

## Article

# Synthesis of Bio-Inspired 1,3-Diarylpropene Derivatives via Heck Cross-Coupling and Cytotoxic Evaluation on Breast Cancer Cells

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**Abstract:** The Heck cross-coupling reaction is a well-established chemical tool for the synthesis of unsaturated compounds by formation of a new C-C bond. In this study, 1,3-diarylpropene derivatives, designed as structural analogues of stilbenoids and dihydrostilbenoids, were synthesised by the palladium-catalysed reactions of 2-amidiodobenzene derivatives with either estragole or eugenol. The products were obtained with high (*E*) stereoselectivity but as two regioisomers. The ratios of isomers were found to be dependent on the nature of the allylbenzene partner and were rationalised by electronic effects exercising a determining influence in the  $\beta$ -hydride elimination step. In addition, the cytotoxic effects of all the Heck reaction products were evaluated against MCF-7 and MDA-MB-231 human breast cancer cells, with unpromising results. Among all, compound **7d** exhibited weak cytotoxic activity towards MCF-7 cell lines with IC<sub>50</sub> values of 47.92  $\mu$ M in comparison with tamoxifen and was considered to have general toxicity (SI value < 2).

**Keywords:** Heck cross-coupling; 1,3-diarylpropene;  $\beta$ -hydride elimination; cytotoxic effects; breast cancer cells



**Citation:** Tan, A.S.; Singh, J.; Rezali, N.S.; Muhamad, M.; Nik Mohamed Kamal, N.N.S.; Six, Y.; Azmi, M.N. Synthesis of Bio-Inspired 1,3-Diarylpropene Derivatives via Heck Cross-Coupling and Cytotoxic Evaluation on Breast Cancer Cells. *Molecules* **2022**, *27*, 5373. <https://doi.org/10.3390/molecules27175373>

Academic Editors: Rafael Chinchilla and Chia-che Chang

Received: 28 June 2022

Accepted: 16 August 2022

Published: 23 August 2022

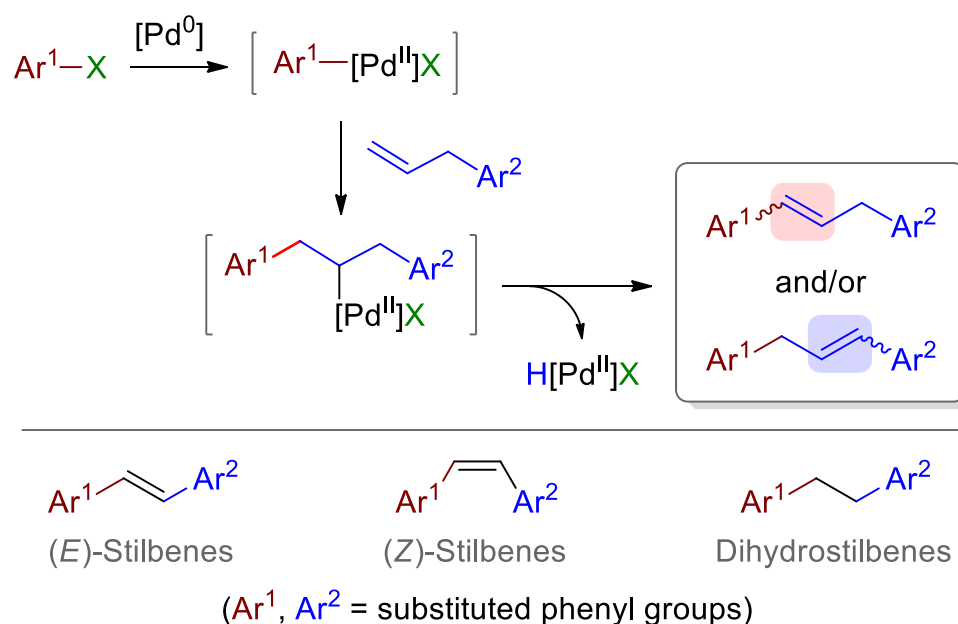
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## 1. Introduction

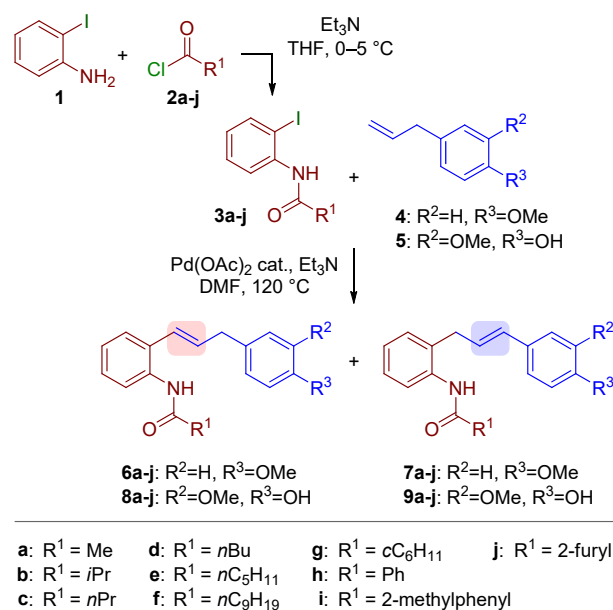
The Heck reaction has perpetuated its significance in synthetic organic chemistry for over half a century. Indeed, the introduction of this carbon-carbon bond-making cross-coupling reaction by Heck and Mizoroki has revolutionised synthetic methodology, thanks to its simplicity and effectiveness [1–5]. Since the first detailed mechanism was proposed by Heck and Nolley in 1972 [2], the elementary steps, reaction parameters and catalytic systems have counted among the major aspects attracting the interest of many researchers [4,6]. One crucial part of the Heck catalytic cycle, that sometimes receives little attention by synthetic chemists, is the  $\beta$ -hydride elimination elementary step. This process plays a key role in enantioselective versions of the reaction, for which it must proceed with suitable regioselectivity [7–10]. Control is also essential in so-called reductive Heck reactions for which, conversely,  $\beta$ -hydride elimination is to be avoided [11]. In relation to this context, the synthesis of 1,3-diarylpropene derivatives by the Heck reaction is especially worthy of study. Indeed, when the two aromatic groups differ, two possible regioisomers can be produced (Scheme 1).



**Scheme 1.** Synthesis of 1,3-diarylpropene derivatives by the Heck reaction. Comparison of the structures of the products with those of stilbenes and dihydrostilbenes.

Moreover, such compounds can be viewed as higher homologues of 1,2-diphenylethylene derivatives (stilbenes), as well as of dihydrostilbenes. In this respect, it is worth pointing out that hydroxylated stilbenes (stilbenoids) and hydroxylated dihydrostilbenes are of special biological importance. Indeed, stilbenoids are produced by various plants in response to stressors such as mechanical injury, e.g., resulting from attack by herbivores, or infection by pathogenic agents [12–14]. Most of these phytoalexin molecules are derived from *trans*-resveratrol, the presence of which in grape vines has been thought to be involved in the “French paradox” [15]. (*E*)-Resveratrol and other naturally occurring (*E*)-stilbene derivatives, such as piceatannol, oxyresveratrol or isorhapontigenin, have attracted much attention and have been the subject of extensive studies. Various interesting pharmacological properties have been disclosed, including antioxidant, anticancer, anti-inflammatory, cardioprotective, antifungal and antibacterial activities [14–19]. Interestingly, dihydrostilbenoids have been reported to exhibit a similar range of biological effects [20]. Some years ago, we studied the preparation of stilbenoid structural analogues having an amido substituent at the *ortho* position of one of the two aromatic parts, using the Heck reaction [21,22]. Some of these molecules were found to possess significant anticancer properties against HT-29, P388, DU-145, MCF-7 and BxPC-3 cancer cell lines, or chemopreventive action [21,22].

In our continuing efforts directed towards the discovery of novel biologically active derivatives, we decided to investigate the application of the Heck reaction to the synthesis of new compounds having a 1,3-diarylpropene skeleton, thus moving from a C6-C2-C6 to a C6-C3-C6 structure, but retaining the pharmacophores, i.e., an amido substituent on one of the phenyl rings and oxygen-based substituents on the other (Scheme 2). It is noteworthy that these new target molecules can be viewed not only as structural analogues of stilbenoids and dihydrostilbenoids, but, in fact, as hybrid compounds having characteristics of both types of molecules.



**Scheme 2.** Synthesis of amido-substituted 1,3-diarylpropene compounds by the Heck cross-coupling reaction.

## 2. Results and Discussion

### 2.1. Synthesis of Amido-Substituted 1,3-Diarylpropene Derivatives

The synthesis of the targeted *o*-amido-substituted 1,3-diarylpropene products is illustrated in Scheme 2. First, the amido-substituted iodobenzene precursors **3a–j** were prepared by *N*-acylation of 2-iodoaniline **1** with the respective acyl chlorides **2a–j**. These compounds were then cross-coupled with estragole **4** or eugenol **5** using the Heck reaction, in the presence of palladium(II) acetate as a catalyst, affording the expected *o*-amido-substituted 1,3-diarylpropene products **6a–j–9a–j** in 36–91% yields (Table 1). In each case, the formation of both possible regioisomers, **6/7** or **8/9**, was observed [23–25].

**Table 1.** Synthesis of *o*-amido-substituted 1,3-diarylpropene products **6a–j–9a–j**.

Compounds	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield *	6/7 or 8/9 Ratio #
<b>6a, 7a</b>	Me	H	OMe	75%	51:49
<b>6b, 7b</b>	<i>i</i> Pr	H	OMe	86%	54:46
<b>6c, 7c</b>	<i>n</i> Pr	H	OMe	80%	48:52
<b>6d, 7d</b>	<i>n</i> Bu	H	OMe	78%	47:53
<b>6e, 7e</b>	<i>n</i> C <sub>5</sub> H <sub>11</sub>	H	OMe	91%	49:51
<b>6f, 7f</b>	<i>n</i> C <sub>9</sub> H <sub>19</sub>	H	OMe	72%	45:55
<b>6g, 7g</b>	<i>c</i> C <sub>6</sub> H <sub>11</sub>	H	OMe	69%	49:51
<b>6h, 7h</b>	Ph	H	OMe	78%	47:53
<b>6i, 7i</b>	2-MePh	H	OMe	58%	49:51
<b>6j, 7j</b>	2-furyl	H	OMe	36%	47:53
<b>8a, 9a</b>	Me	OMe	OH	49%	38:62
<b>8b, 9b</b>	<i>i</i> Pr	OMe	OH	75%	21:79
<b>8c, 9c</b>	<i>n</i> Pr	OMe	OH	79%	26:74
<b>8d, 9d</b>	<i>n</i> Bu	OMe	OH	82%	22:78
<b>8e, 9e</b>	<i>n</i> C <sub>5</sub> H <sub>11</sub>	OMe	OH	56%	21:79
<b>8f, 9f</b>	<i>n</i> C <sub>9</sub> H <sub>19</sub>	OMe	OH	57%	28:72
<b>8g, 9g</b>	<i>c</i> C <sub>6</sub> H <sub>11</sub>	OMe	OH	62%	19:81
<b>8h, 9h</b>	Ph	OMe	OH	81%	29:71
<b>8i, 9i</b>	2-MePh	OMe	OH	79%	22:78
<b>8j, 9j</b>	2-furyl	OMe	OH	83%	26:74

\* isolated yields of unseparated regioisomers. # The ratios were determined by <sup>1</sup>H-NMR spectroscopy of the crude products.

## 2.2. Characterisation of the 1,3-Diarylpropene Heck Products

Compounds **6a–j–9a–j** were characterised by FT-IR, 1D- and 2D-NMR spectroscopies as well as an HRMS analysis. Compounds **8b,9b** were taken as an example to describe the obtained data. The FT-IR spectrum of the **8b/9b** mixture exhibited characteristic absorptions at 3398 (broad, w), 3291 (broad, m), 2970–2873 (w), 1654 (s), 1509 (s) and 1371 (m)  $\text{cm}^{-1}$ , corresponding to O-H stretching, N-H stretching,  $\text{Csp}^3\text{-H}$  stretching, saturated amide C=O stretching, C=C aromatic stretching and  $\text{CH}_3$  bending, respectively. An out-of-plane C-H bending vibration at 753  $\text{cm}^{-1}$  (s) indicated the presence of *ortho*-substituted aromatic rings in compound **8b/9b**. On the other hand, a  $\text{CH}_2$  bending vibration was observed at 1446  $\text{cm}^{-1}$  (m), indicating the presence of a methylene group ( $\text{CH}_2$ ). The *para*-substituted aromatic ring displayed out-of-plane C-H bending vibration bands at 812 (w) and 848 (m)  $\text{cm}^{-1}$ .

Typically, the comprehensive description of all the  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals of mixtures of isomers such as **8b/9b** was not straightforward. However, it could be achieved by first carefully assigning the signals of the few Heck products for which we had managed to obtain samples of pure isomers, including **9b**. This was done on the basis of 1D and 2D NMR experiments: COSY, DEPT135, HSQC and HMBC, as well as by comparison with reported NMR data of simpler compounds sharing structural subunits with our molecules, in particular 1-[(*E*)-cinnamyl]-4-methoxybenzene [23], 1-methoxy-4-[(*E*)-3-phenylprop-1-enyl]benzene [24], 4-[(*E*)-cinnamyl]-2-methoxyphenol [25], *N*-[2-[(*E*)-hex-1-enyl]phenyl]acetamide [26], *N*-(2-allylphenyl)acetamide [27] and *N*-[2-[(*E*)-cinnamyl]phenyl]prop-2-enamide [28]. Once this operation was completed, the corresponding descriptions were used as reference data for the remaining analyses.

The  $^1\text{H}$  NMR spectrum of the **8b/9b** mixture exhibited important characteristic signals within the range  $\delta_{\text{H}}$  1.20–7.95 ppm. A downfield broad singlet for the amide proton ( $\text{NH}$ ) of the major isomer **9b** was observed at  $\delta_{\text{H}}$  7.35 ppm. The seven aromatic protons were distributed in two regions: 7.06–7.95 ppm and 6.72–6.85 ppm. The first area was assigned to the protons attached to the nitrogen-substituted aromatic ring. The doublet of the proton at the *ortho* position relative to the nitrogen atom was characteristic, with a particularly high chemical shift value:  $\delta_{\text{H}}$  7.95 ppm ( $J$  8.0 Hz) for **9b** and  $\delta_{\text{H}}$  7.84 ppm ( $J$  7.6 Hz) for **8b**. The somewhat lower value for the latter was a general observation in all the **6/7** and **8/9** series. The aromatic signals lying in the higher field region were assigned to the methoxyphenol part. They appeared as two sets of overlapping signals: a singlet, accounting for the proton located *ortho* to the methoxyl substituent; and an AB system for the other two protons, with a  $J_{\text{AB}}$  coupling constant of 9.0 Hz. These signals were observed at a markedly lower field in the case of **9b** ( $\delta_{\text{H}}$  6.81–6.87 ppm) than in the case of **8b** ( $\delta_{\text{H}}$  6.72–6.74 ppm), which was a general trend for all **8/9** mixtures.

For each isomer and as expected, the propene unit bridging the two aromatic rings appeared as a doublet (one proton,  $J$  16.0 Hz) for the vinylic CH directly attached to one of the aromatic rings ( $\delta_{\text{H}}$  6.38 ppm for **9b** and 6.42 ppm for **8b**), a doublet of triplets (one proton,  $J$  16.0 and 6.0 Hz) for the central vinylic CH ( $\delta_{\text{H}}$  6.16 ppm for **9b** and 6.27 ppm for **8b**) and a doublet (two protons,  $J$  6.0 Hz) for the allylic protons, in the aliphatic region ( $\delta_{\text{H}}$  3.53 ppm for **9b** and 3.50 ppm for **8b**). The high  $^3J$  coupling constant of 16.0 Hz confirmed the *E* configuration of the  $\text{CH}=\text{CH}$  double bond. The hydroxyl (OH) and methoxyl ( $\text{OCH}_3$ ) protons appeared as two singlets at  $\delta_{\text{H}}$  5.73 and 3.87 ppm, respectively, in the case of **9b**. The OH proton of **8b** came out at a somewhat higher field ( $\delta_{\text{H}}$  5.61 ppm), which was again a general trend in the **8/9** series.

The isopropyl group of **9b** was characterised by an upfield doublet at  $\delta_{\text{H}}$  1.21 ppm ( $J$  7.0 Hz), accounting for the magnetically equivalent six protons of the methyl groups. A septet ( $J$  7.0 Hz) at  $\delta_{\text{H}}$  2.47 ppm was assigned to the neighbouring CH. It is worth mentioning that in the  $^1\text{H}$  NMR spectrum of the **8b/9b** mixture, as well as in several other cases, traces of other products could be detected. Their isolation and characterisation were not attempted, but by analogy with related results reported in the literature [24–26], these were likely to be minor by-products of the Heck reaction, namely *Z* isomers of **8b** and

**9b** and/or the vinylidene product resulting from alternative regioselectivity of the alkene 1,2-insertion step.

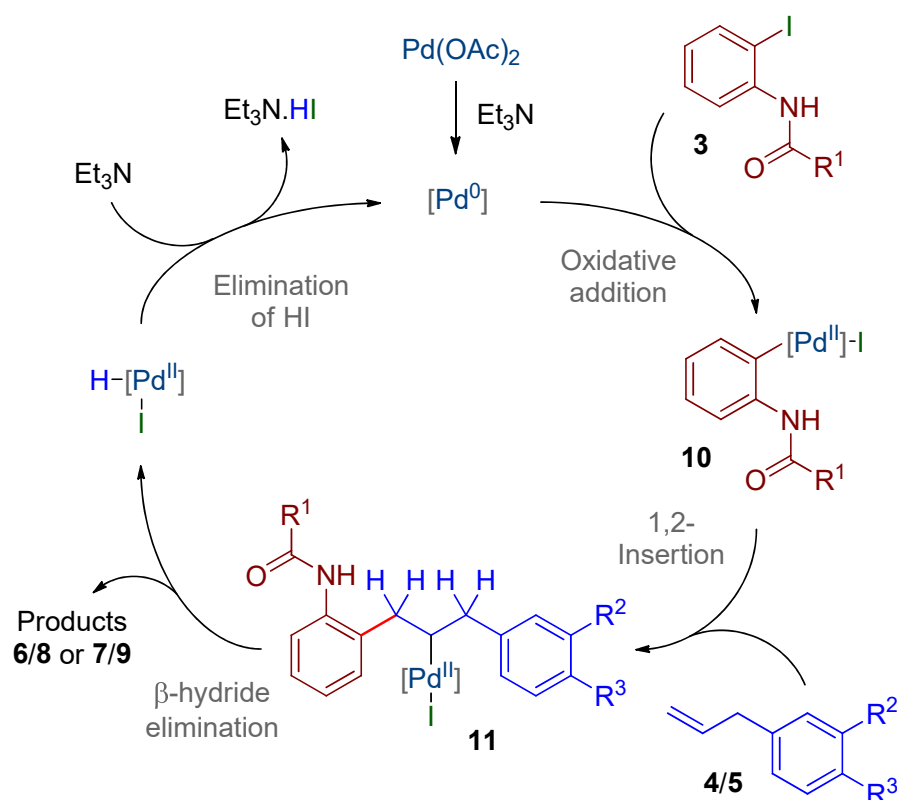
The  $^{13}\text{C}$  NMR spectrum of **8b/9b** exhibited important characteristic signals within the range  $\delta_c$  19.6–175.1 ppm. A total of two sets of 19 carbon signals were observed, with different intensities, with the highest peaks accounting for the major isomer **9b**. The presence of the carbonyl carbon was evidenced by a downfield signal at  $\delta_c$  175.1 ppm. The signals of the twelve aromatic ring carbon nuclei of **8b/9b** were observed in the range  $\delta_c$  107.9–146.7 ppm. The peak of the CH located at the *ortho* position relative to the methoxyl substituent was especially characteristic, with a comparatively low chemical shift value due to the +M electron-donating effect of the substituents of this ring ( $\delta_c$  107.9 ppm for **9b** and 111.2 ppm for **8b**). The signals of the propene subunit also exhibited marked differences depending on the isomers. The  $\text{CH}_2$  group was clearly identifiable, with a chemical shift around 39 ppm for all compounds **8a–j** ( $\delta_c$  39.2 ppm for **8b**) and a value around 36 ppm for **9a–j** ( $\delta_c$  36.1 ppm for **9b**). The chemical shifts of the vinylic carbon atoms were also good markers. For instance, the central vinylic CH appeared at around 134 ppm in the **8** series ( $\delta_c$  134.2 ppm for **8b**) and at around 125 ppm in the **9** series ( $\delta_c$  125.1 ppm for **9b**). The methoxyl substituent (OMe) gave a signal at  $\delta_c$  55.9 ppm for **9b** and 56.0 ppm for **8b**; the isopropyl group was identified by two peaks at  $\delta_c$  36.7 (CH) and 19.6 ppm (Me) for both isomers.

### 2.3. Mechanistic Interpretation of the Results of the Heck Cross-Coupling Reactions

An examination of the literature reveals several examples of related Heck reactions giving mixtures of isomers [29–36]. In several cases, the ratios of isomers were not given and generally, the origin of the selectivities observed was not discussed. In a few instances, the observation of two main products having the same atom connections was interpreted as the formation of *E* and *Z* isomers [31,33], whereas those compounds are perhaps more likely to be regioisomers, as in the present work.

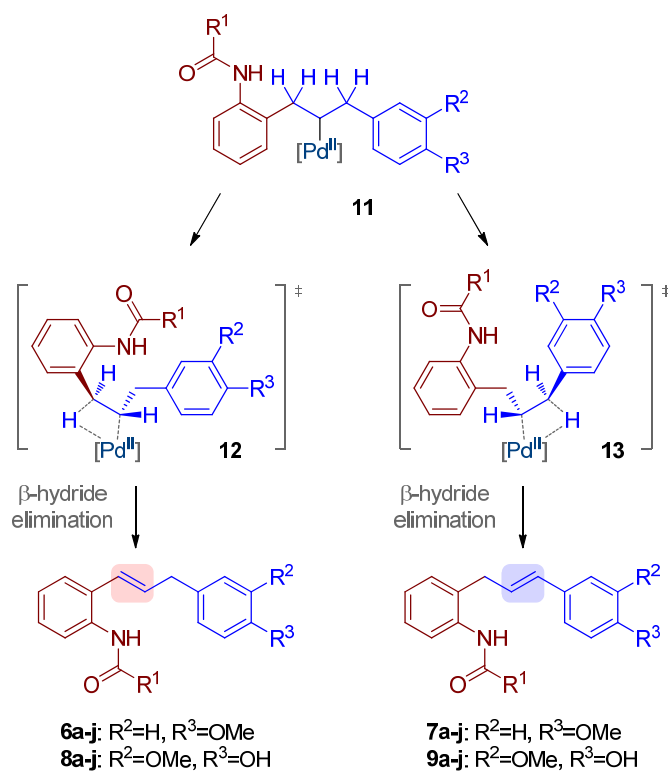
The mechanism of the Heck reaction and the exact nature of the intermediate palladium complexes involved have been extensively studied and discussed [3–6]. A simplified view is displayed in Scheme 3. A pre-activation step generated palladium(0), which then underwent the oxidative addition of the aryl iodide substrate **3**. This produced the intermediate complex **10**, where the palladium atom was attached to the *ortho* amido-substituted aryl group. Coordination of the allylbenzene reactant **4** or **5**, followed by *syn* 1,2-insertion of the C=C bond, gave rise to the alkylpalladium species **11**. The next step was a *syn*  $\beta$ -hydride elimination which, after de-coordination, delivered the product: **6** or **7** from **4** or **8** or **9** from **5**, along with a palladium(II) hydride species. Finally, the palladium(0) catalyst was regenerated in a reductive elimination process.

The crucial elementary step with respect to the stereo- and regioselectivity of the formation of the products was the *syn*  $\beta$ -hydride elimination event taking place from intermediate **11**. Indeed, the outcome was fully determined by which of the four neighbouring hydrogen atoms that are located at the  $\beta$  position relative to the metal centre participates in this process. In our reactions, little regioselectivity was observed when 1-allyl-4-methoxybenzene (estragole) **4** was employed, whereas with 1-allyl-3-methoxy-4-hydroxybenzene (eugenol) **5**, selectivity in favour of product **9** was substantial, ranging from 62:38 to 81:19. In all cases, the (*E*) isomers were produced with high selectivity. The latter stereoselectivity is commonly observed in Heck reactions and it is generally considered that this is the result of kinetic control governed by the Curtin–Hammett principle [3–5].



**Scheme 3.** Simplify mechanism of the Heck cross-coupling reaction of 2-amidoiodobenzenes **3** with allylbenzene derivatives **4** or **5**.

Similarly, it appears that in the present examples, the observed regioselectivities cannot be explained by thermodynamic control. Products **7** and **9** were expected to be stabilised by conjugation of the  $\text{C}=\text{C}$  alkene fragment with the oxygen-substituted aromatic group, whereas in **6** and in **8**, the presence of the *ortho* amido substituent forced the conformation of the neighbouring alkene out of the plane of the aromatic ring, thereby compromising a similar stabilising conjugation effect. Semi-empirical PM7 calculations, performed with  $\text{R}^1 = \text{Me}$  or *i*Pr, support this analysis: **7a**, **7b**, **9a** and **9b** were estimated to be more stable than their respective regioisomers **6a**, **6b**, **8a** and **8b** by 0.87 to 1.83 kcal.mol<sup>-1</sup>. Using estragole **4**, thermodynamic control would thus result in significant **6/7** selectivity in favour of **7**, in contrast to what was experimentally observed. More importantly, the energy difference between **8a** and **9a** was found to be lower than between **6a** and **7a**: 0.87 and 1.39 kcal.mol<sup>-1</sup>, respectively. The same situation was calculated in the case of **8b/9b** vs. **6b/7b**, with respective energy differences of 1.37 and 1.83 kcal.mol<sup>-1</sup>. Pure thermodynamic control would thus lead to lower selectivities with eugenol **5** than with estragole **4**, which is the opposite of what is actually observed. Therefore, regioselectivity is most plausibly under kinetic control. In the reaction of intermediate **11**, four possible transition states can be drawn, among which two, **12** and **13**, account for the formation of the observed major (*E*) isomers (Scheme 4).



**Scheme 4.** Proposed transition states of the  $\beta$ -hydride elimination step from **11**, leading either to regioisomers (*E*)-**6/8** or (*E*)-**7/9**.

The higher selectivity observed using eugenol **5** indicates that the transition state **13** became comparatively more energetically accessible than **12** when the oxygen-substituted aromatic ring (displayed in blue) became more electron-rich. This was consistent with a partial positive charge being developed at the carbon atom of the C–H bond that was being broken in the process. This positive charge was best accommodated by the most electron-rich adjacent aromatic ring. This provides new support for a similar explanation that had been proposed by the group of Sigman to explain the regioselectivities of Heck cross-coupling reactions of allylbenzene with aryldiazonium salts having various electronic properties [34].

#### 2.4. Cytotoxicity Activity

The MTT assay was used to evaluate the toxicity of *N*-(2-cinnamylphenyl)amides on the viability of two types of breast cancer cell lines, i.e., MCF-7 (with a receptor) and MDA-MB-231 (without a receptor). In this study, a normal breast cell line (MCF-10A) was used. MCF-7 is an ER-positive breast cancer cell, whereas MDA-MB-231 is an ER-negative breast cancer cell. These cancer cells have receptor sites that bind to oestrogen, promoting their growth and spread. Tamoxifen is a first-line anti-oestrogen therapy that is used to prevent the production or action of oestrogen.

For the cytotoxicity assays, only pure isomers were submitted for evaluations. The cell lines were treated with different concentrations of the synthesized compounds, i.e., between 10 and 100  $\mu$ M and incubated for 24–72 h. Table 2 displays the IC<sub>50</sub> values, as well as the SI indexes. At 72 h, compound **6i** exhibited weak cytotoxic activity against both MCF7 and MDA-MB-231 cells, with IC<sub>50</sub> values of 91.78  $\mu$ M and 73.79  $\mu$ M, respectively. In addition, compounds **6d**, **7d** and **7e** exhibited weak activity towards both MCF-7 and MCF-10A at 72 h. The IC<sub>50</sub> values recorded were 65.83  $\mu$ M, 47.92  $\mu$ M, 88.46  $\mu$ M and 92.89  $\mu$ M, 71.19  $\mu$ M and 69.18  $\mu$ M, respectively. They were, however, inactive against MDA-MB-231 cells. All other compounds (i.e., isolated pure isomers) tested were inactive for cytotoxicity against all cell lines.

**Table 2.** Cytotoxicities (IC<sub>50</sub> values) and selectivity indexes (SI) of the most active bio-inspired 1,3-diarylpropene Heck reaction products.

Compounds	Time	IC <sub>50</sub> Value (μM)				
		MCF-7	SI	MDA-MB-231	SI	MCF-10A
6d	24 h	94.05 ± 1.26	1.06	>100 ± 0.01	-	>100 ± 0.01
	48 h	93.34 ± 2.15	1.01	>100 ± 0.01	0.94	94.39 ± 9.71
	72 h	65.83 ± 7.33	1.41	>100 ± 0.01	0.93	92.89 ± 8.71
6e	24 h	>100 ± 0.01	0.81	>100 ± 0.01	0.81	80.91 ± 7.58
	48 h	>100 ± 0.01	0.90	>100 ± 0.01	0.90	90.09 ± 8.80
	72 h	>100 ± 0.01	0.99	>100 ± 0.01	0.99	98.50 ± 2.60
6i	24 h	>100 ± 0.01	-	>100 ± 0.01	-	>100 ± 0.01
	48 h	>100 ± 0.01	-	>100 ± 0.01	-	>100 ± 0.01
	72 h	91.78 ± 7.95	1.09	73.79 ± 6.92	1.36	>100 ± 0.01
7d	24 h	58.90 ± 1.81	1.70	>100 ± 0.01	1.00	>100 ± 0.01
	48 h	48.68 ± 3.46	1.54	>100 ± 0.01	0.75	75.03 ± 8.58
	72 h	47.92 ± 2.96	1.49	>100 ± 0.01	0.71	71.19 ± 9.25
7e	24 h	>100 ± 0.01	-	>100 ± 0.01	-	>100 ± 0.01
	48 h	>100 ± 0.01	0.70	>100 ± 0.01	0.70	70.27 ± 1.88
	72 h	88.46 ± 2.37	0.78	>100 ± 0.01	0.69	69.18 ± 0.01
Tamoxifen	24 h	16.22 ± 0.37	0.20	13.62 ± 0.95	0.24	3.24 ± 0.01
	48 h	15.36 ± 1.42	0.22	15.86 ± 0.73	0.21	3.33 ± 0.02
	72 h	15.78 ± 0.10	0.26	14.53 ± 0.08	0.28	4.07 ± 0.09

Tamoxifen, on the other hand, demonstrated strong activity against MCF-7, MDA-MB-231 and MCF-10A, with IC<sub>50</sub> values at 72 h of 15.78 μM, 14.53 μM and 4.07 μM, respectively. The SI value was obtained by dividing the IC<sub>50</sub> value for normal cell lines by the IC<sub>50</sub> for cancerous cell lines. All compounds with SI values less than 2 were considered to have general toxicity, suggesting that they can cause cytotoxicity in normal cells as well [37].

### 3. Materials and Methods

#### 3.1. General

All spectral data were procured using the following instruments: Fourier-transform Infrared (FTIR) spectra were obtained using a PerkinElmer 2000 FTIR Spectrum spectrometer (PerkinElmer, Waltham, MA, USA). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVN 500 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA). Data were analysed with the Top Spin 3.6.1 software package (Bruker Bioscience, Billerica, MA, USA). Chemical shifts were internally calibrated using the residual CHCl<sub>3</sub> solvent peak in CDCl<sub>3</sub> (<sup>1</sup>H, δ 7.26), the CDCl<sub>3</sub> solvent signal (<sup>13</sup>C, δ 77.0) or the tetramethylsilane (TMS) signal (<sup>1</sup>H or <sup>13</sup>C, δ 0.00 ppm). Tetrahydrofuran (THF, QR&C, Grade AR) was freshly distilled from sodium benzophenone ketyl. Dimethylformamide (DMF, QR&C, Grade AR) was dried over 4 Å molecular sieves prior to use. All other commercially available chemicals and materials were used without further purification. Column chromatography was performed using Merck silica gel (0.040–0.063 mm) (Merck & Co., Kenilworth, NJ, USA). Thin Layer Chromatography (TLC) was completed with silica gel-coated aluminium sheets (silica gel 60 F<sub>254</sub>).

The procedure of intermediates and final compounds synthesis and their NMR; ATR-IR and HRMS spectra of the compounds are presented in Supplementary Materials.

#### 3.2. Synthesis Procedures

##### 3.2.1. General Procedure for the Preparation of the Ortho-Amido-Substituted Iodobenzene Precursors

A solution of 2-iodoaniline **1** (1.00 equiv.) and Et<sub>3</sub>N (1.00 equiv.) in dry THF (1.6–2.0 mL per mmol of **1**) was cooled to 0–5 °C. The requisite acyl chloride **2** (1.00 equiv.) was then



added dropwise, with stirring. The cold bath was removed, and the mixture was stirred vigorously overnight at room temperature. The white precipitate of  $\text{Et}_3\text{N}\cdot\text{HCl}$  was filtered off and rinsed with THF ( $3 \times 5$  mL). All the organic fractions were combined and concentrated under reduced pressure to afford the crude amide product **3**, which was then purified by recrystallisation from *n*-hexane/chloroform. Full details and characterisation data for compounds **3a–3j** are attached in the Supporting Information.

### 3.2.2. General Procedure for Preparing the Heck Cross-Coupling Reaction Products

In a dry three-necked flask equipped with a thermometer and a condenser, a solution of *N*-(2-iodophenyl) amide **3** (1.00 equiv.) in dry DMF (4.0 mL per mmol of substrate **3**) was heated up to 120 °C and stirred for 20 min under nitrogen. Palladium(II) acetate (1.00% equiv.), triethylamine (3.50–5.00 equiv.) and the requisite allylbenzene derivative **4** or **5** (1.60 equiv.) were then added successively. The reaction mixture was stirred at 120 °C until the TLC analysis indicated complete consumption of **3** (3–6 h). After cooling, the saturated  $\text{NH}_4\text{Cl}$  aqueous solution (6.0 mL per mmol of starting **3**) was added and the mixture was extracted with EtOAc (three times, with portions of 2.0 mL per mmol of starting **3**). The combined organic fractions were washed with  $\text{H}_2\text{O}$  (6.0 mL per mmol of starting **3**), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The ratio of product isomers was determined by  $^1\text{H}$  NMR spectroscopy of the crude product. Purification by gradient elution column chromatography (*n*-hexane/ethyl acetate, 95:5 to 50:50) then yielded the desired Heck reaction products. Some regioisomers could not be separated and reported as a mixture. Full details for compounds **6a–9j** are attached in the Supporting Information.

*(E)*-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)acetamide **6a**. IR (neat)  $\nu$ : 3286 (m, NH), 3004 (w), 2833 (w), 1653 (s, C=O), 1510 (s), 1453 (m), 1371 (m), 1273 (m), 1242 (s), 1179 (m), 1035 (m, C–O), 821 (m), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.76 (d,  $J = 8.0$  Hz, H-2, 1H), 7.41 (br s, NH, 1H), 7.38 (d,  $J = 8.0$  Hz, H-5, 1H), 7.22 (dd,  $J = 8.0, 7.5$  Hz, H-3, 1H), 7.16 (br d,  $J = 8.5$  Hz, H-11, 2H), 7.11 (dd,  $J = 8.0, 7.5$  Hz, H-4, 1H), 6.87 (br d,  $J = 8.5$  Hz, H-12, 2H), 6.45 (d,  $J = 15.5$  Hz, H-7, 1H), 6.25 (dt,  $J = 15.5, 7.0$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.51 (d,  $J = 7.0$  Hz, H-9, 2H), 2.14 (s, H-16, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 168.4 (C-15), 158.1 (C-13), 134.1 (C-1), 133.9 (C-8), 131.7 (C-10), 130.2 (C-6), 129.5 (C-11), 127.8 (C-3), 126.9 (C-5), 125.6 (C-7), 125.3 (C-4), 123.8 (C-2), 114.00 (C-12), 55.2 (C-14), 38.6 (C-9), 24.2 (C-16). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 282.1475,  $\text{C}_{18}\text{H}_{20}\text{NO}_2$  requires 282.1494.

*(E)*-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)isobutyramide **6b**. IR (neat)  $\nu$ : 3268 (w, NH), 3032 (w), 2969 (w), 1651 (m, C=O), 1511 (s), 1452 (m), 1382 (w), 1287 (w), 1178 (w), 1033 (m, C–O), 834 (w), 746 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.86 (d,  $J = 8.0$  Hz, H-2, 1H), 7.38 (br s, NH, 1H), 7.35 (d,  $J = 8.0$  Hz, H-5, 1H), 7.22 (td,  $J = 8.0, 1.5$  Hz, H-3, 1H), 7.15 (d,  $J = 8.5$  Hz, H-11, 2H), 7.08–7.13 (m, H-4, 1H), 6.87 (d,  $J = 8.5$  Hz, H-12, 2H), 6.40 (d,  $J = 15.0$  Hz, H-7, 1H), 6.26 (dt,  $J = 15.0, 6.6$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.51 (d,  $J = 6.6$  Hz, H-9, 2H), 2.47 (sept,  $J = 6.8$  Hz, H-16, 1H), 1.21 (d,  $J = 6.8$  Hz, H-17, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 175.0 (C-15), 158.2 (C-13), 134.5 (C-8), 134.2 (C-1), 131.5 (C-10), 129.8 (C-6), 129.6 (C-11), 127.8 (C-3), 127.1 (C-5), 125.5 (C-7), 124.9 (C-4), 123.2 (C-2), 114.0 (C-12), 55.3 (C-14), 38.6 (C-9), 36.6 (C-16), 19.6 (C-17). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 310.1823,  $\text{C}_{20}\text{H}_{24}\text{NO}_2$  requires 310.1807.

*(E)*-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)butyramide **6c**. IR (neat)  $\nu$ : 3290 (w, NH), 3005 (w), 2959 (w), 1648 (s, C=O), 1511 (s), 1453 (m), 1381 (w), 1291 (m), 1175 (m), 1159, 1037 (m, C–O), 829 (w), 747 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.84 (d,  $J = 7.6$  Hz, H-2, 1H), 7.36 (d,  $J = 7.6$  Hz, H-5, 1H), 7.34 (br s, NH, 1H), 7.16 (d,  $J = 8.2$  Hz, H-11, 2H), 7.10–7.12 (m, H-3, H-4, 2H), 6.87 (d,  $J = 8.2$  Hz, H-12, 2H), 6.41 (d,  $J = 15.3$  Hz, H-7, 1H), 6.25 (dt,  $J = 15.3, 6.5$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.52 (d,  $J = 6.5$  Hz, H-9, 2H), 2.30 (t,  $J = 7.4$  Hz, H-16, 2H), 1.67–1.72 (m, H-17, 2H), 0.96 (t,  $J = 7.4$  Hz, H-18, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.2 (C-15), 158.2 (C-13), 134.4 (C-8), 134.2 (C-1), 131.6 (C-10), 129.8 (C-6), 129.6 (C-11), 127.8 (C-3), 127.1 (C-5), 125.5 (C-7), 125.1 (C-4), 123.4 (C-2), 114.0 (C-

12), 55.3 (C-14), 39.5 (C-16), 38.6 (C-9), 18.7 (C-17), 13.5 (C-18). HRMS (+ESI)  $[M + H]^+$ : 310.1816,  $C_{20}H_{24}NO_2$  requires 310.1807.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)pentanamide **6d**. IR (neat)  $\nu$ : 3262 (w, NH), 3002 (w), 2959 (w), 1652 (s, C=O), 1509 (s), 1450 (m), 1380 (w), 1292 (w), 1174 (m), 1037 (m, C–O), 813 (w), 747 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$ : 7.88 (d,  $J = 7.8$  Hz, H-2, 1H), 7.38 (br s, NH, 1H), 7.37 (d,  $J = 7.8$  Hz, H-5, 1H), 7.27–7.31 (m, H-3, 1H), 7.18 (d,  $J = 8.5$  Hz, H-11, 2H), 7.10–7.16 (m, H-4, 1H), 6.89 (d,  $J = 8.5$  Hz, H-12, 2H), 6.44 (d,  $J = 15.2$  Hz, H-7, 1H), 6.27 (dt,  $J = 15.2, 6.3$  Hz, H-8, 1H), 3.82 (s, H-14, 3H), 3.54 (d,  $J = 6.3$  Hz, H-9, 2H), 2.34 (t,  $J = 7.5$  Hz, H-16, 2H), 1.64–1.73 (m, H-17, 2H), 1.40–1.46 (m, H-18, 2H), 0.97 (t,  $J = 7.5$  Hz, H-19, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 125.8 MHz)  $\delta$ : 171.3 (C-15), 158.2 (C-13), 134.3 (C-8), 134.2 (C-1), 131.6 (C-10), 129.8 (C-6), 129.5 (C-11), 127.8 (C-3), 127.1 (C-5), 125.6 (C-7), 125.0 (C-4), 123.4 (C-2), 114.0 (C-12), 55.3 (C-14), 38.7 (C-9), 37.4 (C-16), 27.8 (C-17), 22.3 (C-18), 13.7 (C-19). HRMS (+ESI)  $[M + H]^+$ : 324.1958,  $C_{21}H_{26}NO_2$  requires 324.1964.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)hexanamide **6e**. IR (neat)  $\nu$ : 3278 (w, NH), 2952 (w), 2929 (w), 1651 (s, C=O), 1510 (s), 1451 (m), 1378 (w), 1296 (m), 1176 (m), 1037 (m, C–O), 824 (w), 747 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$ : 7.85 (d,  $J = 7.5$  Hz, H-2, 1H), 7.36 (br s, NH, 1H), 7.35 (d,  $J = 7.5$  Hz, H-5, 1H), 7.27–7.30 (m, H-3, 1H), 7.16 (d,  $J = 8.5$  Hz, H-11, 2H), 7.09–7.13 (m, H-4, 1H), 6.87 (d,  $J = 8.5$  Hz, H-12, 2H), 6.43 (d,  $J = 15.0$  Hz, H-7, 1H), 6.24 (dt,  $J = 15.0, 6.8$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.52 (d,  $J = 6.8$  Hz, H-9, 2H), 2.29 (t,  $J = 7.2$  Hz, H-16, 2H), 1.63–1.71 (m, H-17, 2H), 1.34–1.36 (m, H-18, 2H), 1.27–1.29 (m, H-19, 2H), 0.85 (t,  $J = 7.2$  Hz, H-20, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 125.8 MHz)  $\delta$ : 171.3 (C-15), 158.2 (C-13), 134.4 (C-8), 134.3 (C-1), 131.6 (C-10), 129.8 (C-6), 129.5 (C-11), 127.8 (C-3), 127.1 (C-5), 125.6 (C-7), 124.99 (C-4), 123.4 (C-2), 113.99 (C-12), 55.2 (C-14), 38.7 (C-9), 37.8 (C-16), 31.4 (C-18), 25.39 (C-17), 22.4 (C-19), 13.93 (C-20). HRMS (+ESI)  $[M + H]^+$ : 338.2103,  $C_{22}H_{28}NO_2$  requires 338.2120.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)decanamide **6f**. IR (neat)  $\nu$ : 3297 (w, NH), 2954 (w), 2920 (m), 1648 (m, C=O), 1509 (s), 1453 (m), 1378 (w), 1293 (m), 1174 (m), 1034 (m, C–O), 827 (w), 748 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$ : 7.82 (d,  $J = 7.7$  Hz, H-2, 1H), 7.42 (br s, NH, 1H), 7.36 (d,  $J = 7.7$  Hz, H-5, 1H), 7.21–7.25 (m, H-3, 1H), 7.16 (d,  $J = 8.5$  Hz, H-11, 2H), 7.08–7.13 (m, H-4, 1H), 6.87 (d,  $J = 8.5$  Hz, H-12, 2H), 6.44 (d,  $J = 15.5$  Hz, H-7, 1H), 6.24 (dt,  $J = 15.5, 6.5$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.51 (d,  $J = 6.5$  Hz, H-9, 2H), 2.27–2.33 (m, H-16, 2H), 1.62–1.70 (m, H-17, 2H), 1.15–1.28 (m, H-18, H-19, H-20, H-21, H-22, H-23, 12H), 0.89 (t,  $J = 6.9$  Hz, H-24, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 125.8 MHz)  $\delta$ : 171.4 (C-15), 158.2 (C-13), 134.3 (C-1), 134.1 (C-8), 131.6 (C-10), 130.1 (C-6), 129.5 (C-11), 127.8 (C-3), 127.0 (C-5), 125.6 (C-7), 125.0 (C-4), 123.5 (C-2), 113.97 (C-12), 55.2 (C-14), 38.6 (C-9), 37.8 (C-16), 31.81 (C-22), 29.4 (C-21), 29.3 (C-20), 29.2 (C-18, C-19), 25.75 (C-17), 22.6 (C-23), 14.0 (C-24). HRMS (+ESI)  $[M + H]^+$ : 394.2741,  $C_{26}H_{36}NO_2$  requires 394.2746.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)cyclohexanecarboxamide **6g**. IR (neat)  $\nu$ : 3260 (w, NH), 3034 (w), 2931 (w), 1652 (s, C=O), 1511 (s), 1450 (m), 1384 (w), 1300 (w), 1175 (w), 1039 (m, C–O), 824 (w), 747 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$ : 7.88 (d,  $J = 7.8$  Hz, H-2, 1H), 7.38 (br s, NH, 1H), 7.34 (d,  $J = 7.8$  Hz, H-5, 1H), 7.23 (t,  $J = 7.8$  Hz, H-3, 1H), 7.16 (d,  $J = 8.6$  Hz, H-11, 2H), 7.11 (t,  $J = 7.8$  Hz, H-4, 1H), 6.88 (d,  $J = 8.6$  Hz, H-12, 2H), 6.43 (d,  $J = 15.7$  Hz, H-7, 1H), 6.27 (dt,  $J = 15.7, 5.8$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.53 (d,  $J = 5.8$  Hz, H-9, 2H), 2.18 (td,  $J = 11.7, 2.7$  Hz, H-16, 1H), 1.92 (d,  $J = 12.6$  Hz, H-17 $\alpha$ , 2H), 1.75–1.83 (m, H-17 $\beta$ , 2H), 1.65–1.72 (m, H-19 $\beta$ , 1H), 1.40–1.49 (m, H-18 $\alpha$ , 2H), 1.15–1.34 (m, H-18 $\beta$ , H-19 $\alpha$ , 3H);  $^{13}C$  NMR ( $CDCl_3$ , 125.8 MHz)  $\delta$ : 174.1 (C-15), 158.2 (C-13), 134.5 (C-8), 134.3 (C-1), 131.5 (C-10), 130.1 (C-6), 129.7 (C-11), 127.8 (C-3), 127.1 (C-5), 125.6 (C-7), 124.8 (C-4), 123.1 (C-2), 114.0 (C-12), 55.2 (C-14), 46.4 (C-16), 38.6 (C-9), 29.7 (C-17), 25.7 (C-18, C-19). HRMS (+ESI)  $[M + H]^+$ : 350.2123,  $C_{23}H_{28}NO_2$  requires 350.2120.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)benzamide **6h**. IR (neat)  $\nu$ : 3259 (w, NH), 3030 (w), 2834 (w), 1647 (s, C=O), 1512 (s), 1483 (s), 1440 (w), 1300 (m), 1176 (m), 1037 (m, C–O), 815 (w), 753 (s)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$ : 7.98 (d,  $J = 7.9$  Hz, H-2, 1H), 7.75 (br s, NH, 1H), 7.70 (d,  $J = 7.4$  Hz, H-17, 2H), 7.49 (t,  $J = 7.4$  Hz, H-19, 1H), 7.41 (d,

$J = 7.9$  Hz, H-5, 1H), 7.29 (t,  $J = 7.4$  Hz, H-18, 2H), 7.26–7.33 (m, H-3, 1H), 7.08 (d,  $J = 8.7$  Hz, H-11, 2H), 7.06–7.09 (m, H-4, 1H), 6.78 (d,  $J = 8.7$  Hz, H-12, 2H), 6.39 (d,  $J = 15.7$  Hz, H-7, 1H), 6.26 (dt,  $J = 15.7, 6.0$  Hz, H-8, 1H), 3.72 (s, H-14, 3H), 3.45 (d,  $J = 6.0$  Hz, H-9, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 165.4 (C-15), 158.1 (C-13), 134.9 (C-8, C-16), 134.3 (C-1), 131.8 (C-19), 131.4 (C-10), 130.02 (C-6), 129.7 (C-11), 128.8 (C-18), 127.9 (C-3), 127.3 (C-5), 127.1 (C-17), 125.6 (C-7), 125.1 (C-4), 123.1 (C-2), 114.0 (C-12), 55.3 (C-14), 38.6 (C-9). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 344.1674,  $\text{C}_{23}\text{H}_{22}\text{NO}_2$  requires 344.1651.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)-2-methylbenzamide **6i**. IR (neat)  $\nu$ : 3275 (w, NH), 3027 (w), 2997 (w), 1646 (s, C=O), 1514 (s), 1444 (m), 1306 (m), 1271 (m), 1249, 1177 (m), 1037 (m, C–O), 827 (w), 748 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.02 (d,  $J = 7.5$  Hz, H-2, 1H), 7.76 (br s, NH, 1H), 7.43–7.35 (m, H-5, H-19, H-21, 3H), 7.31–7.26 (m, H-3, H-18, 2H), 7.18–7.13 (m, H-4, H-20, 2H), 7.11 (d,  $J = 8.5$  Hz, H-11, 2H), 6.82 (d,  $J = 8.5$  Hz, H-12, 2H), 6.44 (br d,  $J = 15.5$  Hz, H-7, 1H), 6.29 (dt,  $J = 15.5, 6.5$  Hz, H-8, 1H), 3.79 (s, H-14, 3H), 3.50 (br d,  $J = 6.5$  Hz, H-9, 2H), 2.51 (s, H-22, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 168.0 (C-15), 158.1 (C-13), 136.54 (C-16), 136.3 (C-17), 134.6 (C-8), 134.2 (C-1), 131.36 (C-10), 131.28 (C-19), 130.3 (C-6), 130.20 (C-18), 129.6 (C-11), 127.9 (C-3), 127.2 (C-5), 126.57 (C-21), 125.9 (C-20), 125.5, 125.4 (C-4, C-7), 123.3 (C-2), 114.0 (C-12), 55.2 (C-14), 38.5 (C-9), 19.9 (C-22). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 358.1801,  $\text{C}_{24}\text{H}_{24}\text{NO}_2$  requires 358.1807.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)prop-1-en-1-yl)phenyl)furan-2-carboxamide **6j**. IR (neat)  $\nu$ : 3355 (w, NH), 3126 (w), 2934 (w), 1669 (m, C=O), 1510 (s), 1450 (m), 1301 (m), 1164 (m), 1010 (m, C–O), 835 (w), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.44 (br s, NH, 1H), 8.10 (d,  $J = 8.2$  Hz, H-19, 1H), 7.26–7.31 (m, H-2, H-3, H-5, 3H), 7.18 (d,  $J = 7.5$  Hz, H-11, 2H), 7.12–7.15 (m, H-4, H-17, 2H), 6.86 (d,  $J = 7.5$  Hz, H-12, 2H), 6.58 (d,  $J = 15.8$  Hz, H-7, 1H), 6.54–6.57 (m, H-18, 1H), 6.31 (dt,  $J = 15.8, 6.2$  Hz, H-8, 1H), 3.80 (s, H-14, 3H), 3.55 (d,  $J = 6.2$  Hz, H-7, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 158.1 (C-13), 156.1 (C-15), 148.0 (C-16), 144.2 (C-19), 134.8 (C-8), 133.7 (C-1), 131.5 (C-10), 129.7 (C-11), 129.48 (C-6), 127.9 (C-3), 125.5 (C-5), 125.1 (C-7), 125.0 (C-4), 122.6 (C-2), 115.12 (C-17), 114.0 (C-12), 112.5 (C-18), 55.2 (C-14), 38.7 (C-9). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 334.1445,  $\text{C}_{21}\text{H}_{20}\text{NO}_3$  requires 334.1443.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)acetamide **7a**. IR (neat)  $\nu$ : 3286 (m, NH), 3004 (w), 2833 (w), 1653 (s, C=O), 1510 (s), 1453 (m), 1371 (m), 1273 (m), 1242 (s), 1179 (m), 1035 (m, C–O), 821 (m), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.82 (d,  $J = 8.0$  Hz, H-2', 1H), 7.28 (br d,  $J = 8.5$  Hz, H-11', 2H), 7.27 (dd,  $J = 8.0, 7.5$  Hz, H-3', 1H), 7.26–7.29 (m, NH, 1H), 7.23 (d,  $J = 8.0$  Hz, H-5', 1H), 7.13 (dd,  $J = 8.0, 7.5$  Hz, H-4', 1H), 6.84 (br d,  $J = 8.5$  Hz, H-12', 2H), 6.40 (d,  $J = 16.0$  Hz, H-9', 1H), 6.17 (dt,  $J = 16.0, 6.5$  Hz, H-8', 1H), 3.80 (s, H-14', 3H), 3.51 (d,  $J = 6.5$  Hz, H-7', 2H), 2.11 (s, H-16', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 168.3 (C-15'), 159.2 (C-13'), 136.0 (C-1'), 131.1 (C-9'), 130.6 (C-6'), 130.1 (C-5'), 129.4 (C-10'), 127.4 (C-3'), 127.3 (C-11'), 125.4 (C-8'), 125.3 (C-4'), 123.9 (C-2'), 113.96 (C-12'), 55.2 (C-14'), 36.0 (C-7'), 24.3 (C-16'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 282.1475,  $\text{C}_{18}\text{H}_{20}\text{NO}_2$  requires 282.1494.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)isobutyramide **7b**. IR (neat)  $\nu$ : 3268 (w, NH), 3032 (w), 2969 (w), 1651 (m, C=O), 1511 (s), 1452 (m), 1382 (w), 1287 (w), 1178 (w), 1033 (m, C–O), 834 (w), 746 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.94 (d,  $J = 7.5$  Hz, H-2', 1H), 7.38 (br s, NH, 1H), 7.24–7.27 (m, H-3', H-11', 3H), 7.23 (d,  $J = 7.5$  Hz, H-5', 1H), 7.08–7.13 (m, H-4', 1H), 6.84 (d,  $J = 8.7$  Hz, H-12', 2H), 6.38 (d,  $J = 15.8$  Hz, H-9', 1H), 6.18 (dt,  $J = 15.8, 6.5$  Hz, H-8', 1H), 3.80 (s, H-14', 3H), 3.52 (d,  $J = 6.5$  Hz, H-7', 2H), 2.47 (sept,  $J = 6.8$  Hz, H-16', 1H), 1.20 (d,  $J = 6.8$  Hz, H-17', 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 175.1 (C-15'), 159.2 (C-13'), 135.6 (C-1'), 131.2 (C-9'), 130.2 (C-5'), 130.1 (C-6'), 129.4 (C-10'), 127.5 (C-3'), 127.3 (C-11'), 125.3 (C-8'), 125.0 (C-4'), 123.3 (C-2'), 114.0 (C-12'), 55.3 (C-14'), 36.5 (C-16'), 36.1 (C-7'), 19.6 (C-17'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 310.1823,  $\text{C}_{20}\text{H}_{24}\text{NO}_2$  requires 310.1807.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)butyramide **7c**. IR (neat)  $\nu$ : 3290 (w, NH), 3005 (w), 2959 (w), 1648 (s, C=O), 1511 (s), 1453 (m), 1381 (w), 1291 (m), 1175 (m), 1159, 1037 (m, C–O), 829 (w), 747 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.91 (d,  $J = 8.0$  Hz, H-2', 1H), 7.34 (br s, NH, 1H), 7.28 (br dd,  $J = 8.0, 7.5$  Hz, H-3', 1H), 7.27 (br d,  $J = 8.5$  Hz, H-11', 2H),

7.23 (d,  $J = 7.5$  Hz, H-5', 1H), 7.12 (t,  $J = 7.5$  Hz, H-4', 1H), 6.85 (br d,  $J = 8.5$  Hz H-12', 2H), 6.41 (br d,  $J = 16.0$  Hz, H-9', 1H), 6.18 (dt,  $J = 16.0, 6.0$  Hz, H-8', 1H), 3.80 (s, H-14', 3H), 3.52 (br d,  $J = 6.0$  Hz, H-7', 2H), 2.28 (t,  $J = 7.5$  Hz, H-16', 2H), 1.70 (sext,  $J = 7.5$  Hz, H-17', 2H), 0.95 (t,  $J = 7.5$  Hz, H-18', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.2 (C-15'), 159.2 (C-13'), 136.2 (C-1'), 131.2 (C-9'), 130.2 (C-5'), 130.0 (C-6'), 129.4 (C-10'), 127.5 (C-3'), 127.3 (C-11'), 125.3 (C-8'), 125.0 (C-4'), 123.5 (C-2'), 114.0 (C-12'), 55.3 (C-14'), 39.7 (C-16'), 36.2 (C-7'), 19.2 (C-17'), 13.7 (C-18'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 310.1816,  $\text{C}_{20}\text{H}_{24}\text{NO}_2$  requires 310.1807.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)pentanamide **7d**. IR (neat)  $\nu$ : 3262 (w, NH), 3002 (w), 2959 (w), 1652 (s, C=O), 1509 (s), 1450 (m), 1380 (w), 1292 (w), 1174 (m), 1037 (m, C–O), 813 (w), 747 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.94 (d,  $J = 7.7$  Hz, H-2', 1H), 7.38 (br s, NH, 1H), 7.30 (d,  $J = 8.8$  Hz, H-11', 2H), 7.27–7.31 (m, H-3', 1H), 7.25 (d,  $J = 7.7$  Hz, H-5', 1H), 7.10–7.16 (m, H-4', 1H), 6.87 (d,  $J = 8.8$  Hz, H-12', 2H), 6.42 (d,  $J = 15.8$  Hz, H-9', 1H), 6.20 (dt,  $J = 15.8, 6.0$  Hz, H-8', 1H), 3.82 (s, H-14', 3H), 3.54 (d,  $J = 6.0$  Hz, H-7', 2H), 2.32 (t,  $J = 7.5$  Hz, H-16', 2H), 1.64–1.73 (m, H-17', 2H), 1.34–1.39 (m, H-18', 2H), 0.90 (t,  $J = 7.5$  Hz, H-19', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.3 (C-15'), 159.2 (C-13'), 136.3 (C-1'), 131.2 (C-9'), 130.2 (C-5'), 129.9 (C-6'), 129.4 (C-10'), 127.5 (C-3'), 127.3 (C-11'), 125.3 (C-8'), 125.0 (C-4'), 123.3 (C-2'), 114.0 (C-12'), 55.3 (C-14'), 37.6 (C-16'), 36.2 (C-7'), 27.8 (C-17'), 22.4 (C-18'), 13.8 (C-19'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 324.1958,  $\text{C}_{21}\text{H}_{26}\text{NO}_2$  requires 324.1964.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)hexanamide **7e**. IR (neat)  $\nu$ : 3278 (w, NH), 2952 (w), 2929 (w), 1651 (s, C=O), 1510 (s), 1451 (m), 1378 (w), 1296 (m), 1176 (m), 1037 (m, C–O), 824 (w), 747 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.92 (d,  $J = 7.8$  Hz, H-2', 1H), 7.36 (br s, NH, 1H), 7.27–7.30 (m, H-3', 1H), 7.27 (d,  $J = 8.8$  Hz, H-11', 2H), 7.22 (d,  $J = 7.8$  Hz, H-5', 1H), 7.09–7.13 (m, H-4', 1H), 6.84 (d,  $J = 8.5$  Hz, H-12', 2H), 6.40 (d,  $J = 15.5$  Hz, H-9', 1H), 6.18 (dt,  $J = 15.5, 6.5$  Hz, H-8', 1H), 3.80 (s, H-14', 3H), 3.52 (d,  $J = 6.5$  Hz, H-7', 2H), 2.29 (t,  $J = 7.2$  Hz, H-16', 2H), 1.63–1.71 (m, H-17', 2H), 1.34–1.36 (m, H-18', 2H), 1.27–1.29 (m, H-19', 2H), 0.85 (t,  $J = 7.2$  Hz, H-20', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.3 (C-15'), 159.2 (C-13'), 136.3 (C-1'), 131.2 (C-9'), 130.3 (C-5'), 130.2 (C-6'), 129.4 (C-10'), 127.5 (C-3'), 127.3 (C-11'), 125.3 (C-8'), 125.01 (C-4'), 123.3 (C-2'), 114.02 (C-12'), 55.3 (C-14'), 37.6 (C-16'), 36.2 (C-7'), 31.4 (C-18'), 25.43 (C-17'), 22.3 (C-19'), 13.87 (C-20'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 338.2103,  $\text{C}_{22}\text{H}_{28}\text{NO}_2$  requires 338.2120.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)decanamide **7f**. IR (neat)  $\nu$ : 3297 (w, NH), 2954 (w), 2920 (m), 1648 (m, C=O), 1509 (s), 1453 (m), 1378 (w), 1293 (m), 1174 (m), 1034 (m, C–O), 827 (w), 748 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.90 (d,  $J = 7.5$  Hz, H-2', 1H), 7.42 (br s, NH, 1H), 7.27 (d,  $J = 8.6$  Hz, H-11', 2H), 7.23 (d,  $J = 7.5$  Hz, H-5', 1H), 7.21–7.25 (m, H-3', 1H), 7.08–7.13 (m, H-4', 1H), 6.84 (d,  $J = 8.5$  Hz, H-12', 2H), 6.41 (d,  $J = 16.0$  Hz, H-9', 1H), 6.18 (dt,  $J = 16.0, 6.6$  Hz, H-8', 1H), 3.80 (s, H-14', 3H), 3.51 (d,  $J = 6.6$  Hz, H-7', 2H), 2.27–2.33 (m, H-16', 2H), 1.62–1.70 (m, H-17', 2H), 1.15–1.28 (m, H-18', H-19', H-20', H-21', H-22', H-23', 12H), 0.89 (t,  $J = 6.9$  Hz, H-24', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.4 (C-15'), 159.2 (C-13'), 136.2 (C-1'), 131.2 (C-9'), 130.1 (C-5'), 129.9 (C-6'), 129.4 (C-10'), 127.4 (C-3'), 127.2 (C-11'), 125.3 (C-8'), 125.0 (C-4'), 123.5 (C-2'), 113.99 (C-12'), 55.2 (C-14'), 37.5 (C-16'), 36.1 (C-7'), 31.79 (C-22'), 29.4 (C-21'), 29.3 (C-20'), 29.2 (C-18', C-19'), 25.70 (C-17'), 22.6 (C-23'), 14.0 (C-24'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 394.2741,  $\text{C}_{26}\text{H}_{36}\text{NO}_2$  requires 394.2746.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)cyclohexanecarboxamide **7g**. IR (neat)  $\nu$ : 3260 (w, NH), 3034 (w), 2931 (w), 1652 (s, C=O), 1511 (s), 1450 (m), 1384 (w), 1300 (w), 1175 (w), 1039 (m, C–O), 824 (w), 747 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.97 (d,  $J = 7.6$  Hz, H-2', 1H), 7.38 (br s, NH, 1H), 7.28 (d,  $J = 8.8$  Hz, H-11', 2H), 7.24–7.28 (m, H-3', 1H), 7.21–7.24 (m, H-5', 1H), 7.09 (t,  $J = 7.6$  Hz, H-4', 1H), 6.85 (d,  $J = 8.8$  Hz, H-12', 2H), 6.36 (d,  $J = 15.8$  Hz, H-9', 1H), 6.18 (dt,  $J = 15.8, 6.0$  Hz, H-8', 1H), 3.81 (s, H-14', 3H), 3.52 (d,  $J = 6.0$  Hz, H-7', 2H), 2.18 (td,  $J = 11.7, 2.7$  Hz, H-16', 1H), 1.92 (d,  $J = 12.6$  Hz, H-17 $\alpha$ ', 2H), 1.75–1.83 (m, H-17 $\beta$ ', 2H), 1.65–1.72 (m, H-19 $\beta$ ', 1H), 1.40–1.49 (m, H-18 $\alpha$ ', 2H), 1.15–1.34

(m, H-18 $\beta'$ , H-19 $\alpha'$ , 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 174.1 (C-15'), 159.2 (C-13'), 136.4 (C-1'), 131.4 (C-9'), 130.2 (C-5'), 130.1 (C-6'), 129.3 (C-10'), 127.5 (C-3'), 127.3 (C-11'), 125.3 (C-8'), 124.8 (C-4'), 123.2 (C-2'), 114.1 (C-12'), 55.3 (C-14'), 46.5 (C-16'), 36.3 (C-7'), 29.8 (C-17'), 25.7 (C-18', C-19'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 350.2123,  $\text{C}_{23}\text{H}_{28}\text{NO}_2$  requires 350.2120.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)benzamide **7h**. IR (neat)  $\nu$ : 3259 (w, NH), 3030 (w), 2834 (w), 1647 (s, C=O), 1512 (s), 1483 (s), 1440 (w), 1300 (m), 1176 (m), 1037 (m, C–O), 815 (w), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.16 (br s, NH, 1H), 8.04 (d,  $J = 7.7$  Hz, H-2', 1H), 7.70 (d,  $J = 7.4$  Hz, H-17', 2H), 7.43 (t,  $J = 7.4$  Hz, H-19', 1H), 7.29 (t,  $J = 7.4$  Hz, H-18', 2H), 7.26–7.33 (m, H-3', 1H), 7.22 (d,  $J = 8.7$  Hz, H-11', 2H), 7.20–7.23 (m, H-5', 1H), 7.10 (td,  $J = 7.7, 1.2$  Hz, H-4', 1H), 6.80 (d,  $J = 8.7$  Hz, H-12', 2H), 6.42 (d,  $J = 16.0$  Hz, H-9', 1H), 6.17 (dt,  $J = 16.0, 6.0$  Hz, H-8', 1H), 3.76 (s, H-14', 3H), 3.53 (d,  $J = 6.0$  Hz, H-7', 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 165.4 (C-15'), 159.3 (C-13'), 136.6 (C-1'), 134.8 (C-16'), 134.8 (C-8'), 131.7 (C-9', C-19'), 130.3 (C-5'), 129.99 (C-6'), 129.1 (C-10'), 128.7 (C-18'), 127.7 (C-3'), 127.4 (C-11'), 127.0 (C-17'), 125.2 (C-8'), 125.1 (C-4'), 123.1 (C-2'), 114.1 (C-12'), 55.2 (C-14'), 36.8 (C-7'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 344.1674,  $\text{C}_{23}\text{H}_{22}\text{NO}_2$  requires 344.1651.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)-2-methylbenzamide **7i**. IR (neat)  $\nu$ : 3275 (w, NH), 3027 (w), 2997 (w), 1646 (s, C=O), 1514 (s), 1444 (m), 1306 (m), 1271 (m), 1249, 1177 (m), 1037 (m, C–O), 827 (w), 748 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.16 (d,  $J = 7.5$  Hz, H-2', 1H), 7.75 (br s, NH, 1H), 7.37 (br d,  $J = 8.0$  Hz, H-21', 1H), 7.34 (dd,  $J = 7.5, 7.0$  Hz, H-19', 1H), 7.33 (td,  $J = 7.5, 1.0$  Hz, H-3', 1H), 7.27 (dd,  $J = 7.5, 1.0$  Hz, H-5', 1H), 7.23 (d,  $J = 7.5$  Hz, H-18', 1H), 7.17 (br d,  $J = 8.5$  Hz, H-11', 2H), 7.16 (ddd,  $J = 8.0, 7.0, 1.0$ , H-20', 1H), 7.08 (t,  $J = 7.5$  Hz, H-4', 1H), 6.82 (br d,  $J = 8.5$  Hz, H-12', 2H), 6.30 (dt,  $J = 16.0, 1.5$  Hz, H-9', 1H), 6.16 (dt,  $J = 16.0, 6.5$  Hz, H-8', 1H), 3.81 (s, H-14', 3H), 3.55 (dd,  $J = 6.5, 1.5$  Hz, H-7', 2H), 2.48 (s, H-22', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 167.9 (C-15'), 159.2 (C-13'), 136.7 (C-1'), 136.48 (C-16'), 136.2 (C-17'), 131.5 (C-19'), 131.33 (C-9'), 130.3, 130.17 (C-5', C-18'), 129.9 (C-6'), 129.3 (C-10'), 127.6 (C-3'), 127.3 (C-11'), 126.65 (C-21'), 125.8 (C-20'), 125.2 (C-8'), 125.0 (C-4'), 122.9 (C-2'), 113.9 (C-12'), 55.3 (C-14'), 36.3 (C-7'), 19.9 (C-22'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 358.1801,  $\text{C}_{24}\text{H}_{24}\text{NO}_2$  requires 358.1807.

(*E*)-*N*-(2-(3-(4-Methoxyphenyl)allyl)phenyl)furan-2-carboxamide **7j**. IR (neat)  $\nu$ : 3355 (w, NH), 3126 (w), 2934 (w), 1669 (m, C=O), 1510 (s), 1450 (m), 1301 (m), 1164 (m), 1010 (m, C–O), 835 (w), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 8.15 (br s, NH, 1H), 8.10 (d,  $J = 8.2$  Hz, H-19', 1H), 7.39 (d,  $J = 7.5$  Hz, H-2', 1H), 7.29 (d,  $J = 7.6$  Hz, H-11', 2H), 7.26–7.31 (m, H-3', H-5', 2H), 7.12–7.15 (m, H-4', H-17', 2H), 6.85 (d,  $J = 7.6$  Hz, H-12', 2H), 6.54–6.57 (m, H-18', 1H), 6.52 (d,  $J = 15.5$  Hz, H-9', 1H), 6.20 (dt,  $J = 15.5, 6.1$  Hz, H-8', 1H), 3.80 (s, H-14, 3H), 3.61 (d,  $J = 6.1$  Hz, H-7', 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 159.2 (C-13'), 156.0 (C-15'), 148.0 (C-16'), 144.2 (C-19'), 135.9 (C-1'), 131.9 (C-9'), 130.2 (C-5'), 130.0 (C-6'), 129.54 (C-10'), 127.6 (C-3'), 127.3 (C-11'), 125.0 (C-8'), 124.8 (C-4'), 122.9 (C-2'), 115.08 (C-17'), 114.0 (C-12'), 112.4 (C-18'), 55.2 (C-14'), 36.6 (C-7'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 334.1445,  $\text{C}_{21}\text{H}_{20}\text{NO}_3$  requires 334.1443.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)acetamide **8a**. IR (neat)  $\nu$ : 3348 (w, OH), 3229 (w, NH), 3125 (w), 2965 (w), 1636 (m, C=O), 1517 (s), 1460 (w), 1374 (w), 1273 (s), 1236 (m), 1175 (m), 1033 (m, C–O), 868 (w), 822 (w), 797 (w), 756 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.77 (d,  $J = 8.0$  Hz, H-2, 1H), 7.38 (d,  $J = 7.5$  Hz, H-5, 1H), 7.29 (br s, NH, 1H), 6.64–7.17 (m, H-3, H-4, H-11, H-14, H-15, 5H), 6.45 (br d,  $J = 15.5$  Hz, H-7, 1H), 6.26 (dt,  $J = 15.5, 7.0$  Hz, H-8, 1H), 5.56 (s, OH, 1H), 3.89 (s, H-16, 3H), 3.51 (d,  $J = 7.0$  Hz, H-9, 2H), 2.15 (s, H-18, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 168.3 (C-17), 146.6 (C-12), 144.2 (C-13), 134.2 (C-1), 134.0 (C-8), 131.5 (C-10), 130.5 (C-6), 127.9 (C-3), 127.0 (C-5), 125.7 (C-7), 125.4 (C-4), 123.8 (C-2), 121.2 (C-15), 114.43 (C-14), 111.2 (C-11), 55.95 (C-16), 39.2 (C-9), 24.2 (C-18). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 298.1435,  $\text{C}_{18}\text{H}_{20}\text{NO}_3$  requires 298.1443.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)isobutyramide **8b**. IR (neat)  $\nu$ : 3398 (w, OH), 3291 (m, NH), 3016 (w), 2970 (w), 1654 (s, C=O), 1509 (s), 1446 (m), 1371 (w), 1273 (s), 1236 (s), 1155 (m), 1038 (m, C–O), 848 (m), 812 (w), 798 (w), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR

(CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.84 (d,  $J$  = 7.6 Hz, H-2, 1H), 7.43 (d,  $J$  = 7.6 Hz, H-5, 1H), 7.36 (br s, NH, 1H), 7.21 (td,  $J$  = 7.6, 1.7 Hz, H-3, 1H), 7.06 (t,  $J$  = 7.6 Hz, H-4, 1H), 6.72–6.74 (m, H-11, H-14, H-15, 3H), 6.42 (d,  $J$  = 15.8 Hz, H-7, 1H), 6.27 (dt,  $J$  = 15.8, 6.5 Hz, H-8, 1H), 5.61 (br s, OH, 1H), 3.88 (s, H-16, 3H), 3.50 (d,  $J$  = 6.5 Hz, H-9, 2H), 2.47 (sept,  $J$  = 7.0 Hz, H-18, 1H), 1.20 (d,  $J$  = 7.0 Hz, H-19, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 175.1 (C-17), 146.7 (C-13), 144.2 (C-12), 135.7 (C-1), 134.2 (C-8), 131.4 (C-10), 130.0 (C-6), 127.9 (C-3), 127.0 (C-5), 125.6 (C-7), 124.9 (C-4), 122.8 (C-2), 121.3 (C-15), 114.7 (C-14), 111.2 (C-11), 55.9 (C-16), 39.2 (C-9), 36.7 (C-18), 19.6 (C-19). HRMS (+ESI) [M + H]<sup>+</sup>: 326.1755, C<sub>20</sub>H<sub>24</sub>NO<sub>3</sub> requires 326.1756.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)butyramide **8c**. IR (neat)  $\nu$ : 3399 (w, OH), 3269 (w, NH), 3053 (w), 2936 (w), 1646 (s, C=O), 1510 (s), 1453 (m), 1376 (w), 1271 (s), 1229 (s), 1155 (m), 1034 (m, C–O), 849 (w), 806 (w), 794 (w), 756 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.82 (d,  $J$  = 7.7 Hz, H-2, 1H), 7.32 (br s, NH, 1H), 7.37 (d,  $J$  = 7.7 Hz, H-5, 1H), 7.08–7.09 (m, H-3, 1H), 7.01 (t,  $J$  = 7.7 Hz, H-4, 1H), 6.73–6.75 (m, H-11, H-14, H-15, 3H), 6.42 (d,  $J$  = 15.3 Hz, H-7, 1H), 6.26 (dt,  $J$  = 15.3, 7.1 Hz, H-8, 1H), 5.57 (s, OH, 1H), 3.88 (s, H-16, 3H), 3.50 (d,  $J$  = 7.1 Hz, H-9, 2H), 2.29 (t,  $J$  = 7.3 Hz, H-18, 2H), 1.71 (sext,  $J$  = 7.3 Hz, H-19, 2H), 0.96 (t,  $J$  = 7.3 Hz, H-20, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 171.2 (C-17), 146.6 (C-13), 144.2 (C-12), 134.2 (C-1), 134.1 (C-8), 131.4 (C-10), 130.0 (C-6), 127.9 (C-3), 127.0 (C-5), 125.6 (C-7), 125.1 (C-4), 123.5 (C-2), 121.2 (C-15), 114.4 (C-14), 111.2 (C-11), 56.0 (C-16), 39.7 (C-18), 39.2 (C-9), 19.2 (C-19), 13.7 (C-20). HRMS (+ESI) [M + H]<sup>+</sup>: 326.1768, C<sub>20</sub>H<sub>24</sub>NO<sub>3</sub> requires 326.1756.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)pentanamide **8d**. IR (neat)  $\nu$ : 3302 (w, OH), 3270 (w, NH), 3027 (w), 2961 (w), 1647 (s, C=O), 1510 (s), 1452 (m), 1377 (w), 1272 (m), 1229 (s), 1155 (m), 1039 (m, C–O), 850 (w), 818 (w), 782 (w), 755 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.80 (d,  $J$  = 7.5 Hz, H-2, 1H), 7.09–7.41 (m, NH, H-3, H-4, H-5, 4H), 6.72–6.73 (m, H-11, H-14, H-15, 3H), 6.43 (d,  $J$  = 15.3 Hz, H-7, 1H), 6.26 (dt,  $J$  = 15.3, 6.9 Hz, H-8, 1H), 5.64 (s, OH, 1H), 3.88 (s, H-16, 3H), 3.50 (d,  $J$  = 6.9 Hz, H-9, 2H), 2.30 (t,  $J$  = 7.5 Hz, H-18, 2H), 1.63–1.66 (m, H-19, 2H), 1.32–1.37 (m, H-20, 2H), 0.94 (t,  $J$  = 7.5 Hz, H-21, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 171.4 (C-17), 146.6 (C-13), 144.2 (C-12), 134.2 (C-1), 134.0 (C-8), 131.4 (C-10), 130.1 (C-6), 127.8 (C-3), 127.0 (C-5), 125.7 (C-7), 125.1 (C-4), 123.5 (C-2), 121.2 (C-15), 114.4 (C-14), 111.2 (C-11), 55.9 (C-16), 39.2 (C-9), 37.3 (C-18), 27.8 (C-19), 22.31 (C-20), 13.72 (C-21). HRMS (+ESI) [M + H]<sup>+</sup>: 340.1908, C<sub>21</sub>H<sub>26</sub>NO<sub>3</sub> requires 340.1913.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)hexanamide **8e**. IR (neat)  $\nu$ : 3394 (w, OH), 3292 (w, NH), 3027 (w), 2955 (w), 1648 (s, C=O), 1511 (s), 1450 (m), 1372 (w), 1274 (s), 1236 (s), 1154 (m), 1038 (m, C–O), 851 (w), 817 (w), 785 (w), 754 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.81 (d,  $J$  = 8.1 Hz, H-2, 1H), 7.09–7.38 (m, NH, H-3, H-4, H-5, 4H), 6.72–6.73 (m, H-11, H-14, H-15, 3H), 6.44 (d,  $J$  = 15.6 Hz, H-7, 1H), 6.25 (dt,  $J$  = 15.6, 6.9 Hz, H-8, 1H), 5.60 (s, OH, 1H), 3.88 (s, H-16, 3H), 3.50 (d,  $J$  = 6.9 Hz, H-9, 2H), 2.30 (t,  $J$  = 7.2 Hz, H-18, 2H), 1.65–1.68 (m, H-19, 2H), 1.34–1.36 (m, H-20, H-21, 4H), 0.92 (t,  $J$  = 7.2 Hz, H-22, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 171.4 (C-17), 146.6 (C-13), 144.2 (C-12), 134.3 (C-1), 134.1 (C-8), 131.5 (C-10), 130.0 (C-6), 127.9 (C-3), 127.0 (C-5), 125.7 (C-7), 125.1 (C-4), 123.5 (C-2), 121.2 (C-15), 114.4 (C-14), 111.2 (C-11), 55.91 (C-16), 39.2 (C-9), 37.5 (C-18), 31.4 (C-20), 25.4 (C-19), 22.4 (C-21), 13.9 (C-22). HRMS (+ESI) [M + H]<sup>+</sup>: 354.2060, C<sub>22</sub>H<sub>28</sub>NO<sub>3</sub> requires 354.2069.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)decanamide **8f**. IR (neat)  $\nu$ : 3399 (w, OH), 3271 (w, NH), 3068 (w), 2923 (m), 2853 (m), 1650 (s, C=O), 1510 (s), 1452 (m), 1377 (w), 1270 (m), 1226 (s), 1155 (m), 1039 (m, C–O), 850 (w), 822 (w), 787 (w), 753 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.83 (d,  $J$  = 7.9 Hz, H-2, 1H), 7.37 (d,  $J$  = 7.9 Hz, H-5, 1H), 7.32 (br s, NH, 1H), 7.30–7.32 (m, H-3, 1H), 7.07–7.09 (m, H-4, 1H), 6.73–6.74 (m, H-11, H-14, H-15, 3H), 6.44 (d,  $J$  = 15.4 Hz, H-7, 1H), 6.25 (dt,  $J$  = 15.4, 6.8 Hz, H-8, 1H), 5.54 (s, OH, 1H), 3.89 (s, H-16, 3H), 3.50 (d,  $J$  = 6.8 Hz, H-9, 2H), 2.30 (t,  $J$  = 7.3 Hz, H-18, 2H), 1.62–1.70 (m, H-19, 2H), 1.23–1.29 (m, H-20, H-21, H-22, H-23, H-24, H-25, 12H), 0.87 (t,  $J$  = 7.3 Hz, H-26, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 171.4 (C-17), 146.6 (C-13), 144.2 (C-12),

134.1 (C-1), 134.1 (C-8), 131.5 (C-10), 129.9 (C-6), 127.9 (C-3), 127.1 (C-5), 125.1 (C-7, C-4), 123.5 (C-2), 121.2 (C-15), 114.4 (C-14), 111.1 (C-11), 55.9 (C-16, OCH<sub>3</sub>), 39.3 (C-9), 37.7 (C-18), 31.8 (C-24), 29.5 (C-23), 29.4 (C-22), 29.34 (C-20), 29.27 (C-21), 25.8 (C-19), 22.6 (C-25), 14.1 (C-26). HRMS (+ESI) [M + H]<sup>+</sup>: 410.2691, C<sub>26</sub>H<sub>36</sub>NO<sub>3</sub> requires 410.2695.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)cyclohexanecarboxamide **8g**. IR (neat)  $\nu$ : 3394 (w, OH), 3290 (m, NH), 3030 (w), 2928 (m), 1649 (s, C=O), 1512 (s), 1447 (m), 1386 (w), 1280 (m), 1226 (s), 1156 (m), 1039 (m, C–O), 859 (w), 830 (w), 783 (w), 750 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.84 (d, *J* = 8.0 Hz, H-2, 1H), 7.39 (br s, NH, 1H), 7.37 (t, *J* = 8.0 Hz, H-5, 1H), 7.25–7.29 (m, H-3, 1H), 7.08–7.11 (m, H-4, 1H), 6.73–6.74 (m, H-11, H-14, H-15, 3H), 6.38 (d, *J* = 15.3 Hz, H-7, 1H), 6.27 (dt, *J* = 15.3, 6.4 Hz, H-8, 1H), 5.57 (s, OH, 1H), 3.89 (s, H-16, 3H), 3.50 (d, *J* = 6.4 Hz, H-9, 2H), 2.15–2.21 (m, H-18, 1H), 1.92 (d, *J* = 11.5 Hz, H-19 $\alpha$ , 2H), 1.75–1.77 (m, H-19 $\beta$ , 2H), 1.42–1.49 (m, H-20 $\alpha$ , 2H), 1.16–1.28 (m, H-20 $\beta$ , H-21, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 174.2 (C-17), 146.6 (C-13), 144.2 (C-12), 134.3 (C-1), 134.2 (C-8), 131.3 (C-10), 129.4 (C-6), 127.8 (C-3), 127.0 (C-5), 125.6 (C-4), 125.0 (C-7), 123.4 (C-2), 121.3 (C-15), 114.4 (C-14), 111.3 (C-11), 55.92 (C-16), 46.3 (C-18), 39.2 (C-9), 29.8 (C-19), 25.7 (C-20, C-21). HRMS (+ESI) [M + H]<sup>+</sup>: 366.2065, C<sub>23</sub>H<sub>28</sub>NO<sub>3</sub> requires 366.2069.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)benzamide **8h**. IR (neat)  $\nu$ : 3528 (w, OH), 3225 (w, NH), 3062 (w), 3027, 2965 (w), 1649 (m, C=O), 1516 (s), 1484 (m), 1372 (w), 1272 (s), 1247 (m), 1157 (m), 1026 (m, C–O), 866 (w), 819 (w), 793 (w), 754 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 6.68–8.22 (m, NH, H-3, H-4, H-5, H-11, H-14, H-15, H-19, H-20, H-21, 12H), 8.04 (d, *J* = 7.5 Hz, H-2, 1H), 6.47–6.50 (m, H-7, 1H), 6.30–6.37 (m, H-8, 1H), 5.50 (s, OH, 1H), 3.88 (s, H-16, 3H), 3.51 (d, *J* = 6.0 Hz, H-9, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz), characteristic signals,  $\delta$ : 134.7 (C-8), 134.3 (C-1), 128.8 (C-20), 127.9 (C-3), 125.0 (C-4), 123.2 (C-2), 121.3 (C-15), 114.3 (C-14), 111.2 (C-11), 55.85 (C-16), 39.2 (C-9). HRMS (+ESI) [M + H]<sup>+</sup>: 360.1596, C<sub>23</sub>H<sub>22</sub>NO<sub>3</sub> requires 360.1600.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)-2-methylbenzamide **8i**. IR (neat)  $\nu$ : 3388 (w, OH), 3271 (w, NH), 3024 (w), 2965 (w), 1646 (s, C=O), 1515 (s), 1451 (m), 1379 (w), 1267 (s), 1236 (s), 1157 (w), 1032 (m, C–O), 866 (w), 834 (w), 790 (w), 751 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 8.00 (d, *J* = 8.0 Hz, H-2, 1H), 7.74 (br s, NH, 1H), 7.42 (d, *J* = 8.0 Hz, H-5, 1H), 7.36–7.40 (m, H-20, H-21, 2H), 7.35 (d, *J* = 7.5 Hz, H-23, 1H), 7.28 (t, *J* = 8.0 Hz, H-3, 1H), 7.15–7.21 (m, H-4, H-22, 2H), 6.68 (s, H-11, 1H), 6.72 (d, *J* = 8.2 Hz, H-14, H-15, 2H), 6.46 (d, *J* = 15.9 Hz, H-7, 1H), 6.30 (dt, *J* = 15.9, 6.3 Hz, H-8, 1H), 5.50 (s, OH, 1H), 3.80 (s, H-16, 3H), 3.48 (d, *J* = 6.3 Hz, H-9, 2H), 2.50 (s, H-24, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 167.9 (C-17), 146.3 (C-12), 144.3 (C-13), 136.7 (C-18), 136.4 (C-19), 134.3 (C-8), 134.1 (C-1), 131.3 (C-21), 131.2 (C-10), 130.24 (C-20), 130.0 (C-6), 127.9 (C-3), 127.1 (C-5), 126.5 (C-23), 126.1 (C-22), 125.8 (C-7), 125.4 (C-4), 125.0 (C-2), 121.2 (C-15), 114.37 (C-14), 111.2 (C-11), 55.7 (C-16), 39.1 (C-9), 19.9 (C-24). HRMS (+ESI) [M + H]<sup>+</sup>: 374.1743, C<sub>24</sub>H<sub>24</sub>NO<sub>3</sub> requires 374.1756.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)prop-1-en-1-yl)phenyl)furan-2-carboxamide **8j**. IR (neat)  $\nu$ : 3416 (w, OH), 3216 (w, NH), 3039 (w), 2954 (w), 1617 (m, C=O), 1511 (m), 1460 (m), 1350 (m), 1266 (m), 1227 (m), 1153 (m), 1035 (m, C–O), 885 (w), 826 (w), 785 (w), 758 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 8.43 (br s, NH, 1H), 8.12 (d, *J* = 7.9 Hz, H-21, 1H), 7.39 (d, *J* = 7.0 Hz, H-2, 1H), 7.29–7.33 (m, H-3, H-5, 2H), 7.15–7.20 (m, H-4, H-19, 2H), 6.78 (s, H-11, 1H), 6.75–6.77 (m, H-14, H-15, 2H), 6.55–6.58 (m, H-7, 1H), 6.54 (d, *J* = 7.9 Hz, H-20, 1H), 6.30–6.34 (m, H-8, 1H), 5.52 (s, OH, 1H), 3.88 (s, H-16, 3H), 3.54 (d, *J* = 6.0 Hz, H-9, 2H). HRMS (-ESI) [M-H]<sup>-</sup>: 348.1245, C<sub>21</sub>H<sub>19</sub>NO<sub>4</sub> requires 348.1236.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)acetamide **9a**. IR (neat)  $\nu$ : 3348 (w, OH), 3229 (w, NH), 3125 (w), 2965 (w), 1636 (m, C=O), 1517 (s), 1460 (w), 1374 (w), 1273 (s), 1236 (m), 1175 (m), 1033 (m, C–O), 868 (w), 822 (w), 797 (w), 756 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.86 (d, *J* = 8.0 Hz, H-2', 1H), 7.29 (br s, NH, 1H), 7.29 (ddd, *J* = 8.0, 7.5, 1.0 Hz, H-3', 1H), 7.24 (d, *J* = 8.0 Hz, H-5', 1H), 7.15 (dd, *J* = 8.0, 7.5 Hz, H-4', 1H), 6.89–6.82 (m, H11', H14', H15', 3H), 6.38 (dt, *J* = 16.0, 1.5 Hz, H-9', 1H), 6.16 (dt, *J* = 16.0, 6.5 Hz, H-8',

1H), 5.64 (s, OH, 1H), 3.89 (s, H-16', 3H), 3.53 (dd,  $J = 6.5, 1.5$  Hz, H-7', 2H), 2.12 (s, H-18', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$ : 168.2 (C-17'), 146.7 (C-12'), 145.6 (C-13'), 136.1 (C-1'), 131.5 (C-9'), 130.4 (C-6'), 130.3 (C-5'), 129.2 (C-10'), 127.6 (C-3'), 125.4, 125.3 (C-4', C-8'), 123.8 (C-2'), 120.0 (C-15'), 114.5 (C-14'), 108.0 (C-11'), 55.90 (C-16'), 36.1 (C-7'), 24.4 (C-18'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 298.1435,  $\text{C}_{18}\text{H}_{20}\text{NO}_3$  requires 298.1443.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)isobutyramide **9b**. IR (neat)  $\nu$ : 3398 (w, OH), 3291 (m, NH), 3016 (w), 2970 (w), 1654 (s, C=O), 1509 (s), 1446 (m), 1371 (w), 1273 (s), 1236 (s), 1155 (m), 1038 (m, C–O), 848 (m), 812 (w), 798 (w), 753 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.95 (d,  $J = 8.0$  Hz, H-2', 1H), 7.35 (br s, NH, 1H), 7.29 (ddd,  $J = 8.0, 7.5, 1.0$  Hz, H-3', 1H), 7.23 (br d,  $J = 7.5$  Hz, H-5', 1H), 7.13 (t,  $J = 7.5$  Hz, H-4', 1H), 6.85 (s, H-11', 1H), 6.84 (AB system,  $\delta_A = 6.84, \delta_B = 6.85, J_{AB} = 9.0$  Hz, H15', H14', 2H), 6.38 (br d,  $J = 16.0$  Hz, H-9', 1H), 6.16 (dt,  $J = 16.0, 6.0$  Hz, H-8', 1H), 5.73 (br s, OH, 1H), 3.87 (s, H-16', 3H), 3.53 (br d,  $J = 6.0$  Hz, H-7', 2H), 2.47 (sept,  $J = 7.0$  Hz, H-18', 1H), 1.21 (d,  $J = 7.0$  Hz, H-19', 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 175.1 (C-17'), 146.6 (C-12'), 145.5 (C-13'), 136.3 (C-1'), 131.6 (C-9'), 130.2 (C-5'), 130.0 (C-6'), 129.2 (C-10'), 127.5 (C-3'), 125.1, 125.0 (C-4', C-8'), 123.4 (C-2'), 119.9 (C-15'), 114.4 (C-14'), 108.0 (C-11'), 55.9 (C-16'), 36.7 (C-18'), 36.0 (C-7'), 19.6 (C-19'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 326.1755,  $\text{C}_{20}\text{H}_{24}\text{NO}_3$  requires 326.1756.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)butyramide **9c**. IR (neat)  $\nu$ : 3399 (w, OH), 3269 (w, NH), 3053 (w), 2936 (w), 1646 (s, C=O), 1510 (s), 1453 (m), 1376 (w), 1271 (s), 1229 (s), 1155 (m), 1034 (m, C–O), 849 (w), 806 (w), 794 (w), 756 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.92 (d,  $J = 7.7$  Hz, H-2', 1H), 7.32 (br s, NH, 1H), 7.28 (t,  $J = 7.7$  Hz, H-3', 1H), 7.23 (d,  $J = 7.7$  Hz, H-5', 1H), 7.13 (t,  $J = 7.7$  Hz, H-4', 1H), 6.88 (s, H-11', 1H), 6.84 (d,  $J = 8.2$  Hz, H-15', 1H), 6.82 (d,  $J = 8.2$  Hz, H-14', 1H), 6.38 (d,  $J = 15.9$  Hz, H-9', 1H), 6.16 (dt,  $J = 15.9, 6.2$  Hz, H-8', 1H), 5.69 (s, OH, 1H), 3.88 (s, H-16', 3H), 3.52 (d,  $J = 6.2$  Hz, H-7', 2H), 2.29 (t,  $J = 7.3$  Hz, H-18', 2H), 1.71 (sext,  $J = 7.3$  Hz, H-19', 2H), 0.96 (t,  $J = 7.3$  Hz, H-20', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.2 (C-17'), 146.7 (C-12'), 145.5 (C-13'), 136.3 (C-1'), 131.6 (C-9'), 130.2 (C-5'), 130.0 (C-6'), 129.2 (C-10'), 127.5 (C-3'), 125.2, 125.1 (C-4', C-8'), 123.5 (C-2'), 119.9 (C-15'), 114.4 (C-14'), 108.0 (C-11'), 55.9 (C-16'), 39.7 (C-18'), 36.1 (C-7'), 19.2 (C-19'), 13.7 (C-20'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 326.1768,  $\text{C}_{20}\text{H}_{24}\text{NO}_3$  requires 326.1756.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)pentanamide **9d**. IR (neat)  $\nu$ : 3302 (w, OH), 3270 (w, NH), 3027 (w), 2961 (w), 1647 (s, C=O), 1510 (s), 1452 (m), 1377 (w), 1272 (m), 1229 (s), 1155 (m), 1039 (m, C–O), 850 (w), 818 (w), 782 (w), 755 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.91 (d,  $J = 7.8$  Hz, H-2', 1H), 7.37 (br s, NH, 1H), 7.28 (t,  $J = 7.8$  Hz, H-3', 1H), 7.23 (d,  $J = 7.8$  Hz, H-5', 1H), 7.13 (t,  $J = 7.8$  Hz, H-4', 1H), 6.86 (s, H-11', 1H), 6.85 (d,  $J = 8.2$  Hz, H-15', 1H), 6.83 (d,  $J = 8.2$  Hz, H-14', 1H), 6.38 (d,  $J = 15.9$  Hz, H-9', 1H), 6.16 (dt,  $J = 15.9, 6.2$  Hz, H-8', 1H), 5.77 (s, OH, 1H), 3.87 (s, H-16', 3H), 3.52 (d,  $J = 6.2$  Hz, H-7', 2H), 2.30 (t,  $J = 7.4$  Hz, H-18', 2H), 1.63–1.66 (m, H-19', 2H), 1.32–1.37 (m, H-20', 2H), 0.88 (t,  $J = 7.4$  Hz, H-21', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.4 (C-17'), 146.7 (C-12'), 145.5 (C-13'), 136.2 (C-1'), 131.6 (C-9'), 130.2 (C-5'), 130.1 (C-6'), 129.2 (C-10'), 127.5 (C-3'), 125.2, 125.1 (C-4', C-8'), 123.5 (C-2'), 119.9 (C-15'), 114.5 (C-14'), 108.0 (C-11'), 55.8 (C-16'), 37.5 (C-18'), 36.1 (C-7'), 27.8 (C-19'), 22.34 (C-20'), 13.68 (C-21'). HRMS (+ESI)  $[\text{M} + \text{H}]^+$ : 340.1908,  $\text{C}_{21}\text{H}_{26}\text{NO}_3$  requires 340.1913.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)hexanamide **9e**. IR (neat)  $\nu$ : 3394 (w, OH), 3292 (w, NH), 3027 (w), 2955 (w), 1648 (s, C=O), 1511 (s), 1450 (m), 1372 (w), 1274 (s), 1236 (s), 1154 (m), 1038 (m, C–O), 851 (w), 817 (w), 785 (w), 754 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 7.92 (d,  $J = 7.7$  Hz, H-2', 1H), 7.36 (br s, NH, 1H), 7.28 (t,  $J = 7.7$  Hz, H-3', 1H), 7.24 (d,  $J = 7.7$  Hz, H-5', 1H), 7.13 (t,  $J = 7.7$  Hz, H-4', 1H), 6.86 (s, H-11', 1H), 6.85 (d,  $J = 8.2$  Hz, H-15', 1H), 6.84 (d,  $J = 8.2$  Hz, H-14', 1H), 6.38 (d,  $J = 15.9$  Hz, H-9', 1H), 6.15 (dt,  $J = 15.9, 6.2$  Hz, H-8', 1H), 5.73 (s, OH, 1H), 3.87 (s, H-16', 3H), 3.52 (d,  $J = 6.2$  Hz, H-7', 2H), 2.30 (t,  $J = 7.5$  Hz, H-18', 2H), 1.65–1.68 (m, H-19', 2H), 1.28–1.29 (m, H-20', H-21', 4H), 0.86 (t,  $J = 7.5$  Hz, H-22', 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125.8 MHz)  $\delta$ : 171.4 (C-17'), 146.7 (C-12'), 145.6 (C-13'), 136.3 (C-1'), 131.6 (C-9'), 130.2 (C-5'), 130.0 (C-6'), 129.2 (C-10'), 127.5 (C-3'), 125.2, 125.1 (C-4', C-8'), 123.5 (C-2'), 119.9 (C-15'), 114.5 (C-14'), 108.0 (C-11'),



55.86 (C-16'), 37.8 (C-18'), 36.1 (C-7'), 31.4 (C-20'), 25.4 (C-19'), 22.3 (C-21'), 13.8 (C-22'). HRMS (+ESI) [M + H]<sup>+</sup>: 354.2060, C<sub>22</sub>H<sub>28</sub>NO<sub>3</sub> requires 354.2069.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)decanamide **9f**. IR (neat)  $\nu$ : 3399 (w, OH), 3271 (w, NH), 3068 (w), 2923 (m), 2853 (m), 1650 (s, C=O), 1510 (s), 1452 (m), 1377 (w), 1270 (m), 1226 (s), 1155 (m), 1039 (m, C–O), 850 (w), 822 (w), 787 (w), 753 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.93 (d, *J* = 6.8 Hz, H-2', 1H), 7.32 (br s, NH, 1H), 7.29 (t, *J* = 6.8 Hz, H-3', 1H), 7.23 (d, *J* = 6.8 Hz, H-5', 1H), 7.13 (t, *J* = 6.8 Hz, H-4', 1H), 6.86 (s, H-11', 1H), 6.85 (d, *J* = 8.2 Hz, H-15', 1H), 6.83 (d, *J* = 8.2 Hz, H-14', 1H), 6.38 (d, *J* = 15.9 Hz, H-9', 1H), 6.16 (dt, *J* = 15.9, 6.2 Hz, H-8', 1H), 5.65 (s, OH, 1H), 3.88 (s, H-16', 3H), 3.52 (d, *J* = 6.2 Hz, H-7', 2H), 2.30 (t, *J* = 7.3 Hz, H-18', 2H), 1.62–1.70 (m, H-19', 2H), 1.23–1.29 (m, H-20', H-21', H-22', H-23', H-24', H-25', 12H), 0.87 (t, *J* = 7.3 Hz, H-26', 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 171.4 (C-17'), 146.7 (C-12'), 145.5 (C-13'), 136.3 (C-1'), 131.6 (C-9'), 130.2 (C-5'), 129.9 (C-6'), 129.2 (C-10'), 127.6 (C-3'), 125.2 (C-4', C-8'), 123.45 (C-2'), 120.0 (C-15'), 114.5 (C-14'), 107.9 (C-11'), 55.87 (C-16'), 37.9 (C-18'), 36.2 (C-7'), 31.8 (C-24'), 29.4 (C-23'), 29.32 (C-22'), 29.29 (C-20'), 29.2 (C-21'), 25.8 (C-19'), 22.6 (C-25'), 14.1 (C-26'). HRMS (+ESI) [M + H]<sup>+</sup>: 410.2691, C<sub>26</sub>H<sub>36</sub>NO<sub>3</sub> requires 410.2695.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)cyclohexanecarboxamide **9g**. IR (neat)  $\nu$ : 3394 (w, OH), 3290 (m, NH), 3030 (w), 2928 (m), 1649 (s, C=O), 1512 (s), 1447 (m), 1386 (w), 1280 (m), 1226 (s), 1156 (m), 1039 (m, C–O), 859 (w), 830 (w), 783 (w), 750 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 7.96 (d, *J* = 7.6 Hz, H-2', 1H), 7.39 (br s, NH, 1H), 7.28 (t, *J* = 7.6 Hz, H-3', 1H), 7.23 (d, *J* = 7.6 Hz, H-5', 1H), 7.11 (t, *J* = 7.6 Hz, H-4', 1H), 6.87 (d, *J* = 8.2 Hz, H-15', 1H), 6.85 (s, H-11', 1H), 6.84 (d, *J* = 8.2 Hz, H-14', 1H), 6.41 (d, *J* = 15.9 Hz, H-9', 1H), 6.16 (dt, *J* = 15.9, 6.2 Hz, H-8', 1H), 5.69 (s, OH, 1H), 3.88 (s, H-16', 3H), 3.53 (d, *J* = 6.2 Hz, H-7', 2H), 2.15–2.21 (m, H-18', 1H), 1.92 (d, *J* = 11.5 Hz, H-19 $\alpha$ ', 2H), 1.75–1.77 (m, H-19 $\beta$ ', 2H), 1.42–1.49 (m, H-20 $\alpha$ ', 2H), 1.16–1.28 (m, H-20 $\beta$ ', H-21', 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 174.2 (C-17'), 146.7 (C-12'), 145.5 (C-13'), 136.4 (C-1'), 131.8 (C-9'), 130.2 (C-5'), 129.8 (C-6'), 129.2 (C-10'), 127.5 (C-3'), 125.2 (C-8'), 124.9 (C-4'), 123.3 (C-2'), 120.0 (C-15'), 114.5 (C-14'), 107.9 (C-11'), 55.87 (C-16'), 46.5 (C-18'), 36.2 (C-7'), 29.8 (C-19'), 25.7 (C-20', C-21'). HRMS (+ESI) [M + H]<sup>+</sup>: 366.2065, C<sub>23</sub>H<sub>28</sub>NO<sub>3</sub> requires 366.2069.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)benzamide **9h**. IR (neat)  $\nu$ : 3528 (w, OH), 3225 (w, NH), 3062 (w), 3027, 2965 (w), 1649 (m, C=O), 1516 (s), 1484 (m), 1372 (w), 1272 (s), 1247 (m), 1157 (m), 1026 (m, C–O), 866 (w), 819 (w), 793 (w), 754 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 8.22 (s, NH, 1H), 8.12 (d, *J* = 7.5 Hz, H-2', 1H), 7.77 (d, *J* = 7.5 Hz, H-19', 2H), 7.51 (t, *J* = 7.5 Hz, H-21', 1H), 7.36 (t, *J* = 7.5 Hz, H-3', H-20', 3H), 7.29 (d, *J* = 7.5 Hz, H-5', 1H), 7.18 (t, *J* = 7.5 Hz, H-4', 1H), 6.87 (s, H-11', 1H), 6.86 (AB system,  $\delta_A$  = 6.84,  $\delta_B$  = 6.88, *J*<sub>AB</sub> = 8.5 Hz, H15', H14', 2H), 6.46 (br d, *J* = 16.0 Hz, H-9', 1H), 6.22 (dt, *J* = 16.0, 5.5 Hz, H-8', 1H), 5.66 (s, OH, 1H), 3.88 (s, H-16', 3H), 3.61 (d, *J* = 5.5 Hz, H-7', 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 165.4 (C-17'), 146.7 (C-12'), 145.6 (C-13'), 136.7 (C-1'), 134.8 (C-18'), 132.2 (C-9'), 131.8 (C-21'), 130.4 (C-5'), 129.9 (C-6'), 128.9 (C-10'), 128.8 (C-20'), 127.8 (C-3'), 127.1 (C-19'), 125.2 (C-8'), 125.0 (C-4'), 123.2 (C-2'), 120.2 (C-15'), 114.5 (C-14'), 107.9 (C-11'), 55.87 (C-16'), 36.8 (C-7'). HRMS (+ESI) [M + H]<sup>+</sup>: 360.1596, C<sub>23</sub>H<sub>22</sub>NO<sub>3</sub> requires 360.1600.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)-2-methylbenzamide **9i**. IR (neat)  $\nu$ : 3388 (w, OH), 3271 (w, NH), 3024 (w), 2965 (w), 1646 (s, C=O), 1515 (s), 1451 (m), 1379 (w), 1267 (s), 1236 (s), 1157 (w), 1032 (m, C–O), 866 (w), 834 (w), 790 (w), 751 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 8.16 (d, *J* = 7.9 Hz, H-2', 1H), 7.74 (br s, NH, 1H), 7.36–7.40 (m, H-20', H-21', 2H), 7.32 (d, *J* = 7.5 Hz, H-23', 1H), 7.28 (t, *J* = 7.9 Hz, H-3', 1H), 7.23 (d, *J* = 7.9 Hz, H-5', 1H), 7.17 (t, *J* = 7.5 Hz, H-22', 1H), 7.09 (t, *J* = 7.9 Hz, H-4', 1H), 6.76 (s, H-11', 1H), 6.83 (d, *J* = 8.2 Hz, H-14', H-15', 2H), 6.28 (d, *J* = 15.9 Hz, H-9', 1H), 6.14 (dt, *J* = 15.9, 6.2 Hz, H-8', 1H), 5.61 (s, OH, 1H), 3.86 (s, H-16', 3H), 3.56 (d, *J* = 6.2 Hz, H-7', 2H), 2.47 (s, H-24', 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 167.9 (C-17'), 146.6 (C-12'), 145.5 (C-13'), 136.7 (C-18'), 136.5 (C-19'), 136.2 (C-1'), 131.8 (C-9'), 131.3 (C-21'), 130.3 (C-5'), 130.15 (C-20'), 130.0 (C-6'), 129.0 (C-10'), 127.6 (C-3'), 126.7 (C-23'), 125.9 (C-22'), 125.5 (C-4'), 125.2 (C-8'), 124.8 (C-2'),

119.9 (C-15'), 114.39 (C-14'), 108.0 (C-11'), 55.8 (C-16'), 36.3 (C-7'), 19.9 (C-24'). HRMS (+ESI) [M + H]<sup>+</sup>: 374.1743, C<sub>24</sub>H<sub>24</sub>NO<sub>3</sub> requires 374.1756.

(*E*)-*N*-(2-(3-(4-Hydroxy-3-methoxyphenyl)allyl)phenyl)furan-2-carboxamide **9j**. IR (neat)  $\nu$ : 3416 (w, OH), 3216 (w, NH), 3039 (w), 2954 (w), 1617 (m, C=O), 1511 (m), 1460 (m), 1350 (m), 1266 (m), 1227 (m), 1153 (m), 1035 (m, C–O), 885 (w), 826 (w), 785 (w), 758 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 8.43 (br s, NH, 1H), 8.12 (d, *J* = 7.9 Hz, H-21', 1H), 7.29–7.33 (m, H-2', H-3', H-5', 3H), 7.15–7.20 (m, H-4', H-19', 2H), 6.89 (s, H-11', 1H), 6.87 (d, *J* = 8.2 Hz, H-15', 1H), 6.86 (d, *J* = 8.2 Hz, H-14', 1H), 6.55 (d, *J* = 15.9 Hz, H-9', 1H), 6.54 (d, *J* = 7.9 Hz, H-20', 1H), 6.18 (dt, *J* = 15.9, 6.2 Hz, H-8', 1H), 5.62 (s, OH, 1H), 3.88 (s, H-16', 3H), 3.62 (d, *J* = 6.2 Hz, H-7', 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.8 MHz)  $\delta$ : 156.1 (C-17'), 148.0 (C-18'), 146.7 (C-12'), 145.5 (C-13'), 144.1 (C-21'), 136.0 (C-1'), 132.3 (C-9'), 130.3 (C-5'), 130.0 (C-6'), 129.4 (C-10'), 127.7 (C-3'), 125.1 (C-4'), 124.7 (C-8'), 122.9 (C-2'), 120.2 (C-15'), 115.1 (C-19'), 114.3 (C-14'), 112.5 (C-20'), 107.7 (C-11'), 55.9 (C-16'), 36.6 (C-7'). HRMS (-ESI) [M-H]<sup>-</sup>: 348.1245, C<sub>21</sub>H<sub>19</sub>NO<sub>4</sub> requires 348.1236.

### 3.3. Bioassay Assessment

#### 3.3.1. Cell Cultures

MCF-7 and MDA-MB-231 human breast cancer cell lines, as well as MCF-10A human normal breast cell lines, were used in this study. These cells were acquired from the American Type Culture Collection (Manassas, VA, USA). MCF-7 and MDAMB-231 cells were regularly cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Waltham, MA, USA), and supplemented with 10% (*v/v*) foetal bovine serum (FBS; Gibco, Waltham, MA, USA) and 100 U/mL penicillin-streptomycin (PenStrep; Gibco, Waltham, MA, USA). MCF-10A cells were routinely cultured in DMEM/F12 (Gibco, Waltham, MA, USA) medium supplemented with 5% horse serum (Sigma-Aldrich, Burlington, MA, USA), 10  $\mu$ g/mL of insulin (Sigma-Aldrich, Burlington, MA, USA), 20 ng/mL of human epidermal growth factor (hEGF; ThermoFisher, Waltham, MA, USA), 0.5  $\mu$ g/mL of hydrocortisone (Sigma-Aldrich, Burlington, MA, USA) and 1 U/mL PenStrep. All cell lines were maintained in a humidified atmosphere with 5% CO<sub>2</sub> at 37 °C.

#### 3.3.2. Semi-Empirical Calculations

Molecular modelling was performed on compounds **6a**, **7a**, **8a**, **9a**, **6b**, **7b**, **8b** and **9b**. In each case, the most stable conformer was located and its geometry pre-optimised using the molecular mechanics MMFF94 force field [38], with the Avogadro 1.2.0 software [39,40]. Semi-empirical geometry optimisation was then performed using the PM7 method [41], with the MOPAC2016 software [42].

#### 3.3.3. Cytotoxicity Assays

The effects of the *N*-(2-cinnamylphenyl)amide products (i.e., isolated pure isomers) on MCF-7, MDA-MB-231 and MCF-10A were determined using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) proliferation assay. The cell lines were seeded in 96-well plates at a density of 1 × 10<sup>4</sup> cells/well and allowed to grow overnight for cell attachment. The cell lines were then treated with fresh assay medium, supplemented with increasing concentrations of tested compounds (10–100  $\mu$ M) and incubated for 24–72 h at 37 °C. For this assay, the blank and negative controls used were the culture medium alone (without cells) and cells with culture medium only (untreated cells), respectively. For the positive control, MCF-10A cells were treated with 30  $\mu$ M tamoxifen. At each incubation period (24, 48 and 72 h), 10  $\mu$ L of MTT solution (5 mg/mL) was added to each well, and cells were further incubated for 4 h at 37 °C in 5% CO<sub>2</sub>. The solution mixture in each well was replaced with 100  $\mu$ L of dimethyl sulfoxide (DMSO) to solubilise the MTT crystalline products. The optical density (O.D.) of each well was measured using a microplate reader (PowerWave-XS; Bio-Tek Instruments, Winooski, Vermont, USA) at 570 nm. The experiments were conducted in triplicate for each cell line.

A plot of % cell proliferation versus sample concentration was used to show the 50% inhibitory concentration ( $IC_{50}$ ). The selectivity index (SI) was used to indicate the cytotoxic selectivity of the samples against cancer cells and normal cells. It was calculated from the  $IC_{50}$  of the samples in normal cells versus cancer cells. An SI of less than 2 suggests the general toxicity of the drug/sample in cells, while an SI of more than 2 is an indication of the sample selectively targeting cancer cells [37]. All data were analysed and presented as means standard deviation ( $\pm SD$ ). Comparisons between each concentration of 18 samples were evaluated using Student's *t*-test, where  $p < 0.05$ ,  $p < 0.01$  or  $p < 0.001$  were considered as statistically significant relative to the untreated control cells.

#### 4. Conclusions

A series of new bio-inspired (*E*)-1,3-diarylpropene derivatives were synthesised using palladium-catalysed Heck cross-coupling reactions of 2-amidoiodobenzene derivatives with either estragole or eugenol, in 36–91% yields. In each case, two regioisomers were obtained, differing by the position of the (*E*) C=C double bond in the central propene subunit. Higher selectivities were obtained with eugenol, which was rationalised by the  $\beta$ -hydride elimination step being kinetically favoured at the position adjacent to the most electron-rich aromatic substituent. The products could be considered as stilbenoid and dihydrostilbenoid structural analogues, as well as hybrid molecules, and their cytotoxicities were evaluated using MTT proliferation assays against several cancer cell lines. However, only compounds **6d**, **6e**, **7d**, **7i** and **7e** exhibited low growth inhibition against MCF-7 and MDA-MB-231, respectively. Hence, no promising effects were disclosed, in comparison with the reference drug tamoxifen.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/molecules27175373/s1>, The procedure to synthesis of the intermediates and final compounds are shown in this section. Figure S1: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3a** in  $CDCl_3$ ; Figure S2: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3b** in  $CDCl_3$ ; Figure S3: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3c** in  $CDCl_3$ ; Figure S4: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3d** in  $CDCl_3$ ; Figure S5: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3e** in  $CDCl_3$ ; Figure S6: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3f** in  $CDCl_3$ ; Figure S7: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3g** in  $CDCl_3$ ; Figure S8: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3h** in  $CDCl_3$ ; Figure S9: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3i** in  $CDCl_3$ ; Figure S10: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **3j** in  $CDCl_3$ ; Figure S11: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6a,7a** in  $CDCl_3$ ; Figure S12: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **7a** in  $CDCl_3$ ; Figure S13: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6b,7b** in  $CDCl_3$ ; Figure S14: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6c,7c** in  $CDCl_3$ ; Figure S15: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **7c** in  $CDCl_3$ ; Figure S16: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6d,7d** in  $CDCl_3$ ; Figure S17: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6e,7e** in  $CDCl_3$ ; Figure S18: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6f,7f** in  $CDCl_3$ ; Figure S19: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **7f** in  $CDCl_3$ ; Figure S20: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6g,7g** in  $CDCl_3$ ; Figure S21: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6h,7h** in  $CDCl_3$ ; Figure S22: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **7h** in  $CDCl_3$ ; Figure S23: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6i,7i** in  $CDCl_3$ ; Figure S24: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6i** in  $CDCl_3$ ; Figure S25: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **7i** in  $CDCl_3$ ; Figure S26: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **6j,7j** in  $CDCl_3$ ; Figure S27: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **8a,9a** in  $CDCl_3$ ; Figure S28: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **9a** in  $CDCl_3$ ; Figure S29: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **8b,9b** in  $CDCl_3$ ; Figure S30: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **9b** in  $CDCl_3$ ; Figure S31: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **8c,9c** in  $CDCl_3$ ; Figure S32: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **8d,9d** in  $CDCl_3$ ; Figure S33: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **8e,9e** in  $CDCl_3$ ; Figure S34: 500 MHz  $^1H$ - and 126 MHz  $^{13}C$ -NMR spectra of compound **8f,9f** in

CDCl<sub>3</sub>; Figure S35: 500 MHz <sup>1</sup>H- and 126 MHz <sup>13</sup>C-NMR spectra of compound **8g,9g** in CDCl<sub>3</sub>; Figure S36: 500 MHz <sup>1</sup>H- and 126 MHz <sup>13</sup>C-NMR spectra of compound **8h,9h** in CDCl<sub>3</sub>; Figure S37: 500 MHz <sup>1</sup>H- and 126 MHz <sup>13</sup>C-NMR spectra of compound **9h** in CDCl<sub>3</sub>; Figure S38: 500 MHz <sup>1</sup>H- and 126 MHz <sup>13</sup>C-NMR spectra of compound **8i,9i** in CDCl<sub>3</sub>; Figure S39: 500 MHz <sup>1</sup>H- and 126 MHz <sup>13</sup>C-NMR spectra of compound **8j,9j** in CDCl<sub>3</sub>; Figure S40: ATR-FTIR spectrum of compound **3a.**; Figure S41: ATR-FTIR spectrum of compound **3b.**; Figure S42: ATR-FTIR spectrum of compound **3c.**; Figure S43: ATR-FTIR spectrum of compound **3d.**; Figure S44: ATR-FTIR spectrum of compound **3e.**; Figure S45: ATR-FTIR spectrum of compound **3f.**; Figure S46: ATR-FTIR spectrum of compound **3g.**; Figure S47: ATR-FTIR spectrum of compound **3h.**; Figure S48: ATR-FTIR spectrum of compound **3i.**; Figure S49: ATR-FTIR spectrum of compound **3j.**; Figure S50: ATR-FTIR spectrum of compound **6a,7a.**; Figure S51: ATR-FTIR spectrum of compound **6b,7b.**; Figure S52: ATR-FTIR spectrum of compound **6c,7c.**; Figure S53: ATR-FTIR spectrum of compound **6d,7d.**; Figure S54: ATR-FTIR spectrum of compound **6e,7e.**; Figure S55: ATR-FTIR spectrum of compound **6f,7f.**; Figure S56: ATR-FTIR spectrum of compound **6g,7g.**; Figure S57: ATR-FTIR spectrum of compound **6h,7h.**; Figure S58: ATR-FTIR spectrum of compound **6i,7i.**; Figure S59: ATR-FTIR spectrum of compound **6j,7j.**; Figure S60: ATR-FTIR spectrum of compound **8a,9a.**; Figure S61: ATR-FTIR spectrum of compound **8b,9b.**; Figure S62: ATR-FTIR spectrum of compound **8c,9c.**; Figure S63: ATR-FTIR spectrum of compound **8d,9d.**; Figure S64: ATR-FTIR spectrum of compound **8e,9e.**; Figure S65: ATR-FTIR spectrum of compound **8f,9f.**; Figure S66: ATR-FTIR spectrum of compound **8g,9g.**; Figure S67: ATR-FTIR spectrum of compound **8h,9h.**; Figure S68: ATR-FTIR spectrum of compound **8i,9i.**; Figure S69: ATR-FTIR spectrum of compound **8j,9j.**; Figure S70: HR-MS spectrum of compound **3d.**; Figure S71: HR-MS spectrum of compound **3f.**; Figure S72: HR-MS spectrum of compound **6a,7a.**; Figure S73: HR-MS spectrum of compound **6b,7b.**; Figure S74: HR-MS spectrum of compound **6c,7c.**; Figure S75: HR-MS spectrum of compound **6d,7d.**; Figure S76: HR-MS spectrum of compound **6e,7e.**; Figure S77: HR-MS spectrum of compound **6f,7f.**; Figure S78: HR-MS spectrum of compound **6g,7g.**; Figure S79: HR-MS spectrum of compound **6h,7h.**; Figure S80: HR-MS spectrum of compound **6i,7i.**; Figure S81: HR-MS spectrum of compound **6j,7j.**; Figure S82: HR-MS spectrum of compound **8a,9a.**; Figure S83: HR-MS spectrum of compound **8b,9b.**; Figure S84: HR-MS spectrum of compound **8c,9c.**; Figure S85: HR-MS spectrum of compound **8d,9d.**; Figure S86: HR-MS spectrum of compound **8e,9e.**; Figure S87: HR-MS spectrum of compound **8f,9f.**; Figure S88: HR-MS spectrum of compound **8g,9g.**; Figure S89: HR-MS spectrum of compound **8h,9h.**; Figure S90: HR-MS spectrum of compound **8i,9i.**; Figure S91: HR-MS spectrum of compound **8j,9j.** References [43–45] are mentioned in Supplementary Materials

**Author Contributions:** Conceptualization, M.N.A.; methodology, A.S.T., J.S., M.M., N.N.S.N.M.K., Y.S. and M.N.A.; validation, N.S.R., N.N.S.N.M.K., Y.S. and M.N.A.; formal analysis, A.S.T., J.S. and M.M.; investigation, A.S.T., J.S. and M.M.; resources, M.N.A.; data curation, A.S.T., J.S. and M.M.; writing—original draft preparation, A.S.T., J.S., M.M. and M.N.A.; writing—review and editing, N.S.R., N.N.S.N.M.K., Y.S. and M.N.A.; visualization, A.S.T., Y.S. and M.N.A.; supervision, N.S.R., Y.S. and M.N.A.; project administration, M.N.A.; funding acquisition, M.N.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** We are grateful to the Malaysian Ministry of Education (MOHE), and the French Ministry of Europe and Foreign Affairs, the French Ministry of Higher Education, Research and Innovation for the PHC Hibiscus grant (Hubert Curien Partnership) MyPAIR/1/2019/STG01/USM/2.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** This work was carried out in the frame of a collaboration between NPSO, SCS, Universiti Sains Malaysia and LSO, Ecole Polytechnique. The authors wish to thank the Universiti Sains Malaysia Fellowship Scheme (A.S.T.). We are also grateful to Awang K. and Abd. Rahim N. A. for their assistance.

**Conflicts of Interest:** The authors declare no conflict of interest.

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