), 134.7 (C-1′), 132.0 (C-7), 130.6 (C-2′), 129.0 (C-3″, C-5″), 128.5 (C-3′), 127.6 (C-4″), 127.5 (C-2″, C-6″), 127.2 (C-2,C-6), 127.0 (C-3, C-5), 126.9 (C-5′), 125.8 (C-4′), 124.6 (C-6′), 123.6 (C-8), 24.6 (CH_3); HRMS (+ESI) $[M+H]^+$: 314.1540, $C_{22}H_{20}NO$ requires 314.1539. For full crystallographic data refer to CCDC no. 757184.

N-Phenylbenzamide (14a)

Trace amount was isolated. Mp 163–164 °C; δ_H(400 MHz; $CDCl_3$) 7.89 (br s, NH, 1H), 7.86 (d, J = 7.3 Hz, H-9, H-13, 2H), 7.64 (d, J = 8.2 Hz, H-2, H-6, 2H), 7.54 (t, J = 7.3 Hz, H-11, 1H), 7.47 (t, J = 7.5 Hz, H-10, H-12, 2H), 7.36 (t, J = 7.8 Hz, H-3, H-5, 2H), 7.15 (t, J = 7.6 Hz, H-4, 1H); δ_C(100 MHz; $CDCl_3$) 165.9 (C-7), 138.0 (C-1), 135.1 (C-8), 131.9 (C-11), 129.2 (C-3, C-5), 128.9 (C-10, C-12), 127.1 (C-9, C-13), 124.7 (C-4), 120.3 (C-2, C-6).

N-Phenylfuran-2-carboxamide (14b)

Trace amount was isolated. δ_H(400 MHz; $CDCl_3$) 8.14 (br s, NH, 1H), 7.65 (d, J = 7.8 Hz, H-2, H-6, 2H), 7.49 (d, J = 1.8 Hz, H-5′, 1H), 7.35 (t, J = 8.0 Hz, H-3, H-5, 2H), 7.22 (dd, J = 3.6 Hz, 0.92 Hz, H-3′, 1H), 7.13 (t, J = 7.6 Hz, H-4, 1H), 6.54 (dd, J = 3.6 Hz, 1.8 Hz, H-4′, 1H); δ_C(100 MHz; $CDCl_3$) 156.2 (C-7), 147.9 (C-8), 144.3 (C-5′), 137.5 (C-1), 129.2 (C-3, C-5), 124.6 (C-4), 120.0 (C-2, C-6), 115.4 (C-3′), 112.7 (C-4′).

(*E*)-*N*-(2-(2-Methoxystyryl)phenyl)furan-2-carboxamide (15a)

White solid (0.75 g, 49%); mp 128–129 °C; ν_{max}/cm^{-1} (NaCl): 3285, 1671, 1585, 1304, 1247, 751; λ_{max} (MeOH)/nm: 262, 321; δ_H(400 MHz; $CDCl_3$) 8.25 (br s, NH, 1H), 8.04 (d, J = 8.2 Hz, H-6′, 1H), 7.60 (dd, J = 7.8 Hz, 0.92 Hz, H-3′, 1H), 7.56 (dd, J = 7.6 Hz, 1.4 Hz, H-6, 1H), 7.49 (d, J = 0.92 Hz, H-5″, 1H), 7.40 (d, J = 16.5 Hz, H-7, 1H), 7.29 (d, J = 16.8 Hz, H-8, 1H), 7.28–7.33 (m, H-4, H-5′, H-3″, 3H), 7.20 (t, J = 7.1 Hz, H-4″, 1H), 6.98 (t, J = 7.6 Hz, H-5, 1H), 6.91 (d, J = 8.2 Hz, H-3, 1H), 6.55 (dd, J = 3.7 Hz, 1.8 Hz, H-4′, 1H), 3.85 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 157.3 (C-2), 156.4 (C-7′), 148.0 (C-2″), 144.5 (C-5″), 134.1 (C-1′), 130.7 (C-2′), 129.3 (C-4), 128.3 (C-8), 128.2 (C-7), 127.3 (C-6), 127.2 (C-3′), 126.2 (C-1), 125.6 (C-4′), 123.7 (C-5′), 123.5 (C- 6′), 120.9 (C-5), 115.4 (C-3″), 112.7 (C-4″), 111.1 (C-3), 55.5 (OCH_3); HRMS (+ESI) $[M+H]^+$: 320.1285, $C_{20}H_{18}NO_3$ requires 320.1281.

(*E*)-*N*-(2-(3-Methoxystyryl)phenyl)furan-2-carboxamide (15b)

White solid (0.15 g, 33%); mp 96–97 °C; ν_{max}/cm^{-1} (NaCl): 3285, 1669, 1585, 1521, 1304, 1163, 755; λ_{max} (MeOH)/nm: 210, 264, 300; δ_H(400 MHz; $CDCl_3$) 8.17 (br s, NH, 1H), 8.02 (d, J = 8.2 Hz, H-6′, 1H), 7.55 (d, J = 7.8 Hz, H-3′, 1H), 7.50 (d, J = 0.92 Hz, H-5″, 1H), 7.33 (t, J = 7.2 Hz, H-5′, 1H), 7.29 (t, J = 8.0 Hz, H-5, 1H), 7.26 (d, J = 3.2 Hz, H-3′, 1H), 7.22 (d, J = 16.0 Hz, H-8, 1H), 7.21 (t, J = 7.6 Hz, H-4″, 1H), 7.12 (d, J = 7.8 Hz, H-6, 1H), 7.04 (s, H-2, 1H), 7.02 (d, J = 16.5 Hz, H-7, 1H), 6.85 (dd, J = 8.5 Hz, 2.3 Hz, H-4, 1H), 6.56 (dd, J = 3.7 Hz, 1.8 Hz, H-4′, 1H), 3.83 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 160.0 (C-3), 156.4 (C-7′), 147.9 (C-2″), 144.5 (C-5″), 138.5 (C-1), 134.2 (C-1′), 132.9 (C-7), 130.1 (C-2′), 129.9 (C-5), 128.6 (C-5′), 127.3 (C-3′), 125.6 (C-4′), 123.6 (C- 6′, C-8), 119.4 (C-6), 115.6 (C-3″), 113.7 (C-4), 112.7 (C-4″), 112.3 (C-2), 55.4 (OCH_3); HRMS (+ESI) $[M+H]^+$: 320.1281, $C_{20}H_{18}NO_3$ requires 320.1281.

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)phenyl)furan-2-carboxamide (15c)

White solid (0.10 g, 16%); mp 142–144 °C; ν_{max}/cm^{-1} (NaCl): 3239, 1651, 1575, 1514, 1456, 1265, 1157, 1137, 1027, 751; λ_{max} (MeOH)/nm: 210, 252, 326; δ_H(400 MHz; $CDCl_3$) 8.19 (br s, NH, 1H), 8.00 (d, J = 8.2 Hz, H-6′, 1H), 7.52 (d, J = 7.8 Hz, H-3′, 1H), 7.47 (dd, J = 1.8 Hz, 0.92 Hz, H-5″, 1H), 7.29 (t, J = 7.8 Hz, H-5′, 1H), 7.23 (d, J = 2.8 Hz, H-3″, 1H), 7.18 (t, J = 7.8 Hz, H-4′, 1H), 7.07 (d, J = 16.5 Hz, H-8, 1H), 7.05 (d, J = 8.9 Hz, H-6, 1H), 7.03 (s, H-2, 1H), 6.96 (d, J = 16.5 Hz, H-7, 1H), 6.85 (d, J = 8.2 Hz, 2.3 Hz, H-5, 1H), 6.54 (dd, J = 3.4 Hz, 1.8 Hz, H-4″, 1H), 3.89 (s, OCH_3, 3H), 3.88 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 156.4 (C-7′), 149.4 (C-4), 149.2 (C-3), 148.0 (C-2″), 144.5 (C-5″), 134.0 (C-1′), 132.7 (C-7), 130.4 (C-2′), 130.2 (C-1), 128.2 (C-5′), 127.1 (C-3′), 125.6 (C-4′), 123.7 (C-6′), 121.4 (C-8), 120.1 (C-6), 115.4 (C-3″), 112.7 (C-4″), 111.4 (C-5), 109.3 (C-2), 56.1 (OCH_3), 56.0 (OCH_3); HRMS (+ESI) $[M+H]^+$: 350.1411, $C_{21}H_{20}NO_4$ requires 350.1392.

(*E*)-*N*-(2-(4-Methoxystyryl)phenyl)furan-2-carboxamide (15d)

White solid (0.19 g, 36%); mp 120–121 °C; ν_{max}/cm^{-1} (NaCl): 3276, 1669, 1584, 1509, 1251, 755; λ_{max} (MeOH)/nm: 271, 323; δ_H(400 MHz; $CDCl_3$) 8.17 (br s, NH, 1H), 8.04 (d, J = 8.2 Hz,

H-6′, 1H), 7.54 (d, J = 7.8 Hz, H-3′, 1H), 7.50 (d, J = 0.92 Hz, H-5′, 1H), 7.47 (t, J = 7.6 Hz, H-2, H-6, 2H), 7.31 (td, J = 7.3 Hz, 1.3 Hz, H-5′, 1H), 7.26 (d, J = 3.7 Hz, H-3′, 1H), 7.19 (t, J = 7.6 Hz, H-4′, 1H), 7.09 (d, J = 16.5 Hz, H-8, 1H), 7.00 (d, J = 16.5 Hz, H-7, 1H), 6.92 (t, J = 7.6 Hz, H-3, H-5, 2H), 6.56 (dd, J = 3.2 Hz, 1.8 Hz, H-4″, 1H), 3.83 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 159.8 (C-4), 156.3 (C-7′), 148.0 (C-2″), 144.5 (C-5″), 134.0 (C-1′), 132.7 (C-7), 130.4 (C-2′), 129.9 (C-1), 128.2 (C- 5′), 128.1 (C-2, C-6), 127.1 (C-3′), 125.6 (C-4′), 123.5 (C-6′), 121.0 (C-8), 115.5 (C-3″), 114.3 (C-3, C-5), 112.7 (C-4″), 55.5 (OCH_3); HRMS (+ESI) $[M+H]^+$: 320.1302, $C_{20}H_{18}NO_3$ requires 320.1287.

(*E*)-*N*-(2-(3,5-Dimethoxystyryl)phenyl)furan-2-carboxamide (15e)

White solid (0.10 g, 17%); mp 109–110 °C; ν_{max}/cm^{-1} (NaCl): 3282, 1670, 1590, 1520, 1455, 1303, 1204, 1152, 1065, 755; λ_{max} (MeOH)/nm: 239, 269, 308; δ_H(400 MHz; $CDCl_3$) 8.16 (br s, NH, 1H), 8.04 (d, J = 7.8 Hz, H-6′, 1H), 7.54 (dd, J = 7.8 Hz, 1.4 Hz, H-3′, 1H), 7.50 (d, J = 0.92 Hz, H-5″, 1H), 7.33 (td, J = 7.8 Hz, 1.4 Hz, H-5′, 1H), 7.26 (d, J = 3.2 Hz, H-3″, 1H), 7.21 (d, J = 16.0 Hz, H-8, 1H), 7.20 (t, J = 7.5 Hz, H-4′, 1H), 6.99 (d, J = 16.0 Hz, H-7, 1H), 6.66 (s, H-2, H-6, 2H), 6.56 (dd, J = 3.6 Hz, 1.8 Hz, H-4″, 1H), 6.43 (t, J = 1.8 Hz, H-4, 1H), 3.81 (s, 2 × OCH_3, 6H); δ_C(100 MHz; $CDCl_3$) 161.1 (C-3, C-5), 156.3 (C-7′), 147.9 (C-2″), 144.5 (C-5″), 139.1 (C-1), 134.2 (C-1′), 133.0 (C-7), 129.9 (C-2′), 128.6 (C-5′), 127.3 (C-3′), 125.6 (C-4′), 123.9 (C-8), 123.6 (C-6′), 115.6 (C-3″), 112.7 (C-4″), 105.0 (C-2), 100.3 (C-4), 55.9 (2 × OCH_3); HRMS (+ESI) $[M+H]^+$: 350.1412, $C_{21}H_{20}NO_4$ requires 350.1392.

(*E*)-*N*-(2-(1-(2-Methoxyphenyl)vinyl)phenyl)furan-2-carboxamide (16a)

Yield 0.13 g (8%); ν_{max}/cm^{-1} (NaCl): 3390, 1678, 1584, 1526, 1448, 1310, 1245, 754; λ_{max} (MeOH)/nm: 236, 279; δ_H(400 MHz; $CDCl_3$) 8.72 (br s, NH, 1H), 8.37 (d, J = 8.2 Hz, H-6′, 1H), 7.42 (d, J = 0.92 Hz, H-5″, 1H), 7.26–7.32 (m, H-4, H-6, H-5′, 3H), 7.14–7.16 (m, H-3′, H-3″), 7.06 (t, J = 7.3 Hz, H-4″, 1H), 6.96 (t, J = 7.6 Hz, H-5, 1H), 6.84 (d, J = 8.2 Hz, H-3, 1H), 6.50 (dd, J = 3.4 Hz, 1.4 Hz, H-4′, 1H), 5.76 (d, J = 1.8 Hz, H-8b, CH_2, 1H), 5.47 (d, J = 1.8 Hz, H-8a, CH_2, 1H), 3.61 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 156.9 (C-2), 156.1 (C-7′), 148.4 (C-2″), 144.2 (C-5″), 144.0 (C-1′), 134.5 (C-7), 133.5 (C-2′), 130.9 (C-1), 130.1 (C-6), 129.5 (C-4), 129.0 (C-3′), 128.0 (C-5′), 123.9 (C-4′), 121.2 (C-6′), 121.1 (C-8, CH2), 120.9 (C-5), 114.8 (C-3″), 112.5 (C-4″), 111.3 (C-3), 55.5 (OCH_3); HRMS (+ESI) $[M+H]^+$: 320.1284, $C_{20}H_{18}NO_3$ requires 320.1281.

(*E*)-*N*-(2-(1-(3-Methoxyphenyl)vinyl)phenyl)furan-2-carboxamide (16b)

Yield 0.03 g (6%); ν_{max}/cm^{-1} (NaCl): 3389, 1681, 1584, 1527, 1450, 1310, 755; λ_{max} (MeOH)/nm: 210, 250; δ_H(400 MHz; $CDCl_3$) 8.39 (d, J = 8.2 Hz, H-6′, 1H), 8.13 (br s, NH, 1H), 7.39 (t, J = 8.0 Hz, H-5′, 1H), 7.30 (d, J = 1.8 Hz, H-5″, 1H), 7.29 (d, J = 7.8 Hz, H-3′, 1H), 7.22 (d, J = 7.8 Hz, H-5, 1H), 7.16 (td, J = 7.5 Hz, 1.4 Hz, H-4′, 1H), 7.03 (d, J = 3.2 Hz, H-3′, 1H), 6.94–6.90 (m, H-2, H-6, 2H), 6.83 (dd, J = 8.0 Hz, 2.3 Hz, H-4, 1H), 6.43 (dd, J = 3.7 Hz, 1.8 Hz, H-4″, 1H), 5.90 (d, J = 1.4 Hz, H-8b, CH_2, 1H), 5.41 (d, J = 0.92 Hz, H-8a, CH_2, 1H), 3.75 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 160.0 (C-3), 155.9 (C-7′), 147.9 (C-2′), 146.3 (C-7), 144.2 (C-5″), 141.0 (C-1), 134.9 (C-1′), 131.9 (C-2′), 130.4 (C-3′), 129.9 (C-5), 129.0 (C-5′), 124.4 (C-4′), 121.2 (C-6′), 119.5 (C-6), 117.9 (C-8, CH2), 114.9 (C-3″), 113.9 (C-4), 112.7 (C-2), 112.4 (C-4″), 55.3 (OCH_3); HRMS (+ESI) $[M+H]^+$: 320.1284, $C_{20}H_{18}NO_3$ requires 320.1281.

(*E*)-*N*-(2-(1-(3,4-Dimethoxyphenyl)vinyl)phenyl)furan-2-carboxamide (16c)

Yield 0.02 g (4%); ν_{max}/cm^{-1} (NaCl): 3388, 1681, 1584, 1513, 1450, 1311, 1257, 1138, 1025, 756; λ_{max} (MeOH)/nm: 209, 263; δ_H(400 MHz; $CDCl_3$) 8.37 (d, J = 8.2 Hz, H-6′, 1H), 8.15 (br s, NH, 1H), 7.39 (t, J = 7.9 Hz, H-5′, 1H), 7.27–7.30 (m, H-3′, H-5″, 2H), 7.16 (td, J = 7.6 Hz, 0.92 Hz, H-4′, 1H), 7.03 (d, J = 3.6 Hz, H-3″, 1H), 6.94 (d, J = 1.8 Hz, H-2, 1H), 6.83 (dd, J = 8.5 Hz, 2.3 Hz, H-6, 1H), 6.76 (d, J = 8.2 Hz, H-5, 1H), 6.42 (dd, J = 3.2 Hz, 1.8 Hz, H-4″, 1H), 5.81 (d, J = 0.92 Hz, H-8b, CH_2, 1H), 5.31 (d, J = 0.92 Hz, H-8a, CH_2, 1H), 3.83 (s, OCH_3, 3H), 3.82 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 155.9 (C-7′), 149.6 (C-4), 149.2 (C-3), 147.9 (C-2′), 146.0 (C-7), 144.1 (C-5″), 135.0 (C-1′), 132.2 (C-1), 132.1 (C-2′), 130.4 (C-3′), 128.9 (C-5′), 124.4 (C-4′), 121.2 (C-6′), 120.0 (C-6), 116.0 (C-8, CH_2), 114.9 (C-3′), 112.4 (C-4′), 111.1 (C-5), 109.8 (C-2), 56.0 (2 × OCH_3); HRMS (+ESI) $[M+H]^+$: 350.1395, $C_{21}H_{20}NO_4$ requires 350.1387.

(*E*)-*N*-(2-(1-(4-Methoxyphenyl)vinyl)phenyl)furan-2-carboxamide (16d)

Yield 0.05 g (9%); ν_{max}/cm^{-1} (NaCl): 3389, 1682, 1607, 1584, 1526, 1509, 1449, 1309, 1252, 1180, 838, 755; λ_{max} (MeOH)/nm: 205, 261; δ_H(400 MHz; $CDCl_3$) 8.44 (d, J = 8.2 Hz, H-6′, 1H), 8.22 (br s, NH, 1H), 7.39 (t, J = 8.0 Hz, H-5′, 1H), 7.26–7.31 (m, H-2, H-6, H-3′, H-5″, 4H), 7.16 (td, J = 7.6 Hz, 1.4 Hz, H-4′, 1H), 7.04 (d, J = 4.1 Hz, H-3″, 1H), 6.84 (d, J = 8.7 Hz, H-3, H-5, 2H), 6.42 (dd, J = 3.4 Hz, 1.8 Hz, H-4″, 1H), 5.84 (d, J = 0.92 Hz, H-8b, CH_2, 1H), 5.29 (d, J = 1.36 Hz, H-8a, CH_2, 1H), 3.76 (s, OCH_3, 3H); δ_C(100 MHz; $CDCl_3$) 160.0 (C-4), 155.9 (C-7′), 147.9 (C-2″), 145.6 (C-7), 144.2 (C-5″), 135.0 (C-1′), 132.1 (C-2′), 131.8 (C-1), 130.4 (C-3′), 128.8 (C-5′), 128.2 (C-2, C-6), 124.3 (C-4′), 120.9 (C-6′), 115.7 (C-8, CH2), 114.8 (C-3′), 114.1 (C-3, C-5), 112.4 (C-4′), 55.4 (OCH_3); HRMS (+ESI) $[M+H]^+$: 320.1295, $C_{20}H_{18}NO_3$ requires 320.1287.

***N*,*N*′-(Biphenyl-2,2′-diyl)difuran-2-carboxamide (17)**

Yield 0.03 g (7%); mp 173–175 °C; ν_{max}/cm^{-1} (NaCl): 3395, 1671, 1585, 1518, 1458, 1310, 754; λ_{max} (MeOH)/nm: 211, 253; δ_H(400 MHz; $CDCl_3$) 8.49 (d, J = 8.2 Hz, H-6, H-6′, 2H), 8.03 (br s, NH, NH′, 2H), 7.47 (t, J = 7.8 Hz, H-5, H-5′, 2H), 7.22–7.29 (m, H-4, H-4′, H-3, H-3′, H-5″, H-5‴, 6H), 7.01 (d, J = 3.2 Hz, H-3″, H-3‴, 2H), 6.38 (dd, J = 3.2 Hz, 1.8 Hz, H-4″, H-4‴, 2H); δ_C(100 MHz; $CDCl_3$) 156.2 (C-7, C-7′), 147.4 (C-2″, C-2‴), 144.8 (C-5″, C-5‴), 135.5 (C-1, C-1′), 130.6 (C-3, C-3′), 129.9 (C-5, C-5′), 127.3 (C-2, C-2′), 124.9 (C-4, C-4′), 121.7 (C-6, C-6′), 115.3 (C-3″, C-3‴), 112.4 (C-4″, C4‴); HRMS (+ESI) $[M+H]^+$: 373.1192, $C_{22}H_{17}N_2O_4$ requires 373.1188. X-Ray crystallographic details for **17** have been reported.[14]

MTS Cell proliferation assay

HT29 human colon carcinoma cells were supplied by Cancer Research UK, and maintained in DMEM with high glucose (4.5g L^{-1}) and L-glutamine, supplemented with penicillin 100 U ml^{-1}, streptomycin 100 µg ml^{-1} and 10% foetal bovine serum. Cells were maintained in 75 cm^3 tissue culture flasks (Nunc) with a weekly 1 : 10 split. HT29 cells were seeded into a 96 well tissue culture grade plate (Nunc) at 500 cells in 50 µl per well. Plates were incubated at 37 °C, in humidified 5% CO_2 in air for 2–4 h. Test agents were prepared at 100× final concentration in DMSO (Sigma), diluted 1 in 50 in culture medium and 50 µl added to the appropriate wells, to give a final volume of 100 µl. Plates were incubated at 37 °C, in humidified 5% CO_2 in air for 3 days and the MTS reagent was added, 20 µl per well. Plates were incubated at 37 °C, in humidified 5% CO_2 in air, for colour development. Optical density readings at 490 nm were taken at 1–4 h. IC_{50} values were calculated using the pharmacology function in SigmaPlot 11.

MTT Cytotoxicity assay

HepG2 cells were seeded in 96-well plate at a density of 1×10^4 cells per well in a volume of 200 µl and kept under 5% CO_2 at 37 °C. The cells were treated with our stilbenes (**11d**, **11e**, **11f**, **13a**, **15b**, **15c** and **15e**) at concentrations of 0–100 µM. Jurkat cells (1×10^6 cells μl^{-1}) were directly treated with similar concentrations of the compounds. After 24 h incubation, 20 µl of 5 mg ml^{-1} MTT was added to each treated cells and further incubated for 4 h at 37 °C. Subsequently, the total medium was discarded from HepG2 cells whereas 150 µl medium was discarded from Jurkat cells before adding 200 µl and 150 µl DMSO. For complete dissolution, the plate was incubated for 15 min followed with gentle shaking for 5 min. The cytotoxic effect of the stilbenes on HepG2 and Jurkat was assessed by measuring the absorbance of each well at 570 nm. Mean absorbance for each concentration was expressed as a percentage of vehicle control absorbance and plotted *versus* compound concentration.

P388 cells, supplied by the Japan Foundation for Cancer Research, were maintained in RPMI-1640 medium (Nissui Pharm. Co., Ltd) supplemented with 5% fetal calf serum (Mitsubishi Chemical Industry Co., Ltd) and kanamycin (100 µg ml^{-1}). The cells (3×10^3 cells/well) were cultured in Corning disposable 96-well plates containing 100 µl of growth medium per well and were incubated at 37 °C in a humidified atmosphere of 5% CO_2. Various sample concentrations (10 µl) were added to the cultures at day 1 after the transplantation. At day 3, 20 µl MTT solution (5 mg ml^{-1}) per well was added to each cultured medium. After a further 4 h of incubation, 100 µl of 10% SDS – 0.01 N HCl solution was added to each well and the formazan crystals in each well were dissolved by stirring with a pipette. The optical density measurements were made by using a microplate reader (Tohso MPR-A4i) witha a two wavelength system (550 and 700 nm). In all these experiments, 3 replicate wells were used to determine each point.

Measurement of NQO1 activity

NQO1 activity measurements were performed as spectrophotometric assays by measuring the dicoumarol inhibitable reduction of dichlorophenol indophenol (DCPIP) at 600 nm as described by Zafar *et al.*[24] Results were expressed as mol DCPIP reduced/min mg^{-1} protein using the DCPIP molar extinction coefficient of 21000 and the protein concentration of sample.

Western blotting of NQO1

WRL-68 fetal hepatocytes (5.5×10^5 cells) were prepared for SDS-PAGE as described by Zafar *et al.*[24] Cellular proteins were resolved on 12% SDS-PAGE at 150 V followed by electroblotting to polyvinylidene fluoride membranes for 2 h at 100V. The standard immunoblotting procedure was carried out using an *anti* NQO1 monoclonal antibody (Sigma). β-Actin was used as a loading control.

Conclusions

This work demonstrates for the first time the remarkable cytotoxic and chemopreventive properties of some unusual stilbene carboxamides *e.g.* **15d** and **15e**. Altogether fourteen stilbenes were constructed by the Heck reaction and intriguing substituent effects have been observed. The Pd catalyzed union of iodophenyl carboxamides (*e.g* **9f**) with styrenes possessing a single methoxy substituent (*e.g* **10c**) proceeds in higher yield (49%) than that shown in the coupling of **9f** to 3,4-dimethoxystyrene **10a** (16%) or 3,5-dimethoxystyrene **10e** (17%). These "matching" preferences have led us to consider in some details the role of 6-membered ring palladacycles (*e.g* **30**) which incorporate the -N═C(Ar)-*O*-PdL moiety. It is important to observe that intramolecular direct arene arylation is not observed in the chemistry presented in Tables 2 and 3 contrary to what one might have expected. Surprisingly biaryl formation seems to be more facile than intramolecular direct arene arylation (see electronic supplementary information†).

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