Synthetic approaches toward stilbenes and their related structures

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Abstract Compounds belonging to the stilbene family have gained remarkable significance in pharmaceutical as well as material chemistry. The current review covers the various synthetic approaches for the syntheses of stilbene scaffold and related structures over last 30 years. In addition, this review also highlights the role of stilbene intermediates used in the synthesis of important molecules with diverse applications in the field of pharmaceutics and material science.

Keywords Stilbenes and related analogues · Olefination reactions · Palladium catalysis · Cyclization · Benzofluorenes

Introduction

Nature has been a source of medicinal compounds for thousands of years and large number of drugs have been isolated from natural products [1,2]. Stilbene (1,2-diphenylethene) does not exist in nature itself, but its derivatives as plant secondary metabolites are present in various plant species and some of them are considered phytoalexins [2–5]. Stilbene and its analogues hold enormous potential importance due to their diverse spectrum of biological applications such as anticancer [6–10], antiproliferative [11,12], antiangiogenesis [11,12], antimicrobial [13–17], antileukemic [17,18], antioxidant [17,19,20], anti-inflammatory [17], anti-HIV [21,22], anti herpes simplex virus [23] and tyrosine kinase inhibitors [24,25]. Stilbenes exist in E and Z conformations each eliciting different pharmacological activities. Research revealed that the E form or trans exhibits more potent anticancer activity compared to the Z form or cis form. The trans or E form is thermodynamically more stable. Many trans-stilbenes such as resveratrol 1, oxyresveratrol 2, pterostilbene 3, piceatannol 4, isorhapotigenin 5 and cis stilbene, combretastatin 6 (Fig. 1) exhibited varieties of biological activities [1,4,25]. Hydroxy stilbene, i.e., resveratrol (3,4,5-trihydroxystilbene), a non-flavonoid polyphenolic present in grapes, peanuts, berries and red wine was investigated due to its role in plants’ defense against pathogens and pharmacological properties [26–32]. It shows significant effect against cancer, AIDS, antagonistic activity against aryl hydrocarbon receptor (AhR) and estrogenic potency [33,34]. Pterostilbene is used in the treatment of resistant hematoloy malignancies, diabetes and as antimumor agent [34].

Combretastatin A-4 (CA-4), a vascular disrupting agent (VDAs) and a vascular targeting agent (VTAs) present in the bark of Combretum caffrum, acts as antimitotic and exhibited antineoplastic, antioxidant and antiestrogenic properties [1,35–37].

The non-availability of naturally occurring stilbenes in sufficient quantities dictated the development of synthetic methodologies for their preparation at large scale [3] such as Wittig or Horner–Wadsworth–Emmons (HWE) olefination, Perkin aldol condensation, transition metal coupling, i.e., Mizoroki–Heck, Negishi, Stille, Sonogashira, Suzuki–Miyaura, Grubbs & McMurry, Knoevenagel–Doebner, Ramberg–Bucklund reactions [7,34,38,39]. Stilbene derivatives also show industrial applications in electrochemical dyes, dye laser, coloring textiles, organic LED, fluorescent and optical brighteners [40–43]. Likhitwitayawuid identified dimeric stilbenes as tyrosinase inhibitor [44], whereas

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Momotake and Arai wrote a review on photochemistry and photophysics of stilbene dendrimers and related compounds [45]. Shen et al. [46] presented an overview on natural stilbenes. Chaudhary et al. and Nam published reviews on Combretastatin A-4 analogues as anticancer and antimitotic antitumor agents, respectively [35, 36]. Recently, Reinisalo et al. [47] presented a review on polyphenol stilbenes, Jørgensen reviewed the photochemical oxidative cyclization of stilbenes and stilbenoids (the Mallory-reaction) [48], Savage et al. [49] presented a review of semi-rigid, stilbene-containing alternating copolymers, Chong et al. [50] contributed a review on metabolism and roles of stilbenes in plants, and Waldeck reviewed the photoisomerization dynamics of stilbenes [51]. The current review covers the synthetic strategies to develop convenient methods for the construction stilbene architecture and related analogues over the past few decades.

**Synthetic strategies for stilbene analogues**

**Synthesis of stilbene analogues by the Wittig/Horner–Wadsworth–Emmons (HWE) reaction**

Due to effective control of cancer by selenium-containing compounds, Yan et al. [30] prepared benzoselenazole-stilbene by the coupling of stilbene with ebselen as outlined in Scheme 1. For this purpose, phosphonate was prepared in three steps by reacting nitrobenzaldehyde with sodium borohydride in methanol, the resulting product was then treated with phosphorus tribromide in the presence of pyridine and finally refluxed with triethyl phosphite. Further, compound was converted to amino stilbene in 74% yield by reacting with benzaldehydes followed by reduction of nitro group with stannous chloride. Amino stilbene was subsequently coupled with 2-(chloroseleno)benzoyl...
chloride 10 in presence of sodium hydride to accomplish desired benzosenazolostilbene 11 in 55% yield.

Bhat and Pezzuto [52] described chemotherapeutic property of stilbene-based resveratrol. Thus, keeping in mind the perspective applications of resveratrol, Paul et al. [53] synthesized both cis 15 and trans-stilbenes 16 via a Wittig reaction between phosphonium salt 13, which is derived from compound 12 with appropriate aromatic aldehydes 14 but these stilbenes 15 and 16 were formed in 9–52% yields. Mizuno et al. [54] synthesized derivatives of pterostilbene by using a Wittig reaction similar to the route shown in Scheme 2.

Simoni et al. [26] prepared carbamates and uracil derivatives 20a–c from cis-stilbene to test their potential antitumor activity. The Wittig reaction of aldehyde 17 with Wittig salt 13, followed by reduction in the presence of Zn, generated hydrochloride salt 18 in 85% yield. Compound 18 was converted into intermediate isocyanate 19 by treating it with base and trichloromethyl chloroformate. The intermediate isocyanate 19 was finally converted into water soluble urea 20a and carbamates 20b–c in 70–89% yield as outlined in Scheme 3.

Roman et al. [8] prepared E and Z stilbenes as antiinvasive agents by different methods. E-stilbenes 24 were prepared in 48–99% yield using a Wittig reaction, in which benzyl bromide 21 was converted to phosphonate 22 and subsequently transformed to stilbenes 24 in an
E/Z ratio 99:1 by reacting with benzaldehydes 23 under nitrogen atmosphere. A solvent-free Arbuzov reaction generated triethyl phosphate from benzyl bromide followed by a Horner–Wadsworth–Emmons reaction in (THF/KO tBu) and afforded E-selectivity with higher yields as shown in Scheme 4a. Z-stilbenes 28 were formed in 13–87% yield through the Sonogashira coupling of phenylacetylene 25 with aryl iodides 26, which produced alkynes 27 in 92–99% yield. A wide range of alkynes 27 were converted into Z-stilbenes 28 via hydrosilylation (Chalk–Harrod mechanism) and TBAF mediated conversion of vinylsilanes. Lindlar’s catalyst also afforded the Z-stilbenes as shown in Scheme 4b.

Li et al. [5] followed the same Wittig–Horner reaction to generate hydroxy stilbenes 31 as severe acute respiratory syndrome (SARS) inhibitors. Phosphonates of 3,5-dimethoxybenzyl chloride 30 were obtained by an Arbuzov reaction in (n-Bu)_4NI. The reaction of phosphonate anion from compound 30 with aryl aldehydes gave E-stilbenes, which subsequently were demethylated to hydroxylated stilbenes 31 in quantitative yield as outlined in Scheme 5.

Gao et al. [17] synthesized radiolabeled stilbenes 33b and 34b as probes for cancer by treating Wittig salt 13 with 4-fluorobenzaldehyde 32b and 4-nitrobenzaldehyde 32a, respectively. Radiolabel precursors 33a and 34a were formed in 30–60% yield. Treatment of nitro precursors 33a and 34a with K{sup 18}F/Kryptofix{sup 2.2.2} afforded fluorine-18 stilbenes 33b and 34b in 15–20% radiochemical yield as shown in Scheme 6.

Das et al. [55] synthesized pinacolyl boronate stilbenes 38 as lipogenic inhibitors using a Wittig strategy. Wittig salt 36 was formed as white solid in 92% yield from 4,4,5,5-tetramethyl-2-p-tolyl-1,3,2-dioxaborolane 35 in two steps, bromination was followed by a Wittig reaction. Wittig salt 36 on treatment with aldehydes 37 afforded the final products 38 in 72–85% yield as outlined in Scheme 7.

Srivastava and Lee [56] reported the use of a Wittig reaction for the synthesis of hybrid stilbenes 43 and 44 bearing a quinoline moiety to test their anticancer activity. Wittig salt 42 was prepared from benzyl bromide 41 in 60–80% yield while quinoline-3-carbaldehydes 40 were synthesized in 15–89% yield from aniline 39 through a Vilsmeier–Haack reaction. The reaction of Wittig salt 42 with quinoline-3-carbaldehyde 40 resulted in cis-product 43 in 21–75% yield and trans-product 44 in 2–10% yield as described in Scheme 8.
Jung et al. [57] prepared stilbenes (E/Z ratio 1/1) derivatives 50–56 in 77–90% yield as tyrosine phosphatase 1B inhibitors from the reaction of protected aromatic aldehyde 49 and aromatic ylide 47. Deprotection of desired stilbene 50 was accomplished in 86% yield in the presence of tetra-n-butylammonium fluoride. The ester functionality of stilbene derivative 50 was reduced to stilbenes 52 and 53 and their subsequent deprotection afforded 54–56 in 77–90% yields as shown in Scheme 9a. Methyl-4-(chloromethyl) benzoate 57 was transformed into methyl-3-(4-(iodomethyl)phenyl)-2-propenoate 60 in 90% yield via compounds 58 and 59. Phosphonium salt 61 was obtained in 91% yield from compound 60. Reaction of compound 61 with aldehyde 62 provided stilbene 63 in 62% yield. Final phenolic stilbene 64 was obtained in 28% yield by demethylation of stilbene 63 as shown in Scheme 9b. In continuation of their work, Jung et al. [58] obtained amides 65–66 by treating compound 51 with amines. Subsequent deprotection afforded E-stilbenes 67–68 in 60–74% yield as shown in Scheme 9c, and their antioxidant and neuroprotective potential was also evaluated.

Achalkumar and Yelamaggad [59] first reported the coupling of cyclohexane-1,3,5-trione with E-stilbenes 72 and 75 to form light emitting tris(N-salicylideneaniline) [TSANs] 77–78 as shown in Scheme 10. Diethyl(4-nitrobenzyl) phosphate 70 was prepared in 70% yield in two steps from 4-nitrotoluene 69 by benzylic bromination and a Michalis–Arbuzov reaction. The intermediate 70 furnished 1,2-bis(alkoxy)-4-(4-nitrostyryl)-benzenes 72 in 60–62% yield by a HWE reaction with 3,4-dialkoxybenzaldehydes 71 and subsequent reduction using indium as a source of...
reducing agent. 3,4,5-Trialkoxy aldehyde 74 was obtained in 68–80% yield by lithium aluminum hydride mediated reduction of the ester functional group of 73 into alcohols followed by oxidation of alcohols into aldehydes using PCC as oxidizing agent. The reaction of aldehyde 74 with intermediate 70 resulted in a nitrostilbene followed by reduction of nitro group to amine 75 in 60–64% yields. Finally, treatment of triformylphloroglucinol 76 with stilbenes 72 and 75 gave desired TSANs 77 and 78, respectively, in 60–71% yields as yellow crystals.

Belluti et al. [60] understood the biological importance of stilbene analogues and coumarins; therefore, they embedded coumarin units in various stilbene analogues. Methylcoumarines 79 generated intermediate phosphonic acid diethyl esters 80 in 60–81% yield. The intermediate 80 underwent HWE reaction with aldehydes, which afforded stilbene derivatives 81 in an E/Z ratio of 9/1 in 51–72% yield as outlined in Scheme 11.

McNulty and McLeod [61] investigated two Wittig routes for the synthesis of stilbene analogue E-pterostilbene 88. Classical Wittig olefination usually yields poor E/Z stereocontrol, and it is highly desirable to improve stereoselectivity. In route A, phosphonium salt 86 was prepared from 3,5-dihydroxybenzoic acid 82 by converting acid 82 into ester 83 in 95% yield. Reduction of ester 83 into corresponding alcohol 84 was accomplished in 92% yield, which on direct reaction with triphenylphosphine HCl or through formation of benzyl chloride 85 (93% yield) gave compound 86 in 99% yield. However, compound 86 failed to react with 4-hydroxybenzaldehyde 87a, but after protection of hydroxyl group 87b–d gave pterostilbenes 3, 88a–c in 91% yield as shown in Scheme 12a. In route B, p-hydroxyphosphonium salt 90 was obtained in 91% yield using the above procedure. However, protection of the hydroxy group was required for the reaction of phosphonium salt 90 with an aldehyde. Here a deprotected phosphonium salt does not react with an aldehyde. Final product 3 was obtained in an E/Z ratio of 95/5 in 91% yield as shown in Scheme 12b.

Anthracene-based stilbene derivatives 96 containing a 1,3,4-oxadiazole moiety were synthesized by Li and He [62] as shown in Scheme 13, and they also evaluated their optical properties. Anthracene-substituted 1,3,4-oxadiazole intermediate 94 was obtained in 78% yield by refluxing 4-methylbenzohydrazide 91 with anthracene-9-carboxaldehyde 92 giving a yellow solution 93 to which chloramines-T were added and brominated with NBS to furnish compound 94.
Scheme 9  

(a) Synthesis of stilbene analogues 50–56, 

(b) synthesis of stilbene analogues 63–64, 

(c) synthesis of stilbene analogues 65–68
Scheme 10 Synthesis of star-shaped tris(N-salicylideneaniline) bearing trans-stilbene 77–78

R = n-OC₆H₁₇, n-OC₁₀H₂₁, n-OC₁₂H₂₅
Scheme 11 Synthesis of stilbene–coumarin hybrid compounds 81

(a)

\[
\begin{align*}
\text{HO} & \quad \text{dimethyl sulfate} \\
\text{OH} & \quad \text{K}_2\text{CO}_3, \text{acetone} \\
82 & \quad 95\% \\
\text{MeO} & \quad \text{NaBH}_4, \text{MeOH} \\
83 & \quad 92\% \\
\text{MeO} & \quad \text{SOCl}_2, \text{pyridine} \\
84 & \quad 93\% \\
\text{MeO} & \quad \text{PPr}_3, \text{HCl} \\
85 & \quad 99\% \\
\text{RO} & \quad \text{LiOH, H}_2\text{O} \\
86 & \quad 99\% \\
\text{MeO} & \quad \text{PPr}_3, \text{PhMe} \\
87 & \quad 91\% \\
3, 88\text{a–c} & \quad \text{R} = \text{H}, \text{Ts, Bz, THP} \\
87\text{a–d} & \quad \text{R} = \text{H, Ts, Bz, THP}
\end{align*}
\]

(b)

\[
\begin{align*}
\text{HO} & \quad \text{TsCl, TEA} \\
87 & \quad \text{DCM, 95\%} \\
\text{TsO} & \quad \text{NaBH}_4, \text{SiO}_2 \\
89 & \quad \text{MeOH, DCM} \\
90 & \quad 90\% \\
\text{TsO} & \quad \text{PPr}_3, \text{HCl, MeCN} \\
62 + 90 & \quad \text{LiOH, H}_2\text{O} \\
3 & \quad 91\%
\end{align*}
\]

Scheme 12 a Synthesis of pterostilbene 3, 88a–c. b Synthesis of pterostilbene 3
Compound 94 furnished phosphonate ester 95 in 95% yield which, followed by a HWE reaction with aromatic aldehydes, afforded desired products 96 in 83–93% yield.

Lu and He [63,64] synthesized 1,3,4-oxadiazole derivatives containing stilbene and naphthalene units from azomethine. Azomethine 98 was prepared from hydrazide 91 and aldehyde 97 [62]. Reaction of azomethine 98 with chloramine-T gave an intermediate having an oxadiazole ring. Bromination afforded an oxadiazole bearing benzyl bromide 99. Esterification of compound 99 followed by a Wittig–Horner reaction furnished product 101 in 81–91% yield as showed in Scheme 14.

Zhu et al. [43] synthesized conjugated stilbenes carrying an oxadiazole moiety 107 to study their optical properties. Oxadiazole 104 was formed in 60% yield by direct reaction of p-toluic acid 102 with hydrazine hydrate 103 in the presence of polyphosphoric acid. Bromination of oxadiazole 104 followed by esterification with triethylphosphate afforded 106 in 80% yield. A Horner–Wadsworth–Emmons reaction of compound 99 followed by nitro reduction with SnCl2 produced 4,4′-diaminostilbene 113 in 52% yield. Hybrid ODPA-stilbene 115 was formed when ODPA reacted with compound 113 under a nitrogen atmosphere in dry NMP as shown in Scheme 16.

Metal-mediated syntheses of stilbene analogues

Considering the importance of quinazoline and stilbene as bioactive compounds, Mahdavi et al. [67] hybridized trans-stilbene with quinazolines to develop potent anticancer agents. The reaction of styrene 117 with bromobenzaldehyde 116 using palladium-catalyzed Mizoroki–Heck reaction conditions provided stilbene 118 in 90% yield. Treatment of isatoic anhydride 119 with relevant primary amines generated anthranilamide 120 in 85–95% yield, which on reflux with stilbene 118 furnished 121 in 90–95% yields. As described in Scheme 17, compound 121 was oxidized to quinazoline 122 in 75–90% yield using tetrabutylammonium bromide in the presence of base.

As indicated in Scheme 18, Marti-Centelles et al. [68] described palladium-catalyzed preparations of stilbenes 124 by the reaction of styrene 117 with halogenated derivatives 123 under two different reaction conditions (Methods A and
Scheme 14  Synthesis of naphthalene-based stilbene derivatives containing 1,3,4-oxadiazole moiety 101

(a)  

(b)  

Scheme 15  a  Synthesis of highly conjugated stilbene carrying an oxadiazole moiety 107.  b  Synthesis of conjugated stilbenes carrying an oxadiazole moiety 109
B). Both methodologies afforded desired stilbenes in good yields (65–97%). A relatively new route to synthesize antitubulin agent, biaryl aryl stilbene 131 by utilizing Suzuki and Mizoroki–Heck cross coupling reactions, was disclosed by Kumar et al. [10]. Bromination of 3,4,5-trimethoxybenzaldehyde 125 followed by Suzuki cross coupling with aryl boronic acids 127 produced intermediate 4,5,6-trimethoxybiphenyl-2-carbaldehyde 128 in 88–95% yield. Wittig reaction of aldehyde 128 furnished 2,3,4-trimethoxy-6-vinylbiphenyls 129 followed by palladium-catalyzed Mizoroki–Heck coupling with aryl halides 130 afforded biaryl stilbene 131 in 88–90% yield as shown in Scheme 19a. Reddy et al. [69] synthesized nitrovinyl stilbenes 133 by using a similar methodology. Intermediate 126 produced stilbene 132 in 84–97% yield by way of a palladium-catalyzed Mizoroki–Heck reaction.
Heck reaction with styrene. The reaction of compound 132 with nitromethane gave nitrovinyl stilbenes 133 in 79–96% yield as shown in Scheme 19b.

Albert et al. [70] followed a Mizoroki–Heck reaction protocol using triethanolamine, which acts as ligand, solvent as well as base [71] allowing the economic synthesis of \( E \)-stilbenes 3, 137 to evaluate their antimicrobial activity. Substituted styrenes 135 were synthesized in 58–75% yield from benzaldehyde 134 by a Wittig reaction. Then, a Mizoroki–Heck reaction between styrene 135 and halogenated benzene 136 gave \( E \)-stilbenes 3, 137 in good yields as outlined in Scheme 20.

Khan et al. [72] synthesized stilbene derivatives 139 in 40–89% yields by mesylation of 2-iodobenzyl alcohol 138 with dimethylmalonate, which gave intermediate in 68% yield followed by a Mizoroki–Heck reaction with styrenes then gave stilbenes 139 as shown in Scheme 21. Further stilbene derivatives 139 were used in iodonium-promoted carbocyclizations to furnish a mixture of structurally complex indanes 140a in 18–55% yields and tetrhydronaphthalenes 140b in 18–59% yields with three new stereogenic centers.

Kabir et al. [13] reported the Pd-catalyzed regioselective synthesis of \( E \)-stilbene 144 in 74% yield by a Negishi cross coupling between arylvinyl iodide 143 and arylzinc reagent 142. Arylvinyl iodide 143 was prepared in 84% yield [73], whereas arylzinc 142 was obtained by transmetallation of hydrogen-lithium exchange product of arylbromide 141 with zinc(II)chloride as outlined in Scheme 22.

McDonald et al. [74] synthesized aza-stilbenes 147 to check their potency against the c-RAF enzyme. A range of styrenes 146 were created by the palladium-catalyzed Stille coupling of 5-bromo-nicotinonitrile 145 with tributylvinyl
Scheme 20 Synthesis of E-stilbene 3, 137

![Scheme 20]

R = 2-OH, 3-OH, 4-OH, 3-OMe, 4-OMe, 6-F
R¹ = I, Br
R² = H, OMe, OH
R³ = OMe, OH, F, H
R⁴ = H, F, OMe
R⁵ = OMe, OH, F, H

Scheme 21 Synthesis of stilbene derivatives 139

![Scheme 21]

Ar = Ph, 4-Me-C₆H₄, 2-Cl-C₆H₄, 4-Cl-C₆H₄,
2,6-Cl₂-C₆H₃, 1-naphthyl, 2-naphthyl

Scheme 22 Regioselective synthesis of E-stilbene 144

![Scheme 22]

tin. Mizoroki–Heck cross coupling of substituted styrenes 146 with bromo benzene furnished aza-stilbenes 147 mostly in moderate yields as shown in Scheme 23.

Lara-Ochoa et al. [75] reported a new route to stilbene analogue resveratrol 1 using a Sonogashira coupling strategy. Acetylene precursor 150 was obtained in 93% yield under Sonogashira coupling conditions. Subsequent hydrogenation of acetylene 150 with LiAlH₄ gave an E/Z mixture of 16, 17 (96/4 ratio) in quantitative yields. Diphenyldisulfide-assisted isomerization of an E/Z mixture of 16 and 17 gave trans-isomer 17 in 95% yield. Deprotection of the methoxy functional group in 17 in the presence of boron tribromide gave resveratrol 1 in 70% yield as described in Scheme 24.

Utilization of cyclic 1,1-bis(silyl)alkenes 151 to graft double bond on the aromatic ring for the selective preparation of E-stilbenes 154 was reported by Pawluc et al. [76]. Treatment of 151 with various aryl iodides 152 under Mizoroki–Heck coupling conditions furnished compounds 153 in good yields. Various E-stilbenes 154 were formed in good yields (62–92%) when compounds 153 were further coupled with various aryl iodides 152 using [Pd(C₃H₅)Cl]₂ as a catalyst in the presence of TBAF shown in Scheme 25.
An efficient one-pot preparation of stilbene 154 under Mizoroki–Heck reaction conditions was presented by Saiyed and Bedekar [77]. This method reduces work-up, generates less waste and saves time and energy. Initially, styrene 117 was generated by dehydrohalogenation of (2-bromoethyl)benzene 156, whereas the same styrene 117 can also be accessed from aldehyde 157 and phosphonium salt 42 using a Wittig reaction protocol as described in Scheme 26. Product 154 was obtained in 54–88% yield using a standard Mizoroki–Heck reaction as shown in Scheme 26.

Understanding the importance of sonochemistry in accelerating synthetic reactions, Cella et al. [78] utilized ultrasound to generate stilbenes from organotellurium compounds and potassium organotrifluoroborate salts under Suzuki cross coupling reaction conditions. Z-stilbenes 160 were obtained in 60–82% yield by ultrasound irradiation of Z-styryl n-butyltelluride 158 and potassium organotrifluoroborate 159 using Pd(PPh3)4 and Ag2O. Whereas E-stilbenes 163 have been prepared by using E-styryltrifluoroborate 161 and n-butyl(aryl)tellurides 162 with potassium carbonate in 59–91% yield as shown in Scheme 27.

Copolymerization of benzotriazole (BTz) 166, thiophene 168 and stilbene 167 was carried out by Karakus et al. [79] to study their electrochemical properties via Stille cross coupling reaction. Copolymers 169 (P1, P2 and P3) were synthesized in different ratios of BTz and stilbene. Coupling of 4,7-dibromo-2-dodecylbenzotriazole 166, E-1,2-bis(4-bromophenyl)ethane 167 and 2,5-bis(tri-n-butylstannyl) thiophene 168 using dichlorobis(triphenylphosphine)-palladium(II) gave the desired copolymers 169 (P1, P2 and P3) as shown in Scheme 28.

Zhang et al. [80] reported an efficient and simple method to synthesize 2-hydroxylated (Z-stilbenes 172 in good yield by oxidative coupling of 2-hydroxystyrene 170 with arylboronic acid 171 using [CpRhCl2]2 and Cu(OAc)2 at room temperature as shown in Scheme 29, and they further investigated their antiproliferative activity.

Novel double carbocyclizations mediated by selenium were reported by Shahzad and Wirth [81]. Stilbenes 174 were generated from methyl-2-iodobenzoate 173 under palladium-catalyzed Mizoroki–Heck reaction conditions. Reduction of 174 and mesylation of compound 175 followed by subsequent nucleophilic substitution reaction furnished stilbenes 176. On the other hand, 2-iodobenzyl chloride 177 also gave stilbenes 176 using the same route through compound 178. These substituted stilbenes 176 were used as...
precursors to produce dihydronaphthalene 179 in 50–90% yields, which was then transformed to benzofluorenes 180 in 30–90% yields through a one-pot procedure using phenylselenium chloride as selenylating reagent with a Lewis acid as shown in Scheme 30a.

Shahzad et al. [82] used a malonate moiety on an alkene to synthesize dihydronaphthalene and benzofluorenes. Stilbenes 174 were obtained in 80–93% yields from methyl 2-iodobenzoate 173 under Mizaroki–Heck reaction conditions. Hydrolysis of 174 afforded carboxylic acids 175 in 87–100% yields. β-keto ester derivatives of stilbene 181 were obtained in 58–98% yields from corresponding acids 175 using potassium ethyl malonate. Stilbene precursor 181 was transformed to dihydronaphthalene 182 in 50–96% yields using a combination of a selenium electrophile as selenylating reagent with a Lewis acid as shown in Scheme 30b.

Shahzad et al. [83] also used diselenide and disulfide in the synthesis of isocoumarins 184. Stilbene-based carboxylic acids 175 were obtained in 87–100% yields from corresponding esters by using lithium hydroxide. Compound 175 and its analogues were cyclized to dihydroisocoumarins 183 in
Scheme 27 Synthesis of $E$ & $Z$ stilbenes 160 and 163 by using ultrasound irradiation

$$\begin{align*}
\text{Ar}^1 & \equiv \text{TeBu-n} + \text{Ar}^2 \text{BF}_3 \text{K} \\
158 & \quad 159 \\
\text{Ph} & \quad \text{MeOH} \\
\rightarrow & \quad \text{Ar}^1 \equiv \text{Ar}^2 \\
160 & \quad 60-82\% \\
\text{BF}_3 \text{K} & \quad \text{ArTeBu-n} \\
161 & \quad 162 \\
\text{Ph} & \quad \text{MeOH}, \text{Ag}_2 \text{O}, \text{K}_2 \text{CO}_3 \\
\rightarrow & \quad \text{Ar}^1 \equiv \text{Ar}^2 \\
163 & \quad 59-91\% \\
\text{Ar}^1 = & \quad \text{Ph}, 4-\text{ClPh}, 4-\text{MePh}, 4-\text{OMePh, 2-MePh, 1-naphthyl, 1-thiophene} \\
\text{Ar}^2 = & \quad \text{Ph, 4-ClPh, 4-MePh, 4-OMePh, 2-MePh, 1-naphthyl, 1-thiophene, 4-IPh, 4-BrPh} \\
\end{align*}$$

Scheme 28 Synthesis of stilbene-based copolymers 169

$$\begin{align*}
\text{HN} & \equiv \text{N} \\
\text{N} & \equiv \text{N} \\
164 & \quad \text{C}_{12} \text{H}_{25} \\
\text{t-BuOK, EtOH} & \quad \text{C}_{12} \text{H}_{25} \text{Br} \\
\rightarrow & \quad \text{C}_{12} \text{H}_{25} \\
165 & \quad \text{Br} \text{HBr, Br}_2 \\
\rightarrow & \quad \text{Br} \text{166} \\
\text{Br} & \quad \text{SnBu}_3 \\
167 & \quad \text{Bu}_3 \text{Sn} \\
\text{166} + 167 + 168 & \quad \text{THF} \\
\rightarrow & \quad \text{169P}_1 - \text{P}_3 \\
\text{Pn}(x:y) & = \text{P}_1 (1:3.5) \\
& = \text{P}_2 (1:2.1) \\
& = \text{P}_3 (1:1.8) \\
\end{align*}$$

Scheme 29 Synthesis of 2-hydroxylated $(E)$-stilbenes 172

$$\begin{align*}
\text{R} & \equiv \text{H}, 3-\text{OMe}, 2-\text{OMe}, 4-\text{Br}, 4-\text{NO}_2 \\
170 & \quad \text{R}^1 \equiv \text{H}, 4-\text{Me}, 4-\text{Br, 4-OH, 4-CN, 2,4-(OMe)}_2, 3,5-(\text{OH})_2, \\
& \quad 3,5-(\text{OMe})_2, 3,4,5-(\text{OMe})_3, 3,5-\text{Me}_2 \\
\text{171} & \quad \text{[Cp}^* \text{RhCl}_2]_2 \\
\text{Cu(OAc)}_2, \text{MeOH} & \quad \text{172} \\
\rightarrow & \quad 30-85\% \\
\end{align*}$$
Scheme 30  

(a) Synthesis of stilbene precursor 176 and benzofluorene 180. 

(b) Synthesis of stilbenes 175, 181 and biaryls 182 through a convenient synthetic route.

(c) Synthesis of stilbene precursor 175 and one-pot preparation of isocoumarin 184.
Scheme 31 Synthesis of stilbene-based hydroxamates 190

50–97% and isocoumarins 184 in 81–99% yields using N-phenylselenosuccinimide (N-PSS). Because of the high cost of N-phenylselenosuccinimide (N-PSS), another methodology was developed by Shahzad and coworkers using diphenyl diselenide and [bis-(trifluoroacetoxy)iodo]benzene to synthesize isocoumarins 184. Optimization concluded that 10 mol% use of catalyst diphenyl diselenide gave desired isocoumarins in excellent yield as shown in Scheme 30c.

Synthesis of stilbene analogues by Perkin condensation

Kachhadia et al. [84] designed stilbene-based hydroxamates 190 to inhibit histone deacetylases (HDACs), which are the cause of epigenetic states related to cancer. For this purpose, 4-formylcinnamic acid was converted to ester 186, which undergoes Perkin condensation with substituted phenylacetic acids 185 to generate acrylic acids 187 in 47% yield. Compounds 187 were then reduced to alcohols and oxidized into aldehydes 188 in 28% yield using PCC. Compound 188 underwent reductive amination to amine 189. The amines were finally converted into hydroxamic acid 190 in 95–96% yield by treating with hydroxylamine as shown in Scheme 31.

To assess the cytotoxicity of stilbene derivatives, efficient preparation of resveratrol analogue 195 was described by de Lima et al. [1] using Perkin reaction conditions. Condensation of aldehydes 191a–d with phenyl acetic acid 185 provided carboxylic acid-substituted stilbenes 192a–d in 48–49% yields. Compound 194 was formed in 78% yield when copper chromite in quinoline was used for the decarboxylation of compound 192b. Compound 194 was isomerized to trans-analogue 195 in 98% yield in the presence of concentrated HCl. Hydrolysis of compound 192a under basic conditions generated compound 193 in 95% yield as outlined in Scheme 32.

Other synthetic methodologies

Chanawanno et al. [85] prepared and studied the antibacterial activity of pyridinium stilbene 199a, 199b and quinolinium stilbene 203a, 203b. 1,2-Dimethylpyridinium iodide 196 reacted with 4-dimethylaminobenzaldehyde 198 and 4-ethoxybenzaldehyde 197 separately to produce PAM 199a in 61% yield and PET 199b in 66% yield. Replacement of pyridinium iodide 196 with quinolinium iodide 202 generated QAM 203a in 89% yield and QET 203b in 54% yield. When stilbenes 199 and 203 were stirred with a silver salt of 4-substituted benzene sulfonates 200, benzenesulfonates 201, hybrid stilbenes with counter anions were formed in 66–91% yields and 204 in 54–89% yields as shown in Scheme 33.

Xiao et al. [4] reported the creation of hybrid structure coumarin-stilbenes 208 by locking the stilbene double bond in the benzopyrone ring and also studied their anti-tumor properties. 3-Arylcoumarins 207 were formed in 74–93% yield from substituted phenylacetic acids 205 and o-hydroxybenzaldehyde 206. Hydrolysis of compounds 207 with HCl afforded compounds 208 in 90–95% yield as shown in Scheme 34.

Pratap et al. [3] reported the synthesis of stilbenes 211 in 26–81% yield and 212 in 60–65% yield (see Scheme 35).
through a ring transformation between 4-phenyl-3-buten-2-one 210 and 2H-pyran-2-one 209 using KOH.

Giraud et al. [25] developed a new and efficient method to synthesize cis-stilbenes analogue 6 and 215 by hydrosilylation–protodesilylation of diarylalkynes by following the protocol shown in Scheme 36 instead of using Lindlar’s catalyst due to its drawbacks of isomerization and production of alkanes during the reaction. PtO2 proved to be an efficient catalyst for hydrosilylation. Hydrosilylation of diarylalkynes 213 was done using PtO2 and HSiOEtMe2. Removal of HSiOEtMe2 and protodesilylation of vinylsilane...
Scheme 34 Synthesis of coumarin-stilbene hybrid 208

\[
\begin{align*}
\text{COOH} & \quad \text{CHO} \quad \text{OH} \\
\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{OCH}_3 \\
\text{R}^3 = \text{OH}, \text{R}^5 = \text{OAc}
\end{align*}
\]

Scheme 35 Synthesis of \(E\)-stilbenes 211–212

\[
\begin{align*}
\text{Ar} = & \quad 4-\text{CH}_3-\text{C}_6\text{H}_4, 4-\text{Br}-\text{C}_6\text{H}_4, 4-\text{F}-\text{C}_6\text{H}_4, 4-\text{Cl}-\text{C}_6\text{H}_4, \\
& \quad 4-\text{CH}_3-O-\text{C}_6\text{H}_4, 3,4-\text{CH}_2\text{O}_2-\text{C}_6\text{H}_3, 1-\text{naphthyl} \\
\text{R}^1 = & \quad \text{SCH}_3, \text{piperidin-1-yl-CN} \\
\text{R}^2 = & \quad \text{CN}, \text{COOCH}_3
\end{align*}
\]

Scheme 36 Synthesis of \(Z\)-stilbenes 6 and 215 by hydrosilylation-protodesilylation

\[
\begin{align*}
\text{R} = & \quad 4-\text{OMe}, 2,3,4-\text{OMe} \\
\text{R}' = & \quad \text{H, 3-OH, 4-OMe}
\end{align*}
\]

With TBAF afforded \(Z\)-stilbenes 6 and 215 in 49–90% yield.

As shown in Scheme 37, Kumar et al. [86] performed microwave-assisted synthesis of hydroxylated stilbenes 217 in 56–91% yields from cinnamic acid derivatives 216 in a methyl-imidazole promoted decarboxylation.

Wyrzykiewicz et al. [27] introduced piperidine, morpholine and 4-methylpiperidine bearing stilbene moieties and also investigated their antimicrobial activity. Compounds 220 were formed in 13–78% yield by the reaction of \(E\)-4-(bromoalkoxy)stilbenes 218 and were treated with piperidine, morpholine and 4-methylpiperidine 219 separately. \(E\)-4-(bromoalkoxy)stilbenes 218 were prepared by a reported procedure [87] as shown in Scheme 38.

Chang et al. [88] synthesized sulfonyl \((E)\)-stilbenes 222 in 57–88% yield from benzylic sulfones 221 by dimerization-desulfonation shown in Scheme 39. Different bases and additives were used for optimization, and results showed that NaH and PhNO\(_2\) gave good yields.
Scheme 37 Synthesis of stilbenes 217 by microwave irradiation

\[ \text{Scheme 38 Synthesis of (E)-4-[piperidino(4′-methylpiperidino-,morpholino-)-N-alkoxy]stilbenes 220} \]

\[ \text{Scheme 39 Synthesis of sulfonyl E-stilbenes 222 by dimerizative desulfonation} \]

Because of the diverse applications of organosilanes in the chemical industry, Hussain et al. [89] synthesized silicone-based triazine–stilbene compounds 228 in three steps as shown in Scheme 40. In first step, the reaction of 4,4-diaminostilbene-2,2-disulfonic acid 223 with an ice-cold slurry of cyanuric chloride 224 generated intermediate 225. In the second step, intermediate 225 was condensed with aromatic amines at pH 6. In the final step, compound 226 reacted with 3-aminopropyltrimethoxy silane 227 to yield 228 in 92–94%. Um et al. [90,91] used a similar methodology to synthesize triazine–stilbene as fluorescent brighteners. Um et al. [41] prepared substituted triazine–stilbene 232 to test their brightness. Intermediate 230 was produced by reacting stilbene 229 with 2,4,6-trichloro-1,3,5-triazine 224 followed by treatment with different amines. Addition of phenolic derivatives to 231 gave products 232 in 70–98% yield as shown in Scheme 41.

Understanding the photophysical properties of stilbene, Buruiana et al. [92] prepared stilbene-containing polyacrylates 234. The monomers (SUM) 233 were produced in 96% yield by adding 2-isocyanatoethylmethacrylate to trans-4-stilbene methanol. SUM (monomers) 233 were copolymerized with methyl methacrylate (MMA) by free radical mechanism. Stirring the mixture of SUM and MMA in the presence of an initiator (AIBN) gave polyacrylate (SUMMA) 234 in 48% yield as shown in Scheme 42.

**Conclusion**

The significance of stilbenes and their related structures is prominent in the current literature such as publications, reviews, patents and books. In the last decade, different synthetic approaches have been devised to design novel
stilbene-based compounds. The classical approaches involve famous named reactions such as the Wittig reaction/Horner–Wadsworth–Emmons reaction, Mizroki–Heck reaction, Suzuki cross coupling reaction, Stille cross coupling reaction, Sonogashira cross coupling reaction, and Perkin condensation to synthesize stilbenes and related structures. It must be highlighted that these reactions have changed the science of synthesis. The most essential synthetic methodologies to synthesize $E$ and $Z$-stilbene analogues have been summarized in this article. However, in our view, there will be further developments for the production of novel stilbene-based structures in the coming years. We hope will be useful for the scientific community, especially for those interested in the synthesis of stilbene analogues, which have a wide spectrum of applications in medicinal and material chemistry.
Scheme 41 Synthesis of substituted triazine–stilbene 232

R = Ph, 2-SO$_3$NaPh, 3-SO$_3$NaPh, 4-SO$_3$NaPh, CH$_2$Ph

Scheme 42 Synthesis of polyacrylate SUMMA 234
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