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Medicinal chemistry perspective on the structure–activity relationship of stilbene derivatives†

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Stilbenes are a small family of polyphenolic secondary metabolites produced in a variety of closely related plant species. These compounds function as phytoalexins, aiding plant defense against phytopathogens and plants' adaptation to abiotic environmental factors. Structurally, some important phenolic compounds have a 14-carbon skeleton and usually have two isomeric forms, *Z* and *E*. Stilbenes contain two benzene rings linked by a molecule of ethanol or ethylene. Some derivatives of natural (poly)phenolic stilbenes such as resveratrol, pterostilbene, and combretastatin A-4 have shown various biological activities, such as anti-microbial, anti-cancer, and anti-inflammatory properties as well as protection against heart disease, Alzheimer's disease, and diabetes. Among stilbenes, resveratrol is certainly the most popular and extensively studied for its health properties. In recent years, an increasing number of stilbene compounds have been investigated for their bioactivity. This review focuses on the assessment of synthetic stilbene derivatives in terms of their biological activities and structure–activity relationship. The goal of this study is to consider the structural changes and different substitutions on phenyl rings that can improve the desired medicinal effects of stilbene-based compounds beyond the usual standards and subsequently discover biological activities by identifying effective alternatives of the evaluated compounds.

1. Introduction

Stilbene, 1,2-diphenylethylene, gets its name from the Greek word "stilbos", which means "shining".[1] It is a small molecule with a molecular weight of 180 g mol^{-1}.[2] The chemical structure of stilbene is composed of a 14-carbon skeleton. Stilbenes widely exist in nature and may act as phytoalexins, and some plants in response to pathogen attack and other stresses produce stilbenes as defense compounds.[3,4] Stilbenes are abundant in plants with diverse vital biological activities.[5] They are versatile structures composed of two aromatic rings linked by an ethylene moiety and exist in two diastereoisomeric forms, *E*-/*Z*-isomers; thus, they can undergo *E*/*Z* isomerization, altering their general configuration and decreasing their biological activity.[6] Stilbenes show different biological activities such as anti-microbial, anti-oxidant, anti-leukemia, anti-platelet, protein tyrosine kinase inhibitor, anti-inflammatory, anti-cancer, and anti-HIV activities.[7] Thus, stilbenes and their derivatives, which are vital groups of synthetic compounds and natural products, have attracted significant attention for their various pharmacological activities, complicated structures, and useful health properties.[8] In addition to studying the various biological activities of stilbene analogues, the possible application of stilbene analogues as preservatives can be a new research direction.[9] Moreover, these derivatives have attracted significant attention in diverse fields, including food biotechnology, drug discovery and development, and healthcare.[10] The structure of stilbenes is not only limited to pharmaceutical and biological sciences but has also attracted attention from scientists because of their other vital properties, such as large geometrical alteration upon isomerization, high thermal stability of the *Z* isomer, high quantum yield for photochemical isomerization, and direct synthesis.[11,12] Over the past years, increasing articles on stilbene have been found in the literature. Thus, it is a privileged structural scaffold belong to an enormous family of bioactive molecules, including synthetic molecules and natural products.[11,13] More than 400 stilbene derivatives have been identified, which include different structures with various substituents at diverse positions.[14] Hydroxylated stilbenes, such as resveratrol, pterostilbene, pinosylvin, and combretastatin A-4 (CA-4), are natural compounds that exhibit many biological activities (Fig. 1).[12] Resveratrol and its

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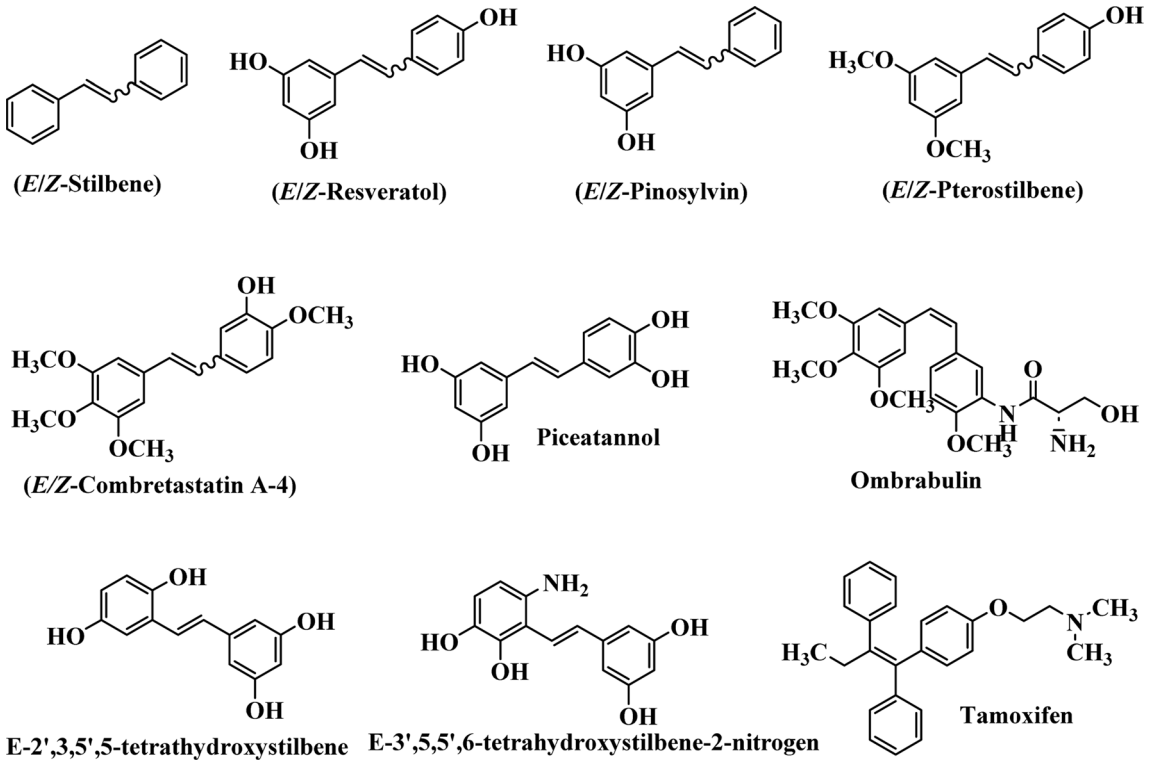

Fig. 1 Some chemical structures of well-known stilbene-based derivatives and drugs.

analogues are well-known for their antioxidant properties against reactive oxygen species (ROS), which cause oxidative damage to biological substances and play a role in aging and inflammation.[15] Resveratrol, a naturally occurring phytoalexin found in grapes and other plants, has been shown to inhibit carcinogenesis and tumor cell cycle progression, as well as interfere with intracellular signal transduction regulating cell survival and apoptosis (programmed cell death) in various human cancer cell lines.[16,17] Piceatannol (PIC) (*E*-2,3′,4′,5-tetrahydroxystilbene) is a phenolic compound (stilbenoid) and a hydroxylated analogue of resveratrol (Fig. 1). Grapes, passion fruit, white tea, Japanese knotweed, Asian legume, and Korean rhubarb are some crucial sources of PIC. However, because the level of PIC in grapes is lower than that of resveratrol, it has received significantly less research attention compared to resveratrol. Scientists have reported that the seeds of passion fruit (*Passiflora edulis*) have a high content of PIC, which displays various biological activities such as protection of the skin from ultraviolet B irradiation, inhibition of melanogenesis, promotion of collagen synthesis, a vasorelaxant effect and Sirt1 induction activity. PIC possesses potent antioxidant activity and has chemopreventive and anti-cancer properties.[18] *Z*-CA-4 is a polyphenol, which was first isolated from an African bush willow tree in 1982, *Combretum caffrum*. It is recognized for its potent anti-angiogenic and anti-tumor activities and potent depolymerizing agents as well as a strong tubulin polymerization inhibitor.[13,19] Numerous derivatives have been developed to search for compounds with higher biological activity, such as ombrabulin, which shows higher activity than CA-4 (Fig. 1). Currently, it is being studied in phase III clinical trials for the treatment of advanced-stage soft-tissue carcinoma.[20] In January 2013, Sanofi said it discontinued the development of ombrabulin after disappointing results from phase III clinical trials. Furthermore, phosphate derivatives have demonstrated good activity and have been used in clinical trials.[21] Interestingly, in 2006, Li *et al.*[3] synthesized stilbene derivatives with substituted hydroxyl groups and found that two of these compounds, *E*-2′,3,5′,5-tetrathydroxystilbene and *E*-3′,5,5′,6-tetrahydroxystilbene-2-nitrogen, inhibited SARS coronavirus replication using an *in vitro* model (Fig. 1). Thus, stilbene-based compounds can also be considered as promising anti-COVID-19 drug candidates due to their ability to disrupt the spike protein.[6] Tamoxifen, a stilbene derivative, is currently used to treat several types of breast cancer in women, as well as a hormone treatment for male breast cancer (Fig. 1).[20] Recently, many scientific institutions have been conducting research on stilbenes as alternative antibiotic growth stimulants. These compounds can be produced in plants by combining coumaric acid and cinnamic acid. Chalcones and flavanols can also be used for their synthesis. They have fungistatic properties (they inhibit fungi growth), toxic properties to fungi (they kill fungi), and estrogenic properties.[22] Stilbenes may decrease obesity by regulating fat metabolism pathways such as adipogenesis, lipogenesis, lipolysis, and thermogenesis. Researchers are also investigating stilbene derivatives for cell proliferation and cytochrome P450 inhibitory activity.[23,24] Natural product research, combined with the powerful possibilities provided by synthetic chemistry may provide an excellent method for

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discovering new structures and identifying therapeutic targets.[13]

Other stilbene-based drugs that have been approved for use include dienestrol, toremifene, clomifene, tapinarof, raloxifene, ospemifene, and hydroxystilbamidine. Furthermore, some derivatives are under continuing clinical trials, such as cystic fibrosis-NCT04166396, chronic obstructive pulmonary disease-NCT03819517, chemoprevention-NCT04266353, combretastatin A1 di-phosphate/CA-1P, also known as OXI-4503 (acute myelogenous leukaemia and myelodysplastic syndromes-NCT02576301), pterostilbene or benvitimod, fispemifene, afimoxifene, droloxifene, and enclomiphene.[11] Moreover, Ramizol, a first-generation stilbene-based antibiotic, is effective against 100 clinical isolates of *C. difficile*,[25] and presently is under pre-clinical testing for the treatment of *C. difficile*-related diseases.[26] Fosbretabulin (CA-4 phosphate) has been investigated in numerous clinical trials as monotherapy and combined therapy with other chemotherapeutic agents, such as carboplatin, paclitaxel, bevacizumab and pazopanib.[27]

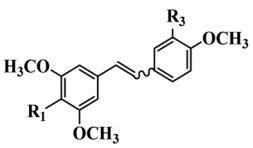
However, despite all these recognized biological activities and advantages, the poor solubility of these analogues presents a critical problem in terms of their bioavailability, and thus prevents stilbene analogues from exhibiting the required activity. Some studies have reported that the complexation of polyphenols with cyclodextrins (CDs) and micellar systems results in a noticeable improvement in their aqueous solubility, and even increases their stability and bioactivity.[10] CDs were shown to be more helpful for improving the solubility of stilbene with the benefit of being less toxic to humans.[24] In addition, nanoformulation techniques have been newly applied to enhance the bioavailability and targeting ability of stilbene analogues.[28] Some researchers conjugated stilbene analogues with mannose, glucose, and galactose to increase their solubility[29] or yield phosphate and carbamate prodrug salts.[30] Another strategy to increase their solubility is added or switching their groups with more polar groups based on the their SAR.[31–34]

This study provides an overview of the synthetic compounds derived from the stilbene scaffold as anti-microbial, anti-cancer, antioxidant, liver enzyme inhibitors, anti-Alzheimer's, anti-diabetes, and other agents. These compounds have undergone chemical modifications, such as the addition of substituents with varying electronic effects or the incorporation of heteroaromatic groups instead of phenyl rings. The biological activity of these compounds is mainly influenced by their chemical structure and the substituent groups attached to them.[35] This comprehensive review mainly focuses on synthetic stilbene derivatives and the structure–activity relationship (SAR) studies on their various biological activities.

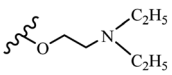
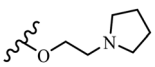
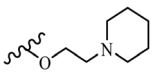
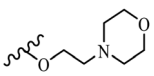
2. Anti-microbial activity

Pathogenic microorganisms have been a threat to humans throughout history, causing significant morbidity and mortality. Until the discovery of the first true antibiotic, penicillin, in 1928 and sulfa drugs in the 1930s, the only means of combating infectious diseases were various types of plant extracts, although their use yielded varying results.[36] Stilbenes have long been recognized as potent anti-bacterial agents, and they continue to pique the interest of many research groups working with various bacteria. The discovery of antibiotic activity against bacteria and fungi sparked interest in stilbene derivative research.[3,4] One example is resveratrol, which naturally exists in plants and has anti-microbial activity against both

Table 1 Anti-microbial activity of *E*/*Z*-CA-4 derivatives



(4a-e)

				MIC (μg/disk)					
Compound	*Z*/*E*	R_1	R_3	*C. albicans*	*N. gonorrhoeae*	*M. luteus*	*S. aureus*	*E. faecalis*	*C. neoformans*
4a	*E*	OH	OH	50–100	12.5–25	—	—	—	6.25–12.5
4b	*Z*	OCH_3		—	50–100	<6.25	25–50	50–100	—
4c	*Z*	OCH_3		—	—	12.5–25	50–100	—	—
4d	*Z*	OCH_3		—	—	—	—	—	—
4e	*Z*	OCH_3		—	50–100	—	—	—	—

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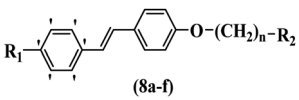
Gram-positive and Gram-negative bacteria.[37] Anti-microbial activity of stilbene derivatives is dependent on the presence of a hydroxyl group in their primary phenyl ring (2-hydroxy, 3-hydroxy, and 4-hydroxy derivatives). If the primary phenyl ring lacks a hydroxyl substituent, 2,5-dihydroxy substituents in the secondary phenyl ring are required for anti-microbial activity. The effect of hydroxyl groups on anti-microbial activity is not surprising, given that phenol is one of the most important anti-microbial agents.[38] The anti-microbial activity increases in derivatives with substituents (F, I, and Br). This can be explained by the change in the partition coefficient and increased permeability of cell membranes to fluoride derivatives, rather than the presence of the substituents themselves.[39,40]

Pettit *et al.*[41] described the synthesis and assessment of the anti-microbial activity of *E*/*Z*-CA-4 analogues. Most analogues were inactive against all strains. Among the synthesized compounds, *Z*-**4b** exhibited the highest anti-microbial activity against *M. luteus*. Also, *E*-**4a** having OH groups in the 4- and 3′-positions on its phenyl ring showed activity against *C. neoformans*; however, none of the compounds showed activity against this strain. Also, the *N*,*N*-diethylamino moiety in compound **4b** in the 3′-position on the phenyl ring was replaced with *N*-pyrrolidinyl in **4c**, which showed less activity against *S. aureus*, *E. faecalis*, and *M. luteus*. In addition, the presence of hydrophilic groups improved the anti-microbial activity compared to lipophilic groups (**4d** and **4e**) against *N. gonorrhoeae*. The results showed that the anti-bacterial activity was greater than anti-fungal activity. According to the obtained results, the *Z*-isomers showed stronger anti-microbial activity than the *E*-isomers (Table 1).

Wyrzykiewicz *et al.*[42] synthesized *E*-piperidino and morpholino stilbenes and assessed their anti-microbial activity. Among the analogues, **8a** showed an anti-microbial effect against all the tested strains (*S. aureus*, *S. faecalis*, *B. subtilis*, *E. coli*, *C. albicans*, and *A. fumigatus*). Among the compounds, **8b** and **8c** exhibited the highest activity against *S. faecalis* and *B. subtilis* (aerobic). These compounds showed almost similar activity as chloramphenicol against these two strains. Also, the presence of an NO_2 group in the 4′-position on the phenyl ring in **8d** compared to **8e** (unsubstituted) displayed higher activity against *S. aureus*, *S. faecalis*, *B. subtilis*, and *A. fumigatus*. It seems that the presence of an electron-withdrawing group (EWG) such as NO_2 in the 4′-position on the phenyl ring plays a vital role in anti-microbial activity. In addition, increasing or decreasing the linker length had no significant effect (*e.g.*, **8a** and **8f**) against *S. faecalis* and *B. subtilis*. Compounds **8a–f** were only endowed with weak anti-microbial activity against *S. aureus* and *A. fumigatus* compared to chloramphenicol and amphotericin B. Most of the screened compounds showed moderate to weak anti-fungal activity (*C. albicans* and *A. fumigatus*). All the tested compounds displayed an insignificant effect against *K. pneumoniae* and *P. aeruginosa*. According to the results, Gram-positive bacteria are more susceptible to the target compounds than Gram-negative bacteria due to the absence of an outer membrane (Table 2).

Chanawanno *et al.*[43] synthesized pyridinium and quinolinium stilbene benzenesulfonate hybrids and evaluated their anti-bacterial activity. The quinolinium derivatives showed better activity compared to pyridinium derivatives. In the first series, quinolinium derivatives **12a–j** exhibited higher activity against Gram-positive than Gram-negative bacteria. Derivatives

Table 2 Chemical structures of *E*-piperidino and morpholino stilbenes



(8a-f)

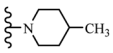
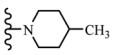
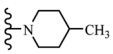
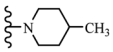
				MIC (μg mL^{-1})					
Compound	*n*	R_1	R	*S. aureus*	*S. faecalis*	*B. subtilis*	*E. coli*	*C. albicans*	*A. fumigatus*
8a	2	H		10	100	100	100	50	50
8b	2	H		7.5	7.5	5	—	50	50
8c	5	NO_2		10	7.5	10	—	—	50
8d	4	NO_2		10	100	10	—	100	10
8e	4	H		—	—	—	—	50	50
8f	4	H		5	100	100	—	—	100
Chloramphenicol	—	—	—	5	5	5	5	—	—
Amphotericin B	—	—	—	—	—	—	—	10	1

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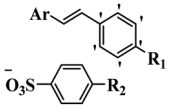
Table 3 Chemical structures of pyridinium and quinolinium stilbene benzenesulfonate derivatives



(12a-j, 15a-j)

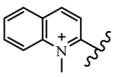
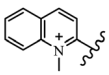
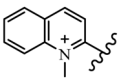
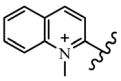
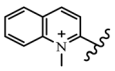
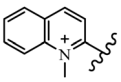
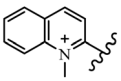
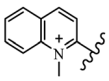
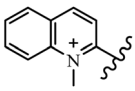
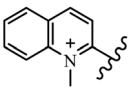
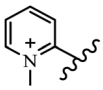
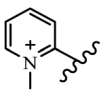
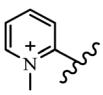
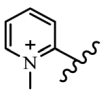
Compound	Ar	R_1	R_2	MIC (μg mL^{-1}) *S. aureus*	*B. subtilis*	*E. faecalis*	*P. aeruginosa*	*S. typhi*	*S. sonnei*
12a		$N(CH_3)_2$	Br	2.34	2.34	2.34	300	300	2.34
12b		$N(CH_3)_2$	Cl	2.34	2.34	2.34	300	300	2.34
12c		$N(CH_3)_2$	CH_3	2.34	2.34	2.34	300	300	2.34
12d		$N(CH_3)_2$	OCH_3	—	75	2.34	300	300	2.34
12e		OC_2H_5	CH_3	—	9.37	37.5	—	—	150
12f		OC_2H_5	Br	300	18.75	37.5	—	—	75
12g		OC_2H_5	OCH_3	—	18.75	75	—	—	150
12h		OC_2H_5	Cl	—	75	75	—	—	300
12i		OC_2H_5	NH_2	37.5	37.5	37.5	—	—	75
12j		$N(CH_3)_2$	NH_2	75	18.75	75	150	75	75
15a		$N(CH_3)_2$	OCH_3	150	150	150	150	150	150
15b		OC_2H_5	OCH_3	150	—	—	—	—	—
15c		OC_2H_5	NH_2	—	—	—	—	—	—
15d		$N(CH_3)_2$	Cl	—	300	—	300	300	—
15e		$N(CH_3)_2$	NH_2	—	—	—	—	—	—

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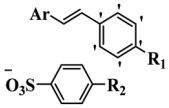
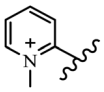
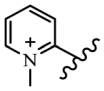
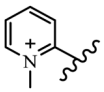
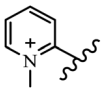
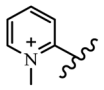
Table 3 (*Contd.*)



(12a-j, 15a-j)

Compound	Ar	R_1	R_2	MIC (μg mL^{-1}) *S. aureus*	*B. subtilis*	*E. faecalis*	*P. aeruginosa*	*S. typhi*	*S. sonnei*
15f		$N(CH_3)_2$	CH_3	300	150	300	150	300	300
15g		OC_2H_5	CH_3	—	300	150	37.5	150	150
15h		OC_2H_5	Br	—	—	—	—	300	300
15i		OC_2H_5	Cl	—	—	—	—	—	—
15j		$N(CH_3)_2$	Br	—	—	—	—	—	—
Benzalkonium chloride	—	—	—	<2.34	150	9.37	300	9.37	—
Vancomycin	—	—	—	9.37	2.34	9.375	2.34	2.34	2.34

12a–c were the most potent compounds against all the tested Gram-positive bacteria. These compounds showed higher activity than that of the benzalkonium chloride drug and vancomycin. All quinolinium analogues were ineffective against *P. aeruginosa* and *S. typhi*. Also, the presence of EWG in the 4-position of the benzenesulfonate moiety resulted in higher anti-bacterial activity toward an electron-donating group (EDG) (*e.g.*, **12a** *vs.* **12d**) against *S. aureus* and *B. subtilis*. Likewise, replacing OC_2H_5 in **12e** with a $(CH_3)_2NH$ group in **12c** in the 4-position on the benzenesulfonate moiety increased the activity against all the strains. The presence of a substitution in the 4-position on the benzenesulfonate moiety increased the activity of the quinolinium derivatives by 2–4 times (**12a–j**). However, substitution in the 4-position of the benzenesulfonate moiety did not significantly improve the anti-bacterial activity of quinolinium derivatives (*e.g.*, **12f**) against *S. aureus* and *B. subtilis*. Compounds **12a–j** were ineffective against all the tested Gram-negative bacteria. In the second series, the compounds containing a $(CH_3)_2NH$ group in the 4′-position on the phenyl ring exhibited better activity than that containing an OC_2H_5 group in the same position (**15a** *vs.* **15b**). All the pyridinium derivatives (**15a–j**) showed less potency than benzalkonium chloride and vancomycin. According to the results, both hydrophilic and lipophilic groups had a similar effect on anti-bacterial activity (Table 3).

He *et al.*[44] synthesized stilbene derivatives containing a 1,3,4-oxadiazole moiety and evaluated their fungicidal activity. Compound **19a** inhibited cucumber *P. cubensis* with significant inhibitory activity comparable to fungicides. Most of the compounds exhibited moderate to weak control efficacy against *S. cucurbitacearum* (*e.g.*, **19b**). Also, changing the position of the NO_2 group on the phenyl ring in 2′-position in **19c** to the 3′- and 4′-positions in **19d** and **19e** enhanced the activity against *P. cubensis* and *C. lagenarium*, respectively. Moreover, among the halogenated compounds, the EWG and small size of F showed the highest activity (**19f**). The shifting of the nitrogen atom from the 2′- to 3′-position of the pyridine ring in compounds **19g** and **19h** increased the activity against *P. cubensis* and decreased the activity against *C. lagenarium* and *S. cucurbitacearum*, respectively. In addition, the presence of an anthracene ring in **19i** showed lower activity than **19j** with a naphthalene ring against *P. cubensis* and *C. lagenarium*. Also, the compounds containing EWG demonstrated better anti-fungal activity compared to that containing EDG (**19k** *vs.* **19l**) against *P. cubensis* and *C. lagenarium*. The results showed that hydrophilic groups were more potent than lipophilic groups (**19c** *vs.* **19m**). Also, the presence of substitution on the phenyl ring reduced the activity (*e.g.*, **19n** and **19b**). In addition, the presence of an extra substitution on the phenyl ring decreased the activity (*e.g.*, **19k** and **19o**) (Table 4).

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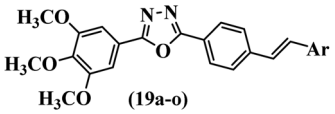
Table 4 Chemical structures of stilbene derivatives containing a 1,3,4-oxadiazole moiety



(19a-o)

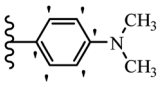
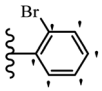
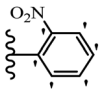
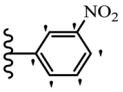
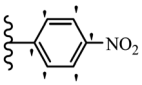
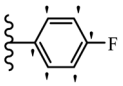
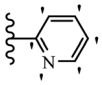
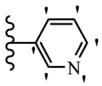
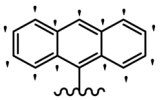
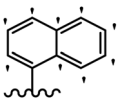
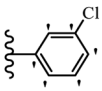
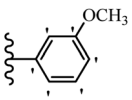
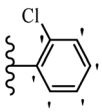
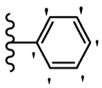
Compound	Ar	Control efficacy (%)		
		P. cubensis	*C. lagenarium*	*S. cucurbitacearum*
19a		71.38	30.26	44.84
19b		8.37	26.38	69.34
19c		48.34	56.07	35.36
19d		50.13	83.82	46.83
19e		63.42	66.72	32.23
19f		52.20	65.14	72.05
19g		18.38	52.88	45.14
19h		42.67	37.58	40.27
19i		15.3	14.29	53.09
19j		36.01	37.98	51.18
19k		65.01	82.43	32.03
19l		44.13	37.90	47.62
19m		32.66	31.48	−9.348
19n		58.77	50.03	55.178

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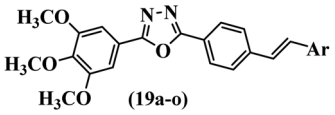
Table 4 (*Contd.*)



(19a-o)

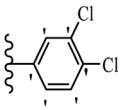
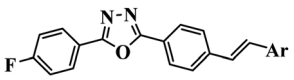
Compound	Ar	Control efficacy (%)		
		P. cubensis	*C. lagenarium*	*S. cucurbitacearum*
19o		−4.08	44.81	8.03
Fungicides	—	*70.13*	*81.57*	*69.02*

Table 5 Synthetic compounds of fluorine-containing stilbene



(20a-f)

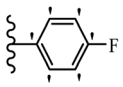
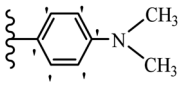
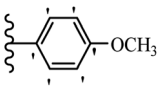
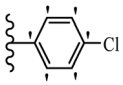
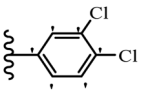
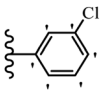
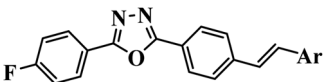
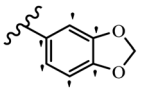
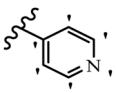
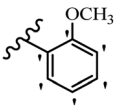
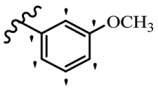
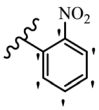
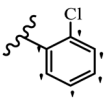
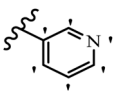
Compounds	Ar	Control efficacy (%)	
		C. lagenarium	*P. cubensis*
20a		83.4	54.6
20b		38.1	70.2
20c		61.3	66.0
20d		54.1	53.5
20e		60.8	34.8
20f		64.3	52.4
Fungicides	—	82.7	72.5

Table 6 Chemical analogues of oxadiazole–stilbene hybrids



(21a-g)

Compounds	Ar	EC_{50} (μg mL^{-1})
21a		144.6
21b		231.3
21c		>400
21d		345.9
21e		382.9
21f		>400
21g		>400
Resveratrol	—	315.6

Jian *et al.*[45] synthesized fluorine-containing stilbene derivatives and assessed their anti-fungal activity. The synthesis method was the same as that in a previous study.[44] Compounds **20a** and **20b** exhibited relatively high fungicidal potency against *C. lagenarium* and *P. cubensis* and were comparable to fungicides against both strains. Moreover, EDG showed higher activity than EWG (**20c** *vs.* **20d**) against *C. lagenarium* and *P. cubensis*. In addition, compound **20e** with two Cl atoms in the 3′- and 4′-positions on the phenyl ring showed lower activity compared to **20f** having one Cl atom in the 3′-position against

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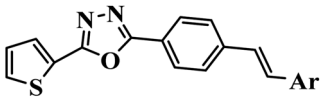
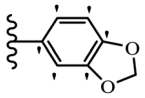
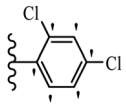
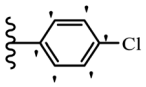
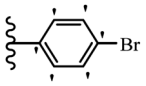
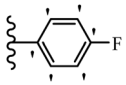
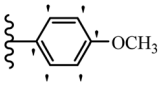
Table 7 1,3,4-Oxadiazole–thiophene-based stilbene derivatives



(22a-f)

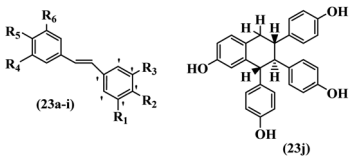
Compounds	Ar	EC$_{50}$ (μg mL^{-1}) *B. cinerea*	*C. lagenarium*
22a		155.4	248.2
22b		172.1	261.7
22c		187.7	279.6
22d		175.5	263.7
22e		180.1	268.9
22f		170.3	259.6
Resveratrol	—	263.1	342.6
Carbendazim	—	124.3	219.7
Fluopyram	—	117.9	223.5

both strains. Also, the anti-fungal activity of the compounds containing hydrophilic groups was better compared to that bearing lipophilic groups (**20b** *vs.* **20f**) (Table 5).

Similarly, a research group[46] reported the synthesis of oxadiazole–stilbene hybrids and evaluated their efficacy against phytopathogenic fungi. The synthesis method was the same as in the previous study.[44] Compounds **21a** and **21b** exhibited superior anti-fungal activity to that of resveratrol. Also, moving the OCH_3 group from the 2′-position of **21c** to the 3′-position on the phenyl ring in **21d** increased the activity. Moreover, the presence of hydrophilic groups resulted in higher activity compared to the lipophilic groups (**21e** *vs.* **21f**). Compound **21b** with a pyridine ring in the 4′-position on the phenyl ring showed stronger activity than compound **21g** with a pyridine ring in the 3′-position. This finding showed that the position of the nitrogen atom in the pyridine ring may play an important role in activity. Also, the compounds containing EWG and EDG showed equal activity (*e.g.*, **21c** and **21f**) (Table 6).

Wen *et al.*[47] synthesized 1,3,4-oxadiazole–thiophene-based stilbene compounds and assessed their anti-fungal activity. In the previous study, the method of synthesized compounds was explained.[44] Compound **22a** exhibited higher activity compared to resveratrol but was weaker than carbendazim and fluopyram against *B. cinerea* and *C. lagenarium*. In addition, increasing the substitution on the phenyl ring displayed the maximum activity (*e.g.*, **22b** and **22c**) against different strains. Furthermore, among the compounds with EWG in the 4′-position on the phenyl ring, compound **22d** with a Br atom exhibited better activity compared to **22c** having a Cl atom and **22e** with an F atom in the same position against both strains. It seems that increasing the atom size improved the activity. Furthermore, the presence of the EDG in the 4′-position on the phenyl ring

Table 8 Chemical structures of resveratrol analogues



Compound	R_1	R_2	R_3	R_4	R_5	R_6	MIC (μg mL^{-1}) *S. aureus*	*E. coli*	*ΔtolC*	Inhibition percent (%) *P. vulgaris*	*S. typhimurium*	*E. coli*	*ΔtolC*	*S. aureus*
23a	H	Br	H	OH	H	OH	25	>100	25	>80	>80	—	90	>80
23b	H	H	H	OH	H	OH	100	>100	100	>80	>80	—	90	>80
23c	H	OH	H	OH	H	OCH_3	100	>100	100	40	40	40	—	—
23d	H	OH	H	H	OH	H	—	—	—	—	—	—	—	—
23e	H		$OCOCH_3$		H						$OCOCH_3$	H	$OCOCH_3$	
—	—	—	—	—	—	—	—							
23f	H	OCH_3	H	OCH_3	OH	OCH_3	—	—	—	—	—	—	—	—
23g	H	OH	H	OCH_3	H	OCH_3	25	>100	25	—	—	—	90	—
23h	OH	OH	H	OH	OH	H	—	—	—	—	—	—	—	—
23i	OH	OH	H	OH	H	OH	—	—	—	—	—	—	—	—
23j	—	—	—	—	—	—	10	>100	10	—	—	—	80	—
Resveratrol	—	—	—	—	—	—	100	>100	100	—	—	—	—	—

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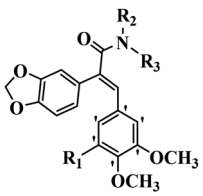
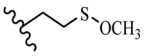
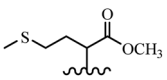
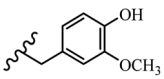
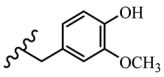
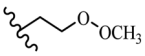
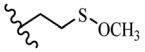
demonstrated greater activity than EWG in the same position (*e.g.*, **22f** and **22d**) against *P. cubensis*. In addition, the antifungal activity of hydrophilic groups showed better activity than that of lipophilic groups (**22f** *vs.* **22c**) (Table 7).

Singh *et al.*[48] reported the anti-bacterial activity of resveratrol structural analogues. Compared to other bacteria tested, resveratrol was more effective against the enteric bacteria *P. vulgaris* and *S. typhimurium*. Compounds **23a** and **23b** exhibited higher inhibition than resveratrol, while compound **23c** exhibited comparable activity against *P. vulgaris*, *S. typhimurium*, and *E. coli*. The other compounds showed lower activity than resveratrol against *P. aeruginosa*. The compounds that were impressive against Gram-negative bacteria were similarly impressive against Gram-positive bacteria (compounds **23a** and **23b** against *S. aureus*). In the case of **23d–f**, no anti-bacterial activity was observed (wild-type or *ΔtolC E. coli*). Compounds **23g** and **23j** were also ineffective against wild type *E. coli*, while their activity was comparable to **23a** and **23b** against *ΔtolC*, the two analogues that were most active against wild-type *E. coli*. Also, the presence of a Br atom in the 4′-position on phenyl ring **23a** showed excellent activity against *S. aureus* compared to **23b**, which was unsubstituted. The antibacterial activity of compound **23c** with an OH group in the 3-position on the phenyl ring was lower than that of **23g** having an OCH_3 group in the same position against *S. aureus*. The inhibitory activity of stilbenes against *S. aureus* reiterated the fact that analogues **23a**, **23g**, and **23h** were more potent than resveratrol against *S. aureus*, while **23b** and **23c** showed comparable activity to resveratrol. When the OH groups in the molecule were replaced with acetoxy or methoxy groups, a significant reduction in antibacterial activity was observed (resveratrol *vs.* compounds **23e** or **23f**). This showed the importance of the OH group for the antibacterial activity. However, increasing the number of OH groups did not result in better antibacterial activity (resveratrol *vs.* **23h** with OH groups in the 3′- and 4′-positions on the phenyl ring or **23i** having OH groups in the 3′- and 5′-position on phenyl ring). The presence of an OH group in the 4′-position on the phenyl ring did not have a significant effect on the activity or inactivity of the molecule (**23b**, **23d**, and **23h**). However, it is worth noting that the best molecules in the series (**23a–c**, **23g**, and **23j**, as well as resveratrol) had an OH group in the 4′-position on the phenyl ring. Partially changing the OH group to other groups resulted in an improvement in antibacterial activity (resveratrol *vs.* **23a** and **23c** or **23g**). The findings showed

Table 9 Structures of 1,3-benzodioxole–stilbene derivatives



(27a-g)

Compound	R_1	R_2	R_3	Fungicidal activity (%)			
				G. theae-sinensis	*A. tenuis Nees*	*F. graminearum*	*R. solani*
27a	H	H		<10	<40	0	<10
27b	H	H		<10	<20	<20	<20
27c	H	H		<20	<10	0	0
27d	OCH_3	H		<20	<20	<20	<20
27e	OCH_3	H		<30	<30	<20	<20
27f	OCH_3	H		<30	<30	<10	<10
27g	OCH_3	H		<10	<20	<30	<20
Piperine	—	—	—	74	55	<30	62
Azoxystrobin	—	—	—	69	55	64	55

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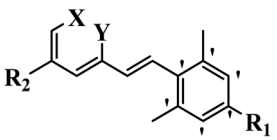
that the lipophilic groups had better activity than the hydrophilic groups (Table 8).

Song *et al.*[21] synthesized and assessed the fungicidal activity of 1,3-benzodioxole-stilbene derivatives. Compound **27a** showed the highest activity against *G. theae-sinensis*, *A. tenuis Nees*, *F. graminearum*, and *R. solani*. This analogue was stronger than piperine and azoxystrobine, but it showed lower activity compared to piperine against *F. graminearum*. Overall, the derivatives showed low inhibitory activity against all the tested strains, while the inhibition rates of the derivatives against most fungi of the tested fungi were not greater than 20%. Replacing propylsulfane linked to an amide moiety in **27a** with methyl-4-(methylthio)butanoate in **27b** showed lower activity against *A. tenuis Nees*. Also, the presence of an OCH_3 group in the 3′-position on the phenyl ring compared to no substitution increased the fungicidal activity (*e.g.*, **27c** and **27d**) against *A. tenuis Nees*, *f. graminearum*, and *R. solani*. Also, hydrophilic groups (*e.g.*, **27e**) and lipophilic groups (*e.g.*, **27f**) are suitable to improve the fungicidal activity against *G. theae-sinensis* and *A. tenuis Nees*. In addition, the presence of cycloalkane and aromatic rings linked to an amide moiety had the same effect on the activity (**27g** *vs.* **27d**) against *A. tenuis Nees* and *R. solani* (Table 9).

Hrast *et al.*[49] described azastilbene derivatives as mur ligase inhibitors and anti-bacterial agents and evaluated the inhibition of four mur ligase subgroups (MurC, MurD, MurE, and MurF). Compound **31a** was the most potent against subgroups MurD, MurE, and MurF. Compound **31b** showed the highest activity against the MurC subgroup among the compounds. In addition, the lipophilic group in **31b** displayed higher activity than the hydrophilic group in **31c** against all the mur ligases. Most of the stilbene derivatives demonstrated poor anti-bacterial activity against both *E. coli* and *S. aureus*. This could be attributed to their low target activity or poor penetration into the bacterial cytoplasm. However, replacing oxazole linked to a pyridine ring on the 4-position phenyl ring in **31c** with imidazole linked to a pyridine ring in same position of **31d** resulted in the highest anti-bacterial activity against *S. aureus* and *E. coli*. Also, the presence of hydrophilic groups resulted in better activity than lipophilic groups against both strains (**31d** and **31b**). Compound **31e** with an OCH_3 group in the 2′-position on the phenyl ring exhibited higher anti-bacterial activity

Table 10 Chemical structures of azastilbene derivatives



(31a-g)

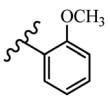
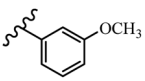
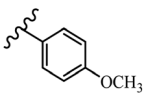
Compound	X	Y	R_1	R_2	Inhibition percent (%)				MIC (mM)	
					MurC	MurD	MurE	MurF	*S. aureus*	*E. coli*
31a	C	N			23	73	55	84	>0.25	>0.25
31b	N	C			56	70	46	58	>0.25	>0.25
31c	N	C			44	45	32	44	0.125	>0.25
31d	N	C			42	47	10	40	0.031	0.25
31e	N	C			35	42	33	0	0.125	>0.25
31f	N	C			15	23	21	18	>0.25	>0.25
31g	N	C			30	30	37	25	0.25	>0.25

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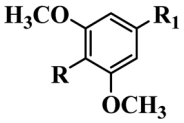
Table 11 Structures of *E*/*Z*-stilbene derivatives



(33a-h, 35a,b)

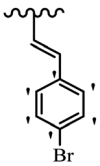
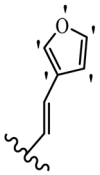
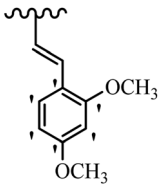
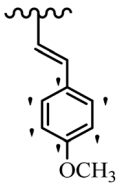
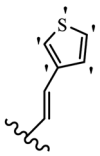
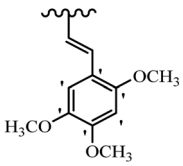
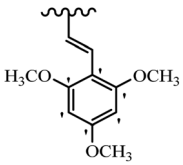
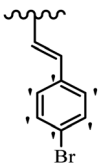
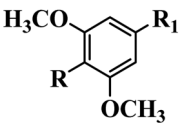
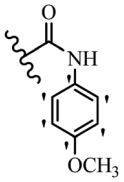
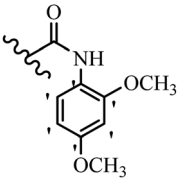
Compound	*E*/*Z*	R	R_1	IC_{50} ($\mu g\ mL^{-1}$) A549	Col2
33a	*Z*	OCH_3		0.01	0.01
33b	*Z*	OCH_3		0.2	0.3
33c	*E*	H		0.8	0.8
33d	*E*	H		0.8	0.9
33e	*Z*	OCH_3		2.1	2.6
33f	Mix	H		>20	>20
33g	Mix	H		3.2	7.2
33h	*E*	OCH_3		4.7	1.6

Table 11 (*Contd.*)



(33a-h, 35a,b)

Compound	*E*/*Z*	R	R_1	IC_{50} ($\mu g\ mL^{-1}$) A549	Col2
35a	—	H		2.6	5.1
35b	—	H		>20	>20
Resveratrol	*E*	—	—	6.9	18.7
Oxyresveratrol	*E*	—	—	>20	>20

compared to compound **31f** having an OCH_3 group in the 3′-position on the phenyl ring and **31g** with an OCH_3 group in the 4′-position on the phenyl ring against *S. aureus* and *E. coli*. It seems that changing the substitution on different positions of the phenyl ring had a positive effect on the anti-bacterial activity (the 2-position showed higher activity than the 4- and 3-positions on the phenyl ring) (Table 10).

3. Anti-cancer activity

Despite the huge effort to develop novel therapies, cancer remains the leading cause of death worldwide. One of the traditional and commonly used methods for cancer treatment is chemotherapy, which targets specific proteins and cellular structures or processes.[50]

Resveratrol as an anti-cancer agent reduces angiogenesis and induces apoptosis *via* the suppression of VEGF and FGF-2.[51] Piceatannol and pterostilbene, stilbene natural derivatives, are remarkably more potent than resveratrol against cancer cell lines.[52] CA-4, a *Z*-stilbenoid analogue, is a strong inhibitor of tubulin polymerization, resulting in cancer cell death.[53] In many experimental models *in vitro* and *in vivo* both *Z*- and *E*-stilbene analogues showed anti-cancer activity but with diverse mechanisms. Some *Z*-isomers of methoxylated stilbenes and their derivatives revealed higher antimetastatic or antiproliferative activity than their *E*-isomers; however, the *E*-isomer of resveratrol displayed higher antiproliferative activity. Moreover, they isomerize during storage, administration, and metabolism in

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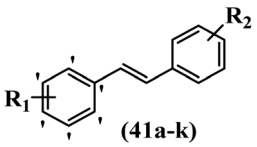
liver microsomes.[54,55] *Z*- and *E*-stilbene analogues have been studied for their cytotoxicity and anti-tubulin activities. The analysis of the results a wide range of stilbene analogues showed that the *Z*-isomer was useful for cytotoxicity and anti-mitotic activity. Tamoxifen, a stilbene analogue, is used for the treatment of some types of breast cancer.[53]

Lee *et al.*[17] synthesized stilbene analogues and evaluated their cytotoxicity. *Z*-**33a** and **b** showed the highest cytotoxicity activity among the compounds. These compounds were stronger than resveratrol and oxyresveratrol against the A549 and Col2 cell lines. Especially, compound **33a** having OCH_3 and Br groups in the 4- and 4′-positions on the phenyl ring exhibited approximately 600-times and 1800-times, respectively, more potent cytotoxicity than resveratrol. In the *E*-isomers, the presence of an extra OCH_3 group in **33c** showed comparable activity to **33d**. Also, replacing the aromatic ring of **33a** with a hetero-aromatic ring in **33b** and **33e** decreased the activity. In the *Z*/*E*-isomers, moving the OCH_3 group from the 5′-position in **33f** to the 6′-position on the phenyl ring in **33g** increased the cytotoxicity. Based on the findings, the *Z*-isomers were more potent than their corresponding *E*-isomers (*e.g.*, **33a** and **33h**). In addition, adding an OCH_3 group to the phenyl ring (**35a** *vs.* **35b**) reduced the cytotoxicity (Table 11).

Lion *et al.*[56] synthesized hydroxylated *E*-stilbenes and assessed their anti-tumor and apoptosis-inducing activity. Compounds **41a** and **41b** showed the highest activity among the compounds and resveratrol against MDA-MB-468 and HCT-116. Also, changing the position of the OH group in **41b** from the 2- to 3- and 4-positions on the phenyl ring in **41c** and **41d** reduced the activity against both cell lines, respectively. Similarly, the compounds having EWG and lipophilic groups showed better activity than that having EDG and hydrophilic groups (*e.g.*, **41e** *vs.* **41f**). Furthermore, the extra OCH_3 group in the 5′-position on the phenyl ring of compound **41g** caused a slight improvement in activity compared to **41h**. This result showed that increasing the number of substitutes on the phenyl ring had a positive effect on activity. Substitution on the phenyl ring resulted in higher activity compared to compound with no substitution (*e.g.*, **41i** and **41j**). With the exception of the relatively insensitive **41k**, the percentage of apoptotic sub-G1/0 MDA-MB-468 cells following drug treatment was higher in all the stilbenes than in resveratrol. Following treatment with compounds **41a**, **41e**, and **41j**, the highest percentage of cells was observed to be in early apoptosis. The induction of apoptosis was again associated with the anti-proliferative activity in MDA-MB-468 cells, particularly for the relatively potent compounds **41j** and **41a**. Particularly, compound **41j** had a much higher percentage of cells in early apoptosis than resveratrol but a much lower percentage than camptothecin. Based on the findings, the presence of EDG and lipophilic groups resulted in the highest apoptosis activity (Table 12).

Pettit *et al.*[41] evaluated *Z*/*E*-CA-4 derivatives for their neoplastic activity. Among the compounds, *Z*-**42a** showed the highest cytotoxicity activity against the BXPC-3, SK-N-SH, SW-1736, NCI-H460, DU-145, and FADU cell lines. In the *Z*-isomers, replacement of the OH group in the 3′-position on the phenyl ring of CA-4 with NO_2, $N(CH_3)_2$, or Br groups in compounds **42b–d** decreased their potency, respectively. In addition, the presence of hydrophilic groups improved the activity compared to lipophilic groups (**42e** and **42f**). The replacement of the bulky group, such as OSO_2CH_3 in **42e**, instead of OH in **42g** reduced the activity. Likewise, the replacement of pyrrolidinyl in the 3′-position on the phenyl ring with piperidinyl in the same position resulted in better activity

Table 12 Chemical structures of hydroxylated *E*-stilbenes



Compounds	R_1	R_2	GI_{50} (μM) HCT-116	GI_{50} (μM) MDA-MB-468	Induced percent (%) Apoptosis
41a	3,5-diOCH_3	3-OH	43.1	0.96	20
41b	3,4-diF	2-OH	15.6	1.1	—
41c	3,4-diF	3-OH	36.0	1.6	—
41d	3,4-diF	4-OH	18.1	19.1	—
41e	2-F	4-OH	38.5	2.8	10
41f	2-OCH_3	4-OH	51.3	3.3	—
41g	3,5-diOCH_3	2-OH	21.3	2.5	—
41h	3-OCH_3	2-OH	58.0	3.1	—
41i	H	3-OH	57.4	7.8	—
41j	2-OCH_3	3-OH	42.3	2.7	15
41k	H	2-OH	58.1	24.9	4
Resveratrol	—	—	49.6	41.1	4
Camptothecin	—	—	—	—	37

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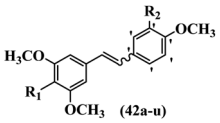
(**42h** *vs.* **42i**) against the BXPC-3, SK-N-SH, SW-1736, NCI-H460, DU-145, and FADU cell lines. In the *E*-isomers, replacement of the NO_2 group in the 3′-position on the phenyl ring in **42j** with Br in the same position of **42k** increased the activity against P-388, BXPC-3, SK-N-SH, DU-145, and FADU. Also, replacing the OCH_3 group with an OH group in the 4′-position on the phenyl ring (*Z*/*E*-**42l**) resulted in a remarkable decrease (about 100-times) in activity. Subsequently, the compounds were tested for their ability to inhibit tubulin protein. Compound **42d** was as active as CA-4, while **42b** and **42e** were about half as active. The *Z*-isomers with bulkier substituents at the 3′-position on the phenyl ring were much less active as inhibitors of assembly (*e.g.*, **42f**; Cl, **42g**; SO_3CH_3 and **42m**; $CO_2NC_4H_8Cl_2$ showed minor or no inhibitory activity). Nevertheless, *Z*-**42n** having an $O(CH_2)_3OH$ group in the 3′-position on the phenyl ring showed better activity than **42o** with 1*H*-imidazol-1-yl in the 3′-position on the phenyl ring. Alternatively, **42p** having *N*-pyrrolyl in the 3′-position on the phenyl ring showed weaker inhibitory activity compared to **42o** and **42n**. This suggests that the aromatic substituent dominated the steric effect that restricts the stilbene–tubulin interaction indirectly based on the inactivity of **42f–i**, **42q–t**, and **42m**. Surprisingly, the more effective tubulin inhibitor (**42o**) had little cytotoxicity, whereas the less effective **42p** was highly cytotoxic in four of the seven cell lines tested. *E*-

Table 13 Structures of *Z*/*E*-CA-4 derivatives



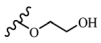
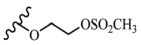
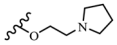
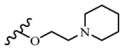
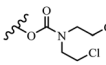
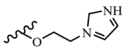
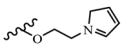
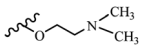
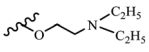
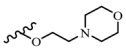
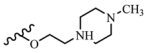
				GI_{50} (μg mL^{-1})							IC_{50} (μM)
Compound	*E*/*Z*	R_1	R_2	P-388	BXPC-3	SK-N-SH	SW1736	NCI-H460	DU-145	FADU	Tubulin
42a	*Z*	OCH_3	NH_2	>0.010	0.00043	0.00023	0.00080	0.00033	0.00033	0.00053	—
42b	*Z*	OCH_3	NO_2	2.4	0.029	0.014	0.0067	0.0038	0.047	0.047	2.6
42c	*Z*	OCH_3	$N(CH_3)_2$	0.9	0.015	0.010	0.80	0.4	0.11	0.090	1.1
42d	*Z*	OCH_3	Br	0.16	0.007	0.002	0.034	0.033	0.027	0.0058	—
42e	*Z*	OCH_3		0.195	0.045	0.028	0.28	0.14	0.32	0.069	2.8
42f	*Z*	OCH_3		2.9	2.7	2.0	4.7	3.7	3.4	4.6	>40
42g	*Z*	OCH_3		2.87	2.7	3.0	1.0	0.42	0.59	0.41	>40
42h	*Z*	OCH_3		0.421	2.0	0.22	0.60	0.34	0.35	0.49	>40
42i	*Z*	OCH_3		0.348	>10.0	1.6	5.1	3.3	3.4	4.2	>40
42j	*E*	OCH_3	NO_2	>10	>10	7.3	2.8	>0.0	>10	3.8	—
42k	*E*	OCH_3	Br	3.08	0.34	0.40	10.8	0.36	0.46	11.4	31
42l	*E*	OCH_3	$O(CH_2)_3OH$	4.9	>10.0	8.1	11.6	>10.0	4.5	2.3	—
42m	*Z*	OCH_3		0.074	2.8	0.14	0.72	0.37	0.31	0.15	>40
42n	*Z*	OCH_3	$O(CH_2)_3OH$	0.63	0.26	0.18	0.38	0.37	0.43	0.63	6.5
42o	*Z*	OCH_3		19.0	0.82	0.31	1.5	0.56	1.5	0.67	7.6
42p	*Z*	OCH_3		0.0232	2.3	0.0064	4.9	0.0033	0.56	0.0030	20
42q	*Z*	OCH_3		0.523	>10.0	0.21	0.64	0.34	0.38	0.47	>40
42r	*Z*	OCH_3		0.255	>10.0	1.5	1.1	3.3	3.4	1.1	>40
42s	*Z*	OCH_3		0.634	2.9	0.22	0.97	0.41	0.40	0.53	>40
42t	*Z*	OCH_3		1.60	>10.0	2.8	>10.0	3.4	4.1	2.9	>40
42u	*E*	OH	OH	4.49	5.0	5.5	>10.0	4.9	6.3	3.2	14
Combretastatin A-4	*E*	—	—	0.0029	0.23	0.00025	0.00061	0.00035	0.00072	0.00045	33
Combretastatin A-4	*Z*	—	—	0.0026	>0.1	0.00026	0.00026	0.00056	0.00076	0.00065	1.2

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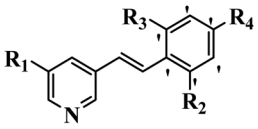
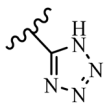
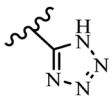
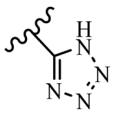
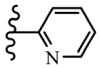
Table 14 Structures of aza-stilbene derivatives



(45a-l)

Compound	n	R_1	R_2	R_3	R_4	pIC_{50} (μM) c-RAF/MEK/ERK	c-RAF
45a	10		—	—	OH	8.4	0.004
45b	5		—	—	H	7.9	—
45c	3	COOH	—	—	—	8.2	—
45d	4	$CONH_2$	—	—	OH	6.8	—
45e	4	$CONH_2$	—	—	—	8.1	—
45f	4		—	—		7.0	—
45g	4	—	CH_3	CH_3	—	6.6	—
45h	1	—	C_2H_5	C_2H_5	—	4.6	—
45i	4	—	CH_3	Cl	—	7.1	—
45j	4	—	Cl	Cl	—	6.6	—
45k	1	—	CH_3	H	—	5.5	—
45l	1	—	Cl	H	—	5.7	—

42k showed comparable activity to *E*-CA-4. *E*-**42u** with an OH group in the 3′- and 4-positions on the phenyl ring showed more than double activity. The results showed that the *Z*-isomers were stronger than the *E*-isomers (Table 13).

McDonald *et al.*[57] synthesized aza-stilbenes and assessed their c-RAF inhibitor activity. Compound **45a** showed the highest c-RAF inhibitory activity. In addition, removing the OH group in the 4′-poition on the phenyl ring of **45a** produced **45b**, which had a slight effect on the enzyme activity. Also, the compounds that had a hydrogen-bond acceptor or donor in the 3-position on the pyridine ring, such as compounds **45c** with a COOH group, **45d** having a $CONH_2$ group, or **45b** with tetrazole, showed higher activity against MEK/ERK. Moreover, replacing the OH group in the 4′-position on the phenyl ring with *N*-methyl carbamate caused a remarkable increase in c-RAF inhibitory activity (**45d** *vs.* **45e**). Also, replacement of the compounds containing tetrazole (**45a** and **45b**) with a 2-pyridine ring (**45f**) resulted in only a minor decrease in c-RAF activity. According to the primary findings, the aza-stilbene scaffold with the two CH_3 groups in the 2′- and 6′-positions on the phenyl ring in compound **45g** was kept to obtain potent c-RAF inhibitors. Also, compound **45h** was 100-times less potent than **45g**, demonstrating a size limitation. In addition, changing the CH_3 group in **45i** with a Cl atom in the 2-position on the phenyl ring of **45j** resulted in a compound that was equal to **45g**. Likewise, the presence of CH_3 or Cl in the 2′-position on the phenyl ring, **45k** and **45l**, showed 10-times less activity than **45g**. When only one of CH_3 group was swapped with a Cl atom on the phenyl ring, as in **45h**, the activity increased by about 3-times compared to **45g** (Table 14).

Gosslau *et al.*[19] reported that *E*/*Z*-stilbene polyphenols induced *p53*-independent apoptosis and rapid perinuclear mitochondrial clustering. Among the *Z*-isomers, **48a** and **48b** were more than 1000-times effective compared to resveratrol against the WI38VA cell line. Furthermore, the addition of an NH_2 group at the 3′-position on the phenyl ring in **48b** resulted in lower activity compared to **48c**. However, attaching an NO_2 group in the 3′-position on the phenyl ring in **48d** reduced the activity compared to **48c**. In the *E*-isomers, the addition of an NO_2 group in the 3′-position on phenyl ring decreased activity (**48e** *vs.* **48f**). As well, appending OCH_3 group in 3′-position on the phenyl ring in **48g** drastically reduced the anti-proliferative activity compared to **48f**. The addition of an OCH_3 group in the 4′-position on the phenyl ring enhanced its anti-proliferative activity at least 10-times (**48h** *vs.* **48i**). Attaching an OCH_3 group in the 4′-position enhanced the activity for both the *Z*- and *E*-isomers by at least 4-times (**48i** *vs.* **48f**, and **48c** *vs.* **48a**). Also, the hydrophilic group showed less activity compared to the lipophilic group (*e.g.*, **48j** and **48i**). In addition, the presence of a Br atom in the 4′-position on the phenyl ring in **48k** resulted in better activity than no substitution in **48l**. *E*-**48f**, the most potent derivative in this series, was 200-times less potent than *Z*-

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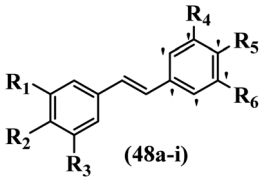
Table 15 Synthetic compounds of *E*/*Z*-stilbene



Compound	*E*/*Z*	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μM) WI38VA
48a	*Z*	OCH_3	OCH_3	OCH_3	—	OCH_3	—	0.02
48b	*Z*	OCH_3	—	OCH_3	NH_2	OCH_3	—	0.05
48c	*Z*	OCH_3	—	OCH_3	—	OCH_3	—	0.03
48d	*Z*	OCH_3	—	OCH_3	NO_2	OCH_3	—	0.5
48e	*E*	OCH_3	OCH_3	OCH_3	NO_2	OCH_3	—	10
48f	*E*	OCH_3	OCH_3	OCH_3	—	OCH_3	—	2
48g	*E*	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	—	—
48h	*E*	OCH_3	OCH_3	—	—	—	—	—
48i	*E*	OCH_3	—	OCH_3	—	OCH_3	—	25–50
48j	*E*	OH	—	OH	—	OH	—	50
48k	*E*	OCH_3	OCH_3	OCH_3	—	Br	—	25–50
48l	*E*	OCH_3	OCH_3	OCH_3	—	—	—	80
Resveratrol	*E*	—	—	—	—	—	—	50

48a. The *Z*-isomer analogues were the most potent *E*-isomer analogues, with IC_{50} values comparable to or better than resveratrol against WI38VA cells. Apoptosis revealed that **48a** activated caspase 3/7 in the WI38VA cells. Similar to **48f**, this compound activated apoptosis in the transformed cells. The findings recommend that mitochondrial clustering can happen in the absence of a main change in microtubule dynamics, implying that microtubule depolymerization is not directly responsible for perinuclear mitochondrial clustering. **48a** and **48f** both inhibited the growth of wild-type and *p53*-null cells. These findings imply that the proapoptotic activity of **48a** and **48f** against cancer cells was not dependent on *p53* (Table 15).

Simoni *et al.*[58] designed stilbene-based derivatives and assessed their anti-tumor activity. Compound **52a** was the most active compound among the derivatives, while it showed weaker or equal activity compared to vincristine, colchicine, and CA-4 against UCI-101, SNU-423, MDA-MB231, and MiaPaCa-2. Most of the compounds showed weak cytotoxicity against SNU-423, MDA-MB231, and MiaPaCa-2. In addition, compound **52b** with *N*-methylpyrrole in the 3- and 4-positions on the phenyl ring exhibited weaker cytotoxicity activity compared with **52a** having $NH_3^+Cl^-$ and OCH_3 groups in the same position against MDA-MB231 and MiaPaCa-2. Also, replacement of the OCH_3 in **52a** with an OH group in the 3′-position on the phenyl ring in **52c** decreased the activity by more than 10-times against the UCI-101 and MDA-MB23 cell lines. In contrast, when the OCH_3 group in the 3-position on the phenyl ring was replaced by bulkier substituents, *i.e.*, ethoxy or isopropoxy groups, as in compounds **52d** and **52e** compared to **52a**, respectively, the activity decreased. Moreover, compound **52f**, with a 2-hydroxyethyl group in the 3′-position on the phenyl ring, still retained its activity. However, the addition of a carboxyl group, as in compound **52g** against UCI-101, completely eliminated its activity, representing unequivocally that the environment cannot tolerate excessive hydrophilicity. Also, the replacement of the OCH_3 group with *N*-methylpyrrole in the 3′- and 4′-positions on the phenyl ring dramatically reduced the activity for **52h** against UCI-101. This result showed that a hydrophobic environment is required for activity. The derivatives with an indole or imidazole ring in **51a**, **51b**, and **51c** showed equal activity against this cell line. Shifting the nitrogen atom in the indole ring from the 1-position in compound **52b** to the 3-position in compound **52i** resulted in weaker activity against UCI-101. It is worth noting that **52b** and **52i** have diverse biological effects, therefore demonstrating a favorable interaction for the CH_3 group in compound **52b**. Among compounds **53a–c**, only **53a** with carbamic acid morpholin-4-yl-ethyl ester in the 3-position on the phenyl ring was active in suppressing the growth of tumor cells, which was 170-times less active than stilbene **52a**. Both **53b** with morpholin-4-yl-ethylureahydrochloride salt in the 3-position on the phenyl ring and **53c** with carbamic acid (2-hydroxyethoxy)ethoxyethyl ester in the same position were not capable of causing remarkable inhibition of cell growth, demonstrating that their activity is lower than **53a**. This could be because compounds **53a–c** were not changed into the active form, stilbene **53a**, under the tissue culture conditions. The tubulin inhibitory activity of the four derivatives **52** that changed substitution in the 3-position on the phenyl ring showed potency following the order of **52f** > **52c** > **52d** > **52j**. Compound **52c**, in particular, has the second-best tubulin inhibitory activity but significantly weaker cytotoxic activity compared to derivatives **52f**, **52d**, and **52j**. When selective second-ring derivatives were tested for tubulin inhibitory activity (**52b** > **52i** > **52a**), their cytotoxicity followed the order of **52b** > **52i** > **52a**. As a result, in addition to tubulin depolymerization, stilbene derivatives may have other mechanisms for inducing cell death (Table 16).

Moon *et al.*[59] synthesized resveratrol derivatives and evaluated their cytotoxicity activity. Compounds **59a** and **59b** were the most potent compounds among them against the XF-498, SK-OV-3, HCT-15, A-549, and SK-MEL-2 cell lines. Furthermore, compound **59a** showed the highest activity in all the cell lines in terms of cytotoxicity. However, none of the compounds exhibited stronger activity than adriamycin against all the cell lines. Besides, compound **59c** with *N*-(4-benzylpiperidine) carbonyl in the 4′-position on the phenyl ring exhibited higher activity than **59d** having *N*-(4-methylpiperidine)carbonyl in the same position against SK-MEL-2, A-549, and HCT-15. However, compound **59d** was inactive against these cell lines. Also, replacement of the aromatic ring in **59e** with a heteroaromatic ring in **59f** decreased the activity against A549, SK-OV-3, SK-MEL-2, and XF-498. In addition, replacing *N*-decylamino-carbonyl in **59g** in the 4′-position with *N*-cyclohexylaminocarbonyl in **59b** on the same position enhanced the activity against all the cell lines (Table 17).

Belluti *et al.*[60] synthesized stilbene–coumarin hybrids and evaluated their cytotoxicity. Compounds **62a** and **62b** displayed higher activity compared to resveratrol against the H460, A431, and JR8 cell lines and were the most potent compounds among

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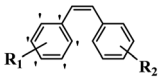
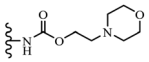
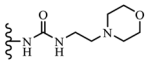
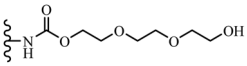
Table 16 Chemical structures of stilbene-based derivatives



(51a-c, 52a-j, 53a-c)

Compound	R_1	R_1	R_2	R_2	IC_{50} (nM) UCI-101	SNU-423	MDA-MB231	MiaPaCa2
51a	3-OCH_3	3-OCH_3		—	250	700	250	200
51b	3-OCH_3	3-OCH_3		—	250	700	250	200
51c	3-OCH_3	3-OCH_3		—	260	1000	800	800
52a	3-OCH_3	3-OCH_3	3-OCH_3	4-$NH_3^+Cl^-$	30	30	30	40
52b	3-OCH_3	3-OCH_3		—	40	30	80	80
52c	3-OH	3-OCH_3	3-OCH_3	4-$NH_3^+Cl^-$	800	2000	800	700
52d	3-OCH_2CH_3	3-OCH_3	3-OCH_3	4-$NH_3^+Cl^-$	80	—	—	—
52e	3-$OCH(H_3C)_2$	3-OCH_3	3-OCH_3	4-$NH_3^+Cl^-$	100	—	—	—
52f	3-$O(H_2C)_2OH$	3-OCH_3	3-OCH_3	4-$NH_3^+Cl^-$	150	200	80	180
52g	3-OCH_2COOH	3-OCH_3	3-OCH_3	4-NH_2	>10.000	—	—	—
52h		—	3-OCH_3	$NH_2x(COOH)_2$	5000	—	—	—
52i	3-OCH_3	3-OCH_3		—	220	—	—	—
52j		—	3-OCH_3	NH_2	200	—	—	—
53a	3-OCH_3	3-OCH_3	OCH_3		5000	5000	—	—
53b	3-OCH_3	3-OCH_3	OCH_3		>10.000	—	—	—
53c	3-OCH_3	3-OCH_3	OCH_3		>10.000	—	—	—
Colchicine	—	—	—	—	30	25	20	25
Vincristine	—	—	—	—	20	10	15	15
Combretastatin A	—	—	—	—	2	6	4	8

the studied compounds. All the compounds were inactive against the A431 and JR8 cell lines except **62a** and **62b**. In this series, compound **62b** appeared to be one of the most active compounds, thus presenting proof for the significance of the OCH_3 group in the 4-position on the coumarin ring as a scaffold. On moving the OCH_3 group from the 4- to 3-position on the coumarin ring in derivative **62b**, resulting in compound **62c**, a dramatic drop in potency was observed, suggesting that the 4-position insertion is also crucial. Furthermore, when the OCH_3 groups of **62b** were replaced with OH, derivative **62g** was 60-times less active than **62b** and 2-times less active than resveratrol against H460. Considering these results, the extra structural changes were made in **62b** focusing on the phenyl ring, a significant decrease in anti-proliferative activity was detected for compound **62d** with an OCH_3 group in the 5′-position and **62e** bearing an OCH_3 group in the 2′-position on the phenyl ring. Besides, the removal of one OCH_3 group in **62b** resulted in a decrease in activity. Also, **62f** showed comparable activity to resveratrol against H460. These findings revealed that the OCH_3 groups in the 3′- and 5′-positions on the phenyl ring had an important role, and their exchange with CH_3, **62a**, showed somewhat greater potency than the corresponding molecule **62b**. Subsequently, **62b** and **62a** was investigated for inducing apoptosis. In particular, the proapoptotic effect of **62b** showed

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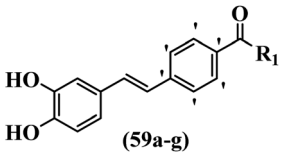
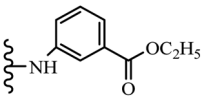
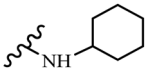
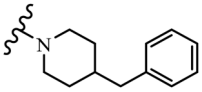
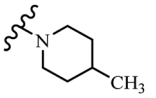
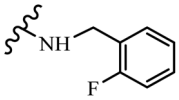
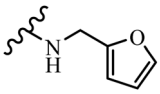
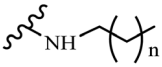
Table 17 Chemical structures of resveratrol analogues



Compound	R_1	IC_{50} (μM)				
		A-549	SK-OV-3	SK-MEL-2	XF-498	HCT-15
59a		8.7	5.7	10.4	11.4	14.4
59b		10.4	6.8	12.4	13.6	17.2
59c		45.7	26.8	43.0	25.4	47.4
59d		—	21.6	—	21.6	—
59e		12.7	9.1	16.2	15.7	21.5
59f		25.6	26.2	22.4	28.0	16.4
59g		16.4	21.7	14.2	19.7	21.2
Resveratrol	—	36.9	42.6	41.4	32.1	35.6
Adriamycin	—	2.8	4.3	2.6	2.1	7.6

a level of apoptosis similar to that of cisplatin and substantially higher than that of resveratrol. Caspase 3 and PARP cleavage were investigated. This effect was linked to a partial cell tumor during the G2/M phase of the cell cycle. In summary, the existence of specific substituents in different positions of both moieties of the hydride compound was confirmed to be serious in discussing the anti-proliferative activity; substitutions shaped the 4-position on the coumarin ring and the 3′- and 5′-positions on the phenyl ring were revealed to be a satisfactory feature for both the anti-tumor and proapoptotic activities (Table 18).

Reddy *et al.*[61] designed resveratrol-based nitrovinylstilbenes and tested their anti-mitotic and anti-tubulin activities. Compound **66a** was the most potent compound among them and showed higher activity than resveratrol against the MCF-7 cell line. However, **66a** showed weaker or equal anti-proliferative activity compared to resveratrol against the SK-N-SH, A-549, and HeLa cell lines. Compound **66b** showed higher anti-proliferative activity compared to resveratrol against MCF-7, SK-N-SH, A549, and HeLa. Also, EDG showed better activity compared to EWG (*e.g.*, **66b** *vs.* **66c**) against SK-N-SH, A-549, and HeLa. Likewise, changing the dioxane ring in the 3′- and 4′-positions (**66d**) with a phenyl ring in the 4′-position on the phenyl ring (**66a**) reduced the activity against all the tested cell lines. In contrast, **66a** showed stronger activity than **66d** against the MCF-7 cell line. Furthermore, increasing the number of OCH_3 groups in different positions on the phenyl ring of **66e** resulted in lower anti-proliferative activity compared to **66f** against the tested cell lines. Also, the presence of a lipophilic group had more favorable anti-proliferative activity than a hydrophilic group on the phenyl ring (**66c** *vs.* **66g**) against the MCF-7, SK-N-SH, and A-549 cell lines. Compounds **66b**, **66d**, and **66g** had higher cytotoxicity activity, which correlated well with their ability to effectively inhibit tubulin. Compound **66b**, as expected, demonstrated the greatest inhibition of tubulin assembly. All the compounds were less potent than colchicine. The findings showed that the compounds inhibited tubulin assembly in the order of **66b** > **66g** > **66d**. The anti-mitotic

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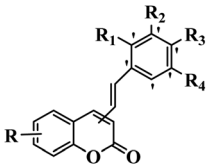
Table 18 Synthetic compounds of stilbene–coumarin hybrids



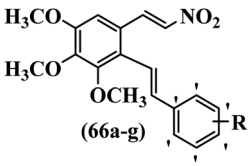
(62a-g)

Compound	Insertion position	IC$_{50}$ (μM) R	R$_1$	R$_2$	R$_3$	R$_4$	H460	A431	JR8	Induced apoptosis (%)
62a	4	7-OCH$_3$	H	CH$_3$	H	CH$_3$	0.29	3.5	3.5	32
62b	4	7-OCH$_3$	H	OCH$_3$	H	OCH$_3$	0.45	3.44	3.2	27
62c	3	7-OCH$_3$	H	OCH$_3$	H	OCH$_3$	>10	—	—	—
62d	4	7-OCH$_3$	H	OCH$_3$	OCH$_3$	OCH$_3$	>100	—	—	—
62e	4	7-OCH$_3$	OCH$_3$	OCH$_3$	OCH$_3$	H	>50	—	—	—
62f	4	7-OCH$_3$	H	OCH$_3$	H	H	12.9	—	—	—
62g	4	7-OH	H	OH	H	OH	27	—	—	—
Resveratrol	—	—	—	—	—	—	12.9	—	—	—

effects of active compounds **66b**, **66g**, and **66d** were tested. These compounds showed higher activity in the G2/M phase of HeLa cells compared to resveratrol. Most of the cells were arrested at the G2/M phase by compounds **66b**, **66d**, and **66g**. These findings support the inhibitory activity of nitrovinylstilbene derivatives (**66b** and **66g**) against the HeLa cell line. The activation of caspase-3 by compounds **66b** and **66g** in HeLa cells was examined. Compared to resveratrol, treatment with compound **66b** resulted in a 12-times increase in caspase-3 activity. In contrast, resveratrol did not cause a significant increase in caspase-3 activation (Table 19).

Csuk *et al.*[20] synthesized *E*-stilbene-based derivatives and evaluated their anti-tumor activity. Compounds **69a** and **69b** showed the highest activity against 518A2, 850C, A253, A549,

Table 19 Chemical structures of resveratrol-based nitrovinylstilbenes



(66a-g)

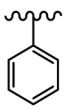
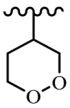
Compounds	R	IC$_{50}$ (pM) MCF-7	SK-N-SH	A549	HeLa	IC$_{50}$ (μM) Tubulin	Inhibition percent (%) G2/M	Fold-increase in Caspase-3
66a		7.2	35.8	44.4	—	—	—	—
66b	4-CH$_3$	42.5	12.5	19.0	4.4	4.27	66.43	10
66c	4-F	19.0	18.8	35.9	12.4	—	—	—
66d		19.2	20.9	16.3	5.4	8.02	50.66	—
66e	3,4,5-triOCH$_3$	13.2	60.9	27.1	—	—	—	—
66f	3,5-diOCH$_3$	19.2	36.2	15.0	10	—	—	—
66g	4-OCH$_3$	21.4	20.7	40.4	7.8	4.90	60.40	11.5
Resveratrol	—	79.1	40.3	44.7	22.5	—	21.29	—
Colchicine	—	—	—	—	—	1.96	—	—

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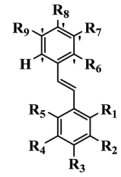
Table 20 Chemical structures of stilbene-based compounds



(69a-k)

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	IC_{50} (μM) 518A2	850C	A253	A549	A2780	DLD1	Lipo	MCF7	NiH3T3	Induced apoptosis (%)
69a	—	OH	OCH_3	—	F	OCH_3	—	OCH_3	—	0.03	0.03	0.03	0.03	0.01	0.04	0.03	0.06	0.05	77.3
69b	—	OH	OCH_3	—	F	—	OCH_3	F	OCH_3	0.20	0.13	0.48	0.18	0.11	0.20	0.21	0.22	0.19	64.1
69c	—	—	OH	—	—	—	OH	—	OH	>30	>30	>30	>30	>30	>30	>30	>30	24.22	—
69d	—	OH	OCH_3	—	—	OCH_3	—	—	OCH_3	0.72	0.86	0.80	0.96	0.87	0.91	0.65	0.54	1.54	—
69e	—	OH	OCH_3	—	—	OCH_3	—	OCH_3	—	1.33	1.33	1.53	1.80	1.27	2.00	1.41	1.64	2.08	—
69f	—	OCH_3	OCH_3	—	—	—	OCH_3	F	OCH_3	18.04	17.72	15.83	22.16	23.92	14.95	16.51	11.20	6.76	—
69g	—	OCH_3	OCH_3	—	—	—	OCH_3	—	OCH_3	2.81	2.46	2.35	3.04	2.06	2.86	2.86	1.89	3.68	77.1
69h	—	OH	OCH_3	—	F	OCH_3	—	—	OCH_3	1.74	2.26	1.34	2.21	2.01	2.26	1.98	2.09	2.66	72
69i	—	OH	OCH_3	—	F	OH	—	—	OH	19.43	16.77	9.88	15.77	10.47	18.00	>30	10.63	21.06	—
69j	—	—	OH	—	—	OH	—	—	OH	28.36	18.70	15.16	12.66	16.62	22.91	17.37	14.17	9.59	—
69k	OH	—	—	—	—	OH	—	—	OH	22.00	24.45	14.53	19.01	12.42	18.11	24.07	13.18	12.38	—
Tamoxifen	—	—	—	—	—	—	—	—	—	7.62	11.09	8.92	9.66	7.77	4.78	8.64	7.10	7.26	—

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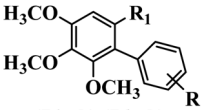
Table 21 Structures of biaryl stilbenes/ethylenes



(74a-h) (76a-h)

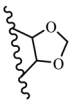
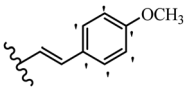
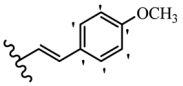
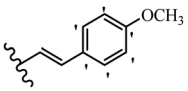
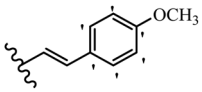
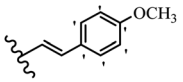
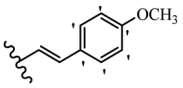
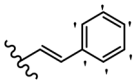
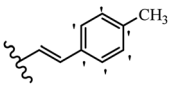
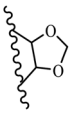
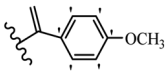
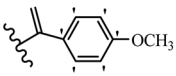
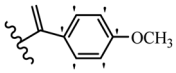
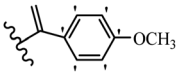
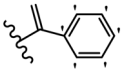
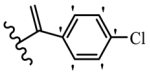
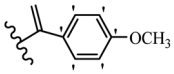
Compound	R	R_1	IC_{50} (μM) A549	Hela	SK-N-SH	DU145	Tubulin	Inhibition mitosis percent (%)
74a			6.3	8.7	8.0	7.3	6.8	73.02
74b	3,4-diF		7.5	9.2	6.9	7.5	9.2	71.16
74c	4-OCH_3		35	19	36	34	—	—
74d	4-Cl		30	49	15	35	—	—
74e	H		36	26	11	51	—	—
74f	3,4-diOCH_3		28	45	42	34	—	—
74g	H		79	89	63	82	—	—
74h	H		54	45	31	101	—	—
76a			5.0	5.4	6.1	6.0	8.6	73.00
76b	3,4-diF		6.5	5.9	7.5	6.8	11.2	70.02
76c	H		22	11	31	8	—	—
76d			15	35	6	46	—	—
76e	H		17	42	34	36	—	—
76f	H		40	34	25	29	—	—
76g	4-Cl		29	30	15	33	—	—

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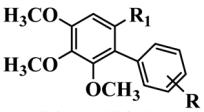
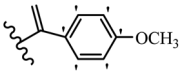
Table 21 (*Contd.*)



(74a-h) (76a-h)

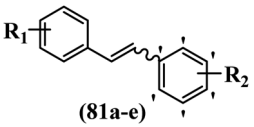
Compound	R	R_1	IC_{50} (μM) A549	Hela	SK-N-SH	DU145	Tubulin	Inhibition mitosis percent (%)
76h	4-OCH_3		14	72	75	37	—	—
Colchicine	—	—	—	—	—	—	1.7	19.4

A2780, DLD1, Lipo, MCF-7, and NiH3T3 cell lines. These compounds were also more potent than tamoxifen. Among the compounds, **69c** exhibited the lowest activity. Switching the OCH_3 group from the 5′- to 4′-position on the phenyl ring (**69d** *vs.* **69e**) decreased the activity against all the tested cell lines. In addition, adding an F atom in the 4′-position on the phenyl ring compared to no substitution resulted in lower activity (**69f** *vs.* **69g**) against the tested cell lines. Also, changing OCH_3 with an OH group in the 2′- and 5′-positions on the phenyl ring reduced the cytotoxicity activity (**69h** *vs.* **69i**). It seems that lipophilic groups show higher activity than hydrophilic groups. Moreover, moving the OH group in the 4- to the 2-position on the phenyl ring showed almost equal cytotoxicity activity (*e.g.*, **69j** and **69k**) against all the cell lines. In addition, the apoptotic activity of the compounds was almost similar to the cytotoxic activity against the A549 cell line (Table 20).

Kumar *et al.*[62] synthesized biaryl stilbenes/ethylenes and assessed their anti-microtubule activity. Among the synthesized compounds in the first series, **74a** and **74b** exhibited the highest activity against the A549, HeLa, SK-N-SH, and DU-145 cell lines. Attaching OCH_3 (**74c**) and Cl groups (**74d**) to the 4-position on the phenyl ring compared to **74e**, which was unsubstituted resulted in lower anti-proliferative activity against the SK-N-SH cell line. In addition, an extra OCH_3 group in the 3-position on phenyl ring decreased the activity (**74c** *vs.* **74f**) against the HeLa and SK-N-SH cell lines. Also, the addition of a CH_3 group in the 4′-position on the phenyl ring of **74h** compared to no substitution (**74g**) enhanced the activity against the A549, HeLa, and SK-N-SH cell lines. Similarly, compounds **76a** and **76b** demonstrated the highest activity in the second series against the A549, HeLa, SK-N-SH, and DU145 cell lines. The compound with no substitution on the phenyl ring (**76c**) displayed higher activity than **76d** having a phenyl on the phenyl ring against HeLa and DU145. However, **76c** showed weaker activity than **76d** against A549 and SK-N-SH. Also, attaching a Cl group in the 4′-position on the phenyl ring compared to no substitution resulted in better activity (**76e** and **76f**). Moreover, according to the SAR studies of both series, it was concluded that the substitutions with a small size and strong electronegativity in the 3- and 4-positions on the phenyl ring may be important for effective anti-proliferative activity (*e.g.*, **74b** and **76b**). Also, the presence of EDG in the 4-position on phenyl showed better activity compared to EWG against A549 (**76h** *vs.* **76g**). The results showed that the second series exhibited stronger activity compared to the first series. Also, **74a** demonstrated the maximum inhibition of tubulin. None of the compounds showed stronger activity than colchicine. **74a**, **74b**, **76a**, and **76b** arrested the majority of the population of cells at the G2/M phase. Overall, these findings indicated that compounds **74a**, **74b**, **76a**, and **76b** inhibited tubulin polymerization more effectively than the other compounds in both series (Table 21).

Roman *et al.*[63] designed some *E*/*Z*-stilbenes and tested their anti-invasive activity. Among the synthesized compounds, *E*-**81a** and Z-**81b** exhibited the highest activity against MCF-7/6. In both isomers, attaching substitutions in the 4′-position phenyl ring enhanced the activity (*e.g.*, **81a** and **81c**). The *Z*-isomers showed better activity than the *E*-isomers (*e.g.*, *Z*-**81d** and *E*-**81d**). Analogues *E*-**81e** and *Z*-**81e**, combining both decoration patterns, displayed very weak potency. Overall, the results showed that two-atom spacers are well tolerated between the aromatic moieties (Table 22).

Table 22 Structures of *E*/*Z*-stilbenes



(81a-e)

Compound	*E*/*Z*	R_1	R_2	IC_{50} (μM) MCF-7/6
81a	*E*	4-OCH_3	4-F	0.01
81b	*Z*	4-F	H	0.01
81c	*E*	4-OCH_3	H	0.1
81d	*E*	3,4,5-triOCH_3	H	0.1
81d	*Z*	3,4,5-triOCH_3	H	0.01
81e	*E*	3,4,5-triOCH_3	4-F	1
81e	*Z*	3,4,5-triOCH_3	4-F	0

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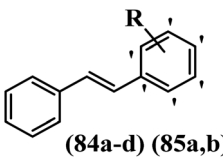
Centelles *et al.*[64] synthesized stilbene derivatives and evaluated their cytotoxicity and inhibitory activity against VEGF. Compound **84a** showed the highest activity against the BAE cell line among the synthesized compounds. Also, it was more potent than resveratrol. Likewise, moving the OH group in the 4′-position of compound **84a** to the 2′- or 3′-position on the phenyl ring in **84b** or **84c** resulted in lower activity against BAE. Moreover, changing the OCH_3 group in the 2′-position on the phenyl ring in **84d** with an OH group in the same position in **84b** resulted in an enhancement in activity against BAE. Further, moving the *O*-allyl moiety from 2′- to 4′-position on phenyl ring reduced activity against BAE (**85a** *vs.* **85b**). In addition, the cytotoxicity of all the compounds was investigated against the HT-29 cell line. Among the synthesized compounds, **85b** showed higher activity compared to resveratrol against HT-29. Moreover, compound **84a** exhibited stronger activity than **84b** and **84c**. Compound **84d** showed weaker cytotoxicity compared to **84b**. Compound **85b** had more potent activity than **85a**. According to the results, changing the position of substitution on the phenyl ring improved the cytotoxicity activity against the HT-29 and BAE cell lines (4′ > 2′ > 3′). Resveratrol and some stilbene analogues reduced the VEGF expression in HT-29 cells. Compounds **84b** and **85a** decreased the VEGF expression to a higher extent than resveratrol and DMSO. Replacement of the OH in the 2′-position on the phenyl ring in **84b** with an OCH_3 group in the same position in **84d** resulted in lower activity against VEGF. The results showed that hydrophilic groups displayed higher activity compared to lipophilic groups. Also, the presence of bulky groups decreased the activity against BAE and expression of VEGF. However, it increased the activity against the HT-29 cell line (Table 23).

Zhang *et al.*[65] synthesized 2-hydroxylated *E*-stilbenes and assessed their anti-proliferative activity. Among the synthesized compounds, **88a** against Colo-205 and MGC80-3, **88b** against HT-29, and **88c** against MDA-468 showed the highest activity. Changing the Br atom in the 4′-position on the phenyl ring (**88d**) with CH_3 (**88e**), OH (**88f**), and CN (**88g**) groups reduced cytotoxicity activity against all the cell lines. It seems that the compounds with a lipophilic group compared to a hydrophilic group showed stronger cytotoxicity activity. Also, the presence of an extra OCH_3 group in the 4′-position on the phenyl ring in **88c** enhanced the cytotoxicity activity compared to **88h** against MDA-468 and MGC80-3. In addition, moving the OCH_3 group from the 3- to 4-position on phenyl improved the cytotoxicity activity (**88i** *vs.* **88h**) against MDA-468 and MGC80-3. Besides, the compounds with substitution on the phenyl ring showed better cytotoxicity activity than no substitution (**88j** *vs.* **88a**) against all the cell lines. In addition, the compounds containing EWG exhibited the higher activity compared to EDG (*e.g.*, **88e** and **88d**) (Table 24).

Table 23 Synthetic compounds of stilbene



(84a-d) (85a,b)

		IC_{50} (μM)		IC_{50} (ng mL^{-1})
Compound	R	BAE	HT-29	VEGF
84a	4-OH	33.6	34.6	—
84b	2-OH	107	112	19
84c	3-OH	91.7	127	—
84d	2-OCH_3	152	42.8	39
85a	2-Oallyl	313	55	20
85b	4-Oallyl	>400	23	—
Resveratrol	—	48	110	30

Morris *et al.*[66] tested the anti-tumor properties of methylated *Z*-resveratrol. Compounds **89e** and **89h** showed lower activity than **89d** against the proliferation of B16-F10. However, the inhibition potency of *Z*-**89f** and **g** was slightly higher than that of **89d**. These results indicated that *Z*-tetra-methoxy inhibited motility more effectively than *Z*-tri- or penta-methoxy. However, isomers of **89a–c** showed no visible activity on β-tubulin expression. It was discovered that **89d** reduced the expression of tubulin in B16-F1 cells, while **89a–c** exhibited no activity. Compared to DMSO, all the tested *Z*-isomers showed a dramatic decrease in intracellular tubulin protein, and in the case of **89f**, the level of expression was below the detectable limit. When compounds **89a–d** were compared, **89d** was the most effective in inhibiting the proliferation of B16-F10 cells, B16-F1 cells, and melanocytes. These findings imply that these cells respond differently to the anti-proliferative effects of **89d**. The *Z*-polymethoxy compounds were created to inhibit cell proliferation compared to DMSO-treated cells, with **89d** being the most potent inhibitor, while analogues **89e**, **89f**, and **89h** were significantly less potent. It is worth noting that neither the *E*-isomer (**89a**) nor any of the counterpart *trans*-polymethoxystilbenes (**89c** and **89i–l**) had a significant effect on B16-F10 cell proliferation. In addition, the present lipophilic groups showed higher activity compared to hydrophilic groups (**89d** *vs.* **89b**). Also, the *Z*-isomers exhibited superior activity in comparison to their corresponding *E*-isomers (Table 25).

Scherzberg *et al.*[67] evaluated resveratrol derivatives against tumor cells. The method for the synthesis of resveratrol derivatives **90a** and **90b** was the same as in the reported study.[26] Compared to *E*-resveratrol, *Z*-**90a** showed 100-times higher anti-proliferative activity against HT-29. Compound *Z*-**90a** inhibited HepG2 cell growth. *E*-Resveratrol exhibited lower activity for HepG2 cells compared to Caco-2. In contrast to Caco-2, the IC_{50} value for *Z*-**90a** in HepG2 is the highest. However, in both proliferation assays, *Z*-**90a** had significantly lower IC_{50} values than *E*-resveratrol. These findings are comparable to that obtained in the Caco-2 cell line. In comparison to the results in tumor cell lines, *Z*-**90a** only had moderate effects on HUVEC cell growth. Compound *Z*-**90a** exhibited no cytotoxic effect on CaCo-2, HT-29, HepG2 cells, and HUVECs. Another distinction was revealed by the cell cycle analysis, where both *E*/*Z*-resveratrol arrested cells in the S-phase, whereas *E*/*Z*-**90a** arrested cells in the G2/M phase. According to the results, lipophilic groups

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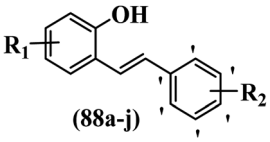
Table 24 Synthetic structures of 2-hydroxylated *E*-stilbenes

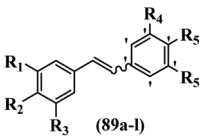


Compound	R_1	R_2	IC_{50} (μM) Colo-205	MDA-468	HT-29	MGC80-3
88a	4-OCH_3	3,4,5-triOCH_3	5.3	5.3	9.7	0.035
88b	5-Br	3,5-diOCH_3	16.4	6.1	9.5	3.3
88c	3-OCH_3	3,4,5-triOCH_3	—	2.6	—	1.1
88d	H	4-Br	21.1	7.4	14.4	—
88e	H	4-CH_3	—	21.9	22.9	—
88f	H	4-OH	—	—	33.5	—
88g	H	4-CN	—	—	—	3.1
88h	3-OCH_3	3,5-diOCH_3	—	—	—	—
88i	4-OCH_3	3,5-diOCH_3	—	8.4	—	0.8
88j	H	H	—	19.3	—	—
Resveratrol	—	—	23.5	45.2	87.2	42

displayed better activity than hydrophilic groups incorporation in BrdU (Table 26).

Yan *et al.*[68] synthesized benzoselenazole-stilbene hybrids and assessed their cytotoxicity activity. Among the analogues, **95a** showed the highest activity, and it was more active than resveratrol and ebselen against the Bel-7402, A549, HeLa, and MCF-7 cell lines. Also, moving the OCH_3 group from the 4′-position in **95b** to the 5′-position on the phenyl ring in **95c** decreased the anti-proliferative activity against the tested cell lines. In addition, the extra OCH_3 group in the 5′-position on the phenyl ring of **95b** produced **95d**, which showed reduced activity against the A549 and HeLa cell lines. However, **95b** and **95d** showed equal activity against the Bel-7402 and MCF-7 cell lines. When the number of OCH_3 groups on phenyl ring decreased, the activity decreased markedly (**95c** *vs.* **95e**). This exhibited that the OCH_3 group is essential for an anti-cancer effect. Consequently, it can be concluded that the compound with two OCH_3 groups, particularly at the 3′- and 4′-positions on the phenyl ring, was active. In contrast, the findings revealed that the OCH_3 groups in the 4- and 5-positions on the phenyl

Table 25 Structures of methylated *E*/*Z*-resveratrol



Compound	*E*/*Z*	R_1	R_2	R_3	R_4	R_5	R_6	Inhibition percent (%) B16-F10, B16-F1, melanocytes	Proliferation B16-F10	Motility B16-F10
89a	*E*	OH	H	OH	H	OH	H	—	—	—
89b	*Z*	OH	H	OH	H	OH	H	—	—	—
89c	*E*	OCH_3	H	OCH_3	H	OCH_3	H	—	—	—
89d	*Z*	OCH_3	H	OCH_3	H	OCH_3	H	75	71	—
89e	*Z*	OCH_3	OCH_3	H	H	OCH_3	H	—	45	50–60
89f	*Z*	OCH_3	H	OCH_3	OCH_3	OCH_3	H	—	45	80–90
89g	*Z*	OCH_3	OCH_3	OCH_3	H	OCH_3	H	—	66	80–90
89h	*Z*	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	—	45	50–60
89i	*E*	OCH_3	OCH_3	H	H	OCH_3	H	—	—	—
89j	*E*	OCH_3	OCH_3	H	H	OCH_3	OCH_3	—	—	—
89k	*E*	OCH_3	OCH_3	OCH_3	H	OCH_3	H	—	—	—
89l	*E*	OCH_3	OCH_3	OCH_3	OCH_3	H	OCH_3	—	—	—
DMSO	—	—	—	—	—	—	—	100	100	—

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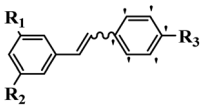
Table 26 Chemical structures of resveratrol derivatives



(Resveratrol, 90a)

Compounds	*E*/*Z*	R_1	R_2	R_3	IC_{50} (μM) HT-29	CaCo-2	HepG2	BrdU incorporation
Resveratrol	*E*	OH	OH	OH	115.9	190.2	110.7	100
Resveratrol	*Z*	OH	OH	OH	—	—	—	>200
90a	Z	OCH_3	OCH_3	OCH_3	0.115	0.145	0.473	0.2–0.5
90a	*E*	OCH_3	OCH_3	OCH_3	—	—	—	5–20

ring had a negative effect on the activity of **95f** against all the tested cell lines compared to the other compounds. When the group in the 4-position on the phenyl ring changed to F or Cl atoms, the anti-proliferative activity remarkably increased (**95g** and **95a**). The findings exhibited that the *E*-isomer stilbene scaffold was favorable for cytotoxic activity compared to the corresponding *Z*-isomers (**95b** *vs.* **98**). Compared with **95b**, the anti-proliferative activity of compound **102** was significantly lower (<10-times), which strongly demonstrated that the benzoselenazole-stilbene hybrids were beneficial for the activity. The *in vitro* inhibition of thioredoxin reductases (TrxR) was tested using the compounds. Compound **95b** revealed the highest activity among the compounds, which was also better than that of ebselen. Compounds **95c** and **95d** exhibited better cell growth inhibition effects compared to **95e** and **95h**. Compounds **95g**, **95a**, **95i**, and **95j**, which have halogen atoms on the phenyl ring, exhibited the highest TrxR inhibitory activity. However, compound **95f**, which demonstrated relatively good inhibitory activity against TrxR, showed less cell growth inhibition. Compound **102**, which is characterized by the absence of a selenium atom, revealed no activity, further demonstrating the requirement of selenium in the derivatives. Furthermore, treatment with compound **95b** resulted in significant cell cycle arrest at the G2/M phase. These findings showed that the compounds could halt cell cycle progression at the mitosis stage. The cell apoptosis assay results showed that resveratrol and compound **95b** caused significant cell apoptosis. Compound **95b** effectively induced cell apoptosis in Bel-7402 cells, eventually leading to cell death according to the data (Table 27).

Mahdavi *et al.*[69] designed *N*-substituted 2-arylquinazolinones and tested their cytotoxicity activity. Among the synthesized compounds, **109a** against MCF-7 and T-47D and **109b** against MDA-MB-231 showed the best cytotoxicity activity. They were also more potent than etoposide against MCF-7, MDA-MB-231, and T-47D. In addition, the compounds containing an aliphatic ring showed increased activity compared to that having an aromatic ring (*e.g.*, **109c** *vs.* **109d**) against MCF-7, MDA-MB-231, and T-47D. Likewise, *N*-alkyl groups were more active than *N*-aryl and *N*-benzyl groups. Compound **109e** with *N*-cyclopentyl was inactive against all the tested cell lines, while **109f** with *N*-propyl showed activity against MCF-7. Most of the *N*-alkyl quinazolinones had similar sensitivity in all the tested cell lines. However, in the case of compound **109g**, the sensitivity of MCF-7 was significantly lower than that of MDA-MB-231 and T-47D. The IC_{50} values of compounds **109d** and **109h–l** indicated that the aryl or benzyl substituents were not favorable for cytotoxicity; however, compound **109k** with a 4-methylbenzyl moiety in the 3-position of quinazolinones showed mild activity against all the tested cell lines. Additionally, there is a similar difference against MCF-7 in **109g** and **109a** having isobutyl and *sec*-butyl groups, respectively. This could be because connecting diverse bonds of *N*-isobutyl and *N*-*sec*-butyl groups to the 3-position of quinazolinones caused diverse steric effects on the 2-aryl ring. Consequently, compounds **109a** and **109c** were tested compared to etoposide for the detection of apoptosis in the MDA-MB-231 and MCF-7 cell lines. Compounds **109c** and **109a** reduced the cell viability and induced apoptosis in MCF-7 and MDAMB-231 cells. Although the screened derivatives caused some necrosis in the treated cells, the results showed that **109a** and **109c** induced apoptosis in MDA-MB-231 cells. The ability of compound **109c** to induce apoptosis in MDA-MB-231 cells was comparable to that of etoposide. The results also revealed that the percentage of MCF-7 cells undergoing apoptosis after exposure to compounds **109a** and **109c** was higher than MDA-MB-231. According to the findings, compounds **109c** and **109a** exhibited cytotoxic activity in the MDA-MB-231 and MCF-7 cell lines *via* apoptosis (Table 28).

Penthala *et al.*[70] synthesized and evaluated the cytotoxicity of heteroaromatic analogues of resveratrol. Compound **112a** was the most potent compound against most of the tested cell lines. Also, hydrophilic groups exhibited higher cytotoxicity activity than lipophilic groups against most of the tested cell lines (**112a** *vs.* **112b**) (Table 29).

Centelles *et al.*[71] synthesized nitrogen-containing heterocyclic stilbene analogues and tested their inhibitory activity against hTERT, VEGF, and c-Myc. Among them, compounds **115a** against HT-29, **115b** against MCF-7, and **118a** and **118b** against HEK-293 showed the highest cytotoxicity activity. These compounds also exhibited stronger activity than resveratrol

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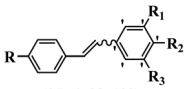
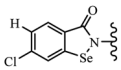
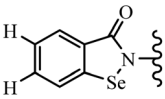
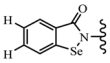
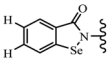
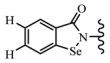
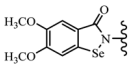
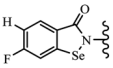
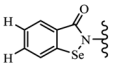
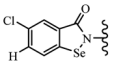
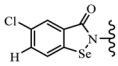
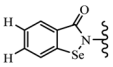
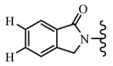
Table 27 Structures of benzoselenazole–stilbene hybrids



(95a-j, 98, 102)

Compound	*E*/*Z*	R_1	R_2	R_3	R	IC_{50} (μM)				Inhibition percent (%)			Induced apoptosis (%)
						Bel-7402	A549	HELA	MCF-7	TrxR	TrxR	G2/M	
95a	*E*	OCH_3	H	OCH_3		0.79	0.52	0.23	0.47	—	36.4	—	—
95b	*E*	OCH_3	OCH_3	H		1.01	1.53	1.52	3.37	3.10	—	44.23	53.4
95c	*E*	OCH_3	H	OCH_3		3.49	3.73	3.80	7.78	8.27	—	—	—
95d	*E*	OCH_3	OCH_3	OCH_3		1.11	3.11	5.67	3.97	5.78	—	—	—
95e	*E*	OCH_3	H	H		13.2	10.4	7.34	9.62	12.8	—	—	—
95f	*E*	OCH_3	H	OCH_3		25.4	52.6	31.6	88.9	7.53	—	—	—
95g	*E*	OCH_3	H	OCH_3		0.99	1.22	0.64	0.51	—	36.6	—	—
95h	*E*	H	H	H		12.4	23.8	35.7	24.8	—	22.4	—	—
95i	*E*	OCH_3	H	OCH_3		—	—	—	—	—	31.2	—	—
95j	*E*	OCH_3	OCH_3	H		6.13	6.95	12.0	16.9	—	38.4	—	—
98	*Z*	OCH_3	OCH_3	H		36.1	43.0	28.4	56.3	9.62	—	—	—
102	*E*	OCH_3	OCH_3	H		>10	>10	>10	>10	—	—		
Resveratrol		—	—	—	—	50.7	>100	47.9	>100	—	26.1	—	—
Ebselen		—	—	—	—	68.2	>100	78.5	>100	8.54	—	—	—

against the HEK-293, MCF-7, and HT-29 cell lines. Most of the compounds showed weaker cytotoxicity than resveratrol. Likewise, moving the OCH_3 group from the 3′-position in **115a** to the 4′-position on the phenyl ring in **115c** reduced the cytotoxicity against all the tested cell lines. Also, moving the nitrogen atom from the 3-position to the 2-position in the pyridine ring mitigated the cytotoxicity activity (**115d** *vs.* **115e**) against the HT-29 and MCF-7 cell lines. However, **115e** had stronger activity than **115d** against the HEK-293 cell line. Also, the conversion of pyridine ring **115f** to pyrimidine ring **115g** reduced the cytotoxicity against the three cell lines. In addition, the lipophilic groups showed greater cytotoxicity activity compared to hydrophilic groups (*e.g.*, **115a** and **118c**) against all the tested cell lines. Also, the HT-29 tumoral cell line was used to study the effect of stilbene derivatives on VEGF secretion and VEGF gene inhibition. Compounds **115h** and **115c** demonstrated significant capability to inhibit VEGF expression. Surprisingly, they showed significantly higher activity than resveratrol. Compound **115a**, the most potent compound, also revealed considerable inhibitory activity against VEGF expression. Compounds **115c** and **115h**, which had the strongest inhibitory activity against VEGF expression, showed significantly lower ability to inhibit VEGF gene expression. In contrast, compound **118c**, which was previously only weakly active in inhibiting

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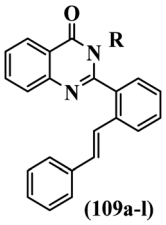
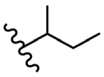
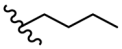
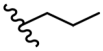
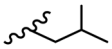
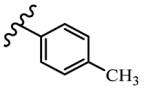
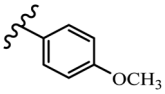
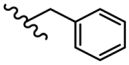
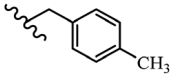
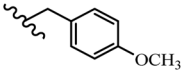
Table 28 Chemical structures of *N*-substituted 2-arylquinazolinones



(109a-l)

Compound	R	IC_{50} (μM)			Induce apoptosis	
		MCF-7	MDA-MB-231	T-47D	MCF-7	MDA-MB-231
109a		3.8	4.9	3.6	26.46	16.55
109b		9.8	4.0	7.9	—	—
109c		5.3	5.5	6.8	25.88	22.4
109d		44.9	>100	>100	—	—
109e		>100	>100	>100	—	—
109f		29.4	>100	>100	—	—
109g		23.3	6.9	9.3	—	—
109h		>100	>100	>100	—	—
109i		>100	>100	>100	—	—
109j		>100	>100	>100	—	—
109k		24.7	23.8	28.2	—	—
109l		>100	>100	>100	—	—
Etoposide	—	7.6	10.3	8.9	—	—

VEGF expression, had the strongest ability to inhibit VEGF gene expression. Compounds **115i**, **115d** and **115h** all had the same capacity to inhibit hTERT gene expression. The remaining compounds, including **115a**, had marginal activity that is slightly lower than the control. However, the trend of activities for inhibiting c-Myc gene expression was demonstrated to be noticeably diverse. Compounds **115i**, **115d**, and **115h** showed significant inhibitory activity on hTERT gene expression, which were much less active in inhibiting c-Myc gene expression. Compounds **115a**, **115c**, **118c**, and **118d**, which previously had such poor activity against hTERT gene expression, were much more active against c-Myc gene expression, mainly **115a** and **118d**, which had the same activity with resveratrol (Table 30).

Centelles *et al.*[72] synthesized resveratrol analogues and assessed their cytotoxicity. Analogue **121a** showed the highest cytotoxicity and it was also better than resveratrol against the

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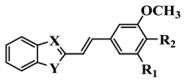
Table 29 Structures of heteroaromatic analogues of resveratrol



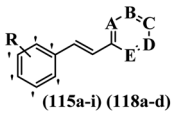
(112a,b)

					GI$_{50}$ (μM)											
Compound	X	Y	R_1	R_2	K562	SR	HOP-92	NCI-H226	HT29	KM12	U251	MDA-MB-435	OVCAR-3	NCI/ADR-RES	A498	UO-31
112a	N	S	OCH_3	OCH_3	0.041	0.036	0.036	0.245	0.038	0.072	0.088	0.024	0.069	0.106	0.041	0.376
112b	CH	S	OCH_3	OCH_3	0.088	0.120	0.322	0.442	0.234	0.213	0.338	0.036	0.224	0.070	0.213	0.513

HEK-293, MCF-7, and HT-29 cell lines. Moreover, moving the OH group from the 2′- to 3′-position on the phenyl ring enhanced the cytotoxicity (**121b** *vs.* **121c**) against HT-29 and HEK-293. Likewise, shifting the OCH_3 group from the 4- in **121d** to 2-position on the phenyl ring in **121e** resulted in lower cytotoxicity against all the tested cell lines. Also, the comparison of compound **121f** having an NH_2 group in the 4-position, **121g** bearing an NH_2 group in the 3-position, and **121h** having an NH_2 group in the 2-position on the phenyl ring showed that **121f** was more potent than **121g** and **121h** against HT-29. In addition, moving the NH_2 group from the 2- to 3-position on the phenyl ring resulted in stronger activity (*e.g.*, **121i** and **121j**) against the MCF-7 and HEK-293 cell lines. In addition, the presence of lipophilic groups compared to hydrophilic groups enhanced the cytotoxicity activity (**121k** *vs.* **121l**) against all the tested cell lines. Also, EWG in **121m** showed higher activity compared to EDG in **121f** against MCF-7. According to the findings, different substitutions in the diverse positions of both phenyl rings had a positive effect on the cytotoxicity (4 > 2 > 3). In addition, compound **121a** showed ability to suppress the expression of h-TERT and c-Myc genes. Compound **121o** was the most active compound among the amide stilbenes. Among the amino stilbenes, those with a methoxy group (**121i**, **121j**, **121n**, and **121a**) exhibited greater activity than that with a hydroxy group (Table 31).

Srivastava *et al.*[73] synthesized quinolino-stilbene derivatives and evaluated their cytotoxicity activity. Among the synthesized *E*/*Z*-compounds, **127a** showed the highest activity against the HeLa, MCF-7, MDA-MB231, MDA-MB468, and 184B5 cell lines. Most of the compounds exhibited better activity compared to paclitaxel, camptothecin, and chloroquine. In the *Z*-isomers, replacing the CF_3 group with an F atom in the 4′-position on the phenyl ring reduced the activity by 2–5 times (**127b** *vs.* **127c**) against five cell lines. In addition, moving the CF_3 group from the 4′- in **127d** to 3′-position on the phenyl ring in **127a** improved the activity by 2-times. However, adding an OCH_3

Table 30 Chemical structures of nitrogen-containing heterocyclic stilbene analogues



(115a-i) (118a-d)

							IC$_{50}$ (μM)			Inhibition percent (%)			
Compound	R	A	B	C	D	E	HT-29	MCF-7	HEK-293	VEGF protein	VEGF gene	hTERT gene	c-Myc gene
115a	3-OCH_3	—	—	N	—	—	44	88	56	52	95	95	50
115b	2-OCH_3	N	—	—	—	—	274	1.7	175	—	—	—	—
115c	4-OCH_3	—	—	N	—	—	61	142	114	42	91	—	63
115d	3-OCH_3	—	N	—	—	—	104	128	123	—	—	57	71
115e	3-OCH_3	N	—	—	—	—	223	204	68	—	—	—	—
115f	4-OCH_3	—	N	—	—	—	299	62	213	—	—	—	—
115g	4-OCH_3	—	N	—	N	—	>500	>500	259	—	—	—	—
115h	2-OCH_3	—	—	N	—	—	76	100	85	37	54	54	64
115i	4-OCH_3	N	—	—	—	—	114	147	199	—	—	52	87
118a	4-OH	—	—	N	—	—	168	16	13	—	—	—	—
118b	2-NH_2	—	—	N	—	—	255	383	13	—	—	—	—
118c	3-NH_2	—	—	N	—	—	168	235	>500	93	48	—	58
118d	4-NH_2	—	—	N	—	—	100	20.6	41	—	—	—	49
Resveratrol	—	—	—	—	—	—	150	71	31	78	65	57	51

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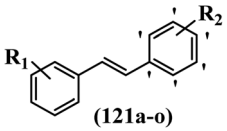
Table 31 Synthetic derivatives of stilbene



(121a-o)

			IC_{50} (μg mL^{-1})				% gene expression	
Compounds	R_1	R_2	HT-29	MCF-7	HEK-293	VEGF	hTERT	c-Myc
121a	4-NH_2	4-OCH_3	0.0036	0.0021	0.012	67	48	69
121b	4-OH	2-OH	22	21	17.5	—	—	—
121c	4-OH	3-OH	6.9	23	1.1	—	—	—
121d	4-OCH_3	4-OH	17.4	11.3	3.9	—	—	—
121e	2-OCH_3	4-OH	24	19	41	—	—	—
121f	4-NH_2	H	4.4	16	11.4	24	65	46
121g	3-NH_2	H	12.9	14	84	—	—	—
121h	2-NH_2	H	17	1.4	1.3	—	—	—
121i	2-NH_2	3-OCH_3	21.2	6.1	0.5	100	35	79
121j	3-NH_2	3-OCH_3	19.6	34	16	23	100	34
121k	3-NH_2	3-OCH_3	16.3	23	11	—	—	—
121l	3-NH_2	2-OH	30.4	24.7	96	38	52	37
121m	3-$NHCO(CH_2)_{10}CH_3$	H	>100	3.5	11.6	—	—	—
121n	3-NH_2	2-OCH_3	25.3	38.7	45	67	52	45
121o	2-$NHCO(CH_2)_{10}CH_3$	H	2.5	12	16	37	53	45
Resveratrol	—	—	34.1	16.1	7.1	65	57	51

group in the 3′-position of the phenyl ring did not have any discernible effect on the anti-proliferative activity when combined with a CF_3 group in the 3-position (**127a** *vs.* **127e**). Moreover, an extra CF_3 group on the phenyl ring had a negative effect on the activity (**127d** *vs.* **127f**). Also, the presence of CF_3 groups at the 3′- and 5′-positions resulted in 5–10 times better activity than the 2′- and 4′-positions (**127f** *vs.* **127g**) and (**127h** *vs.* **127i**) against the HeLa cell line. The addition of a Cl atom at the 4-position of the phenyl ring reduced the activity by 5-times (**127f** *vs.* **127j**) against all the tested cell lines, whereas the addition of an OCH_3 group in the 3-position on the phenyl ring improved the activity by 2-times (**127f** *vs.* **127h**). A methylenedioxy group on the phenyl ring reduced the activity by 10-times against HeLa, MCF-7, MDA-MB231, MDA-MB468, and 184B5 (**127a** *vs.* **127k**). The SAR studies showed that a CF_3 group in the 3′- or 4′-position on the phenyl ring is the best position for anti-proliferative activity. Although an OCH_3 group in the 4-position on the phenyl ring is tolerable, it did not contribute to an enhancement in activity. According to the findings, the stereochemistry and positions of various functional groups are likely to play vital roles in the cytotoxicity. *E*-**127l** with an F atom in the 4′-position on the phenyl ring was very active against the MDA-MB468 cell line and moderately active against the MCF7 cell line. However, it had a low level of activity against HeLa, MDA-MB231, and 184B5. Besides **127l**, the *Z*-stilbene derivatives had higher activity and better anti-cancer effect than the *E*-stilbene derivatives. Compounds **127a** and **127l** inhibited cell cycle progression at the mitosis and S-phase, respectively, eventually leading to apoptosis. Compound **127a** appeared to impede normal G2-M progression, eventually leading to cell death. In MDA-MB231 metastatic breast cancer cells, compound **127a** caused a similar pattern of G2/M arrest and DNA fragmentation. Compound **127a** did not exhibit significant G2/M arrest or DNA fragmentation against MCF10A. In comparison to DMSO, compound **127l** significantly increased the S-phase population in MDA-MB-468 cells. According to the data, **127l** causes DNA damage, which leads to S-phase arrest, and eventually cell death (Table 32).

Kachhadia *et al.*[74] described the synthesis of stilbene derivatives and evaluated their anti-cancer activity. Compound **131a** exhibited the highest inhibitory activity against histone deacetylase (HDAC). Moreover, the secondary amide in **131b** slightly reduced the activity compared with the tertiary amide in **131c**. In addition, the presence of cyclopropyl in compound **131d** increased the activity by 5-times against HDAC compared to **131b**. Also, changing the cyclopropyl ring in **131d** to cyclooctyl in **134e** significantly reduced the activity. Moreover, the HDAC activity decreased when the substitution changed from morpholine to pyrroline (*e.g.*, **131f** and **131g**). Also, aromatic substitutions such as phenyl in **131h** or benzyl in **131i** decreased the activity. Other substitutions, such as benzyloxy **131j** and cyclopentyloxy **131k**, also showed excellent HDAC inhibitory activity. Likewise, replacing the OCH_3 group in the 3-position on the phenyl ring of **131l** with a Cl atom of **131m** in the same position enhanced the activity. In addition, the F atom at the 3′-position of the phenyl ring had a positive effect on the activity when combined with an OCH_3 group at the 4′-position on the phenyl ring (**131n** *vs.* **131o**). In the compounds having a heteroaryl ring, the indol-3-yl in compound **138a** had the highest activity, while the other rings significantly reduced the HDAC

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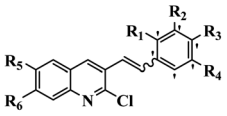
Table 32 Structures of quinolino-stilbene derivatives



(127a-l)

Compound	*E*/*Z*	R_1	R_2	R_3	R_4	R_5	R_6	IC$_{50}$ (μM) HeLa	MCF-7	MDA-MB231	MDA-MB468	184B5	Inhibition percent (%) S-phase
127a	*Z*	H	CF_3	H	H	H	H	2.85	3.53	3.75	3.70	6.15	17
127b	*Z*	H	H	CF_3	H	H	Cl	12.64	6.45	13.55	16.13	26.40	—
127c	*Z*	H	H	F	H	H	Cl	38.62	16.89	42.56	10.91	26.89	—
127d	*Z*	H	H	CF_3	H	H	H	4.22	4.26	5.36	7.38	7.94	—
127e	*Z*	H	CF_3	H	H	OCH_3	H	3.03	2.78	3.28	3.91	5.58	—
127f	*Z*	H	CF_3	H	CF_3	H	H	6.78	7.46	10.13	10.52	13.67	—
127g	*Z*	CF_3	H	CF_3	H	H	H	35.89	10.45	41.76	—	—	—
127h	*Z*	H	CF_3	H	CF_3	OCH_3	H	4.14	4.70	4.47	5.79	7.97	—
127i	*Z*	CF_3	H	CF_3	H	OCH_3	H	>50	>50	>50	>50	>50	—
127j	*Z*	H	CF_3	H	CF_3	H	Cl	41.35	41.71	>50	>50	42.95	—
127k	*Z*	H	CF_3	H	H	OCH_2O	H	20.09	18.90	26.0	>50	16.97	—
127l	*E*	H	H	F	H	H	H	>50	15.13	>50	0.12	38.45	—
Paclitaxel	—	—	—	—	—	—	—	2.29	3.99	2.56	3.87	2.32	41.7
Camptothecin	—	—	—	—	—	—	—	6.13	—	5.77	14.76	4.96	—
Chloroquine	—	—	—	—	—	—	—	29.96	—	36.53	19.86	63.08	—
DMSO	—	—	—	—	—	—	—	—	—	—	—	—	16.9

inhibitory activity. The effect of acrylo phenylacetic acids **139a–c** on the position of the acid group was investigated. The HDAC inhibitory activity of positional isomers **139a–c** was comparable to compounds **131d**, **131p**, **131h**, and **131q**. Encouragingly, compound **139a** with an OCH_3 group in the 4′-position on the phenyl ring was 62-times more potent than compound **131p**. Alternatively, compound **139p** was 38-times less potent than **131a**. The carbonyl group of the amide bond in **131r** reduced to the corresponding amine derivative **135** to produce a secondary amine that is more hydrophilic in nature. Compound **132a** showed 8-times greater HDAC inhibitory activity compared to compound **131d**, while compound **132b** showed 10-times decrease in HDAC inhibitory activity compared to **131q**. Also, the anti-proliferative activity of some compounds was investigated. Among the synthesized compounds, **132a** showed the highest cytotoxicity activity against the NCI-H460, HCT-116, and U-251 cell lines. In addition, compound **131s** with an isopropyl moiety exhibited lower activity than **131d** having cyclopropyl moiety against the tested cell lines. In addition, moving the F atom from the 2′- to 3′-position on the phenyl ring reduced the cytotoxicity against all the tested cell lines (*e.g.*, **131t** and **131n**). Furthermore, the aliphatic groups improved the cytotoxicity compared to aromatic groups (**131u** *vs.* **131k** and **132c** *vs.* **132b**) against the tested cell lines. Also, increasing the number of F atoms in 4′-position of compound **131n** produced **131v**, which showed the highest cytotoxicity activity against all the tested cell lines. Furthermore, compound **131m** with EWG on the phenyl ring showed higher cytotoxicity activity than **131l** having EDG against the tested cancer cell lines (Table 33).

Duan *et al.*[75] designed resveratrol derivatives and tested their activity against LSD1. Compounds **143c** and **d** showed the highest activity against LSD1, and they were more potent than resveratrol and tranylcypromine. In addition, replacing the F atom with an OH group in the 3′-position on the phenyl ring decreased the inhibitory activity against LSD1 (*e.g.*, **143e** and **143f**). Moreover, exchanging the phenyl ring with a pyridine ring (**143g** *vs.* **147**) or indole ring (**143h** *vs.* **149**) resulted in a significant decrease in activity, demonstrating the importance of the phenyl ring in retaining the activity. Also, increasing the atom size improved the activity (*e.g.*, **143c** and **143i**). According to the comparison of **143h** and **144**, changing benzimidamide to benzimidohydrazide significantly reduced the inhibitory activity. Amidoxime in the 3-position on the phenyl ring was preferential; the amidoxime in the 3-position on the phenyl ring of derivatives such as **143g** showed higher inhibitory activity than the corresponding amidoxime in the 4-position on the phenyl ring-substituted derivatives (**143h**) against LSD1. Treatment with **143c** and **143d** resulted in the remarkable buildup of H3K4me2, the substrate of LSD1, without influencing LSD1 expression (Table 34).

Ismail *et al.*[76] synthesized stilbene derivatives and evaluated their tyrosinase inhibitory activity. Compound **152a** showed the highest murine tyrosinase inhibitory activity. This compound exhibited 2-times stronger inhibitory activity than resveratrol against murine tyrosinase. Among the *E*-isomers, compounds **152b** and **152c** showed that fluorination of compound **152d** increased its tyrosinase inhibitory activity. The F-substituted compounds compared to the other halo-substituted

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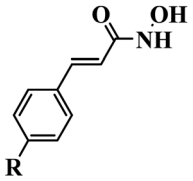
Table 33 Synthetic stilbene derivatives



(131a-v) (139a,b) (132a-c) (135a-c)

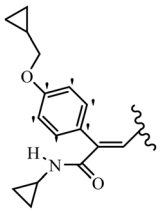
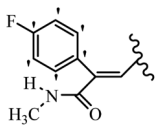
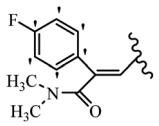
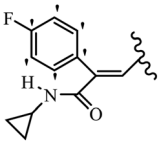
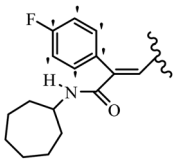
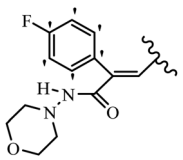
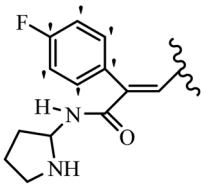
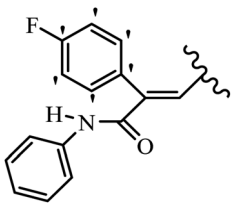
Compounds	R	IC_{50} (nM) HDAC	GI_{50} (μM) NCI-H460	HCT-116	U251
131a		3.7	0.65	0.22	0.05
131b		350	—	—	—
131c		390	—	—	—
131d		48	1.8	1.4	0.02
131e		990	—	—	—
131f		430	—	—	—
131g		410	—	—	—
131h		200	—	—	—

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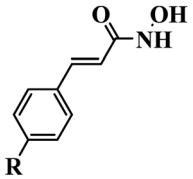
Table 33 (*Contd.*)



(131a-v) (139a,b) (132a-c) (135a-c)

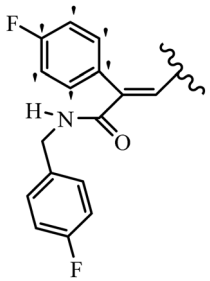
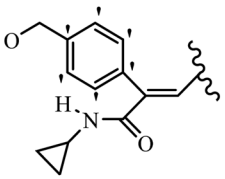
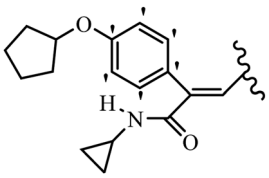
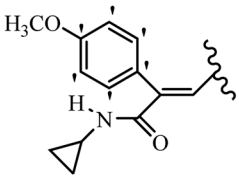
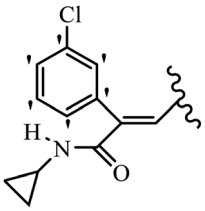
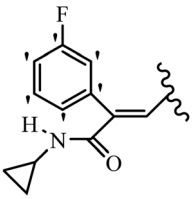
Compounds	R	IC_{50} (nM) HDAC	GI_{50} (μM) NCI-H460	HCT-116	U251
131i		190	—	—	—
131j		39	2.5	2	2
131k		18	0.75	1	1
131l		68	8	3	1.8
131m		30	0.5	0.5	1
131n		40	10	2	4.2

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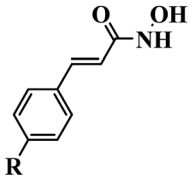
Table 33 (*Contd.*)



(131a-v) (139a,b) (132a-c) (135a-c)

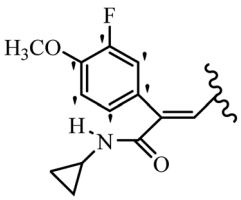
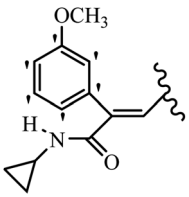
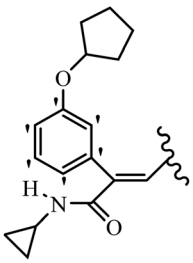
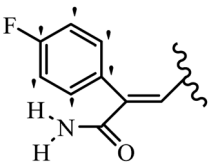
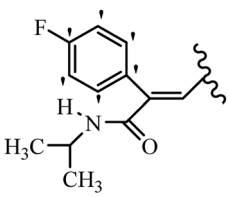
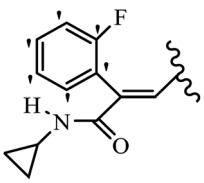
Compounds	R	IC_{50} (nM) HDAC	GI_{50} (μM) NCI-H460	HCT-116	U251
131o		15	9.1	1.1	3
131p		310	—	—	—
131q		56	7	6	6
131r		240	—	—	—
131s		80	11	3	10.5
131t		90	13	6	7

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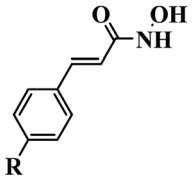
Table 33 (*Contd.*)



(131a-v) (139a,b) (132a-c) (135a-c)

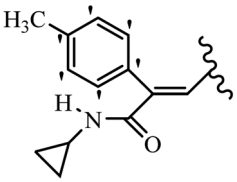
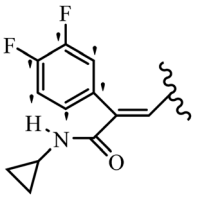
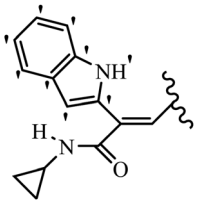
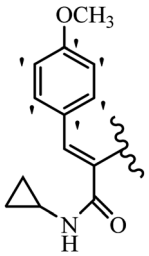
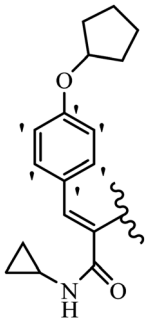
Compounds	R	IC_{50} (nM) HDAC	GI_{50} (μM) NCI-H460	HCT-116	U251
131u		34	0.4	0.5	0.8
131v		30	8	1.8	4
135a		44	0.03	3.5	1.6
139a		5	4	1	2.8
139b		140	—	—	—

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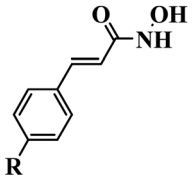
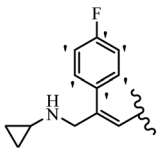
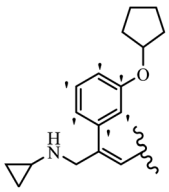
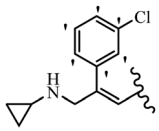
Table 33 (*Contd.*)



(131a-v) (139a,b) (132a-c) (135a-c)

Compounds	R	IC_{50} (nM) HDAC	GI_{50} (μM) NCI-H460	HCT-116	U251
132a		6	0.3	0.02	0.3
132b		600	>100	>100	>100
132c		60	0.2	0.3	0.2

compounds in the 4′-position on the phenyl ring and unsubstituted compounds showed no improvement with an increase in molecular weight (F; **152b** < Br; **152e** < Cl; **152f** < **152d**, H). This implies that the effect of fluorination on the activity of stilbene derivatives cannot be attributed to its effect on lipophilicity but rather to the increase in favorable and specific dipolar interactions. The IC_{50} values of stilbenes substituted with NO_2, CN, CO_2CH_3, OH, and OCH_3 groups supported this hypothesis (**152g**, **152h**, **152i**, **152j**, and **152k**, respectively). Compounds **152k** and **152l** carrying one and four methoxy groups, respectively, reduced the inhibitory activity. Among the *Z*-isomers, compounds **152m**, **152n**, **152o**, and **152p** exhibited no activity compared to the inhibitory activity of stilbenes. It was observed that the introduction of methyl acetate on the linker carbon in **152p** compared to **152o** with a carboxylic acid group in the same position revealed no notable activity on their inhibition potential. The activity studies for compound **152q** indicated that the pyridine ring decreased the inhibitory activity to an excessive range (Table 35).

Katherine *et al.*[77] synthesized stilbene analogues and evaluated their cytotoxicity activity. Compound **185a** showed the highest activity among the synthesized compounds, which was stronger than that of novobiocin against the MCF-7, SK-Br-3, and HCT-116 cell lines. Also, replacing the cyclopropyl linker in compound **182** with a double bond in **181** decreased the activity. The triazole moiety was replaced by a biaryl amide, which resulted in a significant increase in anti-proliferative activity against all the tested cell lines (**185b** *vs.* **185c**). When *N*-methyl-piperidine was replaced with 3-(dimethylamino) propane, the activity decreased as in **185d**, while the activity of **185c** was nearly identical to **185e** against the MCF-7, SKBr3 and HCT-116 cell lines. Interestingly, when *Z*-2-(dimethylamino) ethane was added to the stilbene scaffold, both triazole-containing compounds (**185g** and **185f**) showed improved anti-proliferative activity against all the cell lines. Because **185b** is remarkably less active than the standard, it is clear that the improvement in anti-proliferative activity is due to the triazole moiety replacing the biaryl amide side chain (Table 36).

Duan *et al.*[78] designed stilbene derivatives as LSD1 inhibitors and evaluated their cytotoxicity. Among the synthesized compounds, **190a** and **193a** exhibited the highest activity, and they were more active than ORY-1001. Also, the replacement of the pyridine ring in **190b** with a pyrimidine ring in **190c** intensely reduced the anti-LSD1 activity. In addition, replacing the F in the 3′-position on the pyridine ring of compound **190d** with OH in the same position of **190e** enhanced the activity. Compounds **190f** bearing amine in the 3-position on the phenyl ring showed reduced anti-LSD1 activity comparable to that of **190g** having amidoxime in the same position. However, OH substitution (**190h**, **190i**, and **193b**) led to a dramatic reduction

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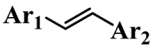
Table 34 Structures of resveratrol derivatives



(143a-i, 144, 147, 149)

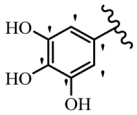
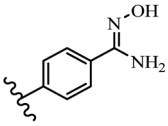
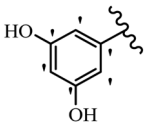
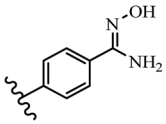
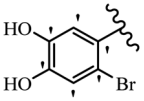
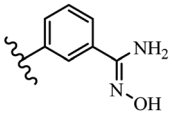
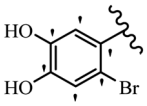
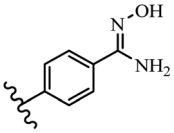
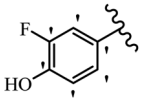
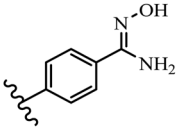
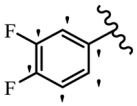
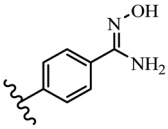
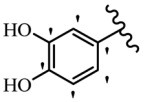
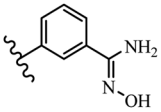
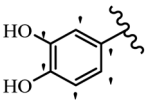
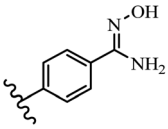
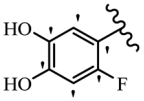
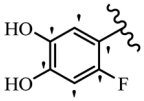
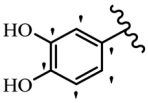
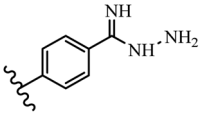
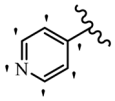
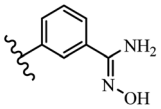
Compound	Ar_1	Ar_2	IC_{50} (μM) LSD1	H3K4me2	CD86 mRNA
143a			—	—	—
143b			—	—	—
143c			0.121	6	7.70
143d			0.123	5.70	9
143e			0.492	—	—
143f			—	—	—
143g			0.333	—	—
143h			0.739	—	—
143i			0.192	—	—
144			—	—	—
147			3.61	—	—

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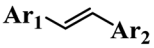
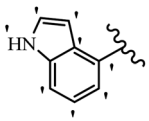
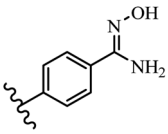
Table 34 (*Contd.*)



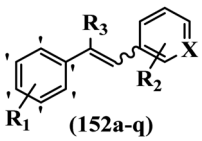
(143a-i, 144, 147, 149)

Compound	Ar_1	Ar_2	IC_{50} (μM) LSD1	H3K4me2	CD86 mRNA
149			—	—	—
Resveratrol	—	—	10.20	—	—
Tranylcypromine	—	—	26.31	—	—

activity. Introducing diverse substituents on the pyridine ring (*e.g.*, **190e**) usually resulted in significantly lower activity compared to no substitution in **190a**. This indicates that substituents at this position are unfavorable. The amidoxime or amino moiety placed in the 3-position on the phenyl ring displayed the highest activity. For example, compounds **190a**, **190f** and **193c** were more potent against LSD1 than the corresponding 4-position-substituted derivatives (**190b** and **193d**). The compounds bearing an OCH_3 group in the 2′-position of the arylbenzene moiety (**190j** and **190k**) showed no activity against LSD1 compared with compounds **190a** and **190f**. It seems that the presence of hydrophilic and small-size groups improved the activity compared to lipophilic and bulk groups, demonstrating the importance of the OH group in maintaining their activities. The synthesized compounds **190a**, **190l**, **193a**, and **193c** with the most potent LSD-inhibitory activity were assessed for their anti-proliferative activities against three MOLM-13, THP-1 and MV-4-11 cell lines. Compound **193a** displayed the best anti-proliferative activity against MOLM-13 and THP-1. Compound **190l** showed fairly higher anti-proliferative activity against MV-4-11, which was more potent than compound **193a** (Table 37).

Singh *et al.*[48] reported the cytotoxicity of resveratrol structural analogues. The compounds showed no cytotoxicity activity against L929. All the compounds showed weaker activity than

Table 35 Chemical structures of *E*/*Z*-stilbene derivatives



(152a-q)

Compound	*E*/*Z*	X	R_1	R_2	R_3	IC_{50} (μM)
152a	*Z*	CH	—	OH	—	5.06
152b	*E*	—	4-F	H	—	79.44
152c	*E*	—	3,5-diF	H	—	56.16
152d	*E*	—	H	H	—	>500
152e	*E*	—	4-Br	H	—	276.56
152f	*E*	—	4-Cl	H	—	319.75
152g	*E*	—	4-NO_2	H	—	360.70
152h	*E*	—	4-CN	H	—	360.70
152i	*E*	—	4-$OCOCH_3$	H	—	>500
152j	*E*	—	4-OH	H	—	17.42
152k	*E*		4-OCH_3	H	—	432.97
152l	*E*	—	4-OCH_3	3,4,5-OCH_3	—	393.99
152m	*Z*	—	4-OCH_3	3,4-OCH_3	COOH	—
152n	*Z*	—	4-OCH_3	4-$OCOCH_3$	COOH	—
152o	*Z*	—	4-OCH_3	3-OCH_3, 4-OH	COOH	—
152p	*Z*	—	4-OCH_3	3-OCH_3, 4-OH	$COOCH_3$	>500
152q	*Z*	N	—	H	—	270.22
Resveratrol	—	—	—	—	—	10.78

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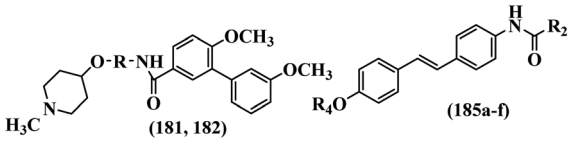
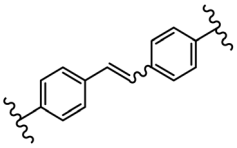
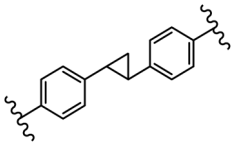
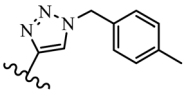
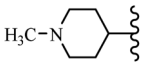
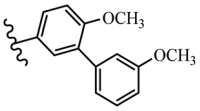
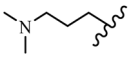
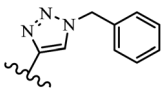
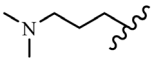
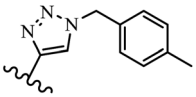
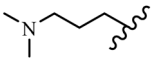
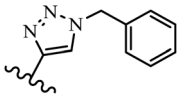
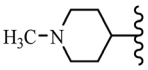
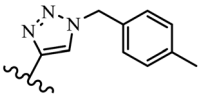
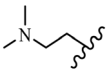
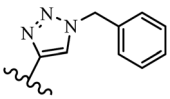
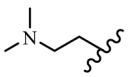
Table 36 Structures of stilbene analogues



Compound	R	R_2	R_4	IC_{50} (μM) MCF-7	SK-Br-3	HCT-116
181		—	—	0.814	0.894	0.801
182		—	—	2.64	1.31	2.90
185a	—			0.092	0.099	0.186
185b	—			5.86	9.68	5.51
185c	—			0.325	0.382	0.350
185d	—			0.494	0.184	0.740
185e	—			0.326	0.231	0.301
185f	—			0.150	0.141	0.179
185g	—			0.234	0.183	0.350
Novobiocin	—	—	—	1.3	0.68	3.68

resveratrol. Compound **194a** exhibited the highest activity against INT407. In addition, the presence of Br on the phenyl ring in **194a** enhanced the activity compared to no substitution in **194b**. According to the results, the compounds with hydrophilic groups on the phenyl rings had a positive effect on cytotoxicity activity (**194c** and **194d**) (Table 38).

Iqbal *et al.*[79] synthesized *E*-stilbene hydrazides and tested their cytotoxicity activity. Analogue **199a** showed the best cytotoxicity activity among the synthesized analogues. It was more potent than doxorubicin against MCF-7. Also, **199b** having a Cl atom in the 4-position exhibited stronger cytotoxicity activity than **199c** bearing an OH group in same position. Moreover, changing its position on the phenyl ring did not change the cytotoxicity activity (**199d** with OH group in 2-position *vs.* **199c**). Likewise, the size of the atom on the phenyl ring did not change the activity (*e.g.*, **199e** and **199f** having a Cl atom and I atom in the 2-position, respectively). All the compounds were more potent than the negative control. Some compounds were stronger than doxorubicin. Analogue **199c** showed higher apoptosis activity than doxorubicin and other compounds.

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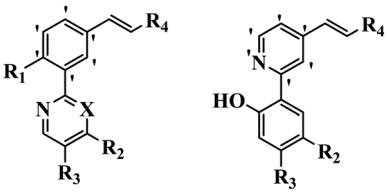
Table 37 Synthetic structures of stilbene derivatives



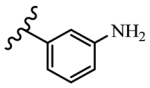
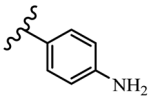
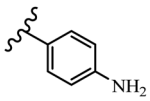
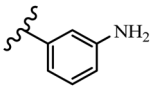
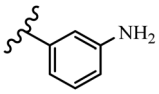
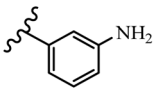
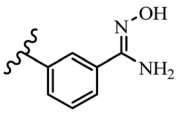
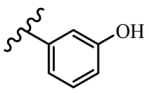
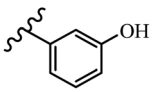
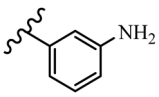
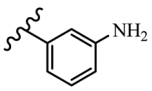
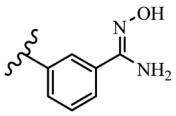
Compound	X	R_1	R_2	R_3	R_4	IC_{50} (μM) LSD1	MOLM-13	THP-1	MV-4-11
190a	—	OH	H	H		0.301	12.51	10.51	10.94
190b	—	OH	H	H		3.57	—	—	—
190c	N	OH	H	H		9.55	—	—	—
190d	—	OH	F	H		—	—	—	—
190e	—	OH	OH	H		1.47	—	—	—
190f	N	OH	H	H		0.859	—	—	—
190g	N	OH	H	H		1.29	—	—	—
190h	—	OH	H	H		4.24	—	—	—
190i	N	OH	H	H		—	—	—	—
190j	—	OCH_3	H	H		—	—	—	—
190k	N	OCH_3	H	H		—	—	—	—
190l	—	OH	H	H		0.72	22.59	7.89	4.71

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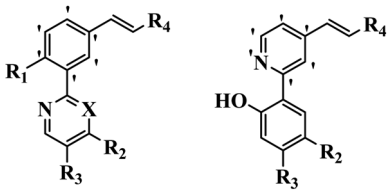
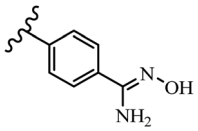
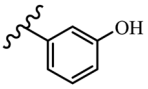
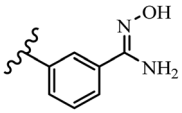
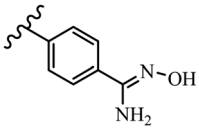
Table 37 (*Contd.*)

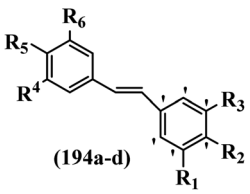


Compound	X	R_1	R_2	R_3	R_4	IC_{50} (μM) LSD1	MOLM-13	THP-1	MV-4-11
193a	—	—	H	F		0.283	8.34	5.76	7.49
193b	—	—	H	H		—	—	—	—
193c	—	—	H	H		0.364	9.05	13.72	15.85
193d	—	—	H	H		0.764	—	—	—
ORY-1001	—	—	—	—	—	11.26	—	>20	—

Substitution of the phenyl ring showed no effect on apoptosis activity (**199g** *vs.* **199e** and **199c**) (Table 39).

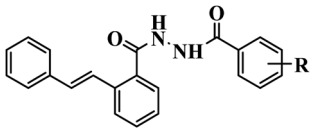
Song *et al.*[21] assessed the cytotoxicity of stilbene derivatives containing a 1,3-benzodioxole moiety. Among the tested compounds, three compounds, **200a**, **200b**, and **200c**, showed activity against HepG-2, but none of them showed activity against the A875 and MARC145 cell lines. These compounds revealed lower activity compared to 5-FU. Also, adding an OCH_3

Table 38 Synthetic compounds of stilbene derivatives



Compound	R_1	R_2	R_3	R_4	R_5	R_6	IC_{50} (μg mL^{-1}) INT 407	L929
194a	H	Br	H	OH	H	OH	28	—
194b	H	H	H	OH	H	OH	38	—
194c	H	OH	H	OH	H	OCH_3	52	—
194d	H	OH	H	OCH_3	H	OCH_3	99	—
Resveratrol	—	—	—	—	—	—	21	—

Table 39 Structure of *E*-hydrazide analogues



Compound	R	MCF-7	Apoptosis (%)
199a	4-NO_2	95	30.09
199b	4-Cl	78	55.98
199c	4-OH	56	80.09
199d	2-OH	60	75.09
199e	2-Cl	86	42.21
199f	2-I	84	48.31
199g	H	73	60.98
Control	—	100	7.30
Doxorubicin	—	62	73.69

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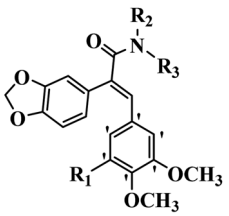
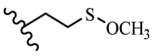
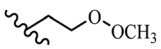
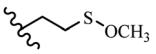
Table 40 Structures of stilbene derivatives containing a 1,3-benzodioxole moiety



(200a-c)

Compound	R_1	R_2	R_3	IC_{50} (μg mL^{-1}) HepG-2	A875	MARC145
200a	H	H		16.53	>40	>40
200b	H	H		22.57	>40	>40
200c	OCH_3	H		25.65	>40	>40
5-FU	—	—	—	9.41	10.66	10.09

group in the 3′-position on the phenyl ring in **200c** showed less activity compared to **200a** with no substitution in the phenyl ring. In addition, large-size and lipophilic groups had a positive effect on activity (**200a** and **200b**, respectively) (Table 40).

Wong *et al.*[80] synthesized stilbene long-chain fatty acid conjugates and assessed their cytotoxicity. Among the compounds, **203a** and **206a** exhibited the highest activity and they were stronger than colchicine against the KB-3-1b, NCI-H460c, and HEK-293 cell lines. All the compounds showed weaker cytotoxicity activity compared to colchicine against MCF-7. *E*-Stilbenes showed lower cytotoxicity than the *Z*-isomer (**206b** *vs.* **206c**) against all four cell lines. Moreover, stilbene **206d** showed considerably decreased cytotoxicity compared to compound **206e** against the HEK-293 cell line. Compound **206f** showed higher activity than **206g** on all the tested cell lines. Compounds **206d** and **206h** exhibited weak activity against all the tested cell lines (Table 41).

Das *et al.*[81] synthesized and tested stilbene-linked 1,2,3-triazoles against six cell lines. All the synthesized compounds showed lower cytotoxicity activity than docetaxel and staurosporine against the HCT-116, Capan-1, K-562, DND-41, Z-138, and NCI-H460 cell lines. Compounds **213a** and **b** exhibited the highest activity among them against the HCT-116, Capan-1, and NCI-H460 cell lines. Furthermore, the replacement of the OCH_3 group in **213c** with a Cl atom in **213d** resulted in lower activity against NCI-H460, HCT-116, and Capan-1. It seems that hydrophilic groups displayed stronger activity than lipophilic groups. In addition, no substitution in **213e** exhibited better activity compared to substitution on the phenyl ring in **213f** against the Capan-1, NCI-H460, DND-41, and K-562 cell lines. Also, the presence of EDG compared to EWG on the phenyl or benzyl ring had a positive effect on cytotoxicity against Capan-1, HCT-116, and NCI-H460 (*e.g.*, **213g** *vs.* **213h**) (Table 42).

4. Liver enzyme inhibitors

Kim *et al.*[82] synthesized *E*-stilbene analogues and evaluated their inhibitory activity on human CYP1A1, CYP1A2, and CYP1B1. Compound **216a** displayed the highest inhibitory activity on CYP1A1, CYP1A2, and CYP1B1. This compound was also more potent than oxyresveratrol. Replacing the OH groups of oxyresveratrol with OCH_3 groups in **216b** improved the inhibitory activity and produced deep variations in selectivity against CYP1A1, CYP1A2, and CYP1B1. A change in the position of the OCH_3 groups on the phenyl ring of compounds **216c** (in 3′-, 4′- and 5′-positions), **216d** (in 3′- and 5′-positions), **216e** (in 3′- and 4′-positions), and **216f** (in 4′-position) resulted in a decrease in potency and selectivity. These findings suggested that the precise location of the OCH_3 groups is a critical feature for selectivity. When the ethylene linker of compound **216b** was replaced with an amide or an imine linker (**220** and **218**), there was no remarkable inhibitory activity on CYPs. In another modification, the phenyl ring was replaced with 4-pyridyl and 3-furanyl rings (**216g** and **216h**), which reduced the activity compared to other compounds. However, **216a** with 2-thiophenyl exhibited the highest inhibitory activity on CYPs, while none of them was as selective as **216b**. Therefore, replacing the OCH_3 group in the 2′-position on the phenyl ring of **216b** with an OH or F in compounds **216i** and **216j** showed less inhibitory activity on CYP1A1, CYP1A2, and CYP1B1, respectively. Also, the presence of lipophilic groups and EWG in **216j** showed higher inhibitory activity than hydrophilic groups and EDG in **216i** (Table 43).

Das *et al.*[83] synthesized pinacolyl boronate-substituted stilbenes and tested them as lipogenic inhibitors. Among the synthesized compounds, **227a** showed the highest lipogenic inhibitory activity, which was greater than that of DMSO. Compound **227b** exhibited the lowest activity among the compounds, which was equal to that of DMSO. Also, replacing the OCH_3 group in the 4′-position on the phenyl ring with an OH group in the same position decreased the activity (**227a** *vs.* **227b**). It seems that the hydrophilic group had a positive effect on activity. In addition, the presence of an OH group in the 6′-position on the phenyl ring in **227c** displayed almost equal activity compared to **227d** (Table 44).

Mikstacka *et al.*[23] synthesized *E*-resveratrol analogues and evaluated their inhibitory activity on some CYPs. Among the synthesized compounds, **226a** and **226b** showed the highest inhibitory activity against CYPs. Also, shifting the OCH_3 group in the 4′- to 5′-position on the phenyl ring reduced the activity (**226c** *vs.* **226d**) on CYP1A1 and CYP1A2. In contrast, **226d** had better inhibitory activity than **226c** on CYP1B1. Compounds having substituents in the 2′- and 4′-positions showed higher affinity to the CYP1A2 active site (**226c**). However, based on the results, CYP1A2 is the most sensitive to changes in the design of methoxy substituents. Compound **226e** with OCH_3 groups in the 3′-, 4′-, and 5′-positions on the phenyl ring did not reduce the affinity of these three OCH_3 groups on the phenyl ring to CYP1A2, but it significantly increased the inhibitory potency against CYP1A1 and CYP1B1. In addition, increasing the

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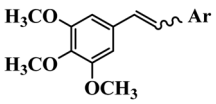
Table 41 Structures of stilbene long-chain fatty acid conjugates



(203a, 206a-h)

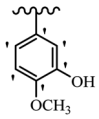
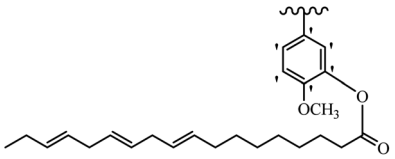
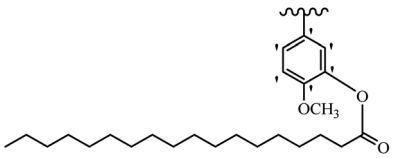
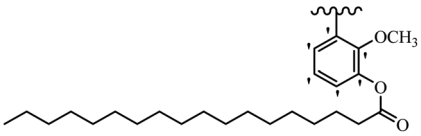
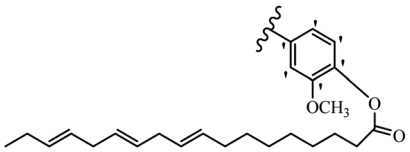
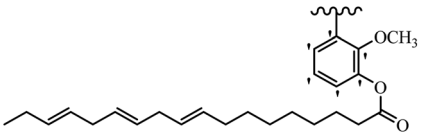
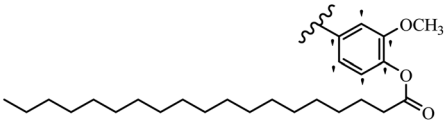
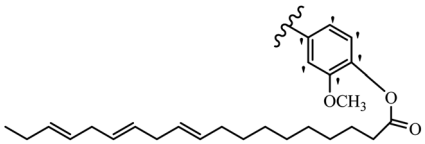
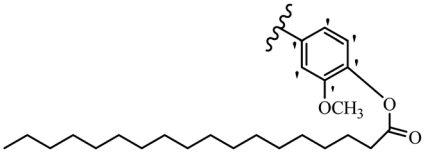
Compound	*E*/*Z*	Ar	IC_{50} (μM)			
			KB-3-1	NCI-H460	HEK-293	MCF-7
203a	*Z*		0.01	0.01	0.01	0.09
206a	*Z*		0.03	0.01	0.023	>10
206b	*Z*		0.03	0.03	0.03	0.24
206c	*E*		>10	>10	2.90	>10
206d	*E*		>100	>100	>100	>100
206e	*E*		2.40	>10	2.40	>10
206f	*Z*		3.10	>10	3.90	7.70
206g	*Z*		>100	>100	>100	>100
206h	*E*		>100	>100	>100	>100
Colchicine	—	—	0.02	0.06	0.02	0.06

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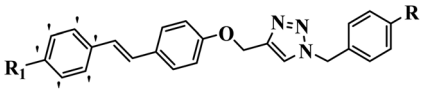
Table 42 Chemical structures of stilbene-linked 1,2,3-triazoles



(213a-h)

Compounds	R_1	R	IC_{50} (μM)					
			Capan-1	HCT-116	NCI-H460	DND-41	K-562	Z-138
213a	F	NO_2	40.2	12.2	11.6	>100	>100	>100
213b	F	H	30.7	46.7	31.7	>100	>100	>100
213c	OCH_3	H	55.3	13.5	35.1	>100	>100	>100
213d	Cl	H	96.4	36.1	>100	>100	19.3	>100
213e	H	H	46.7	29.1	34.3	61.4	39.9	>100
213f	H	NO_2	>100	26.1	78.5	82.1	>100	>100
213g	CH_3	CH_3	52.4	87.4	60.8	>100	>100	>100
213h	F	CH_3	73.4	>100	>100	>100	>100	>100
Docetaxel	—	—	0.0063	0.0008	0.0001	0.0019	0.0034	0.0019
Staurosporine	—	—	0.0046	0.0003	0.0032	0.0064	0.0298	0.0003

number of OCH_3 groups on the phenyl ring improved the inhibitory activity (**226d** *vs.* **226f**). The results showed that the EWG and lipophilic groups had better activity compared to EDG and hydrophilic groups (Table 45).

Mikstacka *et al.*[24] designed *E*-stilbene derivatives and evaluated their inhibitory activity on CYP450. The synthesis method in this study was described in a previous report.[18] Compounds **227a** and **b** showed the highest activity on CYP1A1, CYP1A2, and CYP1B1 among the synthesized compounds. All the compounds strongly inhibited CYP1A1 activity. Compound **227b** was a selective inhibitor of CYP1B1, showing a 90-times higher selectivity for CYP1B1 over CYP1A1 and 830-times higher selectivity for CYP1B1 over CYP1A2. In addition, moving the OCH_3 group in the 3′- to the 5′-position on the phenyl ring enhanced the CYP1A1 inhibition activity (**227c** *vs.* **227d**). Adding an OCH_3 group in the 3′-position on the phenyl ring in **227b** produced **227e**, which exhibited lower activity against CYP1A1, CYP1A2, and CYP1B1. Moreover, attaching an OCH_3 group in the 4′-position on the phenyl ring in **227f** showed stronger activity than **227a** against CYP1A2. In contrast, **227a** and **227f** showed almost equal activity for CYP1A1 and CYP1B1. Also, increasing the number OCH_3 groups on the phenyl ring had a negative effect on activity (*e.g.*, **227e** and **227g**). In addition, changing the position of the OCH_3 group on the phenyl ring in **227f**, **227d**, and **227c** improved the inhibitory activity against CYP1A1. Therefore, according to the results, the activity followed the order of 6′ > 5′ > 4′ (Table 46).

Wierzchowski *et al.*[84] tested *E*-methylthio stilbene derivatives as CYP450 inhibitors. The synthesis method of this study is mentioned in the previous study.[23] All the tested compounds inhibited the CYP1A1 and CYP1B1 activities, but only moderately inhibited CYP1A2. Compounds **228a–c** showed the highest activity and they were stronger than the standard α-naphthoflavone on CYPs. Also, the addition of an OCH_3 group in the 3′-position on the phenyl ring of **228c** enhanced the inhibitory activity compared to no substitution in **228d**. According to the results, both hydrophilic and lipophilic groups on both phenyl rings improved the inhibitory activity (Table 47).

5. Anti-Alzheimer's activity

One of the most common neurodegenerative diseases is Alzheimer's disease (AD). It is assessed that there is one new case of dementia every 3 seconds around the world. Fifty million people worldwide were living with dementia in 2018, and this number is rapidly increasing in countries with an aging population.[85] Although the biology of AD is very complex and not completely determined, some factors such as abnormal Aβ appearance and buildup, reduction of acetylcholine (ACh), tau hyperphosphorylation, dyshomeostasis of biometals, and oxidative stress have been determined to play significant roles in the pathophysiology of AD.[86] In this case, resveratrol has health functional properties in neuronal degenerative pathologies such as AD.[87] Trans-resveratrol and *trans*-piceatannol exhibited a good binding mode *in silico* against AChE. Scirpusin A and cassigarol E displayed inhibitory potential against butyrylcholinesterase (BChE) and AChE compared to tacrine and donepezil.[88]

Lu *et al.*[89] synthesized resveratrol derivatives and tested their Aβ-aggregation inhibitory activity. Compound **233a** showed the highest inhibitory effect on Aβ fibrillization among the synthesized compounds. This compound exhibited stronger activity than curcumin and equal activity to resveratrol. Likewise, changing the position of the dimethylamino group in **233b** from the 2′- to 4′-position on the phenyl ring in compound **233c** resulted in increased activity. Among the four substituted groups (dimethylamino groups; **233a**, pyridyl; **233d**, Br; **233e** and alkyl; **233f**), the dimethylamino group showed the best result. In addition, the inhibitory activity of **237g** was not significantly changed when the dimethylamino group was replaced with one- or two-substituted amino groups. Also, replacing the OCH_3 groups in the 3- and 5-positions on the

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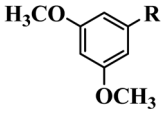
Table 43 Structures of *E*-stilbene analogues



(216a-j, 218, 220)

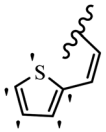
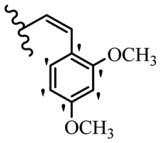
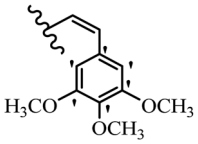
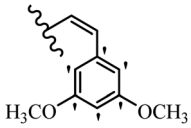
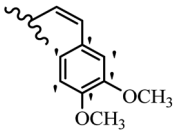
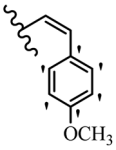
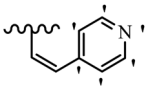
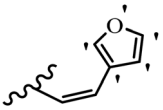
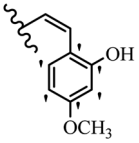
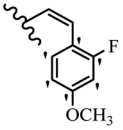
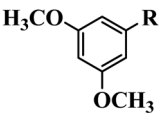
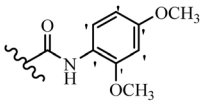
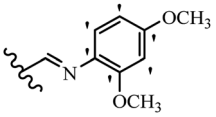
Compound	Ar	IC_{50} (nM) 1A1	1A2	1B1
216a		61	11	2
216b		300	3100	6
216c		140	930	3200
216d		920	198 000	17 600
216e		750	570 000	3000
216f		830	6200	790
216g		1100	290	460
216h		6600	740	2100
216i		980	31 100	390
216j		610	5800	97

Table 43 (*Contd.*)



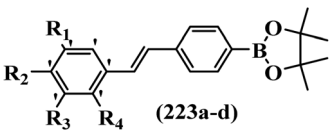
(216a-j, 218, 220)

Compound	Ar	IC_{50} (nM) 1A1	1A2	1B1
218		1500	64 000	670
220		300	>2 × 106	4900
Oxyresveratrol	—	15 000	150 000	34 000

phenyl rings of **232a** compared to **233c** with an OH group in the same position reduced the inhibitory activity. These findings suggested that hydrogen bonds play an important role in the interaction of polyphenols and proteins. Compound **233h**, whose carbon–carbon double bond is reduced compared to the structure of compound **233c**, demonstrated lower activity (Table 48).

Andhare *et al.*[90] designed *E*-distyrylbenzenes and tested their activity against Alzheimer's disease. Compound **236a** showed the highest activity against Aβ-aggregation. Also, changing the position of the nitrostyrylbenzene moiety from the 3-position in **236b** to the 4-position on the phenyl ring in **236c** enhanced the activity. Likewise, the presence of substitution on the phenyl ring between two phenyl stilbene rings decreased the activity (**239a** and **239b**). In addition, replacing the biphenyl ring in **239c** with a phenyl ring in **239d** reduced the activity. Moreover, compound **236d** exhibited the highest inhibitory activity against

Table 44 Structure of analogues of pinacolyl boronate-substituted stilbenes



(223a-d)

Compound	R_1	R_2	R_3	R_4	FAS relative mRNA level
223a	H	OH	H	H	0.39
223b	H	OCH_3	H	H	1.0
223c	Cl	H	Cl	OH	0.57
223d	Cl	H	Cl	H	0.58
DMSO	—	—	—	—	1.0

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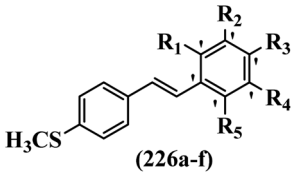
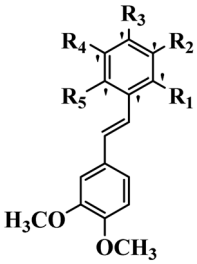
Table 45 Synthetic structures of *E*-resveratrol analogues



(226a-f)

						IC$_{50}$ (μM)		
Compound	R_1	R_2	R_3	R_4	R_5	CYP1A1	CYP1A2	CYP1B1
226a	OCH_3	H	OCH_3	H	OCH_3	0.4	6.5	0.5
226b	Cl	H	H	H	H	1.0	14.5	0.3
226c	OCH_3	H	OCH_3	H	H	2.4	8.1	2.0
226d	OCH_3	H	H	OCH_3	H	3.8	39.5	1.1
226e	H	OCH_3	OCH_3	OCH_3	H	3.6	7.0	2.6
226f	OCH_3	H	OCH_3	OCH_3	H	0.8	15.0	0.9

Table 46 Structures of *E*-stilbene derivatives



(227a-g)

						IC$_{50}$ (μM)		
Compound	R_1	R_2	R_3	R_4	R_5	CYP1A1	CYP1A2	CYP1B1
227a	OCH_3	—	—	—	OCH_3	0.23	2.31	0.31
227b	OCH_3	—	—	—	—	0.36	3.32	0.0040
227c	OCH_3	OCH_3	OCH_3	—	—	5.18	>100	4.17
227d	OCH_3	—	OCH_3	OCH_3	—	1.78	>100	4.44
227e	OCH_3	OCH_3	—	—	—	0.45	16.02	0.37
227f	OCH_3	—	OCH_3	—	OCH_3	0.27	>100	0.30
227g	OCH_3	—	—	OCH_3	—	0.50	>100	0.62

AChE. Compound **236c** showed better activity compared to **236b**. According to the results, the presence of both lipophilic and hydrophilic groups enhanced the activity (**236a**, **236e**, and **236f** and **236d**) against Aβ-aggregation and AChE (Table 49).

Patel *et al.*[86] designed carbazole-stilbene hybrids and tested their anti-Alzheimer's activity. Among the compounds, **245a** against hAChE and **246a** against EqBuChE showed the highest activity. These compounds were weaker than tacrine and donepezil. They were also stronger than *E*-9-ethyl-3-styryl-9*H*-carbazole against hAChE and EqBuChE. In the first series, comparing the compounds with piperidine rings (**245a**, **245b**, and **245c**), compound **245a** ($n = 4$) showed the best inhibitory activity against AChE, while compounds **245b** ($n = 3$) and **245c** ($n = 2$) exhibited the weakest inhibitory activity. A similar pattern was seen for the compounds with pyrrolidine rings (**245d**, **245e**, and **245f**). Compound **245b** exhibited the strongest inhibitory activity against BuChE among them. When the pyrrolidinyl ring in **246b** and piperidinyl ring in **246c** were attached directly to provide urea derivatives, the inhibitory effect against both enzymes was reduced, particularly compared to the first series. When amide linkers (*e.g.*, **245d**) were replaced with urea linkers (*e.g.*, **246d**), there was no significant change in inhibitory activities. In the second series, a comparison of the inhibitory potential of compounds **251a**, **251b**, and **251c** with a pyrrolidine ring revealed that compound **246b** ($n = 2$) had the best profile of AChE and BuChE inhibitory activity, whereas compounds **251a** ($n = 1$) and **251c** ($n = 3$) showed slightly lower AChE and BuChE inhibitory activities. All the urea derivatives inhibited ChEs the

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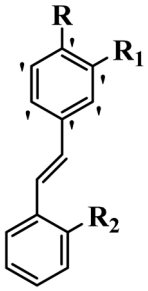
Table 47 Chemical structures of *E*-methylthio stilbene derivatives



(228a-d)

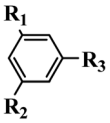
Compound	R	R_1	R_2	IC_{50} (μM) CYP1A1	CYP1A2	CYP1B1
228a	SCH_3	H	OCH_3	0.076	8.38	0.034
228b	OCH_3	OCH_3	SCH_3	0.76	3.54	0.029
228c	OCH_3	OCH_3	OCH_3	0.36	4.93	0.0034
228d	OCH_3	H	OCH_3	0.75	4.13	0.066
ANF	—	—	—	0.012	0.0038	0.0013

most, while compounds **252a** and **252b**, in which the heterocyclic amine was directly attached to form urea, inhibited them the least. When the amide linkers in compound **251d** were replaced with urea linkers in compound **252c**, there was no significant change in AChE inhibitory activity, but the BuChE inhibitory activity increased by 2-times. All the thiourea derivatives demonstrated excellent inhibitory activity against ChEs. Among them, compound **252e** ($n = 2$) was conferred with the highest inhibitory activity against AChE and BuChE. Then, the $A\beta_1$–β_2-aggregation inhibition activity was tested. Compound **252d** showed the highest activity among the compounds, which was better than curcumin. Almost all the compounds showed relatively similar $A\beta_1$–β_2-aggregation inhibitory activity. According to the results, lipophilic groups improved the activity against AChE, BuChE, and $A\beta_1$–β_2-aggregation (Table 50).

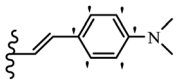
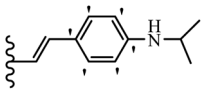
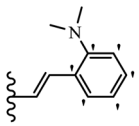
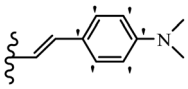
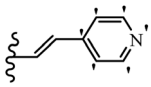
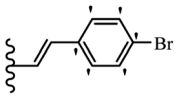
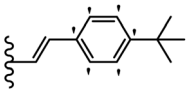
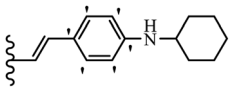
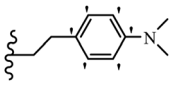
6. Antioxidant activity

The imbalance in antioxidant reactions caused by the buildup of free radicals in the body and oxidation results in oxidative stress.[91] The highest free radicals in cells, mostly formed by mitochondria, are produced by reactive oxygen species (ROS).[92] Excess ROS disturb metabolic function, break down cells and tissues, and lead to diverse health problems.[93] Antioxidants are a group of compounds that aid in neutralizing and trapping free radicals, and thus they can reduce the harm to the body caused by free radicals.[94,95] Natural phenolic derivatives are a vital group of antioxidants investigated and widely used in the nutritional and biopharmaceutical fields to inhibit oxidation processes.[96] Stilbenes, as polyphenolic compounds,[97] possess interesting antioxidant activity.[96] The hydroxy group is important for antioxidant activity, which can be due to the stabilization *via* resonance in the double-bond linker.[98] Resveratrol

Table 48 Structures of resveratrol derivatives



(232a, 233a-h)

Compound	R_2	R_2	R_3	Inhibition percent (%) Aβ-aggregation
232a	OCH_3	OCH_3		7.02
233a	OH	OH		71.65
233b	OH	OH		59.40
233c	OH	OH		65.20
233d	OH	OH		13.56
233e	OH	OH		25.23
233f	OH	OH		43.56
233g	OH	OH		65.50
233h	OH	OH		48.54
Resveratrol	—	—	—	69.73
Curcumin	—	—	—	52.77

exhibited antioxidant activity in tumor initiation, promotion and progression, disturbing its progression by blocking the S and G2 phases of the cell cycle.[99]

Jung *et al.*[15] synthesized *E*-stilbene derivatives and evaluated their antioxidant activity. The synthesis method of this study was mentioned in a previous study.[44] Most of the compounds showed equal antioxidant activity to resveratrol. Compounds **253a** and **253b** exhibited the highest antioxidant activity among the synthesized compounds. These compounds were also better than resveratrol. Compound **253c** with an *N*-tetrahydrofuran-2-ylmethyaminocarbonyl moiety in the 4′-position on the phenyl

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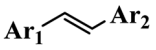
Table 49 Chemical structures of *E*-distyrylbenzenes



(236a-f, 239a-d)

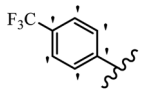
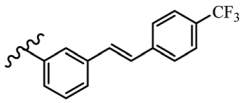
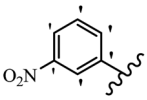
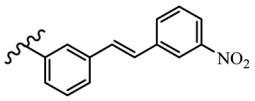
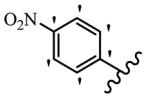
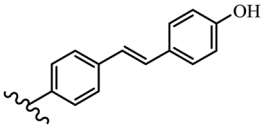
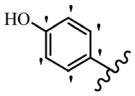
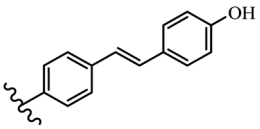
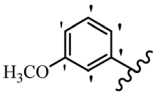
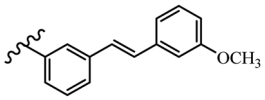
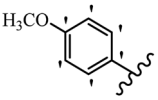
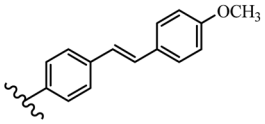
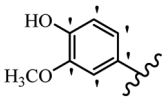
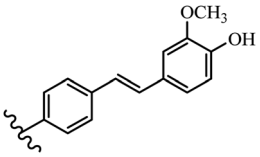
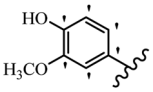
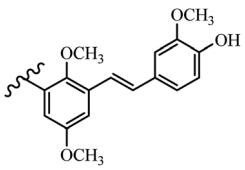
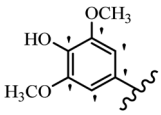
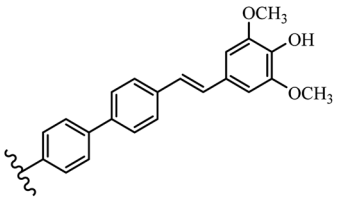
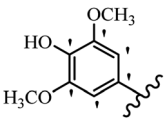
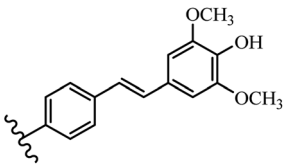
Compound	Ar_1	Ar_2	Aβ-aggregation (μM)	AChE (μM)
236a			40	100
236b			75	180
236c			55	610
236d			45	70
236e			100	55
236f			65	80
239a			35	40
239b			70	40
239c			55	80
239d			45	80

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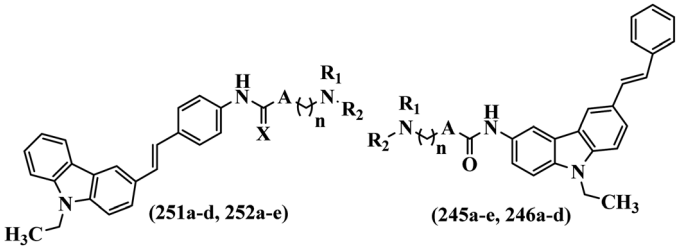
Table 50 Synthetic compounds of carbazole–stilbene derivatives



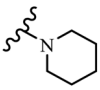
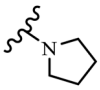
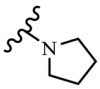
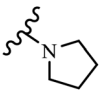
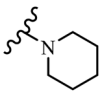
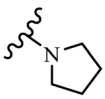
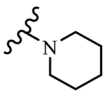
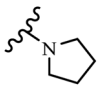
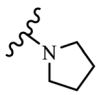
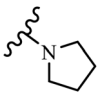
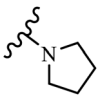
Compound	n	X	A	NR_1R_2	IC_{50} (μM) hAChE	IC_{50} (μM) EqBuChE	Inhibition percent (%) $A\beta_1$–β_2-Aggregation
245a	4	—	—		1.84	2.51	48.09
245b	2	—	—		4.96	1.40	52.08
245c	3	—	—		3.54	2.56	49.88
245d	2	—	—		3.00	1.53	42.72
245e	3	—	—		2.91	1.51	53.92
245f	4	—	—		2.63	3.17	46.72
246a	3	—	NH		3.57	1.02	54.35
246b	—	—	—		6.63	4.48	17.58
246c	—	—	—		5.99	5.01	21.55
246d	2	—	NH		2.65	1.70	52.29
251a	1	O	—		2.98	2.49	51.14
251b	2	O	—		2.36	1.46	54.27
251c	3	O	—		4.77	4.76	53.08

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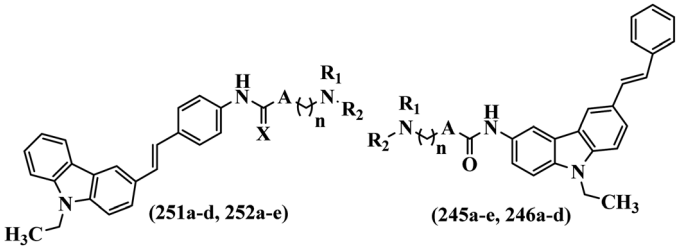
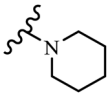
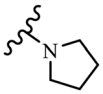
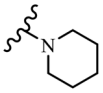
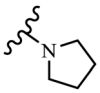
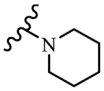
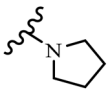
Table 50 (*Contd.*)



Compound	n	X	A	NR_1R_2	IC_{50} (μM) hAChE	IC_{50} (μM) EqBuChE	Inhibition percent (%) $A\beta_1$–β_2-Aggregation
251d	3	O	—		3.29	2.11	49.78
252a	—	O	—		16.22	11.65	42.84
252b	—	O	—		12.37	8.58	44.15
252c	2	O	NH		4.71	2.32	38.90
252d	2	O	NH		3.13	1.20	55.79
252e	2	S	NH		2.64	1.29	51.29
CS-1	—	—	—	—	>100	>100	27.52
Tacrine	—	—	—	—	0.056	0.008	—
Donepezil	—	—	—	—	0.023	1.87	—
Curcumin	—		—	—	—	—	(IC_{50} = 20.43 μM)

ring showed lower activity compared to **253d** having *N*-furan-2-ylmethylaminocarbonyl in the same position. In addition, the presence of *N*-(3-ethoxycarbonylphenyl)aminocarbonyl of **253e** showed higher antioxidant activity than **253f** with no substitution in the same position. The results showed that acyclic amine moieties displayed higher radical-scavenging activity than the cyclic amine moieties in the 4′-position on the phenyl ring (*e.g.*, **253b**, and **253g**). Also, the presence of an aromatic ring compared to an aliphatic ring reduced the activity (**253f** and **253h**) (Table 51).

Lu *et al.*[89] investigated the antioxidant activity of resveratrol compounds. Among the compounds, **254a** demonstrated the highest antioxidant activity, which was comparable to that of resveratrol. Furthermore, a secondary amine in the 4-position on the phenyl ring of **254b** and **254c** displayed higher antioxidant activity than a tertiary amine in **254d** in the same position. The findings indicated that the amine groups in the 4-position on the phenyl ring play a significant role in the antioxidant effect. According to the results, the presence of two propyl chains on the tertiary amine and cyclohexyl ring on the secondary amine resulted in an increase in antioxidant activity (**254e** and **254f**) (Table 52).

Patel *et al.*[86] designed carbazole–stilbene hybrids and evaluated their antioxidant activity. Most of the compounds exhibited weak activity. Among them, **255a** showed the highest activity, but weaker activity than ascorbic acid. In addition, replacing the sulfur atom with oxygen increased the antioxidant activity (**255b** *vs.* **255c**). It seems that increasing the atom size and lipophilic groups improved the antioxidant activity. The other compounds showed almost equal activity (Table 53).

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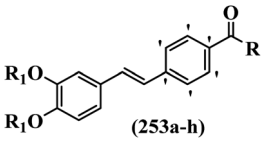
Table 51 Synthetic compounds of *E*-stilbene derivatives



(253a-h)

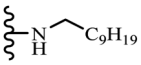
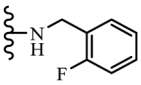
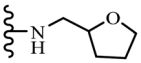
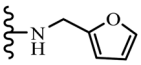
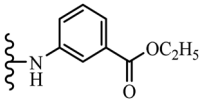
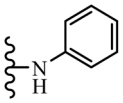
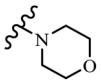
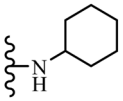
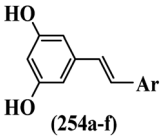
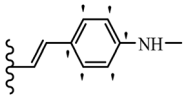
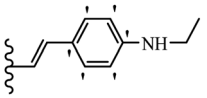
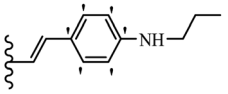
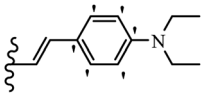
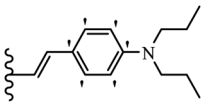
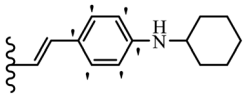
Compound	R	R_1	IC_{50} (μM) Antioxidant activity
253a		H	47.87
253b		H	43.59
253c		H	>200
253d		H	69.0
253e		H	126.63
253f		H	>200
253g		H	>200
253h		H	127.93
Resveratrol	—	—	>200

Table 52 Structures of resveratrol derivatives



(254a-f)

Compound	Ar	ORAC
254a		5.54
254b		5.19
254c		4.33
254d		3.31
254e		2.23
254f		2.25
Resveratrol	—	5.92

7. Antidiabetic activity

Diabetes mellitus is an endocrine metabolic disorder identified by abnormal levels of glucose in the blood stream. Chronic hyperglycemia can cause severe long-term problems including kidney failure, cardiovascular disease, and nerve damage.[100] In this case, resveratrol and rosewood exhibited anti-diabetic activity.[101] Also, stilbenes showed potent inhibitory activity against α-glucosidase.[102,103] In mice nourished by a high-fat diet, they improved the insulin resistance. Resveratrol is also known to regularize hyperglycemia, and significantly improve hyperinsulinemia in diet-induced obese and diabetic mice.[104]

Jung *et al.*[105] synthesized stilbene derivatives and tested their inhibitory activity against protein tyrosine phosphatase 1B (PTP1B). Compound **270a** showed the highest inhibitory activity against PTP1B. It was more potent than molybdate and RK-682. Also, replacing alcohol and aldehyde in **263a** and **264a** instead of methyl ester in **262** reduced the activity. Modifying the molecular structure of a compound by extending a conjugated system within it, from compound **262** to **270a**, resulted in more potent inhibition of PTP1B. However, 3′,4′-dihydroxycinnamic acid **272** and its amide analogs, **274a** and **274b**, exhibited no activity. This indicated that the phenyl ring linked by the double bond is essential for PTP1B inhibition. According to the findings, it seemed that the OH groups in the 3′- and 4′-positions on the phenyl ring and EWGs in the 2- and 4-positions on the phenyl ring, such as ester (**262** and **270a**), aldehyde (**264b**), nitro (**276a** and **276b**) and amides (**264a**) of *E*-stilbene analogues enhanced the inhibitory effect against PTP1B. It is important that *E*-isomers (**270a**) are relatively more potent than *Z*-isomers (**271a**), which may be due to their binding appropriateness to the PTP1B active site (Table 54).

Mizuno *et al.*[106] studied pterostilbene analogues for peroxisome proliferator-activated receptor α (PPARα) activation. The NO_2 group in compounds *E*/*Z*-**280a** and NH_2 group in *E*/*Z*-**281a** in the 4-position on the phenyl ring remarkably activated PPARα. Among the *Z*-isomers, compound **280c** having an OCH_3 group in the 4-position on the phenyl ring had significant activity as a PPARα agonist (>2-times). The introduction of an ester group (**280b** having $COOCH_3$ in the 4-position on the phenyl ring) also resulted in an improvement in activity (>2-

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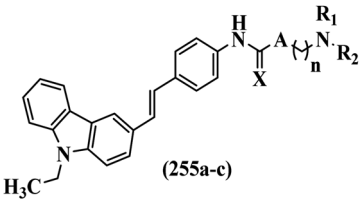
Table 53 Structures of carbazole–stilbene hybrids



(255a-c)

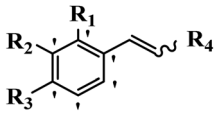
Compound	n	X	A	NR_1R_2	Inhibition percent (%) DPPH
255a	2	S	NH		72.36
255b	3	O	NH		45.95
255c	3	S	NH		70.36
Ascorbic acid	—	—	—	—	98.25

times). To study the role of the vinyl double bond of pterostilbene in the activation of PPARa, saturated compound **283a** was evaluated. Saturation of the double bond changed the conformation of the molecule, resulting in the loss of activity. The most active compound in this series was phosphate derivative **283a**. This displayed that the addition of an acidic group resulted in greater activity. It is possible that **283a** with dihydrogen phosphate in the 4-position on the phenyl ring acts as a prodrug, resulting in the observed increase in activity. In general, compounds *E*-**280b** and *E*/*Z*-**280c** bearing an OCH_3 group in the 4-position on the phenyl ring were also more effective at activating PPAR than ciprofibrate. Considering compounds **280a–c**, **281a** and **b**, and **283a**, having OCH_3 groups in the 3- and 5-positions on the phenyl ring, showed that presence of different groups at the 4′-position determined the activity; thus, methoxy, ester, and phosphate are preferable. Compound **289a** with OH groups in the 3- and 5-positions on the phenyl ring did not show significant PPAR activation. Compound **289b** with an OCH_3 group in the 4′-position on the phenyl ring showed activation on PPARα (>2-times), indicating that the OH groups in the 3- and 5-positions on the phenyl ring are highly effective for activity. The data indicated that the *E*-isomer is more favorable than the *Z*-isomer for activating PPARα (Table 55).

8. Miscellaneous studies

Jung *et al.*[107] described the synthesis of stilbene compounds and assessed their antimalarial activity. The synthesis method of this research is similar to that in previous research.[105] Among the synthesized compounds, **290a** and **b** exhibited the highest

Table 54 Structures of stilbene derivatives



(262, 263a, 264a,b, 270a, 272, 274a, b, 271a, 276a,b)

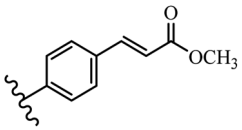
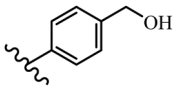
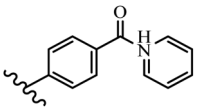
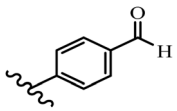
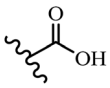
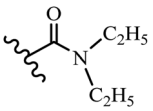
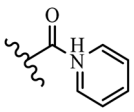
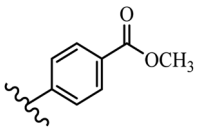
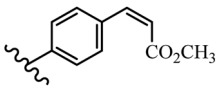
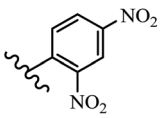
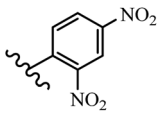
Compound	*E*/*Z*	R_1	R_2	R_3	R_4	IC_{50} (μM) PTP1B
270a	*E*	—	OH	OH		14.9
263a	*E*	—	OH	OH		260
264a	*E*	—	OH	OH		27.2
264b	*E*	—	OH	OH		101
272	—	—	OH	OH		—
274a	—	—	OH	OH		—
274b	—	—	OH	OH		—
262	*E*	—	OH	OH		25.6
271a	*Z*	—	OH	OH		—
276a	*E*	—	OH	OH		190
276b	*E*	OH	OH	—		168
Molybdate	—	—	—	—	—	21
RK-682	—	—	—	—	—	45

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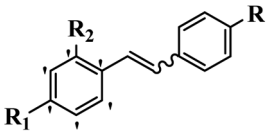
Table 55 Synthetic compounds of pterostilbene analogues



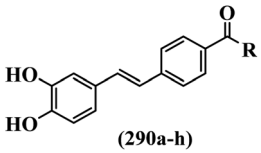
(280a,b, 281a,b, 283a,b, 289a,b)

Compound	*E*/*Z*	R	R_1	R_2
280a	*E*	NO_2	OCH_3	OCH_3
280a	*Z*	NO_2	OCH_3	OCH_3
280b	*E*	$COOCH_3$	OCH_3	OCH_3
280b	*Z*	$COOCH_3$	OCH_3	OCH_3
280c	*E*	OCH_3	OCH_3	OCH_3
280c	*Z*	OCH_3	OCH_3	OCH_3
281a	*E*	NH_2	OCH_3	OCH_3
281a	*Z*	NH_2	OCH_3	OCH_3
281b	*E*	COOH	OCH_3	OCH_3
281b	*Z*	COOH	OCH_3	OCH_3
283a	*E*	OPO_3H_2	OCH_3	OCH_3
283b	*E*	OH	OCH_3	OCH_3
289a	*Z*	OCH_3	OH	OH
289b	*E*	OCH_3	OH	OH

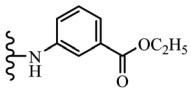
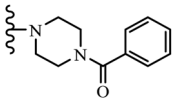
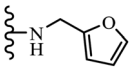
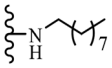
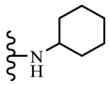
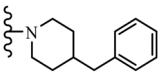
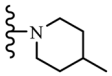
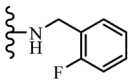
activity, and they were stronger than resveratrol, while they had lower activity compared to chloroquine. Compounds **290a** and **b** were significantly more active than **290c**, which had *N*-(furan-2-ylmethyl)aminocarbonyl. When the carbon chain was replaced with cycloalkane or aromatic ring, the activity was enhanced (*e.g.*, **290d** and **290e**). Also, the presence of *N*-(4-benzylpiperidine)carbonyl in **290f** resulted in lower activity compared to **290g**. In addition, **290c** compared to **290h** having *N*-(2-fluorobenzyl)aminocarbonyl showed a decrease in activity (Table 56).

Kang *et al.*[108] synthesized resveratrol analogues and reported their inhibitory activity against COX-1, COX-2, and NF-κB. Compounds **294a** against COX-1, **294b** against COX-2, and **294c** against NF-κB showed the highest activity among the analogues and they were stronger than resveratrol. All the potent COX-1 inhibitors contained a resorcinol ring, although in **294d**, the OH is replaced by OCH_3 groups. This trend, combined with the observation that the two resveratrol derivatives **294e** and **294f** are equipotent, suggests that for resveratrol to bind COX-1, both rings must rotate out of the plane of the alkene. Analogues **294d**, **294e**, and **294f** displayed potent inhibition against COX-1 and COX-2. This hypothesis is also supported by the SAR, where **294a** with C_2H_5 on carbon number one linker on the alkene was the most potent COX-1 inhibitor, whereas **294g**, which lacked a C_2H_5 substituent on the alkene, was 100-times less active. Although most of the active compounds had EDG in the R_1 position (*e.g.*, **294h** and **294a**), the COX-1 inhibitors showed that the phenol ring of resveratrol tolerates a wide variation of substitution. Thus, it seems reasonable that either the phenol of resveratrol occupies a hydrophobic and large cavity in the COX-1 active site or that area of resveratrol is solvent exposed in the

Table 56 Chemical structures of stilbene derivatives



(290a-h)

Compound	R	IC_{50} (μM) Antiplasmodial
290a		1.56
290b		1.96
290c		11.88
290d		53.92
290e		45.40
290f		51.57
290g		37.84
290h		33.88
Resveratrol	—	0.02
Chloroquine	—	115.35

complex, which improved the effect of **294h** and **294a** slightly to the hydrophobic interactions. However, COX-2, unlike COX-1, recognizes a wide range of substitution patterns on R_3, all of which are EDG, indicating low COX-2 activity. R_1 of the potent COX-2 inhibitors, similar COX-1, showed no particular electronic preference and can accommodate the steric bulk of a naphthalene ring. Also, it is worth noting that the COX-2 inhibitors discovered in the assay showed high (>15 : 1) selectivity for COX-2 over COX-1 (*e.g.*, **294b** and **294i**). Based on the data, **294c** was more potent than resveratrol against NF-κB. Although the pseudo-symmetry of the resveratrol analogues lacking an alkene substituent complicates drawing firm conclusions, it is fairly clear that the catechol occupies the R_3 (resorcinol) site. In this case, it again appears that there is little selectivity for the R_1 ring, beyond a general preference for large and electron-rich rings, again suggesting either a hydrophobic or a solvent-exposed binding site for R_1 (Table 57).

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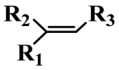
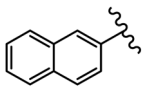
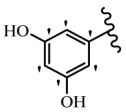
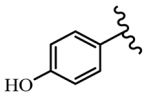
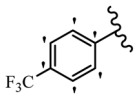
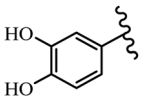
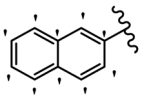
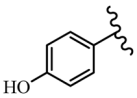
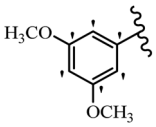
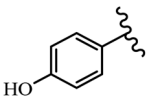
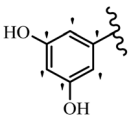
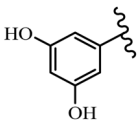
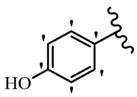
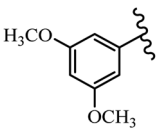
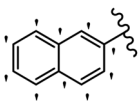
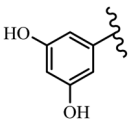
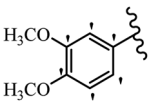
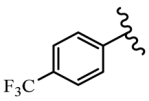
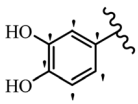
Table 57 Structures of resveratrol analogues



(294a-i)

Compound	R_1	R_2	R_3	IC_{50} (μM) COX-1	COX-2	NF-κB
294a		C_2H_5		0.17	3.3	—
294b		CH_3		36.3	0.47	—
294c		H		—	—	6.91
294d		H		0.7	0.82	19.5
294e		CH_3		1.9	1.57	—
294f		CH_3		1.9	1.78	—
294g		H		18.4	—	—
294h		H		0.29	21.3	—
294i		CH_3		—	1.74	—
Resveratrol	—	—	—	0.83	0.99	16.1

9. Conclusion

Stilbene, a natural compound having anti-microbial, antioxidant, anti-cancer, and anti-Alzheimer properties, has some issues, such as poor water solubility, which reduce its clinical use. Thus, due to the biological importance of this compound, the structure–activity relationship of stilbene derivatives and their biological activities were investigated in this review. The introduction of different substituents on the stilbene scaffold, such as halogens and heterocycles, or the synthesis of hybrid molecules, affects the behavior of the compounds. The goal was to summarize the main structural changes and their associated activities that extend their activities compared to the standard compounds. The conclusions of the present investigations can be summarized as follows:

1. According to the results, the presence of different substitutions on phenyl rings improved the TXRT, anti-microbial, anti-cancer, antioxidant, and CYP inhibitory activity compared

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to unsubstituted compounds. Alternatively, the presence of substitution on the carbon linker reduced the activity against cancer and COX.

2. The results indicated better antibacterial activity compared to antifungal activity. In addition, the findings showed that these compounds were more potent against Gram-positive bacteria than Gram-negative bacteria.

3. *Z*-Isomers displayed higher antibacterial, anti-cancer, Brdu incorporation and tubulin inhibitory activity compared to *E*-isomers. However, *E*-isomers showed better activity than *Z*-isomers on PPARα activation and PTB1B inhibition.

4. The presence of bulky groups on phenyl rings increased the antioxidant activity, while they decreased the anti-microbial and BAE, VEGF, AChE, and HADC inhibitory activities. However, bulky groups on the phenyl rings did not show any change in anti-cancer, and tubulin inhibitory activity.

5. Increasing the number of substitutions on the phenyl rings improved the inhibitory activity of CYPs, but it had a negative effect on the anti-cancer activity. This factor showed no change in anti-microbial activity.

6. The presence of EWG on phenyl rings exhibited the highest inhibitory activity against PTB1B and CYPs and PPARα activation. The presence of EDG on the phenyl rings showed the highest activity on induced apoptosis and against $A\beta_1$–β_2-aggregation. Moreover, both EDG and EWG improved the activity against HADC, LSD1, COX, and cancer, and microbial activity.

7. Results showed that lipophilic groups on the phenyl rings enhanced the activity against VEGF, h-TERT, AChE, BuChE, mur ligase, CYPs, and PTB1B, and on PPARα activation, antioxidant, and anti-cancer activity. Alternatively, hydrophilic groups increased the anti-microbe, induced apoptosis and BAE, LSD1, and COX inhibitory activity.

8. The aliphatic chain attached to the oxygen atom on the phenyl ring and the aliphatic chain on the substituted amide part of the phenyl ring showed better activity than the aliphatic ring on anti-microbial and antioxidant activity. Alternatively, the aliphatic ring on the substituted amide part of the phenyl ring exhibited higher activity than the aliphatic chain in terms of anti-malaria and anti-cancer activity.

9. Aromatic rings showed stronger anti-cancer activity and CYP inhibitory activity than heteroaromatic and aliphatic rings. However, heteroaromatic rings exhibited the highest antimalaria and antioxidant activity.

10. Aliphatic rings showed higher anti-microbial and antimalaria activity and inhibition of HADC than aromatic rings.

11. The presence of amide groups showed inhibitory activity higher than that of amine groups against CYPs.

12. The antioxidant activity and inhibition of HADC of secondary amides were better than that of tertiary amides, while both secondary and tertiary amides showed the highest anti-cancer activity.

13. Expanding a conjugated system increased the inhibitory activity on $A\beta_1$–β_2-aggregation; however, reduced PTB1B and PPARα activation, while this process had the opposite result in anti-cancer activity.

14. The nature and position of substituents on the phenyl ring were significant for $A\beta_1$–β_2-aggregation and AChE inhibitory activity. For example, substituents in the 4-position on the phenyl ring showed higher activity than in the 2- and 3-positions. Also, placing substituents on the phenyl or pyridine rings in all the positions resulted in the highest anti-microbial and anti-cancer activity and inhibition of CYPs and VEGF. The presence of groups in the 4-position was more potent than the 3-position on the coumarin ring anti-cancer activity. 3-Amidaxim on the phenyl ring displayed higher inhibitory activity than 4-amidaxim in the same position against LSD1. Changing the positions did not show any change in anti-microbial activity.

15. Increasing the chain length enhanced the AChE activity, but it had a negative effect on the BuChE inhibitory activity.

16. The presence of a bulky group on the phenyl ring showed strong antioxidant activity. However, the atom size had no effect on anti-microbial and anti-cancer activity.

Author contributions

Saghi Sepehri and Mohammad Mahdavi designed this review. Saghi Sepehri and Mina Khedmati drafted the manuscript. Faezeh Yousef-Nejad revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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