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Accepted Article

Title: Anticancer Activity of Stilbene-based Derivatives

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To be cited as: *ChemMedChem* 10.1002/cmdc.201700045

Link to VoR: http://dx.doi.org/10.1002/cmdc.201700045

A Journal of

ChemPubSoc Europe

WILEY-VCH

www.chemmedchem.org

10.1002/cmdc.201700045

Anticancer Activity of Stilbene-based Derivatives

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Keywords: anticancer drugs, antiproliferative, stilbene analogues, resveratrol.

Abreviations: RAF, rapidly accelerated fibrosarcoma; MAPK, mitogen-activated protein kinase; SAR, structure-activity relationship; MAT2A, methionine S-adenosyl transferase-2; VEGF, vascular endothelial growth factor; hTERT, Telomerase reverse transcriptase; QR2, quinone reductase 1; FGF-2: Fibroblast Growth Factor 2; SULTs: sulfotransferases; GLUTs: glucuronyltransferases; sEH: Epoxide hydrolase; NF-kB: nuclear factor -kB.

Abstract

Stilbene is a very present structural scaffold in nature and stilbene-based compounds are largely described for their biological activity; noteworthy, *E*-resveratrol and its natural stilbene containing derivatives have been extensively investigated as cardioprotective, potent antioxidant, anti-inflammatory, and anticancer agents. Starting from their potent chemotherapeutic activity against a wide variety of cancers, stilbene scaffold has been subjected to synthetic manipulations with the aim to obtaining new analogues with improved anticancer activity and better bioavailability. In the last decade, majority of new synthetic stilbenoids demonstrated significant anticancer activity against a large number of cancer cell lines employed, depending on the type and position of substituents on stilbene skeleton. The present review article focuses on the pharmacological activity

of the key compounds containing stilbene scaffold and classify them on the type of structural modifications in stilbene scaffold.

1. Introduction

Cancer prevention is one of the most widely researched areas today. Since there are many ways involved in the pathophysiology of cancer, different approaches are necessary. Decisive advances in cellular and molecular biology have led to the improvement of chemotherapeutic management of cancer, but further efforts to discover new anticancer agents in order to pass resistance and toxicity concerns, are still necessary. Because natural products are one of the major sources for lead compounds, exhibiting various modes of cytostatic action,[1] in the last decades, much interest has been focused on the use of natural products or their derivative with the scope to develop more efficacious chemotherapeutic agents.[2]

In the last few years, natural compounds with stilbene backbone demonstrated to possess promising activity in cancer prevention, targeting a wide variety of intracellular pathways.[3a-b] Stilbene is a versatile scaffold, characterized by two aromatic rings linked by an ethylene bridge (Figure 1). Stilbenes are defense compounds produced by some plants in response to pathogen attack and other stresses. Stilbenes are abundant in natural products[4] with a variety of important biological activities.[5] Structurally, they are divided into *Z*-type and *E*-type based on the configuration of their central double bond; this can undergo *Z/E* isomerization, changing the overall configuration and reducing the biological activity. In fact, the photoisomerization is a problem that represents a common challenge in optimization work and most quantum chemistry calculation research has focused on the mechanismsof it[6] but has not been concerned about optimizing these compounds to improve their stability and maintain their biological activity.[7-9]

Stilbene containing compounds have always drawn the attention of chemist and pharmacologist over the years mainly because of their important biological properties, such as antioxidant,

hypolipidemic, antiviral, anti-inflammatory and anticancer activities.[14-18] Among these, resveratrol represents one the most extensively studied and its anti-proliferative, antioxidant,[10a-c] anti-inflammatory and anticancer activities[11-13] have been largely reported.

In order to improve the cancer chemopreventive and/or therapeutic activities, as well as the bioavailability with respect to parent drug, new stilbene derivatives are designed, synthesized and tested on multiple cellular targets. These potential, new, chemotherapeutic agents have received much attention from the medicinal chemistry community. Starting from the scaffold of resveratrol, many analogues contain one or both aromatic ring differently substituted. There are clinically used drugs characterized by the presence of stilbene nucleus and numerous hybrid derivatives have been tested on different biological targets.[18a-b]

This review pays attention on the anticancer properties associated with stilbene scaffold. In this paper the focus is the structural aspect of the stilbene-containing derivatives based on their chemical structure, covering the most relevant papers from 2010 to present.

2. Natural anticancer stilbenes

The stilbene moiety is a common structural grouping in nature. Hydroxylated stilbenes, among them *E*-resveratrol **1** (Figure 1), are largely present in nature and play a significant role in the prevention of coronary artery disease due to its antioxidant and anti-inflammatory properties.[11] Resveratrol **1** (3,4',5-trihydroxy-*trans*-stilbene) is a naturally occurring phytoalexin present in grapes, red wine, peanuts, chocolate, and mulberries.

Resveratrol is only present in small amounts in plant sources and its isolation from plant sources is not suitable. It has been shown to possess anti-oxidant,[19] anti-inflammatory, anti-platelet, cancer preventative and anti-cancer properties.[12, 20-23]Although both *Z*- and *E*-isomers of resveratrol are found in nature, it is only the *trans*-isomer that exhibits bioactivity and researchers have been reported that only the *E* form exhibits more potent activity than the corresponding *Z* form across the biological screens including anticancer and anti-oxidant activities.[24]

Resveratrol shows antioxidant activity on molecular targets involved in tumor initiation, promotion and progression disturbing progression through the block of the S and G_2 phases of the cell cycle;[25] its potential cancer chemoprevention is based on its striking inhibitory effects on cellular events. It also induces apoptosis and reduces angiogenesis through the suppression of FGF-2 and VEGF,[26] classifying it as anticancer agent.[27]

In the last decade, numerous reviews have summarized the effects of resveratrol treatment on breast, colorectal, liver, pancreatic, and prostate cancers.[12-13, 27-29] Numerous *in vitro* studies have shown that resveratrol has multiple anti-cancer effects, protecting against both tumor initiation and cancer progression pathways. Despite this, data from rodents and humans are inhomogeneous: *in vivo* studies are still too few due to its poor bioavailability when taken orally.

Some compounds structurally related to resveratrol, are present in nature also showing a wide spectrum of biological activities. Pterostilbene (Figure 1) is a stilbene natural compound found primarily in blueberries and *Pterocarpus marsupium* heartwood. It is a dimethoxy derivative of resveratrol with similar biological activity, even if it is a more potent antioxidant and anticancer molecule.[30a-b] Also, it has a better bioavailability due to the presence of methoxyls that increase the lipophilicity.[31] Trimethoxypterostilbene is a natural product isolated from *Virola elongatae*;[32] it is significantly more potent than parent compound in inhibiting growth of human cancer cells,[33] antiangiogenic activity and better oral bioavailability, longer half-life, greater plasma exposure, and lower clearance than resveratrol.[34]

Piceatannol (Figure 1) is another naturally occurring hydroxystilbene found in grapes, berries, peanuts and sugar cane, synthesized in plants in response to fungal attack, ultraviolet exposure, and microbial infection. Also, piceatannol has been shown to exert various pharmacological effects such as anticancer, anti-inflammatory, anti-oxidant, antiaging, anti-diabetic and cardio-protective activities.[35] Furthermore, the potency of piceatannol usually is greater than that of the resveratrol.[35]

Recently, a series of novel *C* and *O*-prenylated piceatannols has been discovered from propolis in Kangaroo Island of South Australia.[36] An example of synthetic prenylated tetrahydroxystilbenes is reported in Figure 1; they inhibited cell growth in the MTT antiproliferative assay against leukemia K562 cell line in a very low micromolar range and depending on the position of prenyl group.[35-36] Some of resveratrol metabolites are found in red wine, grapes, passion fruit, white tea, as piceatannol (Figure 1). For these compounds, similar biological effects are described. A C-geranylated resveratrol, the amorphastilbol (Figure 1), is the most active compound extracts from the *Robinia pseudoacacia var. umbraculifer* (RPU).[37]

Noteworthy, natural *Z*-stilbene Combretastatin A-4 (CA-4, Figure 1), isolated from the bark of the African willow tree *Combretum caffrum* in 1982, shows biological activities.[38-39] CA-4 belongs to a complex family of potent *Z*-stilbenoids depolymerizing agents and it is a strong inhibitor of tubulin polymerization with cancer cell death.[40] Cytotoxic properties of its *Z*-derivatives have been reviewed by several authors.[39,41] In addition, CA-4 leads to rapid and selective vascular dysfunction in solid tumors by attacking endothelial cells within the tumor vasculature.[42] Unfortunately, its *Z* double bond tends to isomerize to the more thermodynamic stable, but less depolymerizing active *E*.[43] To overcome this shortcoming, a large number of modification for CA-4 has been made and some examples are reported below.[42] In a work published in 2001 by L. A. Stivala *et al.,* it was investigated whether antiproliferative properties are dependent on configuration of the molecule:[19] surprisingly, both of *E* or *Z* configurated synthetic methylated stilbenes stop mitosis at the M phase whereas only *E*-resveratrol blocks cells at the S phase.[44]

Studies on colorectal cancer cell proliferation, conducted with a series of polymethoxy-stilbenes, led to the unexpected result that the strongest effect depends on *Z*-stereochemistry. Computational docking confirmed that *Z*-isomers, apart from *Z*-resveratrol and *Z*-tetramethoxy-stilbene of this series, can be incorporated into the colchicine site of tubulin and all *Z*-isomers substantially overlap the docked structure of CA-4.[41, 45]

Even if resveratrol is a small molecule, structure requirements for biological activity are largely studied. For instance, the presence of additional hydroxy groups, either at the *ortho* or *para* position, further increases the antioxidative activity of the compound, thanks to an intramolecular hydrogen bond that stabilizes the phenoxyl radicals whereas the hydroxyl group at the 4'-position, contributes more to cytotoxic activity than the other hydroxyl group, together with stereoisomery in the *E*-conformation: the 4'-hydroxystyryl moiety is absolutely required for inhibition of cell proliferation.[19] It is clear that the conjugated double bond between the two aromatic rings, is an important structural feature in the inhibition of cancer cell proliferation: reduction of this bond dramatically reduces (about 100-fold) the potency and the resonance property is important also for anti-oxidant effects.

Unfortunately, resveratrol possesses unfavourable pharmacokinetic properties. Various *in vivo* studies have shown that resveratrol is impaired by a short half-life, rapid clearance, and low bioavailability.[41, 45] Its bioavailability is low because it exhibits a high metabolization rate by phase II enzymes, specifically SULTs and GLUTs and this fact significantly reduces its bioavailability in the systemic circulation.[46a-b] Bioavailability of resveratrol could be improved through nanoformulations such as liposomes, polymeric nanoparticles, or cyclodextrins. This aspect has been recently rewieved.[47a] However, interesting studies on its metabolites have been performed *in vivo* and in human liver samples.[47b] Some of these metabolites retain physiological activity and, even at considerably high concentrations, do not induce tumor cell death or prevent their proliferation *in vitro*.[48] For example, five resveratrol sulfate metabolites were synthesized and assessed for cancer chemopreventive showing a relevant degree of activity respect to parent one.[47, 49]

3. Synthetic anticancer stilbenes

Stilbene-based compounds have become of particular interest to chemists because of their range of different biological activities.[50] New stilbene derivatives have been designed and synthesized in

order to find resveratrol analogues with cancer chemopreventive and/or therapeutic activities superior to that of the parent compound.[51a-b]

Resveratrol derivatives, in which all or each single hydroxylic functions were selectively substituted with methyl groups or other substituents, the double bond reduced or incorporated in more complex structures, were synthesized and the biological activity of these compounds was evaluated in order to prepare a novel compounds with greater bioactivity and bioavailability than that of resveratrol. Synthesis and bioactivity evaluation of modified stilbene derivatives received much attention and interests in medicinal chemistry.

In recent years, in order to enhance resveratrol stability, bioavailability and uptake, different biocompatible drug delivery systems containing resveratrol have been developed, using polymeric nanoparticles, liposomes, cyclodextrins, solid lipid nanoparticles or yeast cell as carriers[52a-b] and tested *in vitro*[53] and *in vivo*.[54]

Recently, resveratrol has been conjugated through phosphate bridge(s) to different lipophilic groups related to membrane lipids, such as cholesteryl or diacylglycero moieties. These lipoconjugates were tested towards human neuroblastoma SH-SY5Y cells and proved to be significantly more active than resveratrol, improving its bioavailability.[55]

The stereoisomery of double bond has been object of interest. As previously mentioned, both *Z*- and *E*-stilbene derivatives demonstrated anticancer properties in numerous experimental models *in vitro* and *in vivo* but with different mechanisms. Unlike resveratrol that exhibits higher antiproliferative activity in *E*-conformation, some *Z*-isomers of methoxylated stilbenes and related compounds have shown higher antiproliferative or antimetastatic activity than their *E*-isomers, but they isomerize during storage and administration and during metabolism in liver microsomes.[56-58]

Z- and *E*-stilbene derivatives have been reviewed for their cytotoxic and anti-tubulin properties.[41] SAR analysis and virtual screening conducted on a wide range of stilbene analogues have elucidated the importance of the *Z*-configuration of the olefinic bridge for the cytotoxicity and these studies were useful in the design of novel agents with improved anti-mitotic activity. For instance,

Tamoxifen (Figure 2) is a stilbene derivative currently used for the treatment of several types of breast cancer in women, and as a hormone treatment for male breast cancer.

In recent years, structural modifications of naturally occurring stilbene compounds led to number of compounds with significant antitumor potential.[59]

In this section, we summarize the most important studies of stilbene variously substituted derivatives, based on the type of the main modification made to the stilbene scaffold.

3.1. Polymethoxy stilbenes

Efforts have been made to obtain synthetic analogues with an increased metabolic stability and potentially enhanced antitumor activity. Methoxylation of hydroxyl groups is supposed to prevent polyphenol metabolism and enhance stilbene bioactivity. [60a-b] Methoxylation has been suggested to significantly improve the anti-tumor potential of compounds.[61] The greater the number of methoxy groups that are added, the better the anti-tumor activity of the compound becomes.

Polymethoxystilbenes and related compounds showed promising antitumor properties.

Polymethoxystilbenes and related compounds are a subgroup of resveratrol derivatives frequently much more antiproliferative than parent drug[62] with better antiangiogenic activity, VEGF and NF-kB inhibition,[63] and inhibition of multidrug resistance (MDR) of tumor cells.[64]

Polymethoxystilbenes are able to interact with biomembrane models, undergo a different metabolic conversion and have a higher bioavailability than resveratrol.[65a-c] 3,5,4'-Trimethoxystilbene presented greater anti-tumor activity than the resveratrol, in COLO 205 tumor xenografts.[33]

In order to determine the role of the methoxy position and number, double bond configuration, or the additional hydroxyl groups on anticancer activity and define the structure-activity relationship, a lot of polimethoxylated resveratrol derivatives have been synthesized and tested.[66]

Structure–activity relationship (SAR) studies conducted on methoxylated stilbenes, revealed that 3,5-dimethoxy and 3,4,5-trimethoxy motifs are important to the pro-apoptotic activity while 2-methoxyl group in the stilbene skeleton confers selectivity against cancer cells by targeting

cytochrome P450 CYP1B1, a tumor-specific enzyme. These studies led to obtain two important compounds depicted in Figure 3, **1** and **2**. They are potent apoptosis-inducing agents acting on microtubule polymerization.[67] **1** exhibited superior availability than resveratrol in the colon[68] and effectively reduced adenoma load in ApcMin/þ mice.[69]

3, a hybrid molecule of **1** and **2** (Figure 3), is potent and selective apoptosis-inducing agent; it displayed more potent *in vitro* anti-mitogenic effect on colon cancer cells (Caco-2, HT-29 and SW1116). Moreover, **3** inhibited tumor growth *in vivo* in a colon cancer xenograft model.[67b]

A study carried out on four major metabolites of **1** highlighted the importance of the trimethoxy substitutions and the methoxy group at 4'-position for the antiproliferative activity.[70] In fact, only the metabolite that retained this substitution pattern, exhibited the ability to inhibit of HepG2 and MCF-7 cell proliferation with a similar mechanism of action of **1**. This compound was found to potently inhibit the proliferation of a variety of cancer cells, including HeLa cervical cancer cells, MCF-7 and MDA-MB-435/LCC6 breast cancer cells, HepG2 hepatoma cells, LnCaP prostate cancer cells and HT-29 colon cancer cells.[71] Its analogue *E*-3,5,4′-trimethoxystilbene was the most effective anti-cancer agents among the analogues investigated, and showed improved cytotoxicity compared to resveratrol itself.[72]

Natural resveratrol methyl ethers are described to be more specific and potent inhibitors of cytochromes P450 (CYP) Family 1 in comparison to the parent compound.[73] Also stilbene derivatives with methylthio substituent are selective and potent inhibitors of CYP1 enzymes.[74] **4**, Figure 3, showed a selective inhibition of the isozymes CYP1A1 and CYP1B1, and a very low affinity to CYP1A2.[75] This result was explained by molecular docking studies.[75] The less electronegative sulfur atom respect to the 4'-oxygen atom, reduced toxicity to HEK 293 cells and enhanced the ability of the compound to activate human Sirtuin-1.[76]

4'-Methylthio stilbenes are also reported as efficient inhibitor of NF-kB and AP-1, confirming the crucial role of this transcription factor in tumor pathogenesis in HaCaT keratinocytes.[77] More recently, in a novel series of polymethoxy-*trans*-stilbenes in which the 3,4-dimethoxy motif was

retained, compound **5** (Figure 4) was the most selective inhibitor of both CYP1B1 and CYP1A1 showing very low affinity toward CYP1A2, in nanomolar range.[78] These enzymes are involved in the activation of potential carcinogenesis.[78] Docking studies outlined the importance of methoxy group in 2' position in **5**; this compound showed the energetically favorable orientation into CYP1B1 pocket that allowed van der Waals and π–π stacking interactions.

Recently, N. R. Madadi and coworkers reported the synthesis of a series of *Z*-diarylacrylonitrile analogues of resveratrol; these compounds were evaluated against a panel of 60 human tumor cell lines; the most potent compound **6** (Figure 4) with GI_{50} values of <10 nM against almost all the cell lines in the human cancer cell panel, was also screened against the acute myeloid leukemia cell line, MV4-1. *Z* analogue **7** is more potent than **6** in inhibiting tubulin polymerization in MV4-11 cells; this fact was confirmed by molecular docking studies that indicated a common binding site for **6** and **7** on the α,β-tubulin heterodimer, with a slightly more favorable binding for **7** compared to **6**, which is consistent with the results from microtubule depolymerization assays.[79]

Compound **8** in Figure 4, was largely studied for its apoptotic activity in myeloblastic leukemia cell line HL60 cells (myeloblastic acute leukemia) inducing a partial block of cells in S phase.[27]

Subsequently, compound **8** was checked in an *in vivo* study in immunodeficient mice with HT-29 xenograft[80] in the same study, its 4'-amine analogues *Z*- and *E*-**9** (Figure 4) was more potent. Also, the natural *E*-**8**, was the most growth inhibitory of HT-29 and Caco-2 colon cancer vell lines *in vitro*, among all the stilbenes tested (IC_{50} ¼ 0.04 and 0.08 mM in HT-29 and Caco-2 cells, respectively).[32] Generally, the *Z* analogs demonstrated greater activity than the *E* isomers *in vitro*, but the tumor growth inhibitory effect *in vivo* was different depending of type of substituent in 4' position (amino, ester, methoxy, halogen, hydroxyl). The *Z* -amino analog of **9**, which showed only moderate activity *in vitro*, had the same effect as its *E* isomer *in vivo* due to its isomerization *Z/E*.[80] These compounds decreased the percent of PCNA-labeled cells, being PCNA an auxiliary protein of DNA polymerase δ required for DNA synthesis during S-phase, thus is a useful marker in

reporting cell proliferation.[81] They also increased the levels of p27, a cyclin-dependent kinase inhibitor, that regulates the G0-S transition in cell cycle.[82]

Compounds **9** and **10** were also tested for their activities on 12 anticancer targets, three cancer cell lines and in preliminary animal studies, together with a large library of different 92 compounds.[51a] **9** inhibited ODC induction (IC_{50} of 1.3 μM), modestly inhibited NFkB (IC_{50} of 5.8 μM), induced QR1 by 1.9-fold, and inhibited aromatase with IC_{50} value of 0.31 μM. In the same study, **10** showed a better activity on aromatase inhibition with an IC_{50} of 0.04 μM. Preliminary absorption and metabolism studies were also performed.[51a]

Compounds **9** and its analogue with an additional methoxy group in 4-position, also displayed potent QR2 inhibitory activity (IC_{50} values of 1.7 μM and 0.27 μM, respectively) and their crystal structures in complex with QR2 have been determined. They bind to QR2 in an orientation similar to that of resveratrol: these two compounds interact with a direct hydrogen bond interaction of the amino group and this fact is most likely responsible for enhancing the QR2 inhibitory activity respect to resveratrol (IC_{50} values of 5.1 μM).[83]

The inhibition of QR2 blocks the production of highly reactive species from some quinone substrates; this is very important for the protection of cells.[83] The 4'-amino stilbene scaffold was found to exhibit versatile biological activities including nitric oxide synthase inhibition, aromatase inhibition (IC_{50} 22 μM), and inhibition of TNF-α-induced NF-κB activity.[84] Larger study studies carried out on *E*-**9** (Figure 4) outlined the importance of the *para*-amino group on the 4'-stilbene benzene ring for aromatase inhibitory activity (IC_{50} 0.59 μM), and the introduction of an imidazole moiety on double bond improved the activity greatly in **10** (IC_{50} 36 nM, Figure 4).[83] An analogue of compound **8,** compound **11** (Figure 5) with a methoxy group in 3'-position was found effective for inhibition without inducing cytotoxicity (IC_{50} of 0.16 μM), suggesting that this molecule could be used in combination with other inhibitors to block ABCG2 drug-efflux activity. ABCG2 are resistant cancer cells, in which is overexpression of multidrug ABC ("ATP-binding cassette")

transporters within plasma membranes. This alters the efficiency of chemotherapeutics by lowering their intracellular concentration.[85] **11** was able to chemosensitize the growth of resistant ABCG2-transfected HEK293 cells at submicromolar concentrations.[64] This effect is depended on the number of methoxy substituents, from 1 to 4, and on their positions and the molecular mechanism of inhibition was also studied.

An extraordinary high and wide spectrum of antiproliferative activities was observed for compounds **12** and **13** showed in Figure 5. This evaluation was carried out on four different human cancer cell lines (Colo-205, MDA-468, HT29, and MGC80-3). This study indicated that the nature and the positions of substituents greatly affected the activity profile of these compounds, indeed isomers or derivatives had a narrow spectrum of activity.[86]

Phenols as **14** and **15** (Figure 5) were proved as antiangiogenic agents acting on granulosa cell vascular endothelial growth factor (VEGF) production.[63]

Compounds **14** and **15** showed also high activity on an antiproliferative activity bioassay toward Caco-2 and SHSY5Y cancer cells, GI_{50} value of 3 μM.[87]

Glucosides and galactosides of the active aglycones **14** and **15** lacked antiproliferative activity even if glycosides display antitumor activity or other promising biological properties[88a-b] and resveratroloside showed cytotoxic activity against human tumor cell lines. This fact could be due to poor hydrolysis by intracellular enzymes; they also showed β-glucosidase or β-galactosidase inhibition with IC_{50} values in the approximate range 170-350 μM, compared with the antidiabetic drug acarbose (IC_{50} = 65 μM).[89]

Polymethoxy stilbenes with α,β-unsaturated amide tail were evaluated for anticancer, anti-inflammatory and COX-2 inhibition.[90] Since COX-2 is overexpressed in many human cancers,[91] selective COX-2 inhibition could represent an opportunity for both cancer prevention and therapy.[47b, 92]

Compounds **16**, **17**, and **18** showed in Figure 6, exhibited the most potent antitumor activity against MCF-7, A549 and B16-F10 tumor cell lines and optimal COX-2 inhibitory potency and selectivity

compared with celecoxib. These data were confirmed by further crystallization studies and molecular docking that proved an high binding potency of COX-2.[90]

In a recent work, a series of very simple stilbene derivatives showed a measurable inhibitory effect on angiogenesis, some of them to a higher degree than resveratrol. VEGF is an inducer of angiogenesis and an overexpression in the production of VEGF is implicated in various types of tumors.[93] These compounds caracterized by hydroxyl groups protected by methyl or allyl groups in *ortho* positions (**20-21,** Figure 6),[46a] lead to a decrease in the production of VEGF by 50% in HT-29 cells much more respect to resveratrol. They may be considered a potentially valuable anticancer agent with lower metabolization rate due to no free hydroxyl groups as in resveratrol.

As an extension of this research work, Martì-Centelles and coworkers reported a new series of variously sustituted stilbene derivatives with hydroxyl, methoxy groups and amine and/or amide (Figure 7).[93] These new synthetic stilbene analogues was evaluated on VEGF production and on the expression of the hTERT gene, involved in the process of telomerase activation, an enzyme that has been detected in about 90% of all malignant tumors. Also, the inhibition of expression of c-Myc, an oncogene involved in the transcription factor for hTERT, was measured. Among 39 stilbene derivatives, **22**, Figure 7, showed cytotoxic values in the low nanomolar range for HT-29 and MCF-7 cancer cell lines and it showed a large cytotoxic activity for HEK-293 tumoral cell lines. It inhibited VEFG protein secretion and the expression of the telomerase related hTERT and c-Myc genes at similarly low concentrations.

Highly substituted *E*-configurated stilbenes were compared for their antitumor activity referring to ***Z*-CA-4** on 8 human cancer cell lines and showed cytotoxic activity in micromolar range. Noteworthy, compound **23** (Figure 7) that is configurationally stable, confirmed that *Z*-configuration seems to be not essential for a high cytotoxicity. In fact, combretastatins with a *Z* configurated alkenic bond, possessed *in vitro* a high tendency to undergo *Z/E* isomerization with accompanying decreasing loss of cytotoxicity.[44]

Very interesting role in the chemotherapy of stilbene derivatives, was reported by Reddy *et al.*[94] They synthesized and tested a series of stilbene derivatives variously functionalized with different groups such as methyl, methoxy, methylenedioxy, 3,4,5-trimethoxy, chloro, fluoro, and bromo groups at different positions. These compounds contain an important nitrovinyl side chain that has been described to be able to bound and inhibit human telomerase with resulting in pro-apoptotic activity.[95] Almost all compounds demonstrated significant antiproliferative activity against the four cancer cell lines tested. In particular two of them, compounds **24** and **25** (Figure 7), with a methyl or methoxy groups in *4'*-position on aromatic ring respectively, showed an antiproliferative activity in picomolar range, and an inhibition of tubulin assembly in high percentage, induced cell cycle arrest at the G2/M phase. This fact was explained by docking studies that demonstrated that the position of the trimethoxyphenyl group of compounds **24** and **25** exhibited a binding mode similar to that of the trimethoxy ring of colchicines, a natural compound that inhibits microtubule polymerization.[94]

As a further development of studies on nitrovinyl styrene derivatives, compounds **26** and **27** (Figure 7) having 3,4-(1,3-dioxolane) and 3,4-difluoro groups, respectively, exhibited IC_{50} values below 10 μM against four cancer cells lines, and inhibited tubulin polymerizations by 62% and 55%, respectively at 5 μM concentrations.[96] Also for this compounds, molecular docking analysis demonstrated that they occupied colchicine binding site in tubulin.

3.2. Halogenated stilbenes

In 2009, B. W. Moran *et al*., prepared a series of *trans*-fluorinated analogues of resveratrol some with hydroxyls and others with protected hydroxyl, amino, ether or/and nitro groups.[97] These compounds were assayed in lung cancer and melanoma cell lines. Among them, **28** (Figure 8) displayed greater potency than that of the parent compound resveratrol. This was further evaluated on a panel of 60 cell lines by the National Cancer Institute under the Development Therapeutic

Program (DTP), showing a broad spectrum anticancer activity against leukaemia, colon, lung, breast, melanoma, prostate, ovarian, central nervous system and renal cancer lines.

A panel of fluorinated N,N-dialkylaminostilbenes in particular in ortho position to the stilbene double bond, inhibited Wnt pathway downstream of β-catenin, and repress colorectal cancer cell proliferation; Wnt/β-catenin signaling is an important pathway in development and tumorigenesis,[98] and the block of Wnt signaling is an attractive approach for colorectal cancer chemoprevention and therapeutics. *E*-**29 (**Figure 8) inhibited Wnt signaling at nanomolar levels respect to resveratrol and pterostilbene, that exhibited an inhibition in micromolar range.[99]

In this study, the substitution of an aromatic ring with heterocyclic and polyaromatic systems or the substitution of the N,N-dimethylamino with other alkyl or aryl groups led to a loss of activity.

3.3. Heteroaromatic stilbenes

In literature there are reported studies carried out on derivatives of resveratrol in which one or both of the aromatic rings are replaced with an heteroaromatic one. In a recent study of anticancer stilbenes conducted on a series of derivatives of difluorinated N,N′-dialkylaminostilbenes (FIDAS agents),[99] 2′,6′-dihalostyrylanilines **29**, Figure 8), pyridines **30** and pyrimidines **31** (Figure 8) were tested for their *in vitro* activity against LS174T cells showing citotoxicity in the low nanomolar range on the proliferation of colon and liver cancer cells. They also inhibited the catalytic subunit of MAT2A. This result confirmed the important correlation between the expression of MAT and human colorectal carcinoma.[100] This study led to key findings: aniline and 2-aminopyridine derivatives possess lower IC_{50} values in the inhibition than that of the 5-aminopyridine and the 2-aminopyrimidine ones. The most active FIDAS agents possessed either 2,6-difluorostyryl or 2-chloro-6-fluorostyryl subunits, and small N-alkyl groups, specifically the N-methylamino or the N,N-dimethylamino groups, in a *para* orientation relative to the 2,6-dihalostyryl subunit (Figure 8).[101]

Pyridine and pyrimidine stilbenes were investigated for their cytotoxicity and their ability to inhibit the production of the VEGF and the activation of telomerase on two tumoral cell lines (HT-29 and MCF-7) and one non-tumoral cell line (HEK-293).

Pyridine stilbenes substituted at C-4 and an *ortho* or *meta* methoxy group in the benzene ring, as compounds **32** (Figure 9), showed an action similar to the resveratrol.[102]

In a recent study, heteroaromatic analogs of **1** were evaluated for their anti-cancer activity against a panel of 60 human cancer cell lines (NCI-60 panel) at a concentration of 10^{-5} M.[103] In these compounds, the 4-methoxyphenyl moiety in the **1** molecule was replaced with a heterocyclic ring such as indole, benzofuran, benzothiazole and benzothiophene and the methoxy substitution pattern was also varied. The combination of *E*-3,4,5-trimethoxystyryl moiety and benzothiazole or benzothiophene, respectively (compounds **33** and **34**, Figure 9), exhibited the most potent growth inhibition against most of the tested cancer cell lines and this strongest binding interaction at the colchicine-binding site on tubulin was studied by molecular modeling studies.

The introduction of a cyano group at the olefinic bridge conducted to compounds **35**. Both *E* and *Z* isomers showed nanomolar growth inhibition in a NCl-60-cell lines screen.[104] As an extension of this study, a series of Z-quinolyl cyanostilbene analogs that incorporate 3,4,5-trimethoxyphenyl or 3,5-dimethoxyphenyl, were also synthesized and tested as anti-cancer agents against an extensive panel of human cancer cell lines (compound **36**, Figure 9). These compounds exhibited the most potent growth inhibition in micromolar range, against most of the human cancer cell lines in the panel.[105]

Heteroaromatic *Z*-stilbene vinyl hydroxamic acids are described in the next paragraph.[42, 106]

Heteroaromatic stilbene derivatives are also hybrid molecules, that combine the anticancer properties of stilbene moiety with that of a counterpart with documented ability to modulate one or several pathways relevant for cancer pathogenesis.[107] In medicinal chemistry, polypharmacological compounds represent an innovative strategy to obtain a new chemical entity with a multitarget activities.[108]

In a recent work of Jun Yan and collaborators,[109] the antiproliferative activity of a series of hybrid compounds of resveratrol, was studied. These compounds combine the pharmacophores of resveratrol and ebselen, a selenium-containing compounds that was described for its antiproliferative activity as well as for other biological activities, such as inhibition of cyclooxygenases, lipoxygenases and thioredoxin reductase (TrxR).[110]

TrxR plays an essential functional role in cancer therapy because it is overexpressed in tumor cells. So, a series of benzoselenazole-stilbene hybrids were synthesized and the antiproliferative activity, TrxR inhibitory effect, and ability to increase the intracellular ROS levels against four human cancer cell lines were evaluated. Compound **37** (Figure 10) induced G2/M cell cycle arrest and apoptosis of the human liver carcinoma Bel-7402 cell line and exhibited the best TrxR inhibitory activity. This data confirmed the influence of methoxy groups on blocking the cell cycle as previously reported for resveratrol derivatives.[45]

This fact could explain as the oxidative stress, related to TrxR inhibitory activity, is able to induce apoptosis in cancer cells.

Recently, *E*-stilbene has been coniugated with the *3H*-quinazolin-4-one, a natural bioactive scaffold with a large of documented biological activities among which also the anticancer activity.[111a-b] The nucleus of quinazolinone was substituted in N_3-position with alkyl, aryl or benzyl groups while no structural change was made on the stilbene core bounded in 2-position. These compounds were tested for their cytotoxic activity on three human cancer cell lines including MCF-7, MDA-MB-231, and T-47D using MTT assay. Compounds with N_3-alkyl, N_3-aryl and N_3-benzyl substituents and N_3-*sec*-butyl derivative **38** (Figure 10) showed the best profile of activity showing an IC_{50} of less than 5 μM for all tested cell lines. In this case, stilbene has certainly contributed positively to the activity in reference to what previous reported for structural analogues of 2-aryl quinazolinones.[112]

In a recent study, a series of (E)-styrylbenzoimidazoles **39** (Figure 10) showed an interesting inhibitory acitivity of epoxide hydrolase (sEH) in the range of 1.7 to 2.6 μM on four cancer cell

line.[113] Epoxide hydrolase (sEH) hydrolyses the epoxyeicosatrienoic acids which level is critical for primary tumor growth and metastasis in mouse models of cancer,[114] promoting metastasis by triggering secretion of the vascular endothelial growth factor (VEGF) by the endothelium. Compound with an *ortho*-trifluoromethyl on aromatic ring, was docked in the bonding pocket of catalytic domain of sEH, confirmed its potent sEH inhibition and antiproliferative activities.

3.4. Z- stilbenes

Although *Z* and *E*-isomers of resveratrol occur in nature, the *Z* form is not biologically active. However, methylation at key positions of the *Z* form results in more potent anti-cancer properties, as also reported in the introduction.

In a study conducted by F. Mazué and coworkers, a series of *Z* and *E*-trimethoxy and tetramethoxystilbenes were synthesized and tested for proliferation inhibition of SW480 cell line.[45] Most of the synthetic methoxylated derivatives (*E* or *Z*) stop mitosis at the M phase while *E*-resveratrol inhibits cells at the S phase. The number of methyls present in these molecules, is crucial for determining the inhibitory properties and *Z*-stereoisomers have the strongest effects. Docking studies showed that almost all of the docked structures of *Z*-polymethoxy isomers substantially overlap the docked structure of CA-4, taken as reference compound, apart *Z*-resveratrol and *Z*-tetramethoxy-stilbene, but not most of the *E*-isomers. The most powerful molecule is compound *Z*-**40 (**Figure 11) that showed a very interesting reduction of metastatic mouse melanoma B16 F10 cells, non-metastatic B16 F1 cells, and immortalized melanocytes all which were isolated from C57BL/6 mice.[62]

10.1002/cmdc.201700045

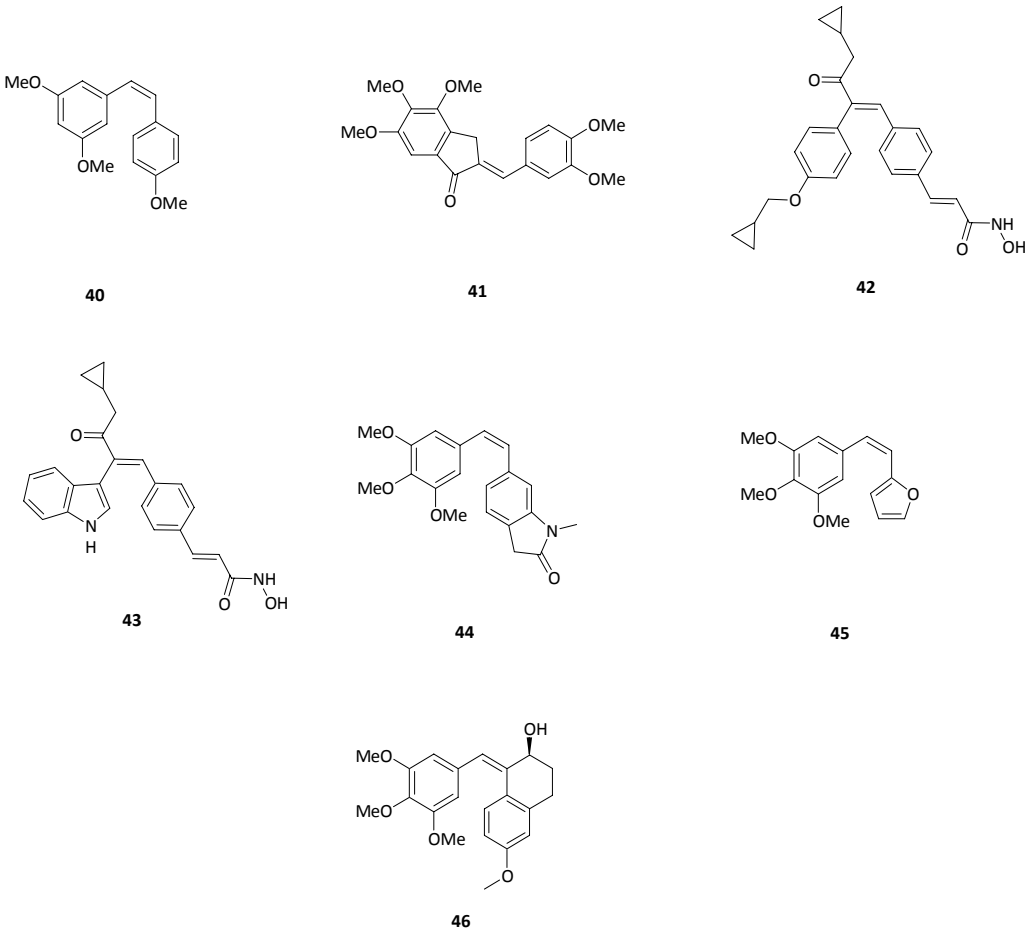

Figure 11: Z-stilbenes **40**-**46**.

New 2-benzyl α,β-unsaturated indanones were studied as tubulin assembly inhibitors.[115] Compound **41** (Figure 11) displayed good anti-proliferative activities with GI_{50} values in the micromole to sub-micromole range on five human cancer cell lines, using an MTT assay. This compound demonstrated that the three methoxyl groups on the 4,5,6-position of the indanone moiety are very important for the inhibition of tubulin polymerization in HeLa cell line arresting cell-cycle progression at the G2/M phase in a concentration-dependent manner; this is in agreement with most of the antimitotic agents.

Vinyl hydroxamic acids linked to *Z*-stilbene were described as orally available HDAC inhibitors.[116] Most of 42 tested compounds showed a good HDAC inhibition (IC_{50} < 100 nM) and good anti-proliferative activity study in three different cancer cell line (HCT-116, NCIH-460,

U251), GI_{50} ranging from 0.01 μM to 3 μM. In Figure 11, are depicted two of the best vinyl hydroxamic acids as examples, **42** and **43**.[106]

The most active compound **44** (Figure 11) of a series of 28 *Z*- and *E*-styrylbenzoxazolones, containing 3,4,5-trimethoxystyryl fragment in position 6 of benzoxazolone, showed highest antiproliferative effect against HepG2, EA.hy926 and K562 cancer cell lines and on additional cell lines, with IC_{50} similar or better compared to CA-4. It showed to induce of mitotic arrest in G2/M phase like CA-4, as confirmed by X-ray studies.[42]

The combretastatin-based hybrid **45** (Figure 11) and its analogues, were tested *in vitro* for potential antitumor and cytotoxic activities on the HeLa tumor cell line and non-tumor Vero cell line. This derivative showed an high potential antitumor activity with an IC_{50} value of low micromolar.[117]

Z-constrained stilbenes, analogues of CA-4, were synthesized and tested for their ability to inhibit tumor cell growth on the HT-29 and SKOV3 cancer cell lines. *In vitro* and *in vivo* best activity was detected for compound **46**, Figure 11. Studies of *Z/E* isomerization with UV-VIS spectrophotometric analysis have been also performed for some of these compounds.[98]

4. Conclusions

Stilbene is an extensively explored aromatic nucleus introduced in the scaffold of novel agents implicated in a wide variety of pathophysiological conditions, for the antioxidant, antiaging, anti-inflammatory, anti-diabetic and cardio-protective and anticarcinogenic properties. Natural stilbenes such as resveratrol and combretastatins, as well as their synthetic analogues, become of a great interest to the medicinal chemists. In the last decades, different researches have been devoted to the development of stilbene based compounds with potential clinical utility in the treatment a variety of different tumors.

This review summarize the main natural and synthetic compounds containing stilbene scaffold and ranking them on the basis of type of substitution of stilbene skeleton. These collection aims to

provide an important insight into stilbene containing compounds providing a useful tool to design new therapeutic agents with potential activity on the different pathways involved in cancer therapy.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

This study was supported by University "G. d'Annunzio" of Chieti local grants.

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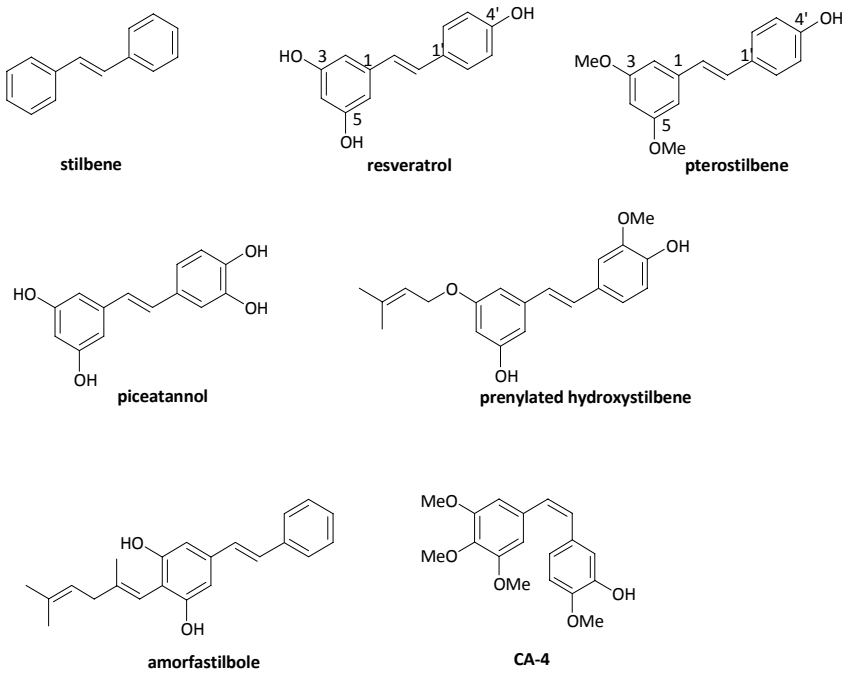

Figure 1: stilbene and some derivatives.

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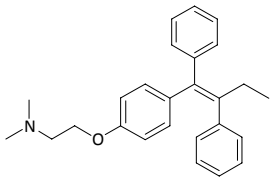

Figure 2: Tamoxifen.

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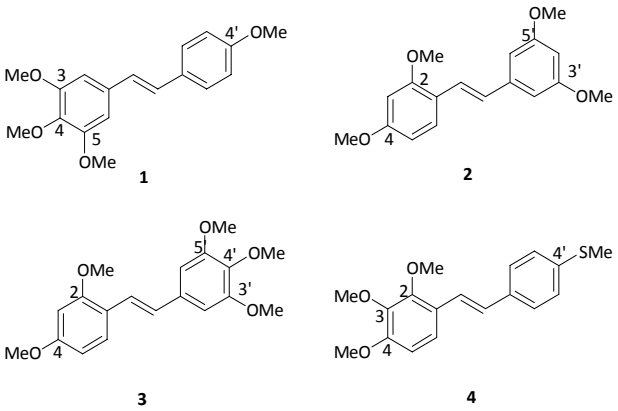

Figure 3: Polymethoxylated stilbenes **1-4**.

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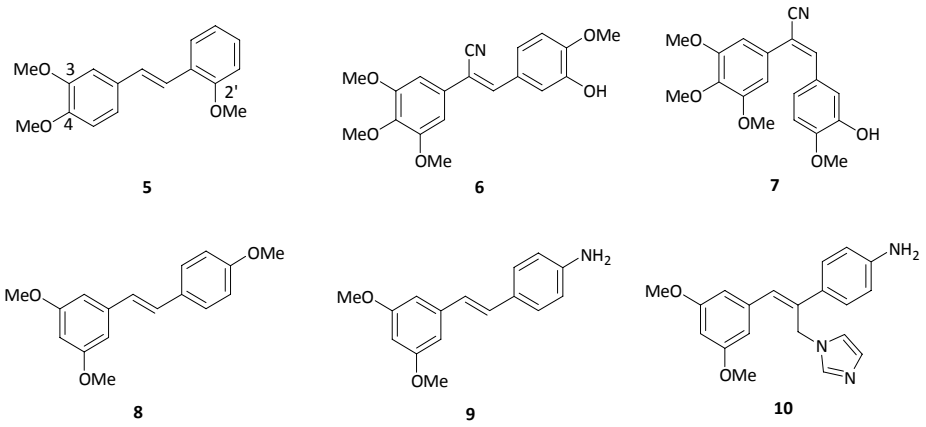

Figure 4: Polymethoxylated stilbenes **5-10**.

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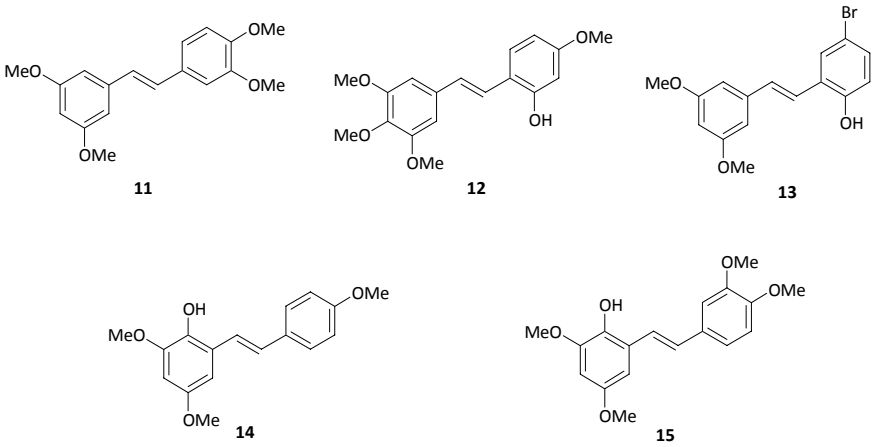

Figure 5: Polymethoxylated stilbenes **11-15**.

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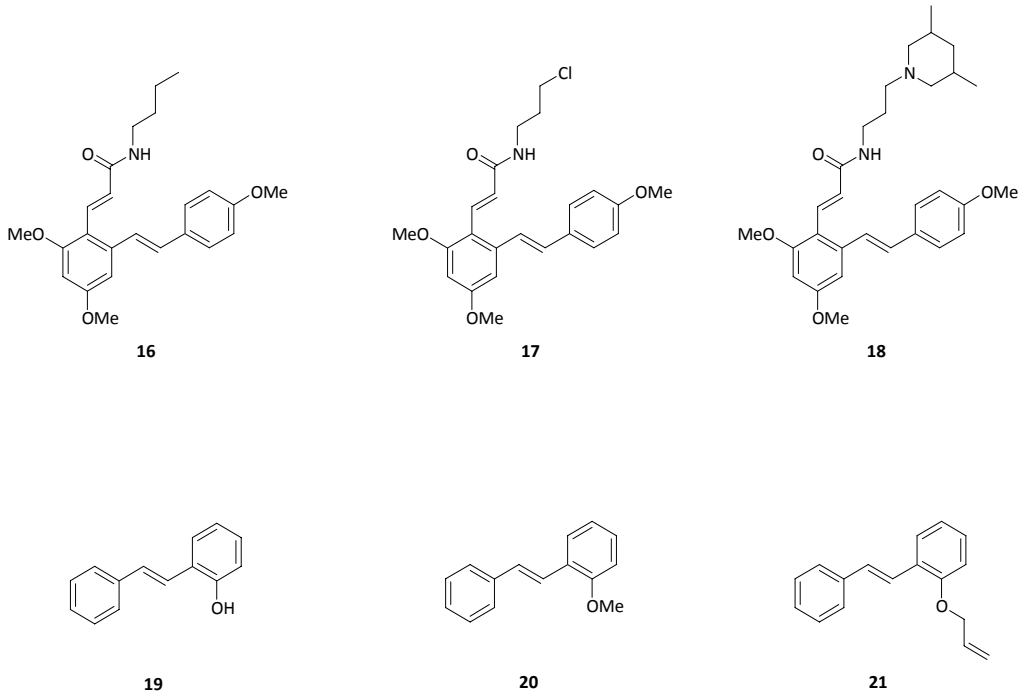

Figure 6: Stilbene derivatives **16-21**.

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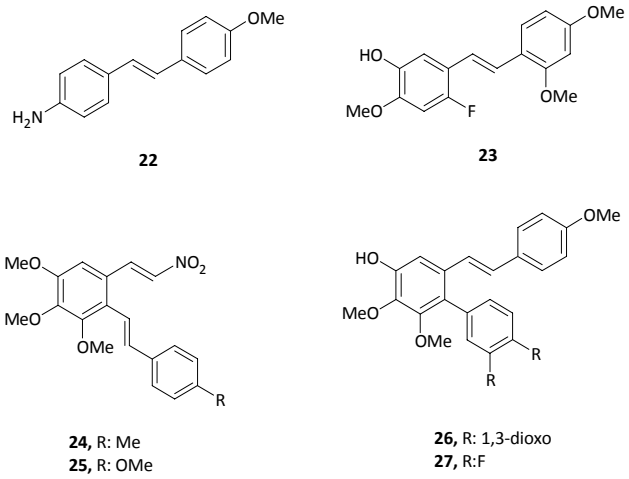

Figura 7: Stilbene derivatives **22-27**.

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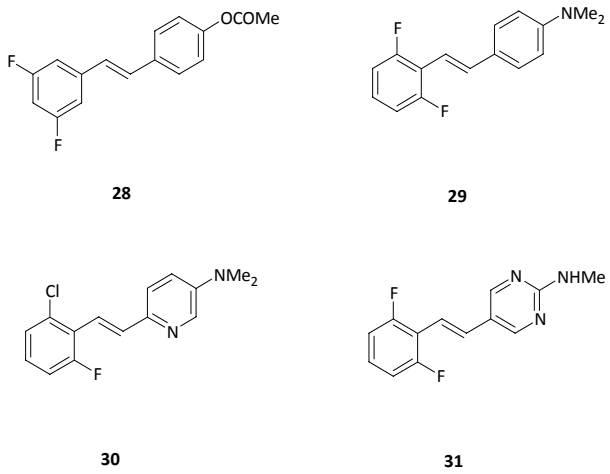

Figure 8: Halogenated stilbenes **28-31**.

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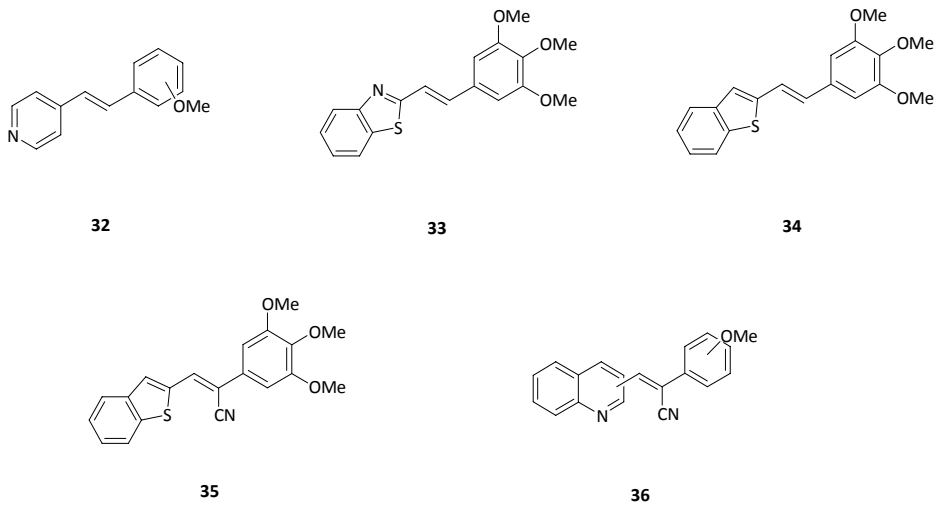

Figure 9: Heteroaromatic stilbenes **32-36**.

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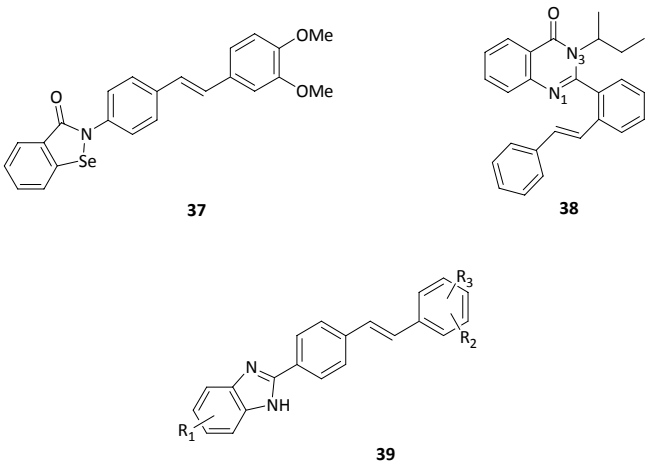

Figure 10: Hybrid stilbenes **37**-**39**.

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Captions

Figure 1: stilbene and some derivatives.

Figure 2: Tamoxifen.

Figure 3: Polymethoxylated stilbenes **1-4**.

Figure 4: Polymethoxylated stilbenes **5-10**.

Figure 5: Polymethoxylated stilbenes **11-15**.

Figure 6: Stilbene derivatives **16-21**.

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Figure 10: Hybrid stilbenes **37-39**.

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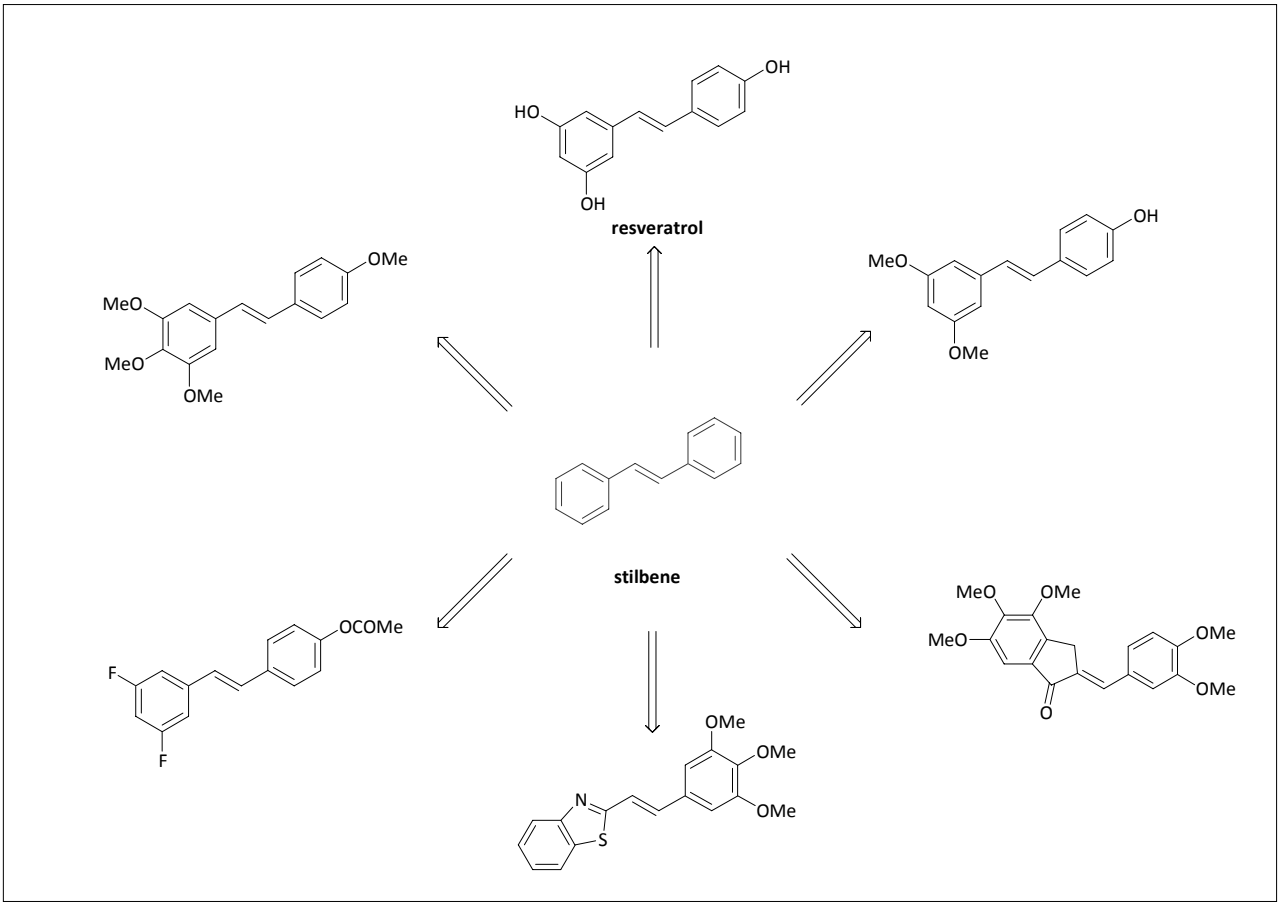

stilbene containing anticancer compounds

10.1002/cmdc.201700045

Biographical sketchs

Dr. Barbara De Filippis

Dr. Barbara De Filippis has a degree in Pharmaceutical Chemistry and Technology and conferred the PhD title in Medicinal Chemistry Sciences at the "G. D'Annunzio "in Chieti, Italy. She is Assistant Professor of Medicinal Chemistry at University of Chieti where teaches a course of Medicinal Chemistry.

The main research topics are related to metabolic diseases and cancer. Her work is centered around synthesis and biological evaluation of fibrates derivatives active on Peroxisome Proliferator-Activatet Receptors (PPARs), nuclear receptors involved in lipoprotein metabolism. Currently, the research interest has shifted towards the synthesis of resveratrol derivatives useful as potential anticancer and antioxidant agents.

Dr. Alessandra Ammazzalorso

Dr. Alessandra Ammazzalorso obtained her PhD in Pharmaceutical Sciences from the University of Chieti (Italy) in 2001. Since 2004 she is researcher at Pharmacy Department of University of Chieti. Her research interests include the design and synthesis of small molecule drugs, mainly compounds targeting Peroxisome Proliferator-Activated Receptors.

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Prof. Rosa Amoroso

Prof. Rosa Amoroso completed the degree in Pharmaceutical Chemistry and Technology (1989) and the PhD in Organic Chemistry (1992) at University of Bologna, Italy. Nowadays she is Associate Professor of Medicinal Chemistry at University of Chieti, Italy. The scientific interests of prof. Rosa Amoroso are mainly directed towards medicinal chemistry and the research topics are the cardiovascular agents and Nitric Oxide Synthase inhibitors.

Dr. Marialuigia Fantacuzzi

MarialuigiaFantacuzzi earned her Honor degree in Medicinal Chemistry and Pharmaceutical Technology and the Ph.D. in Drug Science at the “G. d'Annunzio” University of Chieti (Italy). Nowadays she is researcher and lecturer of Medicinal Chemistry at the Department of Pharmacy. Her research interests are in the field of design, synthesis and biological evaluation of molecules acting on Nitric Oxide Synthases or Peroxisome Proliferator-Activated Receptors.

Dr. Cristina Maccallini

10.1002/cmdc.201700045

Cristina Maccallini received her PhD in Pharmaceutical Sciences in 2002 from the University "G. d'Annunzio" of Chieti (Italy). From 2005 she is Assistant Professor at the Pharmacy Department at the University of Chieti. Her research focuses on the synthesis and pharmaceutical analysis of non amino acidic analogs of L-arginine and of aryloxy acid derivatives as bioactive compounds.

Dr. Letizia Giampietro

Dr. Letizia Giampietro graduated in Pharmacy (2000) and held a Ph.D in Medicinal Chemistry (2003) at "G. D'Annunzio" University of Chieti (Italy). Nowadays she is Assistant Professor of Pharmaceutical Analysis at Pharmacy Department of University of Chieti (Italy). She has experience in research area of medicinal chemistry; in particular, her scientific interests are above all focused towards the synthesis of fibrate derivatives active on Peroxisome Proliferator-Activated Receptors (PPARs) and of L-Arginine analogues as Nitric Oxide Synthase inhibitors. Furthermore, in the last years her research interest was directed about aromatase inhibitors and stilbene analogues as antioxidant agents.

10.1002/cmdc.201700045