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Synthesis, structural characterisation and biological evaluation of fluorinated analogues of resveratrol

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ABSTRACT

Resveratrol is a potential chemopreventive agent and can be isolated from grape skins and other dietary sources. The Wittig reaction and the decarbonylative Heck reaction were employed to synthesise analogues of this stilbene. Fluorinated derivatives of this stilbene were synthesised maintaining the 3,4′,5-substitution pattern. The hydroxyl groups were also replaced by amino groups and the biological activity evaluated. The compounds were assayed on a variety of cell lines, primarily the non-small lung carcinoma cell line DLKP-A. Analogues were evaluated alone and in combination with a known chemotherapeutic agent epirubicin.

1. Introduction

Secondary phenolic metabolites from plants display diverse biological activities. Epicatechins from green tea and the isoflavanoid genistein from soya products, have been shown to prevent tumour formation[1] and osteoporosis,[2] respectively. Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) **1** is a naturally occurring phytoalexin present in grapes and other food products. It has been shown to possess anti-oxidant, anti-inflammatory, anti-platelet, cancer preventative and anti-cancer properties.[3–5]

Resveratrol came to prominence during the course of research into the so-called 'French paradox'.[6] This concept stems from the observation that the population of France have a relatively high fat diet accompanied by a steady, albeit moderate intake of alcohol in the form of red wine, whilst their incidence of coronary heart disease is lower than expected. This trihydroxy stilbene has displayed in vitro growth inhibition in a number of human cancer cell lines.[7] In spite of its wide range of activity, the mechanistic basis of the in vivo activity of resveratrol remains unknown.[8] Numerous studies have pointed to its ability to function as a cellular anti-oxidant while others have demonstrated the inhibition of signalling kinases as its key function.[9] In addition to its potential as a tool to study protein signalling, it may also serve as a therapeutic lead, a disease preventative dietary supplement,[10] or as a topical treatment.[11]

Resveratrol is only present in small amounts in plant sources and its quantity depends on the stress situation of the plant. Isolation from plant sources is not viable, as it has been reported that only 92 μg of resveratrol are present in one gram of dried grape skins. Although both *cis*- and *trans*-isomers of resveratrol are found in nature, it is only the *trans*-isomer that exhibits bioactivity.[12] Reliable and efficient synthetic routes to resveratrol are therefore highly desirable. The majority of published routes for the synthesis of resveratrol are based on Wittig-like reactions. However stereoselective synthetic routes such as the Heck, Stille and Negishi reactions have more recently been employed.[13]

We now report the synthesis, structural characterisation and biological evaluation of fluorinated analogues of resveratrol. Maintaining the 3,4′,5-substitution pattern of resveratrol may result in novel stilbenes with improved biological activity.

2. Chemistry

A series of fluorinated analogues were synthesised maintaining the resveratrol substitution pattern in order to prepare a novel compound with greater bioactivity than that of resveratrol **1** (Fig. 1). Fluorinated resveratrol analogues were synthesised, some with hydroxyl groups and others with protected hydroxyl groups. In addition, novel compounds containing the known hydroxyl bioisostere, the amino group were also prepared.

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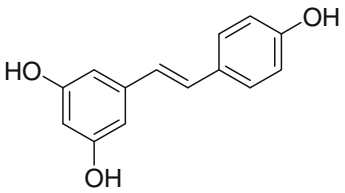


Figure 1. Resveratrol **1**.

The decarbonylative Heck reaction was employed as an efficient method for the synthesis of resveratrol (Scheme 1).[14,15] Utilising this reaction, compounds **2–8** were synthesised (Table 1). Compound **9** was prepared via the acetoxy analogue **7**, which was subsequently deprotected.[16] Analogue **10** was prepared in a similar fashion but in this case ammonium acetate only deprotected one of the available two acetoxy groups of compound **8**.

A second series of analogues (**11**–**19**) was prepared maintaining fluorine atoms at the 3 and 5 positions with an amino group replacing the 4′-hydroxyl group (Table 2). These amino derivatives were synthesised by reduction of the corresponding nitro analogue. The classic Wittig reaction yielded the nitrostilbene isomers **11** and **12** (Scheme 2). The nitro isomers were separated via fractional crystallisation from ethanol, but could not be differentiated by proton NMR studies due to overlap of signals.

Crystals of isomer **11** were grown from toluene for single crystal X-ray studies and were shown to be those of the *trans*-isomer. The monoclinic unit cell of nitrostilbene **11** is shown in Figure 2. This compound **11** crystallises in the monoclinic space group $P2_1/n$ with four independent molecules per asymmetric unit. The hydrogen bonding contacts to both oxygen and fluorine are also indicated in the unit cell diagram. The contact distance between hydrogen and oxygen is 2.530 Å and between hydrogen and fluorine is 2.567 Å.

Reduction of the nitro stilbene was achieved using iron(III) chloride hexahydrate and iron pindust.[17] Reduction of both isomers was carried out separately in quantitative yields affording the *trans* and *cis* amino derivatives (**13** and **14**). An amino acetyl **15**, an amino trifluoroacetyl analogue **16** and a tertiary amine derivative, (*E*)-3,5-difluoro-4′-dimethylaminostilbene **17** were subsequently prepared.

Amino acid derivatives were also synthesised. A BOC-protected amino acid derivative **18** was prepared by coupling (*E*)-3,5-difluoro-4′-aminostilbene **13** to BOC-protected glycine using the standard coupling reaction with *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) as an activation agent.[18,19] Deprotection of the BOC-glycine analogue **18** was achieved by stirring in a 50% solution of trifluoroacetic acid in dichloromethane, resulting in a quantitative yield of (*E*)-3,5-difluoro-4′-aminoglycinestilbene trifluoroacetate salt **22**. This procedure was also employed using different amino acids to generate further analogues **19**–**21**.

Stilbene analogues (**23**–**35**) with nitrogen substituents at the 3 and 5 positions and a fluorine atom at the 4′ position were synthesised (Table 3). Synthesis of (*E*)-3,5-dinitro-4′-fluorostilbene **23** was carried out via the decarbonylative Heck reaction. The *cis*-isomer, (*Z*)-3,5-dinitro-4′-fluorostilbene **24** was prepared via the classical Wittig reaction for comparative purposes.

Reduction of the 3,5-dinitro-4′-fluorostilbenes (**23** and **24**) via the iron(III) chloride reduction procedure furnished the diamino isomers (**25** and **26**). By controlling the equivalents of reducing agents used in the reaction, it was possible to isolate stilbenes with only one nitro group reduced. This was carried out using both dinitro-isomers (**23** and **24**) individually, thereby producing (*E*)-3-nitro-5-amino-4′-fluorostilbene **27** and (*Z*)-3-nitro-5-amino-4′-fluorostilbene **28**.

The acetyl derivatives of the 3,5-diamino-4′-fluoro series (**29** and **30**) were also synthesised. BOC-protected amino acid derivatives (**31**–**34**) were prepared using the standard EDC coupling reaction.

Table 1
Fluorinated resveratrol derivatives **2**–**10**

Compound	Isomer	R	R′	R″	Yield
2	(*E*)	F	F	F	48
3	(*E*)	F	F	OCH_3	22
4	(*E*)	OCH_3	OCH_3	F	26
5	(*E*)	F	F	OCH_2CH_3	19
6	(*E*)	OCH_2CH_3	OCH_2CH_3	F	29
7	(*E*)	F	F	$OCOCH_3$	58
8	(*E*)	$OCOCH_3$	$OCOCH_3$	F	65
9	(*E*)	F	F	OH	81[a]
10	(*E*)	OH	$OCOCH_3$	F	76[a]

[a] Yield of deprotection step.

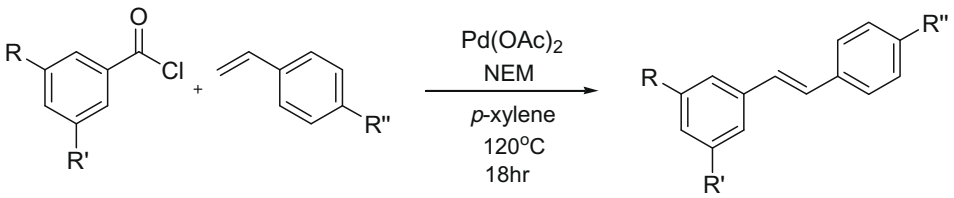
Table 2
4′-Nitro and amino resveratrol analogues

Compound	Isomer	R	R′	R″	Yield
11	(*E*)	F	F	NO_2	49[a]
12	(*Z*)	F	F	NO_2	46[a]
13	(*E*)	F	F	NH_2	88[b]
14	(*Z*)	F	F	NH_2	80[b]
15	(*E*)	F	F	$NHCOCH_3$	70[c]
16	(*E*)	F	F	$NHCOCF_3$	62[c]
17	(*E*)	F	F	$N(CH_3)_2$	32[a]
18	(*E*)	F	F	NH-BOC-glycine	17[d]
19	(*E*)	F	F	NH-BOC-L-alanine	18[d]
20	(*E*)	F	F	NH-BOC-β-alanine	12[d]
21	(*E*)	F	F	NH-BOC-L-valine	11[d]
22	(*E*)	F	F	NH-glycine*	92[e]

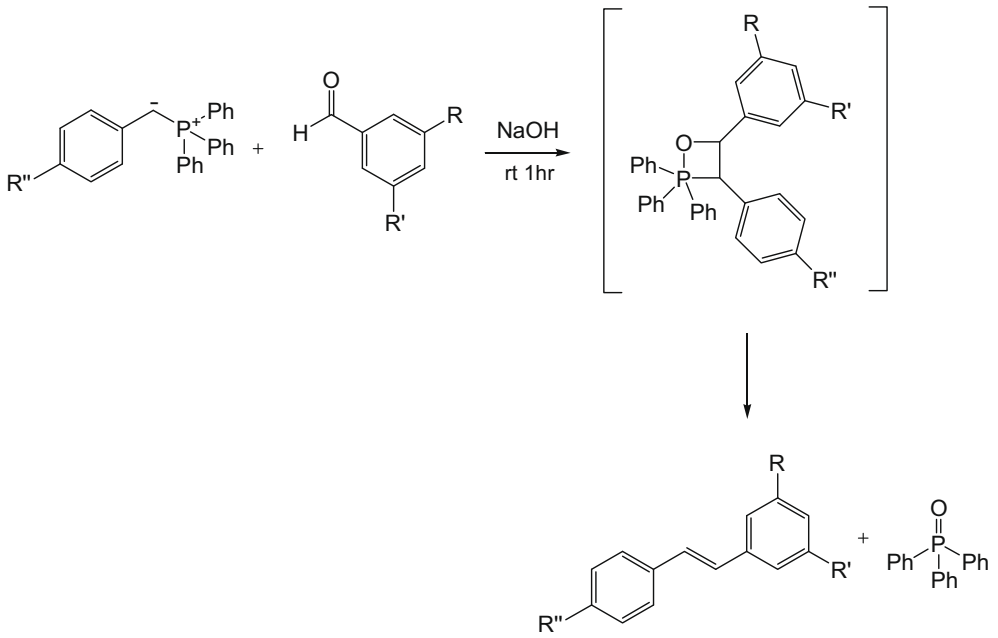
[a] Yield of stilbene formation.
[b] Yield of nitro reduction.
[c] Yield of amine acylation.
[d] Yield of amino acid coupling.
[e] Yield of amino acid deprotection.
* Isolated as trifluoroacetate salt.

3. Biological evaluation

Resveratrol **1** has been shown to prevent and slow the progression of a wide variety of illnesses, including cancer, cardiovascular disease and ischaemic injuries.[3–5] It also enhances stress resistance



Scheme 1. Synthesis of (*E*)-3,5-4′-substituted stilbene via Heck reaction.



Scheme 2. Synthesis of (*E*)-3,4′,5-substituted stilbene via Wittig reaction.

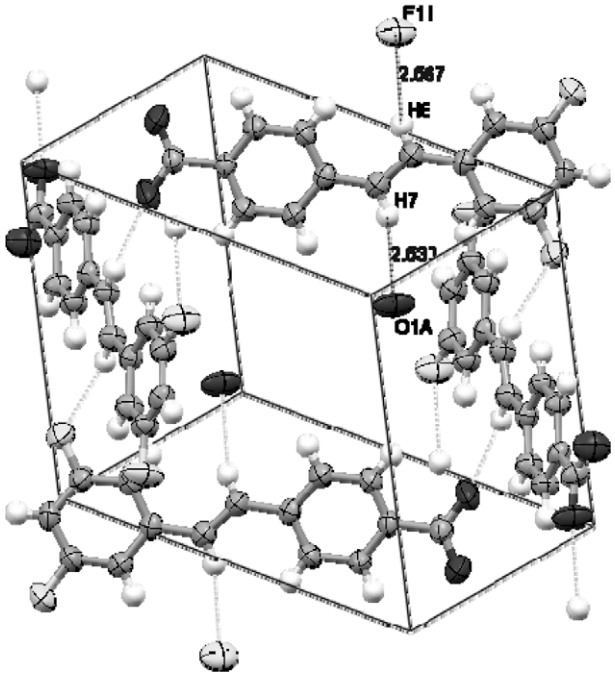


Figure 2. X-ray crystal structure and unit cell of (*E*)-3,5-difluoro-4′-nitrostilbene **11** with hydrogen-bonding interactions.

Table 3
3,5-Dinitro and/or diamino resveratrol derivatives

Compound	Isomer	R	R′	R″	Yield
23	(*E*)	NO_2	NO_2	F	65[a]
24	(*Z*)	NO_2	NO_2	F	35[a]
25	(*E*)	NH_2	NH_2	F	77[b]
26	(*Z*)	NH_2	NH_2	F	65[b]
27	(*E*)	NO_2	NH_2	F	17[b]
28	(*Z*)	NO_2	NH_2	F	23[b]
29	(*E*)	$NHCOCH_3$	$NHCOCH_3$	F	78[c]
30	(*E*)	$NHCOCF_3$	$NHCOCF_3$	F	56[c]
31	(*E*)	NH-BOC-glycine	NH-BOC-glycine	F	56[d]
32	(*E*)	NH-BOC-L-alanine	NH-BOC-L-alanine	F	38[d]
33	(*E*)	NH-BOC-β-alanine	NH-BOC-β-alanine	F	60[d]
34	(*E*)	NH-BOC-L-valine	NH-BOC-L-valine	F	12[d]
35	(*E*)	NH-glycine*	NH-glycine*	F	95[e]

[a] Yield of stilbene formation.
[b] Yield of nitro reduction.
[c] Yield of amine acylation.
[d] Yield of amino acid coupling.
[e] Yield of amino acid deprotection.
* Isolated as trifluoroacetate salt.

and extends the lifespan of various organisms from yeasts to vertebrates.[20] Cancer prevention is one of the mostly widely researched areas today. In vitro and in vivo studies have identified resveratrol as an effective candidate for cancer chemoprevention as it blocks each step in the carcinogenesis process.[21] These properties are mainly due to its antioxidant activity on molecular targets involved in tumour initiation, promotion and progression.[22]

Multidrug resistance (MDR) is a phenomenon whereby previously sensitive tumour cells develop resistance to a wide variety of structurally unrelated compounds. One mechanism of resistance is the upregulation of cellular transporter proteins belonging to the ABC superfamily. These transporters confer resistance by preventing the intercellular accumulation of chemotherapeutic drugs. The most widely studied member of this family is ABCB1 or P-glycoprotein (P-gp) and is one of the major reasons for failure of cancer therapy. Another member that has been proven responsible for treatment failure is the multidrug resistance protein family. Overcoming MDR has become the key focus in the treatment of many tumours. Modulation of an ABC transporter protein can occur in a number of ways, including down-regulation of its protein or mRNA levels, direct inhibition of its transport function or by competing with other substrates thus decreasing the efflux of drugs from the cell.

Herein we report the biological activity of fluorinated and amino derived resveratrol analogues. Preliminary assessment of the bioactivity of the resveratrol derivatives was determined by assay-

ing in non-small cell lung carcinoma and melanoma cell lines. The in vitro models chosen for investigating the potential of the resveratrol compounds were DLKP, DLKP-A and HT-144. The DLKP-A cell line is a daughter cell line of DLKP, a poorly differentiated squamous non-small cell lung carcinoma. The P-glycoprotein (P-gp) membrane pump is the main mechanism of multidrug resistance (MDR) of the DLKP-A cell line.[23] It highly expresses P-gp, while expressing very low levels of multidrug resistance protein 1 (MRP1). DLKP, on the other hand, expresses highly active MRP1, while lacking the P-gp cell membrane transporter. Derivatives that showed inhibitory potency against the lung cell lines were then subjected to further investigations in combination studies with a known chemotherapeutic agent epirubicin **36** (Fig. 3). The chemotherapeutic drug epirubicin, is used for both MDR transporter proteins as it is a well known P-gp and MRP1 substrate. A cross section of some 10 compounds synthesised were selected for biological studies. The compounds were selected based on their solubility in aqueous solutions and also when added to cell media. A minimum amount of dimethylsulfoxide (DMSO) was used to solubilise the compounds, before solubility of the solution was tested in media. A minimum concentration of 0.5 mg/ml in the media was required for a compound to undergo biological evaluation. This is due to the toxicity of the solvent DMSO in cell culture systems if present at higher concentrations.

The compounds tested have the greatest anti-proliferative activity in the DLKP cell line, followed closely by DLKP-A as shown by their IC_{50} values. The melanoma cell line, HT-144, is up to four times less sensitive to resveratrol and its analogues. Compounds **7** (7 ± 1 μM), **9** (6 ± 0.3 μM) and **22** (<10 μM) have similar toxicity to resveratrol **1** (10 ± 2 μM) on the DLKP cells (Table 4). Compounds **8** (25 ± 5 μM), **10** (21 ± 5 μM), **15** (39 ± 2 μM), **25** (>50 μM), **29** (∼50 μM), **30** (28 ± 4 μM) and **35** (>50 μM) showed a decrease in cytotoxicity when compared to resveratrol. Resveratrol **1** (15 ± 3 μM) and compound **7** (10 ± 2 μM) were the most potent anti-proliferation agents in the DLKP-A cell line. The 3,5-diacetyl analogue **29** and the 3,5-diamino acid salt **35**, had an IC_{50} value greater than 50 μM, as did the *trans*-diamino stilbene **25**, which is outside the parameters of the experimental design. The HT-144 melanoma cell line had the greatest resistance to resveratrol and the four fluorinated resveratrol analogues (**7**–**10**). Due to this insensitivity, the amino derivatives were not tested in this cell line. Resveratrol **1** (40 ± 9 μM) and compound **7** (36 ± 1 μM) had the greatest cytotoxic effects on HT-144. Compounds **8** (56 ± 2 μM), **9** (59 ± 3 μM) and **10** (54 ± 3 μM) had very similar IC_{50} values in the HT-144 cell line. Both DLKP and DLKP-A were seeded at the same density (1×10^3 cell/well) whereas HT-144 was seeded at 3×10^3 cells/well. The increased cell number employed with HT-144 assays was due to the requirement of contact for cell growth, in other words, HT-144 cells need to grow at higher density and establish cell to cell contacts to proliferate at a rate appropriate for in vitro toxicity assays. All cell lines had 5 day drug exposure

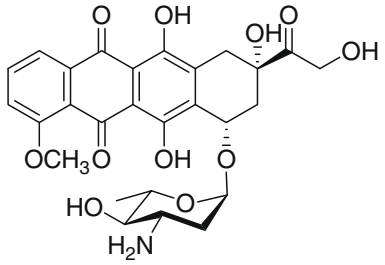


Figure 3. Epirubicin **36**.

Table 4
IC_{50} values (μM) of selected resveratrol derivatives on the non-small lung cell carcinoma cell lines, DLKP and DLKP-A and the melanoma cell line HT-144

Compound	DLKP	DLKP-A	HT-144
1	10 ± 2	15 ± 3	40 ± 8
7	7 ± 1	10 ± 2	36 ± 1
8	25 ± 5	19 ± 3	56 ± 2
9	6 ± 0.3	14 ± 2	59 ± 3
10	21 ± 5	21 ± 2	54 ± 3
15	39 ± 2	n/a[a]	—
22	<10	20 ± 10	—
25	>50	>50	—
29	∼50	∼50	—
30	28 ± 4	20 ± 10	—
35	>50	>50	—

[a] Due to DMSO effects, IC_{50} calculation not possible.

treatment. The end point determinations were made using the acid phosphatase assay.[24]

With regard to the MDR status of resveratrol and its 10 analogues, resveratrol had a slight interaction with both the MRP1 and P-gp transporter proteins while compound **30** was a modulator of the P-gp but not of the MRP1 transporter protein (Fig. 4). In both the DLKP and DLKP-A cell lines, resveratrol acted in an additive manner when in combination with epirubicin (Epi. 0.01 μM and Res. 10 μM). This was not the case with the HT-144 cell line. The combination of the fluorinated/amino derivatives (10 μM) with the P-gp/MRP1 substrate, 0.01 μM epirubicin, resulted in no change in the anti-proliferative potential of epirubicin on the DLKP cells. Therefore, these compounds did not affect the transporter function of MRP1. A similar outcome was observed on the HT-144 cell line. On the other hand, a change in the potency of 1.5 μM epirubicin on the DLKP-A cells was observed when in combination with compounds **8**, **9**, **10**, **22**, **30** and **35**. Similar to the interaction observed between resveratrol and epirubicin on this cell line, compounds **8**, **9**, **10**, **22** and **35** also acted in an additive manner when combined with epirubicin. In Figure 4, 1.5 μM epirubicin caused a 34% decrease in proliferation, 10 μM compound **30** caused a 16% reduction in proliferation, however when they were combined they collectively reduced proliferation by 80%. This increased anti-proliferative effect by the ditrifluoroacetyl derivative **30** is known as synergism and is characteristic of an MDR modulator (Tables 5 and 6).

Four compounds namely **2**, **3**, **4** and **7** were accepted for anticancer assessment by the National Cancer Institute under the Development Therapeutic Program (DTP). The compounds were first assessed using a primary anticancer screen. Previous work carried out by the DTP used an in vitro model consisting of 60 human tumour cell lines as the primary anticancer screen. Analysis of this data indicated that approximately 95% of the actives from the 60 cell line screen can be identified using only three lines. For this reason the DTP is now using a three cell line panel consisting of MCF7 (Breast), NCI-H460 (Lung) and SF-268 (CNS) as its primary anticancer assay. This 3-cell line, one dose assay has been in use by the DTP for several years for the evaluation of combinatorial libraries and has proven to be an effective pre-screen. The inclusion of this assay allows for a more detailed evaluation of agents that have exhibited some ability to inhibit the growth of human tumour cells in culture.

In this assay each cell line was inoculated and preincubated on a microtiter plate. Test agents were then added at a single concentration and the culture was incubated for 48 h. End point determinations were made with alamar blue. Results for each test agent were reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds that reduced the growth of any one of the cell lines to approximately 32% or less

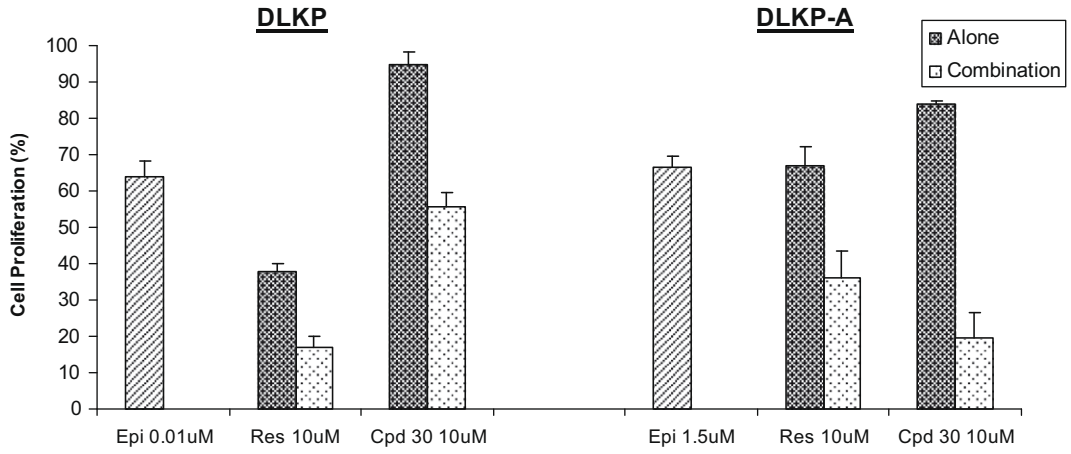


Figure 4. Combination assay of resveratrol, **1**, and its amino derivative, **30**, with epirubicin (0.01 μM and 1.5 μM) on the DLKP and DLKP-A cell lines.

Table 5
Combination assay data of **1**, **7**, **8**, **9** and **10** with epirubicin on the DLKP, DLKP-A and HT144 cell lines

Cell proliferation (%)	Alone	St dev (%)	Combination	St dev (%)
DLKP				
Epirubicin 0.01 μM	83.8	*14*		
Resveratrol 10 μM	38	*2*	18	*4*
7 5 μM	52	*23*	40	*4*
8 5 μM	100	*5*	10	*2*
9 5 μM	74	*11*	70	*40*
10 5 μM	98	*6*	96	*4*
DLKP-A				
Epirubicin 10 μM	78.6	*7*		
Resveratrol 10 μM	66	*5*	36	*5*
7 5 μM	50	*20*	50	*30*
8 5 μM	89	*5*	68	*8*
9 5 μM	85	*5*	56	*12*
10 5 μM	90	*6*	75	*4*
HT144				
Epirubicin 0.005 μM	91	*8*		
Resveratrol 20 μM	100	*10*	82	*18*
7 20 μM	85	*3*	75	*13*
8 20 μM	100	*5*	90	*20*
9 20 μM	105	*5*	93	*8*
10 20 μM	110	12	*100*	*10*

Table 6
Combination assay data of **1**, **15**, **22**, **25**, **29**, **30** and **35** with epirubicin on the DLKP and DLKP-A cell lines

Cell proliferation (%)	Alone	St dev (%)	Combination	St dev (%)
DLKP				
Epirubicin 0.01 μM	64	*4*		
Resveratrol 10 μM	38	*2*	17	*3*
15 10 μM	75	*1*	49	*2*
22 10 μM	25	*9*	21	*11*
25 10 μM	87	*1*	58	*6*
29 10 μM	94	*4*	56	*5*
30 10 μM	95	*3*	56	*4*
35 10 μM	91	*3*	54	*3*
DLKP-A				
Epirubicin 1.5 μM	66	*3*		
Resveratrol 10 μM	67	*5*	36	*8*
15 10 μM	78	*2*	59	*5*
22 10 μM	85	*11*	42	*25*
25 10 μM	98	*1*	76	*1*
29 10 μM	96	*1*	86	*2*
30 10 μM	84	*1*	19	*7*
35 10 μM	92	*8*	58	*17*

Table 7
The growth percentage of human tumour cells in culture when treated with various fluorinated analogues of resveratrol compared to the untreated control cells

Compound	Concn μM	Breast	Lung	CNS
2	100	82	101	111
3	100	84	105	111
4	100	67	60	105
7	100	22	7	1

Table 8
Pharmacological values (μM) of compound **7** against a selection of tumour cell lines

Tumour cell line	GI_{50} μM	IC_{50} μM
Leukaemia HL-60 (TB)	116.7	54.6
Lung EKVX	116.7	78.7
Colon HT29	80.6	73.7
CNS SNB-75	90.9	60.3
Melanoma SK-MEL-28	83.1	70.1
Ovarian SK-OV-3	96.5	83.1
Renal RXF 393	202.4	75.9
Prostate DU-145	127.7	100.5
Breast T-47D	127.7	79.8

were passed on for evaluation in the full panel of 60 cell lines over a 5-log dosage.

The results of this assay indicated that fluorinated analogues of resveratrol may have potential as anticancer agents. Analogues **2** and **3** showed mild toxicity against the breast tumour cell line with approximately 20% inhibition recorded but no inhibition of growth was measured in the lung or CNS cell lines. Compound **4** showed improved activity in both the breast and lung cell lines with 40% inhibition recorded for the lung tumour cell lines. The difluoro derivative, compound **7** was the most potent analogue in breast, lung and central nervous system tumour cells. It was shown to limit the growth of breast cancer by 78%. Growth of lung cancer cells only increased by 7% when treated with compound **7**. The most interesting result was that compound **7** limited the growth of CNS tumour cells by 99% over a two-day period. This compound was then assessed in the 60 cell line assay that included human tumour cells from leukaemia, lung cancer, colon cancer, central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. The GI_{50}, IC_{50}, LC_{50} and TGI values were calculated for each cell line (Tables 7 and 8).

Compound **7** displayed broad spectrum anticancer activity. It was most active against the leukaemia cell line giving an IC_{50} value

of 54.29 μM. It inhibited the growth of cancer most effectively with the colon tumour cell line HT29 with a GI_{50} value of 80.6 μM. The cytotoxicity of compound **7** is comparable to previously published results.[25] The biological activities of resveratrol analogues have been best utilised by chemoprevention and cancer growth inhibition. Cytotoxicity has not been shown to be an essential component of potent growth inhibition and chemopreventative agents.

4. Conclusions

In conclusion, the resveratrol derivatives **2–35** were synthesised, fully characterised and a selection of these resveratrol analogues were assayed in lung cancer and melanoma cell lines. Several display a potency equal to and in the case of (*E*)-3,5-difluoro-4′-acetoxystilbene **7**, greater than that of the parent compound resveratrol. Compound **7** was further evaluated on a panel of 60 cell lines by the National Cancer Institute under the Development Therapeutic Program (DTP). The results of this assay indicated that compound **7** was a broad spectrum anticancer derivative, as activity was observed against leukaemia, colon, lung, breast, melanoma, prostate, ovarian, central nervous system and renal cancer lines. It was also shown that in combination studies with epirubicin (*E*)-3,5-di(trifluoroacetylamino)-4′-fluorostilbene **30** gave the greatest synergy and the greatest anti-proliferative effect, suggesting a possible interaction with the multi-drug resistance pump, P-glycoprotein.

5. Experimental

5.1. General procedures

All chemicals were purchased from Sigma–Aldrich, Lennox Chemicals or Fluorochem Limited and used as received. A commercially purchased sample of resveratrol **1** (Sigma–Aldrich, *R5010*) was used as a control in all biological assays performed and acid phosphatase assay kit purchased from Sigma–Aldrich (*CS0704*). Commercial grade reagents were used without further purification. When necessary all solvents were purified and dried; and stored under argon. Triethylamine was distilled and stored over potassium hydroxide pellets. Riedel-Haën silica gel was used for thin layer and column chromatography. Melting point determinations were carried out using a Stuart melting point (SMP3) apparatus and are uncorrected. Elemental Analysis was carried out by the Microanalytical Laboratory at University College Dublin. Electrospray ionisation mass spectra were obtained on a Bruker Esquire 3000 series ion trap mass spectrometer. IR spectra were obtained on a Perkin–Elmer Spectrum GX FT-IR system. UV spectra were obtained on a UV–vis–NIR Perkin–Elmer Lambda 900 spectrometer. NMR spectra were obtained on a Bruker AC 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR, 376 MHz for ^{19}F NMR and 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (δ) are relative to tetramethylsilane and the ^{19}F NMR chemical shifts (δ) are relative to trifluoroacetic acid. All coupling constants (J) are in hertz (Hz).

5.2. Synthesis of resveratrol derivatives

5.2.1. (*E*)-3,4′,5-Trifluorostilbene (2)

3,5-Difluorobenzoyl chloride (1.45 g, 8.2 mmol) and 4-fluorostyrene (1.0 g, 8.2 mmol) were added to a solution of palladium acetate (0.092 g, 0.41 mmol) and *N*-ethylmorpholine (3.37 g, 8.2 mmol) in xylene (50 ml). The solution was heated at 120 °C for 18 h and then filtered. The solvent was removed in vacuo to yield a crude brown solid. Recrystallisation from hexane/ethyl acetate 50:1 gave the title product **2** as white crystalline needles (0.93 g, 48%).

Mp 48–50 °C. Lit.[26] mp 47 °C.

Anal. Calcd for $C_{14}H_9F_3$: C, 71.79; H, 3.87. Found: C, 72.04; H, 3.99.

IR (KBr): ν 2956, 2857, 1597, 1510, 1233, 961, 831 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69–7.73 (2H, m, –Ar*H* 2′ and 6′), 7.48 (1H, d, J = 16.4 Hz, –C*H*), 7.38–7.41 (2H, m, –Ar*H* 3′ and 5′), 7.24–7.32 (3H, m, –Ar*H* 2, 6 and –C*H*), 7.15–7.20 (1H, m, –Ar*H* 4).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2 (d, –Ar*C* 3), 162.3 (d, –Ar*C* 4′), 161.8 (d, –Ar*C* 5), 141.4 (t, –Ar*C* 1), 133.2 (d, –Ar*C* 1′), 130.6 (–*C*H), 129.0 (d, –Ar*C* 2′ and 6′), 126.4 (d, –*C*H), 116.0 (–Ar*C* 3′ and 5′), 109.6 (d, –Ar*C* 2), 109.4 (d, –Ar*C* 6), 102.9 (t, –Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −34.8 to −34.9 (2F, m), −37.8 to −37.9 (1F, m).

5.2.2. (*E*)-3,5-Difluoro-4′-methoxystilbene (3)

The experimental procedure is identical to the preparation of compound **2** except 3,5-difluorobenzoyl chloride (1.32 g, 7.5 mmol) and 4-vinylanisole (1.0 g, 7.5 mmol) were used. Recrystallisation from hexane/ethyl acetate 12:1 furnished **3** as yellow crystalline needles (0.41 g, 22%).

Mp 107–109 °C. Lit.[26] Mp 108–110 °C.

Anal. Calcd for $C_{15}H_{12}O_1F_2$: C, 73.16; H, 4.91. Found: C, 72.93; H, 4.98.

IR (KBr): ν 2963, 2833, 1586, 1511, 1240, 962, 838 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.35 (1H, d, J = 16.4 Hz, –C*H*), 7.27–7.30 (2H, m, –Ar*H* 2 and 6), 7.01–7.10 (2H, m, –Ar*H* 4 and –C*H*), 6.96 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 3.76 (3H, s, –OC*H*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2 (d, –Ar*C* 3), 161.8 (d, –Ar*C* 5), 159.8 (–Ar*C* 4′), 141.8 (t, –Ar*C* 1), 131.4 (–*C*H), 129.2 (–Ar*C* 1′), 128.5 (–Ar*C* 2′ and 6′), 124.2 (t, –*C*H), 114.5 (–Ar*C* 3′ and 5′), 109.3 (d, –Ar*C* 2), 109.1 (d, –Ar*C* 6), 102.4 (t, –Ar*C* 4), 55.4 (–O*C*H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −35.0 (2F, t, J^{C-F} = 5.2 Hz).

5.2.3. (*E*)-3,5-Dimethoxy-4′-fluorostilbene (4)

The experimental procedure is identical to the preparation of compound **2** except 3,5-dimethoxybenzoyl chloride (1.65 g, 8.2 mmol) and 4-fluorostyrene (1.0 g, 8.2 mmol) were used. Recrystallisation from hexane/ethyl acetate 50:1 furnished **4** as yellow crystalline needles (0.55 g, 26%).

Mp 48–49 °C. Lit.[26] Mp 46–48 °C.

Anal. Calcd for $C_{16}H_{15}O_2F_1$: C, 74.4; H, 5.85. Found: C, 73.49; H, 5.35.

IR (KBr): ν 2933, 2830, 1598, 1506, 1306, 961, 847 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62–7.66 (2H, m, –Ar*H* 2′ and 6′), 7.28 (1H, d, J = 16.4 Hz, –C*H*), 7.19–7.23 (2H, m, –Ar*H* 3′ and 5′), 7.13 (1H, d, J = 16.4 Hz, –C*H*), 6.78 (2H, d, J = 2.4 Hz, –Ar*H* 2 and 6), 6.43 (1H, t, J = 2.4 Hz, –Ar*H* 4), 3.78 (6H, s, –OC*H*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1 (d, –Ar*C* 4′), 161.0 (–Ar*C* 3 and 5), 139.3 (–Ar*C* 1), 133.8 (–Ar*C* 1′), 128.7 (–*C*H), 128.6 (d, –Ar*C* 2′ and 6′), 128.0 (–*C*H), 115.9 (d, –Ar*C* 3′ and 5′), 104.7 (–Ar*C* 2 and 6), 100.2 (–Ar*C* 4), 55.5 (–O*C*H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −38.8 to −38.9 (1F, m).

5.2.4. (*E*)-3,5-Difluoro-4′-ethoxystilbene (5)

The experimental procedure is identical to the preparation of compound **2** except 3,5-difluorobenzoyl chloride (1.83 g, 6.7 mmol) and 4-ethoxystyrene (1.0 g, 6.7 mmol) were used. Recrystallisation from hexane/ethyl acetate 25:1 furnished **5** as yellow spherical crystals (0.32 g, 19%).

Mp 82–84 °C.

Anal. Calcd for $C_{16}H_{14}O_1F_2$: C, 73.83; H, 5.42. Found: C, 73.61; H, 5.85.

IR (KBr): ν 2907, 2357, 1610, 1042, 844, 647 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 7.52 (2H, d, J = 8.8 Hz, –Ar*H* 2′ and 6′), 7.35 (1H, d, J = 16.4 Hz, –C*H*), 7.27–7.31 (2H, m, –Ar*H* 2 and 6), 7.03–7.09 (2H, m, –Ar*H* 4 and –C*H*), 6.94 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 4.03 (2H, q, J = 6.8 Hz, –O*CH*$_2$–), 1.32 (3H, t, J = 6.8 Hz, –OCH$_2$*CH*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2 (d, –Ar*C* 3), 161.8 (d, –Ar*C* 5), 159.1 (–Ar*C* 4′, 141.9 (t, –Ar*C* 1), 131.4 (–*C*H), 129.0 (–Ar*C* 1′), 128.5 (–Ar*C* 2′ and 6′), 124.1 (–*C*H), 115.0 (–Ar*C* 3′ and 5′), 109.2 (d, –Ar*C* 2), 109.1 (d, –Ar*C* 6), 102.4 (t, –Ar*C* 4), 63.4 (–O*CH*$_2$–, –VE DEPT), 14.9 (–OCH$_2$*CH*$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −35.0 (2F, t, J^{C-F} = 5.2 Hz).

5.2.5. (*E*)-3,5-Diethoxy-4′-fluorostilbene (6)

The experimental procedure is identical to the preparation of compound **2** except 3,5-diethoxybenzoyl chloride (1.87 g, 8.2 mmol) and 4-fluorostyrene (1.0 g, 8.2 mmol) were used. Recrystallisation from hexane/ethyl acetate 25:1 furnished **6** as yellow crystalline needles (0.68 g, 29%).

Mp 58–60 °C.

Anal. Calcd for $C_{18}H_{19}O_2F_1$: C, 75.50; H, 6.68. Found: C, 75.60; H, 6.59.

IR (KBr): ν 2974, 2351, 1591, 1505, 1382, 1184, 968, 832 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 7.61–7.65 (2H, m, –Ar*H* 2′ and 6′), 7.27 (1H, d, J = 16.0 Hz, –C*H*), 7.20 (2H, t, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.10 (1H, d, J = 16.4 Hz, –C*H*), 6.74 (2H, d, J = 2.4 Hz, –Ar*H* 2 and 6), 6.39 (1H, t, J = 2.4 Hz, –Ar*H* 4), 4.03 (4H, q, J = 7.2 Hz, –O*CH*$_2$–), 1.33 (6H, t, J = 7.2 Hz, –OCH$_2$*CH*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0 (d, –Ar*C* 4′), 160.2 (–Ar*C* 3 and 5), 139.2 (–Ar*C* 1), 133.9 (d, –Ar*C* 1′), 128.7 (–Ar*C* 2′ and 6′), 128.6 (–*C*H), 127.9 (–*C*H), 115.9 (d, –Ar*C* 3′ and 5′), 105.1 (–Ar*C* 2 and 6), 100.9 (–Ar*C* 4), 63.3 (–O*CH*$_2$–, –VE DEPT), 14.9 (–OCH$_2$*CH*$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −38.8 to −38.9 (1F, m).

5.2.6. (*E*)-3,5-Difluoro-4′-acetoxystilbene (7)

The experimental procedure is identical to the preparation of compound **2** except 3,5-difluorobenzoyl chloride (4.38 g, 24.6 mmol) and 4-acetoxystyrene (4.0 g, 24.6 mmol) were used. Recrystallisation from hexane/ethyl acetate 12:1 furnished **7** as yellow planar crystals (3.94 g, 58%).

Mp 142–144 °C.

Anal. Calcd for $C_{16}H_{12}O_2F_2$: C, 70.07; H, 4.41. Found: C, 69.72; H, 4.46.

IR (KBr): ν 2926, 2351, 1752, 1616, 1208, 968 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 7.63 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.44 (1H, d, J = 16.4 Hz, –C*H*), 7.32–7.36 (2H, m, –Ar*H* 2 and 6), 7.23 (1H, d, J = 16.4 Hz, –C*H*), 7.17 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.08–7.14 (1H, m, –Ar*H* 4), 2.29 (3H, s, –C*H*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5 (–*C*=O), 164.2 (d, –Ar*C* 3), 161.8 (d, –Ar*C* 5), 150.7 (–Ar*C* 4′), 141.4 (t, –Ar*C* 1), 134.3 (–Ar*C* 1′), 130.8 (–*C*H), 128.1 (–Ar*C* 2′ and 6′), 126.6 (–*C*H), 122.5 (–Ar*C* 3′ and 5′), 109.6 (d, –Ar*C* 2), 109.5 (d, –Ar*C* 6), 102.7 (t, –Ar*C* 4), 21.1 (–*C*H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −34.8 (2F, t, J^{C-F} = 8.6 Hz).

5.2.7. (*E*)-3,5-Diacetoxy-4′-fluorostilbene (8)

The experimental procedure is identical to the preparation of compound **2** except 3,5-diacetoxybenzoyl chloride (1.03 g, 4.0 mmol) and 4-fluorostyrene (0.48 g, 4.0 mmol) were used. Recrystallisation from hexane/ethyl acetate 3:1 furnished **8** as white crystalline needles (0.82 g, 65%).

Mp 161–162 °C.

Anal. Calcd for $C_{18}H_{15}O_4F_1$: C, 68.78; H, 4.81. Found: C, 68.91; H, 4.65.

IR (KBr): ν 3119, 2929, 1774, 1655, 1509, 1401, 1197, 912 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.48 (2H, m, –Ar*H* 2′ and 6′), 7.03–7.13 (5H, m, –Ar*H* 2, 6, 3′, 5′ and –C*H*), 6.94 (1H, d, J = 16.0 Hz, –C*H*), 6.84 (1H, t, J = 2.4 Hz, –Ar*H* 4), 2.32 (6H, s, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (–*C*=O), 162.9 (d, –Ar*C* 4′), 151.6 (–Ar*C* 3 and 5), 139.9 (–Ar*C* 1), 133.2 (d, –Ar*C* 1′), 129.8 (–*C*H), 128.6 (d, –Ar*C* 2′ and 6′), 127.1 (d, –*C*H), 117.2 (–Ar*C* 2 and 6), 116.1 (d, –Ar*C* 3′ and 5′), 114.2 (–Ar*C* 4), 21.5 (–*C*H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$): δ −38.0 to −38.1 (1F, m).

5.2.8. (*E*)-3,5-Difluoro-4′-hydroxystilbene (9)

Ammonium acetate (4.5 g, 54.4 mmol) was added to a solution of (*E*)-3,5-difluoro-4′-acetoxystilbene (2.0 g, 7.3 mmol) in aqueous methanol (4:1) and the solution was stirred at room temperature for 3 h. The title product was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed in vacuo to furnish **9** as an orange solid (1.03 g, 81%).

Mp 142–144 °C. Lit.[27] Mp 141–142 °C.

Anal. Calcd for $C_{14}H_{10}O_1F_2$: C, 72.40; H, 4.34. Found: C, 72.27; H, 4.61.

IR (KBr): ν 3364, 2926, 1592, 1246, 1104, 961 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 8.04 (1H, s, –O*H*), 7.43 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.24–7.31 (3H, m, –Ar*H* 2, 6 and –C*H*), 6.97–7.01 (2H, m, –Ar*H* 4 and –C*H*), 6.81 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2 (d, –Ar*C* 3), 161.8 (d, –Ar*C* 5), 158.3 (–Ar*C* 4′), 142.0 (t, –Ar*C* 1), 131.8 (–*C*H), 128.7 (–Ar*C* 2′ and 6′), 127.6 (–Ar*C* 1′), 123.1 (d, –*C*H), 116.0 (–Ar*C* 3′ and 5′), 109.0 (d, –Ar*C* 2), 108.9 (d, –Ar*C* 6), 102.1 (t, –Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −35.0 (2F, t, J^{C-F} = 8.6 Hz).

5.2.9. (*E*)-3-Acetoxy-5-hydroxy-4′-fluorostilbene (10)

The experimental procedure is identical to the preparation of compound **9** except (*E*)-3,5-diacetoxy-4′-fluorostilbene (0.1 g, 0.32 mmol) was used. The title product was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was removed in vacuo to furnish **10** as a white powder (1.05 g, 76%).

Mp 118–120 °C.

Anal. Calcd for $C_{16}H_{13}O_3F_1$: C, 70.58; H, 4.81. Found: C, 70.35; H, 5.00.

IR (KBr): ν 3336, 2364, 1770, 1586, 1509, 1206, 852 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.43 (2H, m, –Ar*H* 2′ and 6′), 7.01–7.06 (2H, m, –Ar*H* 3′ and 5′), 6.97 (1H, d, J = 16.6 Hz, –C*H*), 6.85 (1H, d, J = 16.6 Hz, –C*H*), 6.78 (2H, d, J = 8.8 Hz, –Ar*H* 2 and 6), 6.49 (1H, t, J = 2.0 Hz, –Ar*H* 4), 6.13 (1H, s, –O*H*), 2.33 (3H, s, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 (–*C*=O), 162.9 (d, –Ar*C* 4′), 157.2 (–Ar*C* 3), 151.9 (–Ar*C* 5), 140.1 (–Ar*C* 1), 133.3 (d, –Ar*C* 1′), 129.1 (–*C*H), 128.5 (d, –Ar*C* 2′ and 6′), 127.6 (–*C*H), 116.0 (d, –Ar*C* 3′ and 5′), 111.9 (–Ar*C* 6), 111.6 (–Ar*C* 2), 108.8 (–Ar*C* 4), 21.6 (–*C*H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$): δ −39.3 to −39.4 (1F, m).

5.2.10. (*E*/*Z*)-3,5-Difluoro-4′-nitrostilbene (11/12)

3,5-Difluorobenzyl triphenyl phosphonium bromide (11.7 g, 25 mmol) and 4-nitrobenzaldehyde (4.7 g, 31.25 mmol) were dissolved in dichloromethane (150 ml) and stirred at room temperature. A 50% w/v sodium hydroxide solution was added dropwise to the stirred solution [0.4 ml NaOH solution per 1 mmol of aldehyde]. The solution was stirred at room temperature for 1 h then washed with brine and water. The solvent was removed in vacuo to yield both isomers as a yellow solid. Recrystallisation from ethanol gave the *trans*-isomer as a bright yellow powder **11** (3.2 g, 49%). Crystals of **11** suitable for X-ray analysis were grown from toluene. The resulting mother liquor was evaporated to dryness to yield the *cis* product as a pale yellow powder **12** (3.0 g, 46%).

5.2.10.1. *trans*-Isomer (11). Mp 199–201 °C.

Anal. Calcd for $C_{14}H_9N_1O_2F_2$: C, 64.37; H, 3.47; N, 5.36. Found: C, 64.12; H, 3.47; N, 5.21.

IR (KBr): ν 3085, 2929, 2831, 2442, 2209, 1927, 1793, 1726, 1618, 1589, 1509, 1439, 1336, 1116, 974, 865, 748, 707, 691, 665 cm^{-1}.

UV (λ_{max}) (ACN): 337 nm.

^1H NMR (400 MHz, DMSO-d_6): δ 8.27 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.86 (2H, d, J = 9.2 Hz, –Ar*H* 2′ and 6′), 7.59 (1H, d, J = 16.4 Hz, –C*H*), 7.51 (1H, d, J = 16.4 Hz, –C*H*–), 7.43 (2H, m, –Ar*H* 2 and 6), 7.21 (1H, tt, J = 2.4 and 9.2 Hz, –Ar*H* 4).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (d, J = 244.2 Hz, –*C*F), 162.6 (d, J = 244.0 Hz, –*C*F), 146.6 (–Ar*C* 4′), 143.1 (–Ar*C* 1′), 140.2 (t, J = 9.9 Hz, (–Ar*C* 1), 130.8 (–*C*H), 129.3 (–*C*H), 127.6 (–Ar*C* 2′ and 6′), 124.1 (–Ar*C* 3′ and 5′), 109.9 (d, J = 25.6 Hz, –Ar*C* 2 and 6), 103.6 (t, J = 25.9 Hz, –Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −109.82 (2F, t, J^{C-F} = 9.4 Hz).

5.2.10.2. *cis*-Isomer (12). Mp 73–75 °C.

Anal. Calcd for $C_{14}H_9N_1O_2F_2$: C, 64.37; H, 3.47; N, 5.36. Found: C, 64.35; H, 3.67; N, 5.16.

IR (KBr): ν 3106, 3081, 2836, 2442, 1928, 1640, 1587, 1503, 1447, 1432, 1340, 1321, 1179, 1127, 1104,996, 970, 882, 860, 842, 767, 750, 732, 695, 666 cm^{-1}.

UV (ACN): λ_{max} 314 nm.

^1H NMR (400 MHz, DMSO-d_6): δ 8.17 (2H, d, J = 9.2 Hz, –Ar*H* 3′ and 5′), 7.48 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.17 (1H, tt, J = 2.4 and 9.4 Hz, –Ar*H* 4) 6.84–6.92, (4H, m, –Ar*H* 2 and 6, –C*H*, –C*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.4 (d, J = 245.0 Hz, –*C*F), 162.3 (d, J = 244.7 Hz, –*C*F), 146.4 (–Ar*C* 4′), 143.0 (–Ar*C* 1′), 139.6 (t, J = 9.9 Hz, –Ar*C* 1), 130.9 (–*C*H), 130.4 (–*C*H), 129.8 (–Ar*C* 2′ and 6′), 123.7 (–Ar*C* 3′ and 5′), 111.6 (d, J = 25.5 Hz, –Ar*C* 2 and 6), 103.3 (t, J = 25.8 Hz, –Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −109.57 (2F, t, J^{C-F} = 8.0 Hz).

5.2.11. (*E*)-3,5-Difluoro-4′-aminostilbene (13)

(*E*)-3,5-Difluoro-4′-nitrostilbene (1.42 g, 5.4 mmol) was dissolved in a 10:1 mixture of ethanol and acetic acid (22 ml) and heated to reflux temperature. Iron(III) chloride hexahydrate (0.25 g, 0.93 mmol), followed by iron pindust (2.22 g, 39.7 mmol) was added with vigorous stirring and the solution refluxed for 3 h. The solution was filtered and diluted with water. The product was extracted with diethyl ether and dried over sodium sulfate. Purification by column chromatography with hexane/ethyl acetate as eluant yielded compound **13** as a brown powder (1.1 g, 88%).

Mp 110–112 °C.

Anal. Calcd for $C_{14}H_{11}N_1F_2$: C, 72.72; H, 4.79; N, 6.06. Found: C, 72.48; H, 4.90; N, 5.97.

Mass Spectrum: $[M+H]^+$ found 232.4.

$C_{14}H_{12}N_1F_2$ requires, 232.24.

IR (KBr): ν 3483, 3466, 3396, 3380, 3206, 3091, 3025, 1894, 1617, 1586, 1447, 1429, 1312, 1268, 1183, 1138, 1116, 997, 979, 965, 881, 839, 818, 670 cm^{-1}.

UV (ACN): λ_{max} 315 nm; 242 (sh), 339 (sh) nm.

^1H NMR (400 MHz, DMSO-d_6): δ 7.20–7.30 (5H, m, –Ar*H* 2′, 6′, –C*H*, –Ar*H* 2 and 6), 7.00 (1H, tt, J = 2.2 and 9.4 Hz, –Ar*H* 4), 6.89 (1H, d, J = 16.4 Hz, –C*H*), 6.57 (2H, d, J = 8.4 Hz, –Ar*H* 3′ and 5′), 5.45 (2H, s, –NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7 (d, J = 242.9 Hz, –*C*F), 162.6 (d, J = 243.0 Hz, –*C*F), 149.4 (–Ar*C* 4′), 142.1 (t, J = 9.8 Hz, –Ar*C* 1), 132.1 (–*C*H), 128.1 (–Ar*C* 2′ and 6′), 123.7 (–Ar*C* 1′), 120.3 (–*C*H), 113.7 (–Ar*C* 3′ and 5′), 108.2 (d, J = 25.1 Hz, –Ar*C* 2 and 6), 101.2 (t, J = 26.1 Hz, –Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.55 (2F, t, J^{C-F} = 7.5 Hz).

5.2.12. (*Z*)-3,5-Difluoro-4′-aminostilbene (14)

The experimental procedure is identical to the preparation of compound **13** except (*Z*)-3,5-difluoro-4′-nitrostilbene (1.0 g, 3.8 mmol) was used. Purification by column chromatography with hexane/ethyl acetate as eluant furnished **14** as a brown oil (1.0 g, 80%).

Bp 180–185 °C.

Anal. Calcd for $C_{14}H_{11}N_1F_2$: C, 72.72; H, 4.79; N, 6.06. Found: C, 72.52; H, 4.93; N, 5.88.

IR (ATR): ν 3461, 3372, 3214, 3010, 1616, 1603, 1583, 1514, 1445, 1429, 1307, 1176, 1113, 988, 966, 871, 830, 794, 666 cm^{-1}.

UV (ACN): λ_{max} 238 nm; 314, 336 (sh) nm.

^1H NMR (400 MHz, DMSO-d_6): δ 7.05 (1H, tt, J = 2.2 and 9.2 Hz, –Ar*H* 4) 6.93 (4H, d, J = 8.4 Hz, –Ar*H* 2, 6, 2′ and 6′), 6.55 (1H, d, J = 12.4 Hz, –C*H*), 6.46 (2H, d, J = 8.4 Hz, –Ar*H* 3′ and 5′), 6.29 (1H, d, J = 12.4 Hz, –C*H*), 5.34 (2H, s, –NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3 (d, J = 243.8 Hz, –*C*F), 162.2 (d, J = 243.7 Hz, –*C*F), 148.7 (–Ar*C* 4′), 141.6 (t, J = 9.9 Hz, –Ar*C* 1), 133.0 (–*C*H), 129.7 (–Ar*C* 2′ and 6′), 123.3 (–*C*H), 122.8 (–Ar*C* 1′), 113.4 (–Ar*C* 3′ and 5′), 111.2 (d, J = 25.1 Hz, –Ar*C* 2 and 6), 102.0 (t, J = 25.8 Hz, –Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.47 (2F, t, J^{C-F} = 8.8 Hz).

5.2.13. (*E*)-3,5-Difluoro-4′-acetylaminostilbene (15)

(*E*)-3,5-Difluoro-4′-aminostilbene (0.96 g, 4.16 mmol) was dissolved in ethyl acetate (5ml) and three drops of pyridine. Acetic anhydride (1.18 ml, 12.47 mmol) was added dropwise to this solution and the reaction was stirred at room temperature for 40 min before washing with water and brine. Recrystallisation from hexane/ethyl acetate yielded the title compound **15** as a white powder (0.79 g, 70%).

Mp 217–220 °C.

IR (KBr): ν 3290, 3098, 3047, 3021, 1663, 1619, 1584, 1522, 1408, 1369, 1314, 1118, 980, 961, 847, 810, 673 cm^{-1}.

UV (ACN): λ_{max} 327 nm.

^1H NMR (400 MHz, DMSO-d_6): δ 10.07 (1H, s, –N*H*–), 7.62 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.53 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.30–7.38 (3H, m, –Ar*H* 2, 6 and –C*H*), 7.06–7.16 (2H, m, –Ar*H* 4 and –C*H*), 2.06 (3H, s, –CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3 (–*C*=O), 162.7 (d, J = 243.0 Hz, –*C*F), 162.6 (d, J = 243.1 Hz, –*C*F), 141.4 (t, J = 9.7 Hz, –Ar*C* 1), 139.5 (–Ar*C* 1′), 131.1 (–*C*H), 131.0 (–Ar*C* 4′), 127.3 (–Ar*C* 2′ and 6′), 124.6 (–*C*H), 119.0 (–Ar*C* 3′ and 5′), 108.9 (d, J = 12.0 Hz, –Ar*C* 2 and 6), 102.2 (t, J = 26.0 Hz, –Ar*C* 4), 24.0 (–*C*H_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.26 (2F, t, J^{C-F} = 7.5 Hz).

5.2.14. (*E*)-3,5-Difluoro-4′-(trifluoroacetyl)aminostilbene (16)

The experimental procedure is identical to the preparation of compound **15** except (*E*)-3,5-difluoro-4′-aminostilbene (1.45 g, 6.28 mmol) was used. Recrystallisation from hexane/ethyl acetate yielded compound **16** as a beige powder (1.27 g, 62%).

Mp 188–191 °C.

Anal. Calcd for $C_{16}H_{10}N_1O_1F_5$: C, 58.72; H, 3.08; N, 4.28. Found: C, 58.58; H, 3.09; N, 4.19.

IR (KBr): ν 3296, 3095, 1705, 1619, 1589, 1541, 1450, 1291, 1248, 1186, 1155, 1118, 984, 958, 913, 841, 808, 734, 669 cm^{-1}.

UV (ACN): λ_{max} 321 nm.

^1H NMR (400 MHz, DMSO-d_6): δ 11.38 (1H, s, –N*H*–), 7.73 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.65 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.42 (1H, d, J = 16.8 Hz, –C*H*), 7.36 (2H, m, –Ar*H* 2 and 6), 7.24 (1H, d, J = 16.8 Hz, –C*H*), 7.13 (1H, tt, J = 2.2 and 9.2 Hz, –Ar*H* 4).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (d, J = 243.7 Hz, –*C*F), 162.6 (d, J = 243.6 Hz, –*C*F), 154.4 (q, J = 36.8 Hz, –C=O), 141.0 (t, J = 9.8 Hz, –Ar*C* 1), 136.3 (–Ar*C* 1′), 133.6 (–Ar*C* 4′), 130.6 (–*C*H), 127.4 (–Ar*C* 2′ and 6′), 126.1 (–*C*H), 121.1 (–Ar*C* 3′ and 5′), 115.7

(q, J = 286.9 Hz, –CF_3), 109.2 (d, J = 25.4 Hz, –ArC 2 and 6), 102.6 (t, J = 26.0 Hz, –ArC 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −73.83 (3F, s, –CF_3), −110.14 (2F, t, J^{C-F} = 7.5 Hz).

5.2.15. (*E*)-3,5-Difluoro-4′-dimethylaminostilbene (17)

The experimental procedure is identical to the preparation of compounds **11/12** except 3,5-difluorobenzyl triphenyl phosphonium bromide (2.5 g, 5.33 mmol) and 4-dimethylaminobenzaldehyde (0.99 g, 6.66 mmol) were used. Recrystallisation from ethanol gave the *trans* product **17** as yellow crystals (0.45 g, 32%).

Mp 139–141 °C.

Anal. Calcd for $C_{16}H_{15}N_1F_2$: C, 74.11; H, 5.83; N, 5.40. Found: C, 74.19; H, 5.96; N, 5.38.

IR (KBr): ν 3094, 3020, 2898, 2862, 2810, 2359, 1883, 1599, 1522, 1445, 1355, 1316, 1220, 1194, 1116, 977, 964, 876, 841, 805, 674 cm^{-1}.

UV (ACN): λ_{max} 364 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.24–7.31 (3H, m, –Ar*H* 2, 6 and –C*H*), 6.93–7.03 (2H, m, –Ar*H* 4 and –C*H*), 6.72 (2H, d, J = 8.8 Hz, –Ar*H* 2′ and 6′), 2.94 (6H, s, –CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.2 (d, J = 243.0 Hz, –*C*F), 162.7 (d, J = 243.0 Hz, –*C*F), 150.3 (–ArC 1′), 142.1 (t, J = 9.5 Hz, –ArC 1), 132.0 (–CH), 128.0 (–ArC 3′ and 5′), 123.9 (–ArC 4′), 121.1 (–CH), 112.0 (–ArC 2′ and 6′), 108.4 (d, J = 19 Hz, –ArC 2 and 6), 101.4 (t, J = 26.5 Hz, –ArC 4), 39.8 (–CH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.52 (2F, t, J^{C-F} = 7.5 Hz).

5.2.16. (*E*)-3,5-Difluoro-4′-*N*-(BOC-glycine)aminostilbene (18)

(*E*)-3,5-Difluoro-4′-aminostilbene (0.8 g, 3.85 mmol) was dissolved in dichloromethane (20 ml). *N*-*tert*-Butoxycarbonyl-glycine (0.68 g, 3.85 mmol), 1-hydroxybenzotriazole (0.52 g, 3.85 mmol) and triethylamine (0.54 ml, 3.85 mmol) were added to stirred solution. The reaction mixture was cooled to 0 °C, and *N*-ethyl-*N*′-(3-dimethylaminopropyl) carbodiimide (0.74 g, 3.85 mmol) was added. After 30 min the solution was raised to room temperature and the reaction was allowed to proceed for 48 h. The solution was washed with brine, satd potassium hydrogen carbonate, 10% citric acid and dried over sodium sulfate. The solvent was evaporated in vacuo and purification was achieved by column chromatography with hexane/ethyl acetate. Recrystallisation from ethyl acetate/hexane furnished **18** as a white powder (0.25 g, 17%).

Mp 189–191 °C.

Anal. Calcd for $C_{21}H_{22}N_2O_3F_2$: C, 64.94; H, 5.71; N, 7.21. Found: C, 64.81; H, 5.70; N, 7.12.

IR (KBr): ν 3414, 3277, 3195, 2977, 1679, 1603, 1509, 1447, 1414, 1371, 1313, 1277, 1166, 1117, 1056, 962, 844, 670 cm^{-1}.

UV (ACN): λ_{max} 321 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (1H, s, –N*H*) 7.63 (2H, d, J = 8.4 Hz, –Ar*H* 3′ and 5′), 7.55 (2H, d, J = 8.8 Hz, –Ar*H* 2′ and 6′), 7.31–7.38 (3H, m, –Ar*H* 2, 6 and –C*H*), 7.15 (1H, d, J = 16.4 Hz, –C*H*), 7.06–7.12 (2H, m, –Ar*H* 4 and –N*H*), 3.73 (2H, d, J = 6.0 Hz, –CH_2), 1.40 (9H, s, t-CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3 (–*C*OCH$_2$), 162.8 (d, J = 243.3 Hz, –*C*F), 162.6 (d, J = 243.6 Hz, –*C*F), 155.9 (–*C*OO*t*-Butyl), 141.4 (t, J = 9.9 Hz, –ArC 1), 139.1 (–ArC 4′), 131.2 (–CH), 131.1 (–ArC 1′), 127.4 (–ArC 2′ and 6′) 124.8 (–CH), 119.1 (–ArC 3′ and 5′), 109.0 (d, J = 25.4 Hz, –ArC 2 and 6), 102.0 (t, J = 26.2 Hz, –ArC 4), 78.0 (–*C*(CH$_3$)$_3$), 43.8 (–CH$_2$, –VE DEPT), 28.2 (–C(*C*H$_3$)$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.28 (2F, t, J^{C-F} = 7.5 Hz).

5.2.17. (*E*)-3,5-Difluoro-4′-*N*-(BOC-L-alanine)aminostilbene (19)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-difluoro-4′-aminostilbene (1.7 g, 7.36 mmol) and *N*-*tert*-butoxycarbonyl-L-alanine (1.39 g, 7.36 mmol) were used. Purification by column chromatography with hexane/ethyl acetate as eluant gave the title compound **19** as a white powder (0.54 g, 18%).

Mp 227–229 °C.

Anal. Calcd for $C_{22}H_{24}N_2O_3F_2$: C, 65.66; H, 6.01; N, 6.96. Found: C, 65.38; H, 5.96; N, 6.80.

IR (KBr): ν 3335, 2986, 2939, 1674, 1587, 1517, 1444, 1411, 1366, 1316, 1250, 1161, 1112, 1073, 979, 959, 841, 666, 630 cm^{-1}.

UV (ACN): λ_{max} 325 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.08 (1H, s, –N*H*) 7.66 (2H, d, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.56 (2H, d, J = 8.8 Hz, –Ar*H* 2′ and 6′), 7.32–7.39 (3H, m, –Ar*H* 2, 6 and –C*H*), 7.06–7.18 (3H, m, –C*H*, –Ar*H* 4 and –N*H*), 4.13 (1H, quin, J = 7.2, α-H), 1.39 (9H, s, t-CH_3), 1.28 (3H, d, J = 7.2 Hz, –CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9 (–*C*OCH$_2$), 162.8 (d, J = 243.5 Hz, –*C*F), 162.6 (d, J = 243.5 Hz, –*C*F), 155.2 (–*C*OO*t*-Butyl), 141.3 (t, J = 10.0 Hz, –ArC 1), 139.2 (–ArC 4′), 131.2 (–CH), 131.0 (–ArC 1′), 127.4 (–ArC 2′ and 6′) 124.7 (–CH), 119.2 (–ArC 3′ and 5′), 109.0 (d, J = 25.3 Hz, –ArC 2 and 6), 102.3 (t, J = 26.1 Hz, –ArC 4), 78.0 (–*C*(CH$_3$)$_3$), 50.4 (α-*C*), 28.2 (–C(*C*H$_3$)$_3$), 17.9 (–*C*H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.24 (2F, t, J = 9.4 Hz).

5.2.18. (*E*)-3,5-Difluoro-4′-*N*-(BOC-β-alanine)aminostilbene (20)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-difluoro-4′-aminostilbene (0.58 g, 2.51 mmol) and *N*-*tert*-butoxycarbonyl-β-alanine (0.48 g, 2.51 mmol) were used. Purification by column chromatography with hexane/ethyl acetate as eluant furnished **20** as a white powder (0.12 g, 12%).

Mp 213–215 °C.

Anal. Calcd for $C_{22}H_{24}N_2O_3F_2$: C, 65.66; H, 6.01; N, 6.96. Found: C, 65.28; H, 6.07; N, 6.77.

IR (KBr): ν 3353, 2985, 1682, 1619, 1588, 1521, 1446, 1411, 1343, 1281, 1248, 1167, 1113, 980, 958, 841, 667 cm^{-1}.

UV (ACN): λ_{max} 326 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (1H, s, –N*H*), 7.64 (2H, d, J = 8.4 Hz, –Ar*H* 3′ and 5′), 7.54 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.31–7.38 (3H, m, –Ar*H* 2, 6 and –C*H*), 7.06–7.17 (2H, m, –C*H*, –Ar*H* 4), 6.90 (1H, t, J = 5.6 Hz, –N*H*), 3.23 (2H, q, J = 6.4 Hz, β-*H*), 2.47–2.52 (m, α-H), 1.38 (9H, s, t-CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5 (–*C*OCH$_2$), 162.8 (d, J = 243.0 Hz, –*C*F), 162.7 (d, J = 243.0 Hz, –*C*F), 155.5 (–*C*OO*t*-Butyl), 141.3 (t, J = 10.0 Hz, –ArC 1), 139.3 (–ArC 4′), 131.0 (–CH), 131.0 (–ArC 1′), 127.3 (–ArC 2′ and 6′) 124.7 (–CH), 119.1 (–ArC 3′ and 5′), 109.0 (d, J = 25.0 Hz, –ArC 2 and 6), 102.3 (t, J = 26.0 Hz, –ArC 4), 77.6 (–*C*(CH$_3$)$_3$), 36.8 (α-*C*, –VE DEPT), 36.4 (β-*C*, –VE DEPT), 28.2 (–C(*C*H$_3$)$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.25 (2F, t, J = 7.5 Hz).

5.2.19. (*E*)-3,5-Difluoro-4′-*N*-(BOC-L-valine)aminostilbene (21)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-difluoro-4′-aminostilbene (0.97 g, 4.20 mmol) and *N*-*tert*-butoxycarbonyl-L-valine (0.91 g, 4.20 mmol) were used. Purification by column chromatography with hexane/ethyl acetate as eluant yielded **21** as a white powder (0.20 g, 11%).

Mp 177–180 °C.

Anal. Calcd for $C_{24}H_{28}N_2O_3F_2$: C, 66.96; H, 6.56; N, 6.51. Found: C, 66.71; H, 6.57; N, 6.51.

IR (KBr): ν 3337, 2964, 2871, 1666, 1588, 1516, 1447, 1412, 1367, 1310, 1246, 1168, 1116, 982, 961, 844, 668 cm^{-1}.

UV (ACN): λ_{max} 307 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.06 (1H, s, –N*H*), 7.65 (2H, d, J = 8.4 Hz, –Ar*H* 3′ and 5′), 7.55 (2H, d, J = 8.4 Hz, –Ar*H* 2′ and 6′), 7.32–7.39 (3H, m, –Ar*H* 2, 6 and –C*H*), 7.07–7.18 (2H, m, –C*H*, –Ar*H* 4), 6.94 (1H, d, J = 8.8 Hz, –N*H*), 3.92 (1H, t, J = 7.8 Hz, α-*H*),

1.96–2.01 (m, –C*H*(CH_3)$_2$), 1.38 (9H, s, t-C*H*$_3$), 0.90 (6H, d, *J* = 6.4 Hz, –C*H*(CH_3)$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8 (–*C*OCH$_2$), 162.8 (d, *J* = 243.5 Hz, –*C*F), 162.6 (d, *J* = 243.5 Hz, –*C*F), 155.6 (–*C*OOt–Butyl), 141.3 (t, *J* = 9.8 Hz, –Ar*C* 1), 139.0 (–Ar*C* 4′), 131.3 (–*C*H), 131.0 (–Ar*C* 1′), 127.3 (–Ar*C* 2′ and 6′) 124.8 (–*C*H), 119.3 (–Ar*C* 3′ and 5′), 109.0 (d, *J* = 25.3 Hz, –Ar*C* 2 and 6), 102.3 (t, *J* = 26.0 Hz, –Ar*C* 4), 78.0 (–*C*(CH_3)$_3$), 60.6 (α-*C*), 30.3 (–*C*(CH_3)$_2$), 28.1 (–C(*C*H$_3$)$_3$), 19.2 (–*C*H$_3$), 18.4 (–*C*H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −110.25 (2F, t, *J* = 7.5 Hz).

5.2.20. (*E*)-3,5-Difluoro-4′-(aminoglycine)stilbene trifluoroacetate salt (22)

(*E*)-3,5-difluoro-4′-(amino-BOC-glycine)stilbene (0.22 g, 0.57 mmol) was dissolved in dichloromethane (5 ml). Trifluoroacetic acid (5 ml) was added and the reaction was stirred at room temperature for 1 h. The reaction was monitored by thin layer chromatography. The solvent and excess TFA was evaporated with nitrogen stream. The crude residue was recrystallised from ethyl acetate to yield the title product **22** as a white powder (0.21 g, 92%)

Mp 196–199 °C.

IR (KBr): *v* 3260, 3116, 2360, 1677, 1589, 1546, 1509, 1434, 1315, 1263, 1201, 1139, 1121, 958, 842, 800, 724, 670 cm^{-1}.

UV (ACN): λ_{max} 318 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (1H, s, –N*H*) 8.25 (3H, s, –NH_3^+), 7.66 (2H, d, *J* = 8.8 Hz, –Ar*H* 3′ and 5′), 7.61 (2H, d, *J* = 8.8 Hz, –Ar*H* 2′ and 6′), 7.39 (1H, d, *J* = 16.4 Hz, –C*H*), 7.34 (2H, m, –Ar*H* 2 and 6), 7.19 (1H, d, *J* = 16.4 Hz, –C*H*), 7.11 (1H, tt, *J* = 2.2 and 9.4 Hz, –Ar*H* 4), 3.83 (2H, s, –CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9 (–*C*O), 162.8 (d, *J* = 243.5 Hz, –*C*F), 162.6 (d, *J* = 243.5 Hz, –*C*F), 158.3 (q, *J* = 30.0 Hz, –*C*OCF$_3$), 141.2 (t, *J* = 9.8 Hz, –Ar*C* 1), 138.3 (–Ar*C* 4′), 131.9 (–Ar*C* 1′), 130.9 (–*C*H), 127.6 (–Ar*C* 2′ and 6′), 125.2 (–*C*H), 119.2 (–Ar*C* 3′ and 5′), 117.2 (d, *J* = 298.0 Hz, –*C*F$_3$), 109.1 (d, *J* = 25.3 Hz, –Ar*C* 2 and 6), 102.4 (t, *J* = 26.4 Hz, –Ar*C* 4), 41.0 (–*C*H$_2$, −VE DEPT).

^{19}F NMR (376 MHz, DMSO-d_6): δ −73.61 (3F, s), −110.20 (2F, t, J^{C-F} = 9.4 Hz).

5.2.21. (*E*)-3,5-Dinitro-4′-fluorostilbene (23)

The experimental procedure is identical to the preparation of compound **2** except 3,5-dinitrobenzoyl chloride (1 g, 4.35 mmol) and 4-fluorostyrene (0.53 g, 4.35 mmol) were used. Recrystallisation from hexane/ethyl acetate 50:1 gave the title product **23** as a mustard yellow powder (0.91 g, 65%).

Mp 228–230 °C.

Anal. Calcd for $C_{14}H_9N_2O_4F_1$: C, 58.34; H, 3.15; N, 9.72. Found: C, 58.35; H, 3.12; N, 9.83.

IR (KBr): *v* 3012, 2870, 1789, 1592, 1533, 1506, 1411, 1343, 1233, 1214, 1161, 1075, 962, 860, 815, 783, 731, 704, 652 cm^{-1}.

UV (ACN): λ_{max} 280 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (2H, d, *J* = 2.0 Hz, –Ar*H* 2 and 6), 8.68 (1H, t, *J* = 1.8 Hz, –Ar*H* 4), 7.73–7.78 (3H, m, –Ar*H* 2′, 6′ and –C*H*), 7.54 (1H, d, *J* = 16.4 Hz, –C*H*), 7.29 (2H, t, *J* = 8.8 Hz, –Ar*H* 3′ and 5′).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.31 (d, *J* = 245.0 Hz, –*C*F), 148.5 (–Ar*C* 3 and 5), 140.9 (–Ar*C* 1), 132.6 (–*C*H), 132.6 (d, *J* = 3.3 Hz, –Ar*C* 1′), 129.1 (d, *J* = 8.2 Hz, –Ar*C* 2′ and 6′), 125.9 (–Ar*C* 2 and 6), 124.4 (d, *J* = 2.3 Hz, –*C*H), 116.4 (–Ar*C* 4), 115.8 (d, *J* = 21.5 Hz, –Ar*C* 3′ and 5′).

^{19}F NMR (376 MHz, DMSO-d_6): δ −112.26 to −112.34 (1F, m).

5.2.22. (*Z*)-3,5-Dinitro-4′-fluorostilbene (24)

The experimental procedure is identical to the preparation of compounds **11/12** except 3,5-dinitrobenzyl triphenyl phosphonium bromide (2.22 g, 4.64 mmol) and 4-fluorobenzaldehyde (0.59 g, 5.57 mmol) were used. Recrystallisation from ethanol gave the *trans*-isomer **23** as a mustard yellow powder (0.47 g, 35%). The resulting mother liquor was evaporated to dryness to yield the *cis*-isomer **24** as a pale yellow powder (0.62 g, 46%).

Mp 93–96 °C.

IR (KBr): *v* 3102, 2954, 2922, 2869, 2359, 2341, 1903, 1600, 1535, 1506, 1342, 1314, 1218, 1158, 1076, 955, 916, 860, 841, 826, 816, 752, 730, 644 cm^{-1}.

UV (ACN): λ_{max} 262 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (1H, t, *J* = 2.2 Hz, –Ar*H* 4), 8.40, (2H, d, *J* = 2.0 Hz, –Ar*H* 2 and 6), 7.31–7.34 (2H, m, –Ar*H* 2′ and 6′), 7.17 (2H, t, *J* = 8.8 Hz, –Ar*H* 3′ and 5′), 6.99 (1H, d, *J* = 12.0 Hz, –C*H*), 6.87 (1H, d, *J* = 12.4 Hz, –C*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.6 (d, *J* = 244.4 Hz, –*C*F), 147.9 (–Ar*C* 3 and 5), 139.7 (–Ar*C* 1), 133.3 (–*C*H), 131.5 (d, *J* = 3.5 Hz, –Ar*C* 1′), 130.5 (d, *J* = 8.1 Hz, –Ar*C* 2′ and 6′), 128.6 (–Ar*C* 2 and 6), 126.1 (–*C*H), 116.7 (–Ar*C* 4), 115.7 (d, *J* = 21.3 Hz, –Ar*C* 3′ and 5′).

^{19}F NMR (376 MHz, DMSO-d_6): δ −112.98 to −113.05 (1F, m).

5.2.23. (*E*)-3,5-Diamino-4′-fluorostilbene (25)

The experimental procedure is identical to the preparation of compound **13** except (*E*)-3,5-dinitro-4′-fluorostilbene (1.4 g, 4.86 mmol) was used. The title product **25** was purified by column chromatography with hexane/ethyl acetate as eluant, furnishing in a brown powder (0.85 g, 77%).

Mp 157–160 °C.

Anal. Calcd for $C_{14}H_{13}N_2F_1$: C, 73.66; H, 5.74; N, 12.27. Found: C, 72.93; H, 5.87; N, 11.94.

IR (KBr): *v* 3436, 3397, 3360, 3316, 3198, 3062, 3047, 3021, 1896, 1593, 1507, 1464, 1362, 1333, 1225, 1192, 1159, 1097, 963, 834, 788, 682 cm^{-1}.

UV (ACN): λ_{max} 312 nm; 260 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59 (2H, m, –Ar*H* 2′ and 6′), 7.17 (2H, t, *J* = 8.8 Hz, –Ar*H* 3′ and 5′), 6.90 (2H, d, *J* = 2.0 Hz, *HC*=*CH*), 6.04 (2H, d, *J* = 2.0 Hz, –Ar*H* 2 and 6), 5.80 (1H, t, *J* = 1.8 Hz, –Ar*H* 4), 4.76 (4H, s, –NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.3 (d, *J* = 242.9 Hz, –*C*F), 149.3 (–Ar*C* 3 and 5), 137.5 (–Ar*C* 1), 133.9 (d, *J* = 3.0 Hz, –Ar*C* 1′), 130.0 (d, *J* = 2.1 Hz, –*C*H), 128.0 (d, *J* = 7.8 Hz, –Ar*C* 2′ and 6′), 125.1 (–*C*H), 115.5 (d, *J* = 21.2 Hz, –Ar*C* 3′ and 5′), 101.7 (–Ar*C* 2 and 6), 100.1 (–Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −114.93 to −115.01 (1F, m).

5.2.24. (*Z*)-3,5-Diamino-4′-fluorostilbene (26)

The experimental procedure is identical to the preparation of compound **13** except (*Z*)-3,5-dinitro-4′-fluorostilbene (1.39 g, 4.83 mmol) was used. Purification by column chromatography with hexane/ethyl acetate as eluant yielded **26** as a brown oil (0.72 g, 65%).

Bp 190–195 °C.

Anal. Calcd for $C_{14}H_{13}N_2F_1$: C, 73.66; H, 5.74; N, 12.27. Found: C, 73.12; H, 5.76; N, 12.05.

IR (KBr): *v* 3424, 3339, 3208, 3010, 1614, 1585, 1505, 1460, 1420, 1349, 1218, 1190, 1157, 1095, 863, 834, 787, 674 cm^{-1}.

UV (ACN): λ_{max} 252 nm; 222, 286 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32 (2H, m, –Ar*H* 2′ and 6′), 7.05 (2H, t, *J* = 9.0 Hz, –Ar*H* 3′ and 5′), 6.39 (2H, d, *J* = 3.2 Hz, *HC*=*CH*), 5.72 (3H, m, –Ar*H* 2, 4 and 6), 4.68 (4H, s, –NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9 (d, *J* = 242.6 Hz, –*C*F), 149.3 (–Ar*C* 3 and 5), 137.7 (–Ar*C* 1), 133.5 (d, *J* = 3.1 Hz, –Ar*C* 1′), 131.8 (d, *J* = 1.0 Hz, –*C*H), 130.6 (d, *J* = 7.9 Hz, –Ar*C* 2′ and 6′), 127.1 (–*C*H), 114.8 (d, *J* = 21.1 Hz, –Ar*C* 3′ and 5′), 102.9 (–Ar*C* 2 and 6), 99.3 (–Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −114.89 to −114.98 (1F, m).

5.2.25. (*E*)-3-Nitro-5-amino-4′-fluorostilbene (27)

The experimental procedure is identical to the preparation of compound **13** except (*E*)-3,5-dinitro-4′-fluorostilbene (0.54 g, 1.88 mmol) was used. The title product **27** was purified by column chromatography with hexane/ethyl acetate as eluant, furnishing an orange powder (0.08 g, 17%).

Mp 138–141 °C.

Anal. Calcd for $C_{14}H_{11}N_2O_2F_1$: C, 65.11; H, 4.29; N, 10.85. Found: C, 64.99; H, 4.32; N, 10.86.

IR (KBr): *v* 3472, 3372, 3224, 3082, 1895, 1620, 1600, 1578, 1531, 1509, 1447, 1413, 1352, 1333, 1241, 1159, 1091, 964, 856, 841, 778, 742, 666 cm^{-1}.

UV (ACN): λ_{max} 290 nm.

^1H NMR (400 MHz, DMSO-d_6): δ 7.70 (2H, m, –Ar*H* 2′ and 6′), 7.58 (1H, s, –Ar*H* 2), 7.17–7.31 (5H, m, –Ar*H* 4, 3′, 5′ and *HC*=C*H*), 7.14 (1H, s, –Ar*H* 6), 5.86 (2H, s, –NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7 (d, *J* = 242.9 Hz, –*C*F), 150.1 (–Ar*C* 3), 149.2 (–Ar*C* 5), 138.9 (–Ar*C* 1), 133.09 (d, *J* = 3.0 Hz, –Ar*C* 1′), 130.04 (d, *J* = 2.1 Hz, –*C*H), 128.0 (d, *J* = 7.8 Hz, –Ar*C* 2′ and 6′), 127.0 (–*C*H), 117.2 (–Ar*C* 6), 115.6 (–Ar*C* 3′ and 5′), 107.8 (–Ar*C* 2), 106.3 (–Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −113.55 to −113.62 (1F, m).

5.2.26. (*Z*)-3-Nitro-5-amino-4′-fluorostilbene (28)

The experimental procedure is identical to the preparation of compound **13** except (*Z*)-3,5-dinitro-4′-fluorostilbene (1.39 g, 4.83 mmol) was used. Purification by column chromatography with hexane/ethyl acetate as eluant furnished compound **28** as an orange powder (0.11 g, 23%).

Mp 116–118 °C.

IR (KBr): *v* 3438, 3356, 3232, 3085, 3017, 1635, 1600, 1526, 1508, 1343, 1238, 1221, 1159, 998, 877, 840, 807, 767, 745, 663 cm^{-1}.

UV (ACN): λ_{max} 270 nm.

^1H NMR (400 MHz, DMSO-d_6): δ 7.26 (3H, m, –Ar*H* 4, 2′ and 6′), 7.12 (3H, m, –Ar*H* 2, 3′ and 5′), 6.80 (1H, s, –Ar*H* 6), 6.69 (1H, d, *J* = 12.4 Hz, –*CH*), 6.59 (1H, d, *J* = 12.0 Hz, –*CH*), 5.80 (2H, s, –NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4 (d, *J* = 214.9 Hz, –*C*F), 150.1 (–Ar*C* 1), 148.8 (–Ar*C* 3), 147.4 (–Ar*C* 5), 138.5 (–Ar*C* 1′), 130.6 (d, *J* = 8.0 Hz, –Ar*C* 2′ and 6′), 130.3 (–CH), 128.7 (–CH), 119.4 (–Ar*C* 6), 115.3 (d, *J* = 21.2 Hz, –Ar*C* 3′ and 5′), 109.7 (–Ar*C* 2), 106.0 (–Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −113.94 to −114.02 (1F, m).

5.2.27. (*E*)-3,5-Diacetylamino-4′-fluorostilbene (29)

The experimental procedure is identical to the preparation of compound **15** except (*E*)-3,5-difluoro-4′-aminostilbene (0.5 g, 2.19 mmol) was used. Recrystallisation from hexane/ethyl acetate yielded the product **29** as a white powder (0.53 g, 78%).

Mp 213–215 °C.

Anal. Calcd for $C_{18}H_{17}N_2O_2F_1$: C, 69.22; H, 5.49; N, 8.97. Found: C, 68.85; H, 5.63; N, 8.83.

IR (KBr): *v* 3268, 3099, 1667, 1615, 1599, 1556, 1509, 1456, 1420, 1371, 1276, 1227, 1159, 1038, 998, 964, 848, 609 cm^{-1}.

UV (ACN): λ_{max} 258 nm, 298, 307 (sh) nm.

^1H NMR (400 MHz, DMSO-d_6): δ 9.99 (2H, s, –N*H*), 7.76 (1H, s, –Ar*H* 4), 7.69 (2H, m, –Ar*H* 2′ and 6′), 7.52 (2H, d, *J* = 1.2 Hz, –Ar*H* 2 and 6), 7.21 (2H, t, *J* = 9.0 Hz, –Ar*H* 3′ and 5′), 7.14 (1H, d, *J* = 16.4 Hz, –*CH*), 7.03 (1H, d, *J* = 16.4 Hz, –*CH*), 2.05 (6H, s, –CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4 (–*C*=O), 161.7 (d, *J* = 244.0 Hz, –*C*F), 139.8 (–Ar*C* 3 and 5), 137.4 (–Ar*C* 1), 133.3 (d, *J* = 2.0 Hz, –Ar*C* 1′), 128.5 (–Ar*C* 2′ and 6′), 128.4 (–*C*H), 127.2 (–*C*H), 115.5 (d, *J* = 21.0 Hz, –Ar*C* 3′ and 5′), 112.0 (–Ar*C* 2 and 6), 109.5 (–Ar*C* 4), 24.0 (–*C*H_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ −114.05 to −114.13 (1F, m).

5.2.28. (*E*)-3,5-Di(trifluoroacetylamino)-4′-fluorostilbene (30)

The experimental procedure is identical to the preparation of compound **15** except (*E*)-3,5-difluoro-4′-aminostilbene (0.56 g, 2.46 mmol) was used. Recrystallisation from hexane/ethyl acetate yielded the title product **30** as a white powder (0.58 g, 56%).

Mp 247–250 °C.

Anal. Calcd for $C_{18}H_{11}N_2O_2F_7$: C, 51.44; H, 2.64; N, 6.67. Found: C, 51.85; H, 2.86; N, 6.47.

IR (KBr): *v* 3410, 3325, 3107, 1888, 1732, 1711, 1598, 1562, 1568, 1458, 1322, 1216, 1149, 1006, 959, 938, 914, 890, 849, 815, 791, 738, 674, 623 cm^{-1}.

UV (ACN): λ_{max} 260 nm; 296, 307 (sh) nm.

^1H NMR (400 MHz, DMSO-d_6): δ 11.47 (2H, s, –N*H*), 8.02 (1H, t, *J* = 1.6 Hz, –Ar*H* 4), 7.70–7.74 (4H, m, –Ar*H* 2, 6, 2′ and 6′), 7.16–7.28 (4H, m, –Ar*H* 3′, 5′ and *HC*=C*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ 161.9 (d, *J* = 243.8 Hz, –*C*F), 154.7 (q, *J* = 36.9 Hz, –*C*=O), 138.3 (–Ar*C* 1), 137.1 (–Ar*C* 3 and 5), 133.0 (d, *J* = 3.0 Hz, –Ar*C* 1′), 128.7 (d, *J* = 7.9 Hz, –Ar*C* 2′ and 6′), 128.7 (–*C*H), 127.3 (–*C*H), 115.7 (q, *J* = 287.1 Hz,–*C*F3), 116.2 (–Ar*C* 2 and 6), 115.6 (d, *J* = 21.4 Hz, –Ar*C* 3′ and 5′), 113.1 (–Ar*C* 4).

^{19}F NMR (376 MHz, DMSO-d_6): δ −73.87 (6H, s), −113.49 to −113.57 (1F, m).

5.2.29. (*E*)-3,5-Di(*N*-BOC-glycine)amino-4′-fluorostilbene (31)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-diamino-4′-fluorostilbene (0.29 g, 1.27 mmol) and *N*-*tert*-butoxycarbonyl-glycine (0.67 g, 3.81 mmol) were used. Purification by column chromatography using hexane/ethyl acetate as eluant gave a solid. Recrystallisation from ethyl acetate/hexane furnished **31** as a white powder (0.26 g, 56%).

Mp 138–140 °C.

Anal. Calcd for $C_{28}H_{35}N_4O_6F_1$: C, 61.98; H, 6.50; N, 10.33. Found: C, 61.58; H, 6.66; N, 9.82.

IR (KBr): *v* 3300, 3103, 2976, 2929, 1675, 1599, 1507, 1452, 1366, 1225, 1160, 1052, 959, 847, 791, 681 cm^{-1}.

UV (ACN): λ_{max} 257 nm; 298, 309 (sh) nm.

^1H NMR (400 MHz, DMSO-d_6): δ 9.99 (2H, s, –N*H*) 7.80 (1H, s, –Ar*H* 4), 7.70 (2H, m, –Ar*H* 2′ and 6′), 7.55 (2H, s, –Ar*H* 2 and 6), 7.15–7.24 (3H, m, –Ar*H* 3′, 5′ and –*CH*), 7.04–7.08 (3H, m, –*CH* and –N*H*–), 3.75 (4H, d, *J* = 6.4 Hz, –CH_2), 1.41 (18H, s, t-CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3 (–*C*OCH$_2$), 161.7 (d, *J* = 243.6 Hz, –*C*F), 155.9 (–*C*OOt–Butyl), 139.5 (–Ar*C* 3 and 5), 137.6 (–Ar*C* 1), 133.3 (d, *J* = 3.1 Hz, –Ar*C* 1′), 128.5 (–*C*H), 128.5 (–Ar*C* 2′ and 6′), 127.4 (–*C*H), 115.6 (d, *J* = 21.4 Hz, –Ar*C* 3′ and 5′), 112.1 (–Ar*C* 2 and 6), 109.6 (–Ar*C* 4), 78.0 (–*C*(CH$_3$)$_3$), 43.7 (–CH$_2$, −VE DEPT), 28.2 (–C(CH_3)$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −113.98 to −114.05 (1F, m).

5.2.30. (*E*)-3,5-Di(*N*-BOC-L-alanine)amino-4′-fluorostilbene (32)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-diamino-4′-fluorostilbene (1.21 g, 5.31 mmol) and *N*-*tert*-butoxycarbonyl-L-alanine (3.01 g, 15.92 mmol) were used. Purification by column chromatography with hexane/ethyl acetate as eluant furnished the product **32** as a white powder (1.15 g, 38%).

Mp 139–141 °C.

Anal. Calcd for $C_{30}H_{39}N_4O_6F_1$: C, 63.14; H, 6.89; N, 9.82. Found: C, 63.42; H, 6.72; N, 9.66.

IR (KBr): *v* 3292, 2977, 2931, 1672, 1600, 1508, 1452, 1366, 1288, 1164, 1070, 1021, 960, 846, 790, 711, 681 cm^{-1}.

UV (ACN): λ_{max} 258 nm; 298, 307 (sh) nm.

^1H NMR (400 MHz, DMSO-d_6): δ 9.98 (2H, s, –N*H*) 7.84 (1H, s, –Ar*H* 4), 7.69 (2H, m, –Ar*H* 2′ and 6′), 7.55 (2H, s, –Ar*H* 2 and 6), 7.14–7.23 (3H, m, –Ar*H* 3′, 5′ and –*CH*), 7.04–7.08 (3H, m, –*CH* and –N*H*), 4.14 (2H, quin, *J* = 7.2 Hz, α-*H*), 1.39 (18H, s, t-CH_3), 1.27 (6H, d, *J* = 7.2 Hz, –CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0 (–*C*OCH$_2$), 161.7 (d, J = 243.5 Hz, –*C*F), 155.1 (–*C*OO*t*-Butyl), 139.6 (–Ar*C* 3 and 5), 137.5 (–Ar*C* 1), 133.3 (–Ar*C* 1′), 128.54 (–*C*H), 128.46 (–Ar*C* 2′ and 6′) 127.4 (–*C*H), 115.6 (d, J = 21.3 Hz, –Ar*C* 3′ and 5′), 112.3 (–Ar*C* 2 and 6), 109.9 (–Ar*C* 4), 78.0 (–*C*(CH$_3$)$_3$), 50.4 (α-*C*), 28.2 (–C(*C*H$_3$)$_3$), 18.0 (–*C*H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −113.99 to −114.07 (1F, m).

5.2.31. (*E*)-3,5-Di(*N*-BOC-β-alanine)amine-4′-fluorostilbene (33)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-diamino-4′-fluorostilbene (0.52 g, 2.28 mmol) and *N*-*tert*-butoxycarbonyl-β-alanine (1.3 g, 6.84 mmol) were used. Purification by column chromatography with hexane/ethyl acetate as eluant yielded **33** as a white powder (0.52 g, 60%).

Mp 113–116 °C.

Anal. Calcd for $C_{30}H_{39}N_4O_6F_1$: C, 63.14; H, 6.89; N, 9.82. Found: C, 62.95; H, 7.24; N, 9.64.

IR (KBr): ν 3303, 3095, 2975, 2928, 1680, 1599, 1508, 1450, 1366, 1247, 1165, 1068, 961, 846, 789 cm^{-1}.

UV (ACN): λ_{max} 257 nm, 298, 308 (sh) nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (2H, s, –N*H*) 7.79 (1H, s, –Ar*H* 4), 7.68 (2H, m, –Ar*H* 2′ and 6′), 7.56 (2H, s, –Ar*H* 2 and 6), 7.21 (2H, t, J = 8.8 Hz, –Ar*H* 3′ and 5′), 7.13 (1H, d, J = 16.2 Hz, –C*H*), 7.03 (1H, d, J = 16.2 Hz, –C*H*), 6.86 (2H, t, J = 5.4 Hz, –N*H*), 3.24 (4H, q, J = 6.4 Hz, –C*H*$_2$), 2.47–2.50 (m, –C*H*$_2$), 1.38 (18H, s, t-C*H*$_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5 (–*C*OCH$_2$), 161.7 (d, J = 243.5 Hz, –*C*F), 155.5 (–*C*OOt–Butyl), 139.7 (–Ar*C* 3 and 5), 137.4 (–Ar*C* 1), 133.3 (d, J = 3.1 Hz,–Ar*C* 1′), 128.5 (–Ar*C* 2′ and 6′), 128.4 (–*C*H), 127.2 (–*C*H), 115.6 (d, J = 21.5 Hz,–Ar*C* 3′ and 5′), 112.2 (–Ar*C* 2 and 6), 109.7 (–Ar*C* 4), 77.6 (–*C*(CH$_3$)$_3$), 36.7 (–*C*H$_2$, –VE DEPT), 36.5 (–*C*H$_2$, –VE DEPT), 28.2 (–C(*C*H$_3$)$_3$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −114.03 to −114.11 (1F, m).

5.2.32. (*E*)-3,5-Di(*N*-BOC-L-valine)amino-4′-fluorostilbene (34)

The experimental procedure is identical to the preparation of compound **18** except (*E*)-3,5-diamino-4′-fluorostilbene (0.62 g, 2.72 mmol) and *N*-*tert*-butoxycarbonyl-L-valine (1.35 g, 6.21 mmol) were used. Purification by column chromatography with hexane/ethyl acetate as eluant gave the title product **34** as a brown wax (0.20 g, 12%).

IR (KBr): ν 3305, 3091, 2964, 2924, 2873, 2358, 2336, 1670, 1508, 1451, 1366, 1227, 1164, 1024, 847 cm^{-1}.

UV (ACN): λ_{max} 258 nm; 296, 310 (sh) nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.06 (2H, s, –N*H*) 7.88 (1H, s, –Ar*H* 4), 7.70 (2H, m, –Ar*H* 2′ and 6′), 7.60 (2H, s, –Ar*H* 2 and 6), 7.16–7.23 (3H, m, –Ar*H* 3′, 5′ and –C*H*), 7.08 (1H, d, J = 16.4 Hz, –C*H*), 6.89 (2H, d, J = 8.4 Hz, –N*H*), 3.99 (2H, t, J = 7.8 Hz, α-*H*), 1.94–2.10 (2H, m, –C*H*), 1.41 (18H, s, t-C*H*$_3$), 0.94 (12H, d, J = 6.0 Hz, –CH(C*H*$_3$)$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8 (–*C*OCH$_2$), 161.7 (d, J = 243.0 Hz, –*C*F), 155.5 (–*C*OO*t*-Butyl), 139.4 (–Ar*C* 3 and 5), 137.6 (–Ar*C* 1), 133.3 (d, J = 3.0 Hz, –Ar*C* 1′), 128.5 (–*C*H), 128.4 (–Ar*C* 2′ and 6′) 127.4 (–*C*H), 115.5 (d, J = 22.0 Hz, –Ar*C* 3′ and 5′), 112.5 (–Ar*C* 3 and 5), 110.0 (–Ar*C* 4), 78.0 (–*C*(CH$_3$)$_3$), 60.6 (α-*C*), 30.3 (–*C*H–), 28.1 (–C(*C*H$_3$)$_3$), 18.4 and 19.2 (–CH(*C*H$_3$)$_2$).

^{19}F NMR (376 MHz, DMSO-d_6): δ −113.98 to −114.03 (1F, m).

5.2.33. (*E*)-3,5-Di(aminoglycine)-4′-fluorostilbene trifluoroacetate salt (35)

The experimental procedure is identical to the preparation of compound **22** except 3,5-di(amino-BOC-glycine)-4′-fluorostilbene (0.22 g, 0.41 mmol) was used. The crude residue was recrystallised from ethyl acetate to yield the title product **35** as a white powder (0.22 g, 95%)

Mp 204–206 °C.

IR (KBr): ν 3095, 3002, 1670, 1626, 1560, 1509, 1458, 1199, 1136, 847, *798*, 722 cm^{-1}.

UV (ACN): λ_{max} 254 nm; 298 nm.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (2H, s, –N*H*) 8.24 (6H, s, –NH$_3^+$), 7.88 (1H, s, –Ar*H* 4), 7.71 (2H, m, –Ar*H* 2′ and 6′), 7.57 (2H, d, J = 1.2 Hz, –Ar*H* 2 and 6), 7.23 (3H, m, –Ar*H* 3′, 5′ and –C*H*), 7.07 (1H, d, J = 16.0 Hz, –C*H*), 3.28 (4H, s, –C*H*$_2$).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9 (–*C*O), 161.5 (d, J = 243.8 Hz, –*C*F), 158.4 (q, J = 32.0 Hz, –*C*O), 139.0 (–Ar*C* 3 and 5), 138.0 (–Ar*C* 1), 133.1 (d, J = 3.2 Hz, –Ar*C* 1′), 128.6 (d, J = 7.9 Hz, –Ar*C* 2′ and 6′), 128.1 (–*C*H), 127.9 (–*C*H), 116.9 (d, J = 297.0 Hz, –*C*F$_3$), 115.6 (d, J = 21.5 Hz, –Ar*C* 3′ and 5′), 112.6 (–Ar*C* 2 and 6), 109.6 (–Ar*C* 4), 41.0 (–*C*H$_2$, –VE DEPT).

^{19}F NMR (376 MHz, DMSO-d_6): δ −73.84 (6F, s, –*C*F$_3$), −113.72 to −113.80 (1F, m, 4′-F).

6. Supplementary data

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 685944 for **11**. Copies of the data can be obtained free of charge from The Director, CCDC, 12, Union Road, Cambridge, CB2 1 EZ, UK. [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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