Supplementary material

Medicinal Chemistry Perspective on Structure-Activity Relationship of Stilbene Derivatives

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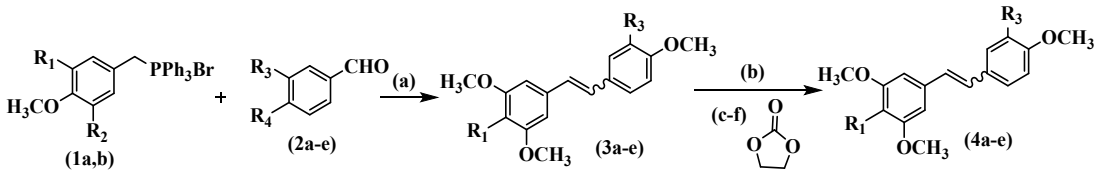
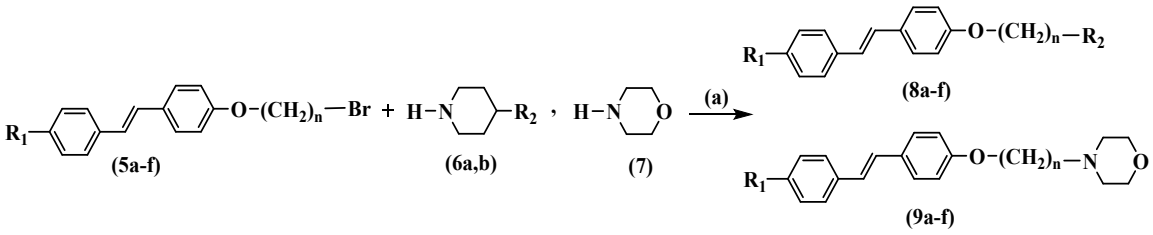
Pettit *et al*. described synthesis and assessment anti-microbial activity of *E/Z*-CA-4 analogues. Reaction of phosphonium bromides **1a,b** with aryl aldehydes **2a-e** produced *E/Z*-isomers **3a-e**. Derivatives of **4a-e** were produced with suitable reagents (Scheme **1**).



SCHEME 1 Synthesis of *E/Z*-CA-4 analogues. Reagents and conditions: (a) Tetrahydrofuran, *n*-BuLi, THF, Cat. 15-crown-5, -23 ˚C; (b) *n*-Bu_4NF, THF; (c) Ethylene carbonate, base, K_2CO_3, DMF, heat; (d) $CH_3SO_2OCH_2CH_2Cl$, NaH, DMF, 0 ˚C; (e) Aminoethyl halide, sodium hydride, NaH, 90 ˚C, HCl; (f) Dry pyridine, $(ClCH_2CH_2)_2NC(O)Cl$, heat, over 54 h

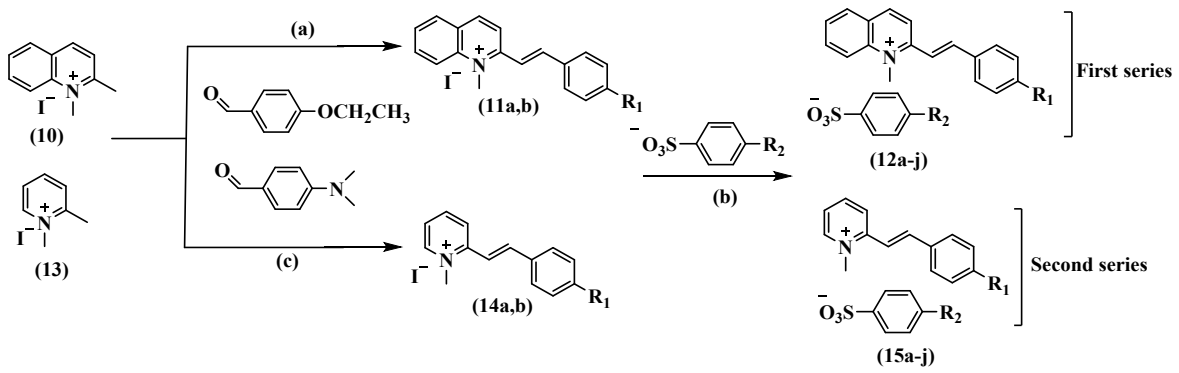
Wyrzykiewicz *et al*. synthesized *E*-piperidino and morpholino stilbenes and assessed their anti-microbial activity.

Compounds **8a-f** and **9a-f** were synthesized by the reaction of the **5a-f** with piperidine **6a**,**b** and **7** (Scheme **2**).



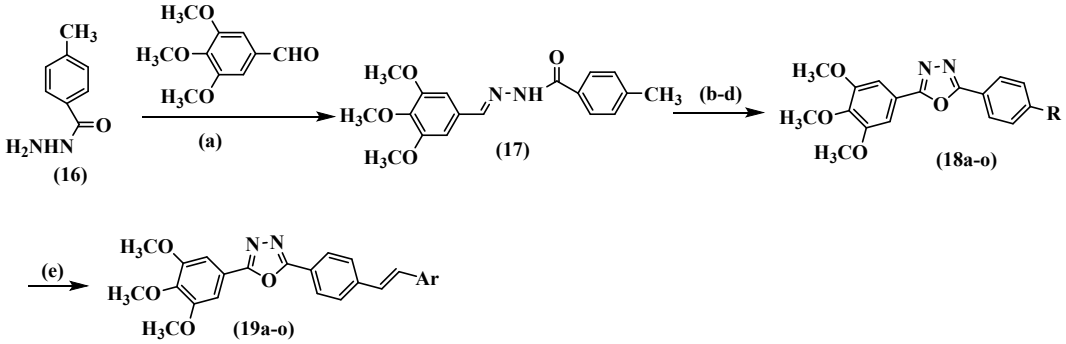
SCHEME 2 Synthesis of *E*-piperidino and morpholino stilbenes. Reagents and conditions: (a) DMF, TEA, NaOH, DMSO, room temperature

Chanawanno *et al*. synthesized pyridinium, and quinolinium stilbene benzenesulfonate hybrids and evaluated their anti-bacterial activity. Intermediates **11a**,**b** and **14a**,**b** were synthesized by compounds **10** and **13**, respectively. After that, compounds **12a-j** and **15a-j** were provided with the same method using exchanging silver (I) 4-methylbenzenesulfonate with other derivatives of silver (I) in 4-position on benzenesulfonate (Scheme **3**).



SCHEME 3 Synthesis of quinolinium, and pyridinium stilbene benzenesulfonate. Reagents and conditions: (a) CH_3OH, refluxed, 50-55 ˚C, 4 h, N_2 atmosphere and 6h; (b) CH_3OH, stirred, 50 ˚C, 0.5 h; (c) CH_3OH, refluxed, 50- 55 ˚C, N_2 atmosphere and 6 h

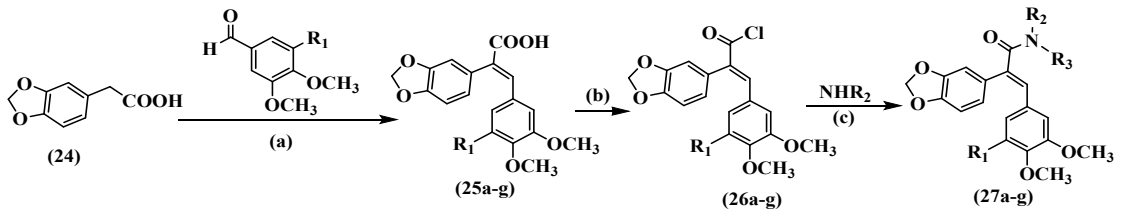
He *et al.* synthesized stilbene derivatives containing an 1,3,4-oxadiazole moiety and evaluated their fungicidal agents. Compound **16** and 3,4,5-trimethoxybenzaldehyde provided compound **17**. Intermediate **18a-o** was prepared by intermediate chloramine-T which was synthesized by compound **17**. Then, their bromine and phosphonate derivatives were produced. After that, the reaction of phosphonate **18a-o** with different aldehyde derivatives produced derivatives **19a-o** (Scheme **4**).



SCHEME 4 Synthesis of stilbene derivatives. Reagents and conditions: (a) CH_3OH, refluxed, 1h; (b) CH_3OH, refluxed, 4h; (c) NBS, CCl_4, refluxed, 8h; (d) $P(OC_2H_5)_2$, refluxed, 5h; (e) *t*-BUOK, DMF, 5h.

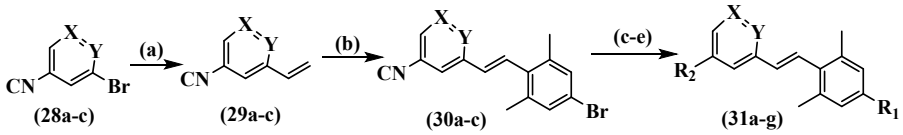
Song *et al*. synthesized and assessed fungicidal activity of 1,3-benzodioxole-stilbene derivatives. The intermediates **25a-g** were provided by reacting the 3,4-methylenedioxyphenylacetic acid **24** with the appropriate substituted arylaldehyde. Then,

corresponding acyl chlorides bearing diarylethene analogue **26a-g** reacted with numerous amines to offer the compounds **27a-g** (Scheme **5**).



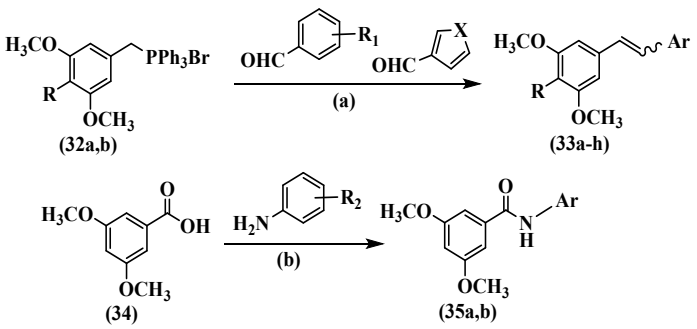
SCHEME 5 Synthesis of 1,3-benzodioxole-stilbene derivatives. Reagents and conditions: (a) AC_2O, DIPEA, 120 ˚C; (b) $(COCl)_2$, DMF, DCM, 0 ˚C; (c) DCM, TEA, 0 ˚C

Hrast *et al.* described azastilbene derivatives as mur ligase inhibitors and anti-bacterial agents. Compounds **28a-c** and tributyl(vinyl)tin were used to produce **29a-c**. Then, this intermediate with 5-bromo-2-iodo-1,3-dimethylbenzene produced the corresponding *E*-isomer stilbene derivatives **30a-c**. Finally, analogues **31a-g** were produced using the corresponding reagents (Scheme **6**).



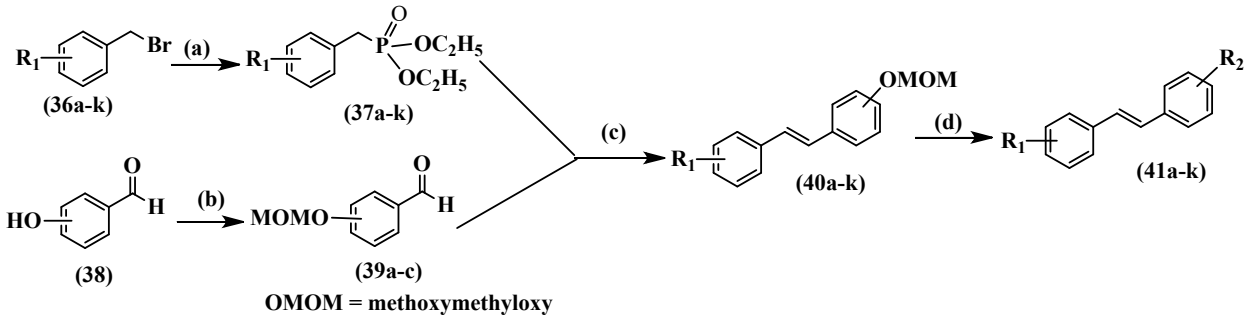
SCHEME 6 Synthesis of azastilbene. Reagents and conditions: (a) LiCl, $Pd(PPh_3)_2Cl_2$, DMF, 70 ˚C; (b) Pd_2dba_3, TEA, $P(o\text{-}Tol)_3$, DMF, 95 ˚C; (c) $Pd(OAc)_2$ and xantphos(4,5-bis (diphenylphosphino)-9,9-dimethylxanthene), corresponding boronic acids, K_2CO_3, $Pd(PPh_3)_4$, H_2O, THF, 100 ˚C; (d) NH_4Cl, NaN_3, DMF, 110 ˚C; (e) Cat. S, ethanolamine, ethylenediamine

Lee *et al.* synthesized stilbene analogues and evaluated their cytotoxicity activity. First, condensation of **32a**,**b** and the appropriate aldehydes afforded a mixture of *E*/*Z*-**33a-h**. On the other hand, compound **34** reacted with suitable amines to give amides **35a**,**b** (Scheme **7**).



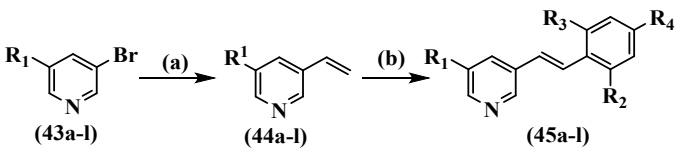
SCHEME 7 Synthesis of stilbene analogues. Reagents and conditions: (a) Cat.18-crown-6, KOH, DCM, 2 h, room temperature; (b) CCl_3CN, Ph_3P, DCM, 1 h, room temperature, TEA

Lion *et al.* synthesized hydroxylated *E*-stilbenes and assessed their anti-tumor and apoptosis-inducing activity. Compounds **36a-k** and triethyl phosphite produced compounds **37a-k**. Alternatively, compound **38** and chloromethyl methyl ether produced **39a-c**. Next, acetic acid was added to **37a-k** and **39a-c** to afford **40a-k**. Finally, pyridinium *p*-toluene sulfonate was added to compounds **40a-k** to give the substituted hydroxylated *E*-stilbenes **41a-k** (Scheme **8**).



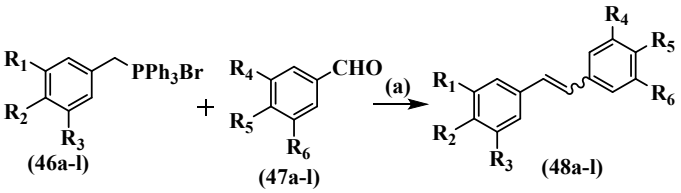
SCHEME 8 Synthesis of hydroxylated *E*-isomer stilbenes. Reagents and Conditions: (a) $P(OC_2H_5)_3$, dry DMF, sodium methoxide, 18/6-crown ether; (b) CH_3OCH_2Cl, DCM; (c) CH_3ONa, stirred, room temperature, 5 min, DMF, 100 ˚C; (d) CH_3OH

McDonald *et al*. synthesized aza-stilbenes and accessed their c-RAF inhibitor activity. The vinyl intermediate **44a-l** was created by coupling compound **43a-l** with tributylvinyl tin. Then, compounds **45a-l** were produced by the reaction between **44a-l**, arylbromide(iodide) and tris(dibenzylideneacetone)dipalladium (Scheme **9**).



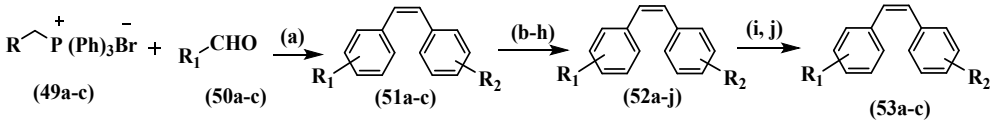
SCHEME 9 Synthesis of Aza-stilbenes. Reagents and Conditions: (a) Tributylvinyl tin, LiCl, BHT, $Pd(PPh_3)_2Cl_2$, DMF, 70 °C; (b) Arylbromide(iodide), tris(dibenzylideneacetone)dipalladium, TEA, P(*o*-tol)$_3$, DMF, 95 °C, tributyl tin azide, toluene, refluxed, dimethylamine, CH_3OH, room temperature

Gosslau *et al*. reported that *E*/*Z*-stilbene polyphenols induced *p53*-independent apoptosis and rapid perinuclear mitochondrial clustering. The reaction of various benzaldehydes **47a-l** with phenyltriphenylphosphonium bromide **46a-l** produced suitable products **48a-l** (Scheme **10**).



SCHEME 10. Synthesis of *E/Z*-stilbene polyphenols. Reagents and conditions: (a) n-BuLi, THF, -23 °C

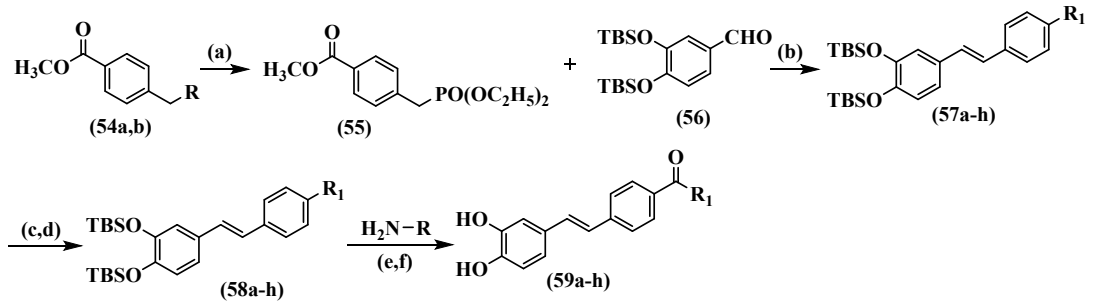
Simoni *et al*. designed stilbene-based derivatives and assessed their anti-tumor activity. In the first step, stilbene derivatives **51a-c** were produced by the reaction of the appropriate phosphonium salt **49a-c** with aldehyde **50a-c**. In the second step, stilbene derivatives **52a-j** were produced by the corresponding reagents and compounds **51a-c**. Finally, **52a-j**, trichloromethyl chloroformate and 2-morpholino-1-ethylamine formed urea derivatives **53a-c** (Scheme **11**).



SCHEME 11 Synthesis stilbene-based. Reagent and conditions: (a) NaH, THF, room temperature; (b) Tetrabutylammonium fluoride, tert-butyldimethylsilyl, DCM, room temperature; (c) CH_3I, KOH, DMSO, dimethylsulfoxide; (d) *P*-toluenesulfonic acid, CH_3OH; (e) LiOH, CH_3OH, 50 °C, 24h; (f) (i) Zn, AcOH, room temperature; (ii) HCl, CH_3OH; (g) (i) Zn, AcOH, room temperature;

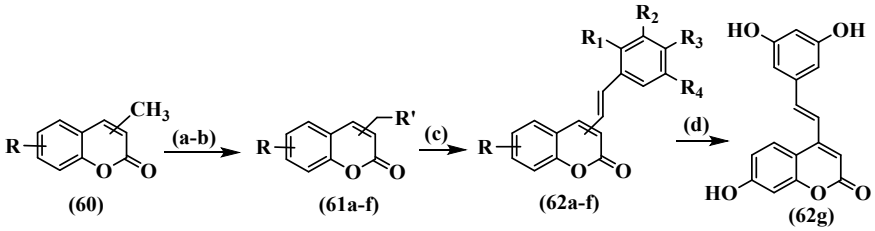
(h) (i) Zn, AcOH, room temperature; (ii) Oxalic acid, THF; (i) Trichloromethyl chloroformate, dioxane, 60 ˚C, 3 h; (j) (i) 2-Morpholino-1-ethylamine; (ii) HCl, CH_3OH

Moon *et al.* synthesized resveratrol derivatives and evaluated their cytotoxicity activity. By treating compounds **54a**,**b** with triethyl phosphite, they were converted to phosphonate **55**. This compound reacted with **56** to produce **57a-h**. Then, compounds **57a-h** gave compounds **58a-h** during the reaction with the corresponding reagents. Afterwards, **58a-h** was coupled with several amines. Finally, compounds **59a-h** were deprotected by removing *tert*-butyldimethylsilyl from their dihydroxy moieties (Scheme **12**).



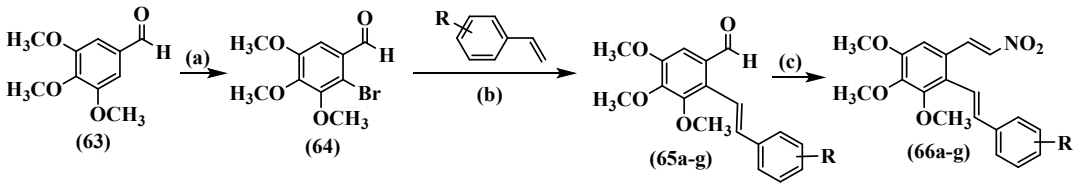
SCHEME 12 Synthesis resveratrol derivatives. Reagents and conditions: (a) $P(OC_2H_5)_3$, 160 ˚C, 3 h; (b) *n*-BuLi, THF, -20 ˚C, 1 h; room temperature, 12 h, NaH, DCM, 0 ˚C, 16 h; (c) DIBAL-H, DCM, -78 ˚C, 1h; (d) DMSO, $(COCl)_2$, TEA, DCM, -78 ˚C, 1 h, or TPAP, *N*-methylmorpholine-*N*-Oxide, THF, room temperature, 30 min, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, 0 ˚C, 16 h; (e) 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate, DCM, room temperature, 16 h; (f) TFA, DCM, room temperature, 1 h, TBAF, THF, 0 ˚C, 30 min

Belluti *et al*. synthesized stilbene-coumarin hybrids and evaluated their cytotoxicity activity. The 3/4-methylcoumarin derivatives **60** reacted with triethylphosphate and yielded the analogous phosphonic acid diethyl ester derivatives **61a-f**. The provided compounds were then reacted with the appropriate aldehydes in the presence of sodium methoxide, yielding stilbene derivatives **62a-f**. The methoxy functions of compound **62b** were cleaved with BBr_3 to yield **62g** (Scheme **13**).



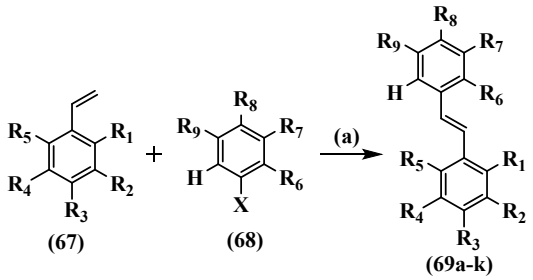
SCHEME 13 Synthesis of stilbene-coumarin hybrid. Reagents and conditions: (a) NBS, $(PhCOO)_2O$, CCl_4, refluxed; (b) $PO(OC_2H_5)_3$, 150 ˚C; (c) Ar-CHO, $NaOCH_3$, DMF, 0-100 ˚C; (d) DCM, 0 ˚C, room temperature

Reddy *et al*. designed resveratrol-based nitrovinylstilbenes and tested their anti-mitotic and anti-tubulin activities. The bromination of benzaldehyde **63** resulted in analogue **64**. Then, the intermediates **65a-g** were prepared by reaction of aryl halide **64** with different styrenes. Finally, nitromethane was used to convert stilbenes **65a-g** to target compounds **66a-g** (Scheme **14**).



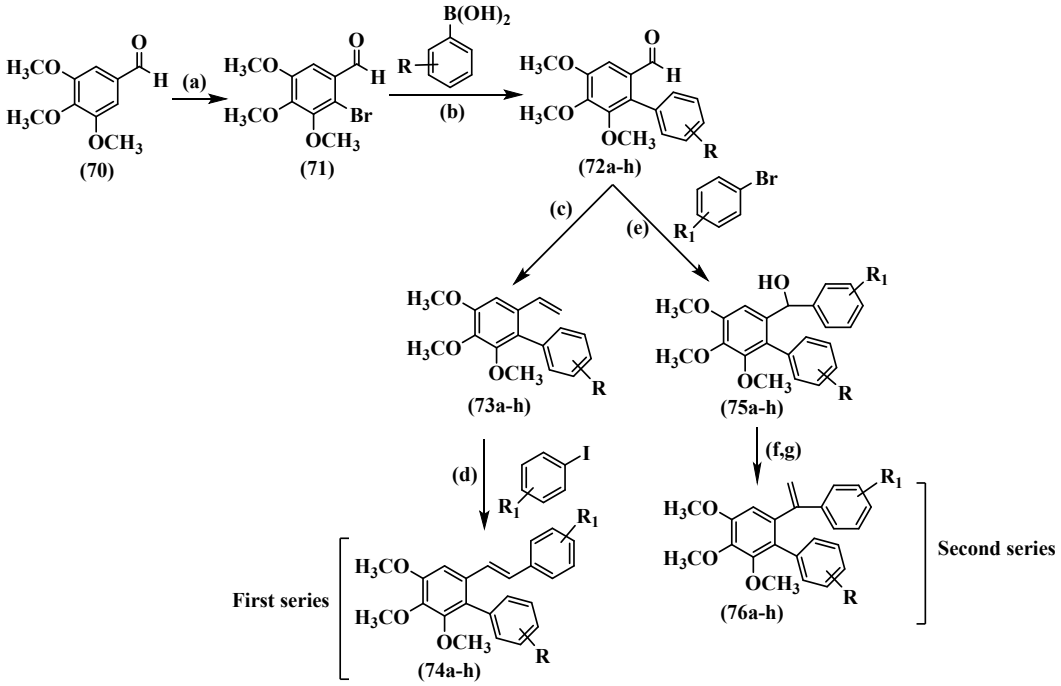
SCHEME 14. Synthesis of nitrovinylstilbenes. Reagents and conditions: (a) Br_2, CH_3COOH, room temperature, 2h; (b) $Pd(OAc)_2$, dimethylacetamide, K_3PO_4, 130 ˚C; (c) CH_3NO_2, NH_4OAc, 100 ˚C, 3h

Csuk *et al*. Synthesized *E*-stilbene-based derivatives and evaluated their anti-tumor activity. Compounds **67** and **68** reacted together to give **69a-k** (Scheme **15**).



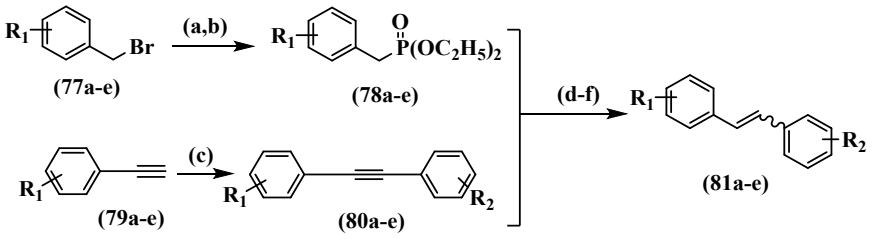
SCHEME 15 Synthesis of *E*-stilbene-based. Reagents and conditions: (a) Triethanolamine, $Pd(OAc)_2$, 24 h, 100 ˚C

Kumar *et al.* synthesized biaryl stilbenes/ethylenes and assessed their anti-microtubule activity. In the first step, compound **71** was prepared by the bromination of **70**. In the second step, joining **71** with aryl boronic acids yielded the compounds **72a-h**. In the third step, the compounds **74a-h** were achieved from the reaction of **72a-h**, **73a-h** and aryl magnesium halides. In the fourth step, different aryl magnesium halides produced compounds **75a-h**. In the fifth step, the oxidation of compounds **75a-h** has been done. Finally, the produced compound reacted with methylenetriphenylphosphorane to form **76a-h** (Scheme **16**).



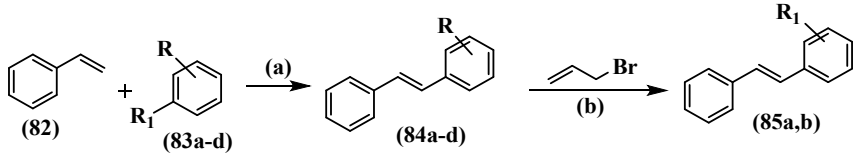
SCHEME 16 Synthesis of biaryl aryl stilbenes/ethylenes. Reagents and conditions: (a) Br_2, CH_3COOH, room temperature, 2 h; (b) $Pd(PPh_3)_4$, H_2O: C_2H_5OH, 80 ˚C, 6 h; (c) $CH_3P(Ph)_3Br$, *t*-BuOK, THF, room temperature, 24 h; (d) $Pd(OAC)_2$, K_3PO_4, DMA,140 ˚C, 12 h; (e) Mg, THF, 2 h; (f) PCC, DCM, room temperature, 2 h; (g) $CH_3P(Ph)_3Br$, *n*-BuLi, THF, -78 ˚C, 12 h

Roman *et al.* designed some of *E*/*Z*-stilbenes and tested their anti-invasive activity. The required phosphonates **78a-e** were yielded by the appropriate benzyl bromides **77a-e**. During another reaction, compounds **79a-e** and $PdCl_2(PPh_3)_2$ produced **80a-e**. The derivatives were produced using the respective reagents produced *E*/*Z*-compounds **81a-e** (Scheme **17**).



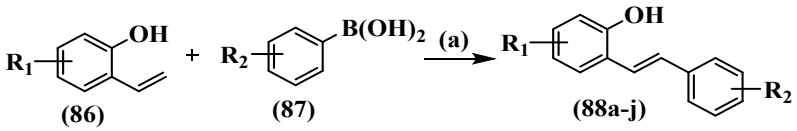
SCHEME 17 Synthesis of *E*/*Z*-stilbenes analogues. Reagents and conditions: (a) PPh_3, dry $(C_2H_5)_2O$, N_2, heat, 12 h; (b) $P(OC_2H_5)_3$, heat, 130 °C, 5 h; (c) $PdCl_2(PPh_3)_2$, H_2O/sec-$BuNH_2$, Ar, room temperature (d) KOtBu, dry $(C_2H_5)_2O$, N_2, heat, 1 h, 0 °C to heat; (e) NaOMe, dry DMF, 0 °C to room temperature, 1 h, heat, overnight; (f) $C_2H_5OMe_2SiH$, PtO_2, N_2, 60 °C, 15 h, TBAF, THF, N_2, 0 °C to room temperature, 15 h

Centelles *et al*. synthesized stilbene derivatives and evaluated their cytotoxicity activity and inhibitory activity against VEGF. First, styrene **82** and **83a-d** in presence of K_2CO_3 gave analogues **84a-d**. Next, the reaction between compounds **84a-d** and allyl bromide produced compounds **85a**,**b** (Scheme **18**).



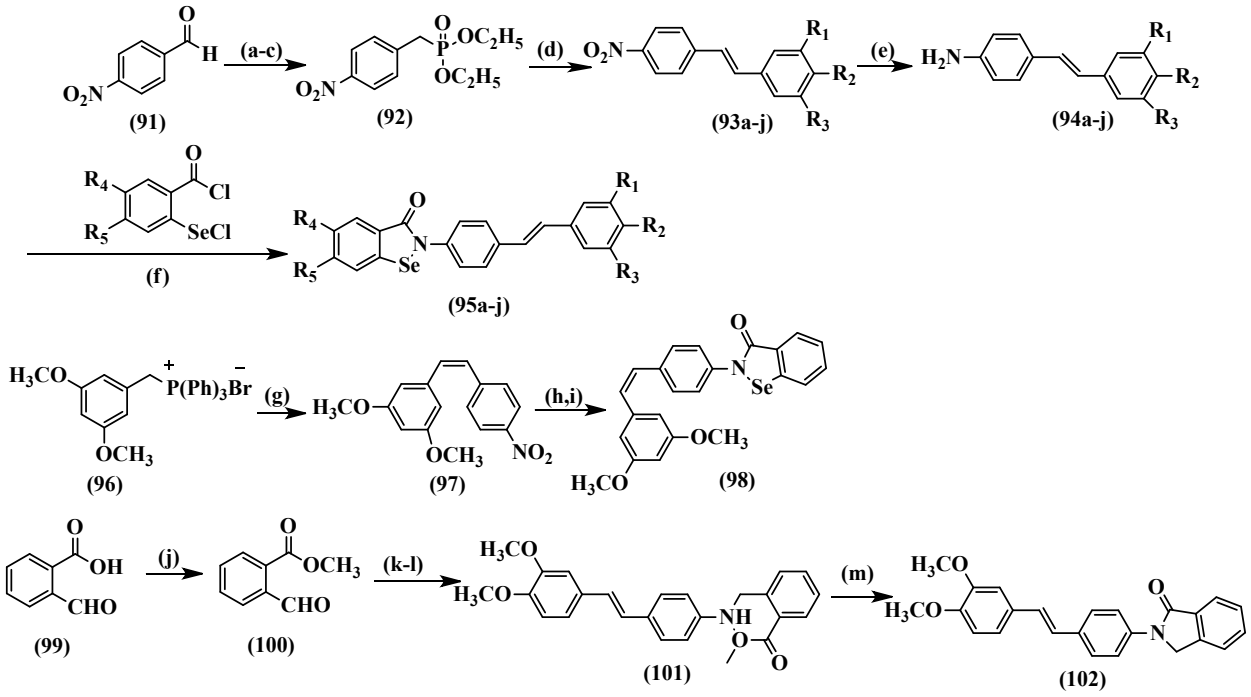
SCHEME 18 Synthesis of stilbene derivatives. Reagents and conditions: (a) Pd(0), K_2CO_3, 170 °C, MW (70 W, 10 min); (b) K_2CO_3, acetone, room temperature, 24 h

*Z*hang *et al*. synthesized 2-hydroxylated *E*-stilbenes and assessed their anti-proliferative activity. Synthesis of **88a-j** was accomplished by oxidative joining of 2-hydroxystyrenes **86** and arylboronic acids **87** (Scheme **19**).



SCHEME 19 Synthesis of 2-hydroxylated *E*-isomer stilbenes. Reagents and conditions: (a) $[CpRhCl_2]_2$, $Cu(OAc)_2$, CH_3OH, room temperature

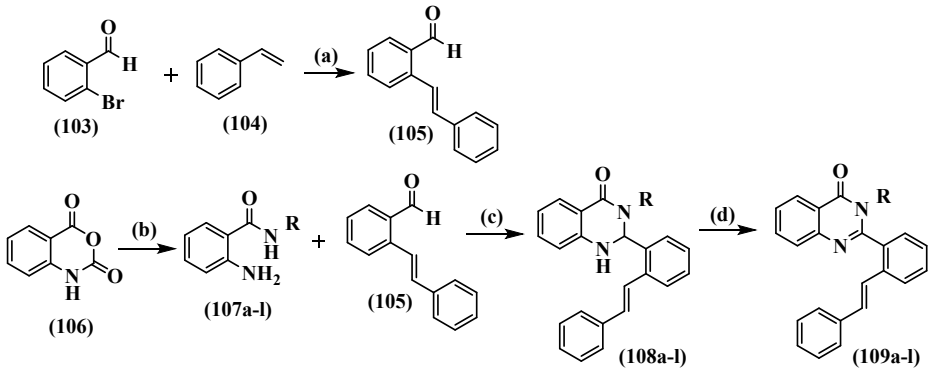
Yan *et al*. synthesized benzoselenazole-stilbene hybrids and assessed their cytotoxicity activity. 4-Nitrobenzaldehyde **91** was first reacted with sodium borohydride to produce (4-nitrophenyl)methanol. The reaction of (4-nitrophenyl)methanol with phosphorus tribromide produced 1-(bromomethyl)-4-nitrobenzene. Next, this compound reacted with pyridine and triethyl phosphate to give the intermediate **92**. After, intermediate **92** reacted with different substituted aldehydes to yield stilbene derivatives **93a-j**. Afterward, amines **94a-j** was reduced by compounds **93a-j**, reacted with diverse 2-(chloroseleno)benzoyl chlorides to provide the target compounds **95a-j**. On the other hand, compound **98** was found via the reaction of phosphonium salt **96**, *p*-nitrobenzaldehyde **97**, and 2-(chloroseleno)benzoyl chloride. Besides, the methyl esterification of 2-formylbenzoic acid **99** produced compound **100**. Flowingly, compound **100** was treated with *E*-4-(4-fluoro-3,5-dimethoxystyryl)aniline to give **101**. Finally, CH_3ONa was added to **101** to provide derivative **102** (Scheme **20**).



Scheme 20 Synthesis of benzoselenazole-stilbene hybrids. Reagents and conditions: (a) $NaBH_4$, CH_3OH, 0 ˚C, room temperature; (b) PBr_3, pyridine, DCM, 0 ˚C, room temperature; (c) triethyl phosphate, 120 ˚C; (d) Different aldehydes, CH_3ONa, 0 ˚C, 1 h, room temperature, 12 h; (e) $SnCl_2.2H_2O$, AcOEt, 90 ˚C; (f) NaH, THF, 0 ˚C, room temperature; (g) *p*-nitrobenzaldehyde, n-BuLi, THF, -78 ˚C; (h) $Na_2S_2O_4$, acetone/H_2O; (i) NaH, THF, 0 ˚C, room temperature; (j) $SOCl_2$,

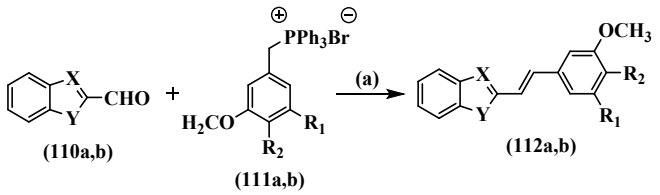
CH_3OH; (k) Na_2SO_4, C_2H_5OH, room temperatur; (l) $NaBH_4$, C_2H_5OH; (m) $NaOCH_3$, CH_3OH, refluxed

Mahdavi *et al*. designed *N*-substituted 2-arylquinazolinones and tested their cytotoxicity activity. 2-Bromobenzaldehyde **103** reacted with styrene **104** to give *E*-**105**. In another category, the anthranilamide derivatives **107a-l** were provided by the reaction of suitable primary amine with isatoic anhydride **106**. Next, the reaction of compound **107a-l** with aldehyde **105** yielded the intermediates **108a-l**. Lastly, intermediates **108a-l** were converted to final compounds **109a-l** (Scheme **21**).



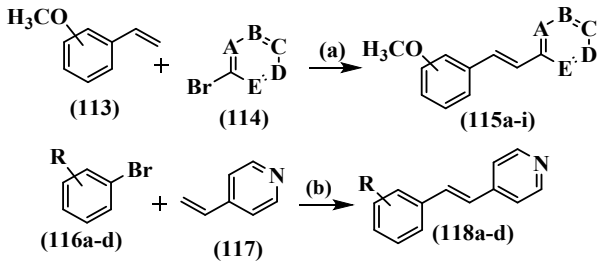
SCHEME 21 Synthesis of *N*-substituted 2-arylquinazolinones bearing *E*-stilbene scaffold. Reagents and conditions: (a) $Pd(OAc)_2$, NaOAc, polyethylene glycol, 100 °C, 3h; (b) R-NH_2, H_2O, room temperature, 3-5h; (c) K_2CO_3, CH_3OH, refluxed, 2-4 h; (d) Potassium *tert*-butoxide, TBAB, dry THF, room temperature, 4-6h

Penthala *et al.* synthesized and evaluated cytotoxicity activity of heteroaromatic analogues of resveratrol. Analogues of **112a**,**b** were synthesized by carbaldehyde derivatives **110a**,**b** with a diversity of triphenyl phosphonium bromide salts **111a**,**b** in sodium methoxide (Scheme **22**).



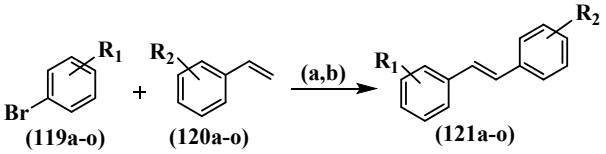
SCHEME 22 Synthesis of resveratrol analogues. Reagents and conditions: (a) 5% $NaOCH_3$, CH_3OH, 3-5 h, room temperature

Centelles *et al.* synthesized nitrogen-containing heterocyclic stilbene analogues and tested their inhibitory activity against hTERT, VEGF, and c-Myc. To produce stilbene derivatives **115a-i**, bromopyridine or bromopyrimidine derivatives **114** reacted with styrene derivatives **113**. On the other hand, 4-vinylpyridine **117** with the appropriate bromo aniline or bromo phenol **116a-d** together reacted to yield compounds **118a-d** (Scheme **23**).



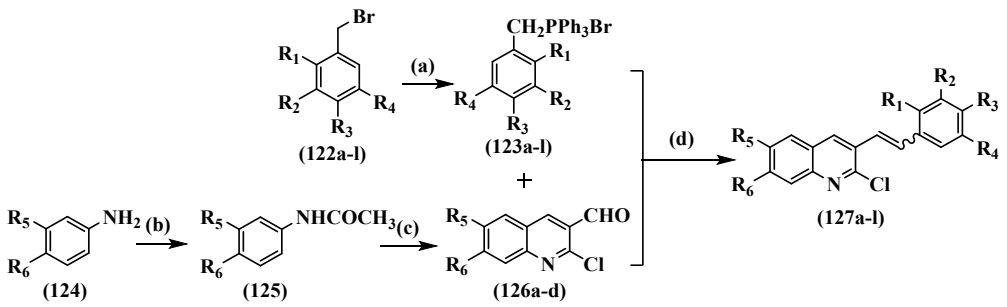
SCHEME 23 Synthesis of nitrogen-containing heterocyclic stilbene analogues. Reagents and conditions: (a) *Tri-n*-butylamine, TBAB, H_2O, $Pd(NH_3)_2Cl_2$, EtOAc, microwave 70 W, room temperature to 140 ˚C, 1.5 h, H_2O, EtOAc; (b) $Pd(NH_3)_2Cl_2$, piperidine, DMF, microwave 70 W, room temperature, 140 ˚C, 1.5 h

Centelles *et al.* synthesized resveratrol analogues and assessed their cytotoxicity activity. Stilbene derivatives **121a-o** were produced by reaction of bromo derivatives **119a-o** with the corresponding styrene derivatives **120a-o** (Scheme **24**).



SCHEME 24 Synthesis of stilbenes related to resveratrol. Reagents and conditions: (a) $Pd(PPh_3)_4$, piperidine, DMF, 180 ˚C, 3 h; (b) $Pd(NH_3)_2Cl_2$, Bu_3N, TBAB, H_2O, 140 ˚C, 1.5 h

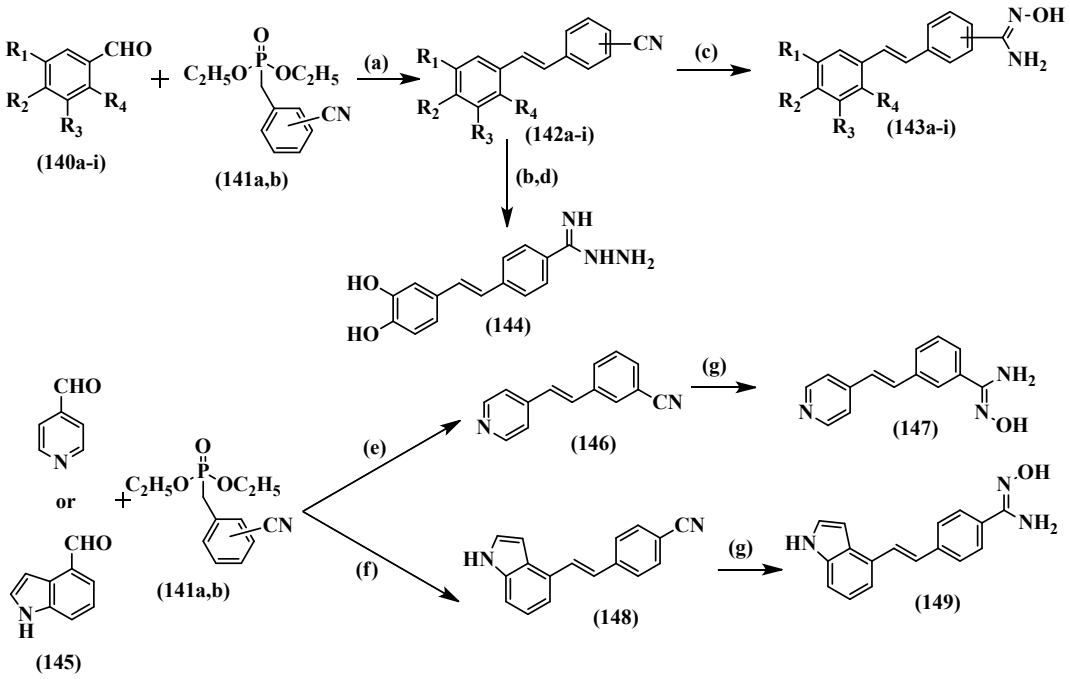
Srivastava *et al*. synthesized quinolino-stilbene derivatives and evaluated their cytotoxicity activity. Analogues **122a-l** were dissolved with triphenylphosphine and refluxed to get salt **123a-l**. On the other hand, compounds **125a-l** were produced by **124a-l**. Then, substituting acetanilide **125** with $POCl_3$ provided quinoline-3-carbaldehydes **126a-d**. Afterword, reactions on substituted **126a-d** and salts **123a-l** produced *E*/*Z*-**127a-l** (Scheme **25**).



SCHEME 25 Synthesis of quinolino-stilbene derivatives. Reagents and conditions: (a) PPh_3, toluene, refluxed, 110 °C, 1-3 h; (b) dil. HCl, acetic anhydride, room temperature; (c) $POCl_3$, DMF, ice, 90 °C, refluxed; (d) NaOH, DMSO, room temperature, 30 min

Kachhadia *et al.* described synthesis of stilbene derivatives and evaluated their anti-cancer activity. First, phenylacetic acid **128** reacted with methyl-4-formylcinnamate **129** to yield acrylic acid **130**. Then, it treated with substituted amine to yield **131**. Compound **130** was converted to anhydride by methyl chloroformate. This compound reduced to alcohol and oxidized to yield aldehyde. The ester was then obtained by reductive amination of aldehyde with suitable amine via sodium borohydride. The change of the esters into hydroxamic acids **131a-o** and **132a-o** were carried out with methanolic hydroxylamine. In the case of compounds **135a-d**, suitable heteroaryl acetic acid was used instead of phenylacetic acid and the procedure was similar to what was described above. On the other hand, the given method was followed to make the compounds 1**39a-c** from compound **138**, which is the same method used to produce **131a-o** and **132a-o** (Scheme **26**).

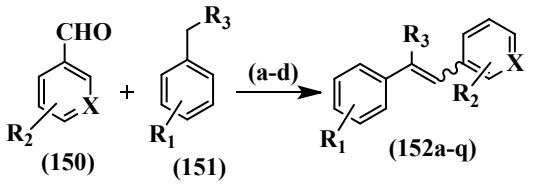
Duan *et al*. designed resveratrol derivatives and tested them against LSD1. First, the reaction of **141a**,**b** with suitable benzaldehydes **140a-i** resulted in stilbene derivatives **142a-i**. Next, treatment of **142a-i** with hydroxylamine and triethylamine provided amidoximes **143a-i**. After that, compound **144** was prepared from *E*-4-(3,4-dihydroxystyryl)benzonitrile **142a-i** by treatment with hydrazine. On the other hand, isonicotinaldehyde or 1*H*-indole-4-carbaldehyde reacted with **141a**,**b** to produce **146** and **148**. Finally, TEA and $NH_2OH.HCl$ were added to **146** and **148** to afford stilbene derivatives **147** and **149** (Scheme **27**).



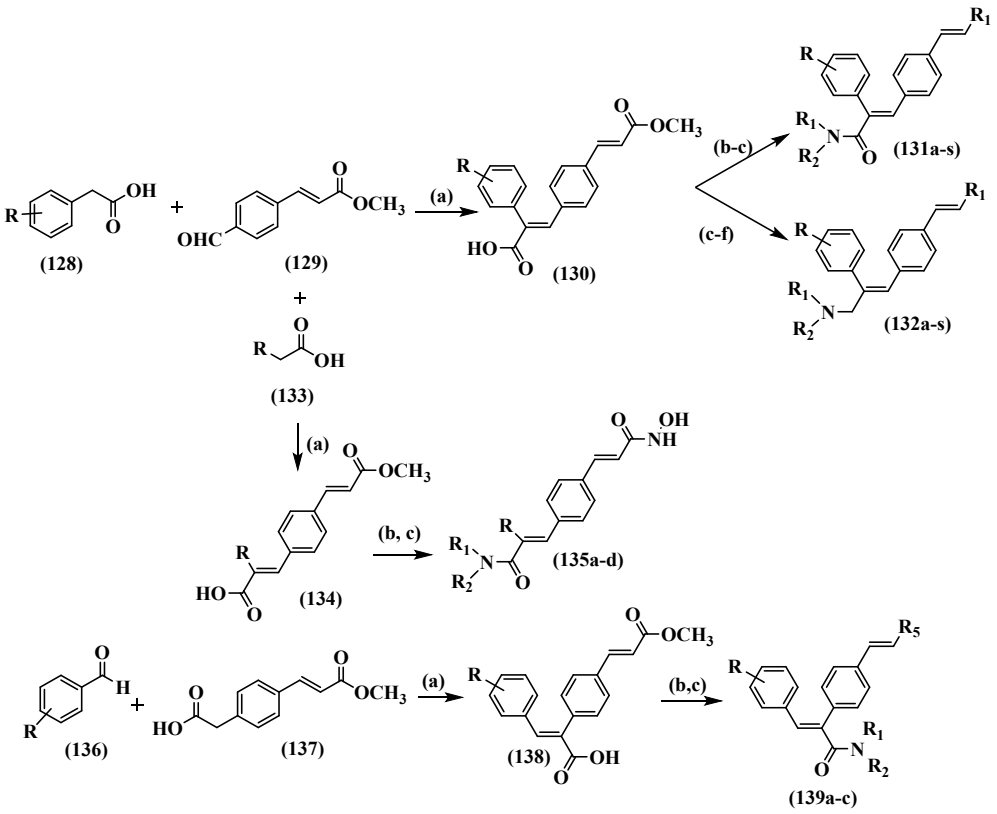
SCHEME 27 Synthesis of compounds resveratrol derivatives. Reagents and conditions: (a) DMF, *t*-BuOK, 0 ˚C, room temperature, 0.5-2 h; (b) BBr_3, DCM, -35 ˚C, room temperature, overnight; (c) $NH_2OH.HCl$, TEA, CH_3OH, refluxed, 3-5 h; (d) (i) *E*-isomer 4-(3,4-dihydroxystyryl)benzonitrile, C_2H_5OH, HCl (gas), 0 ˚C, room temperature, 2 h; (ii) $NH_2NH_2.H_2O$, C_2H_5OH, room temperature, 3 h; (e) *t*-BuOH, *t*-BuOK, 0 ˚C, room temperature, 1 h; (f) DMF, *t*-BuOK, 0 ˚C, room temperature, 2 h; (g) $NH_2OH.HCl$, TEA, CH_3OH, refluxed, 5h

Ismail *et al.* synthesized stilbene derivatives and evaluated their tyrosinase inhibitory activity.

The reaction between compounds **150** and **151** produced the final compound *E*/Z-**152a-q** (Scheme **28**).



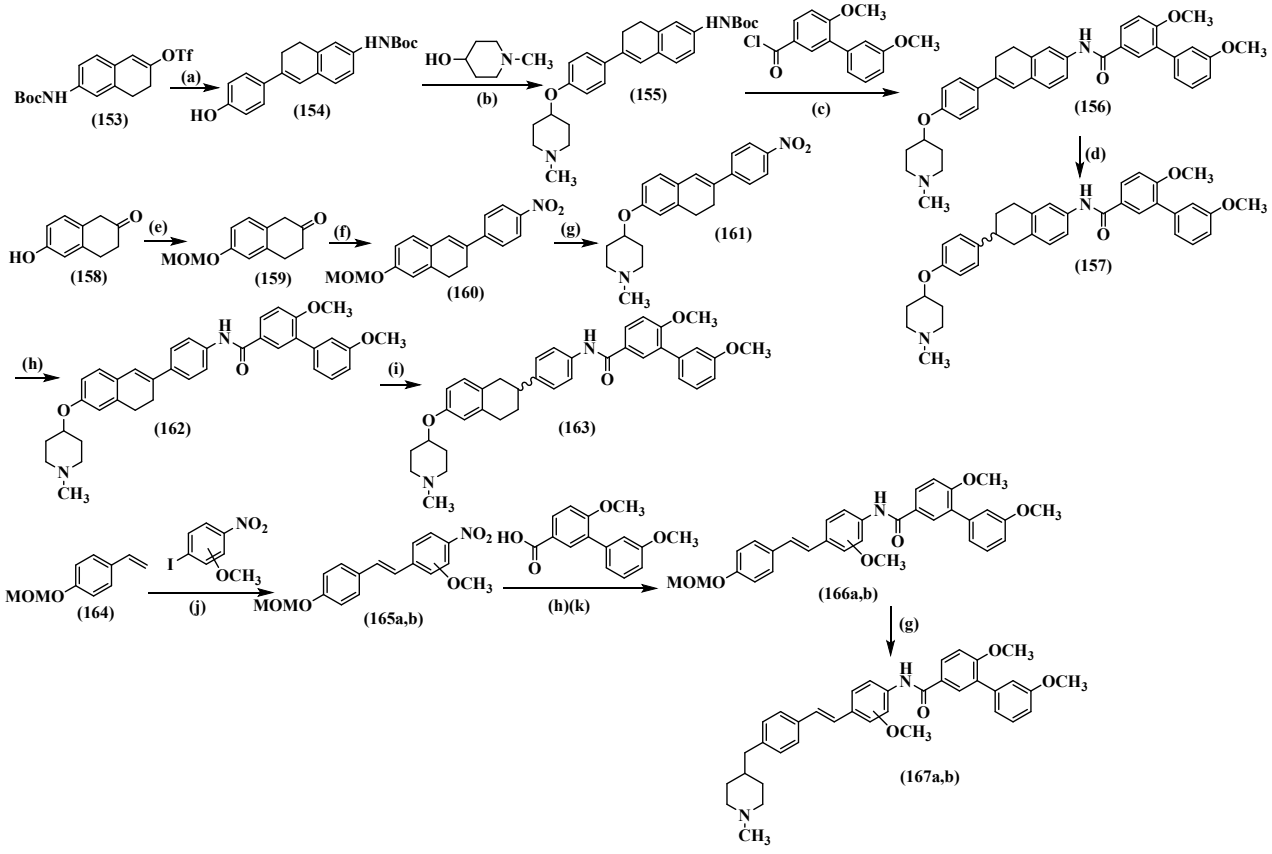
SCHEME 28 Synthesis of stilbene derivatives. Reagents and conditions: (a) $NaOH/H_2O$, DCM; (b) I_2, hexane; (c) $NaOCH_3/CH_3OH$, THF; (d) piperidin, pyridine, 115 ˚C

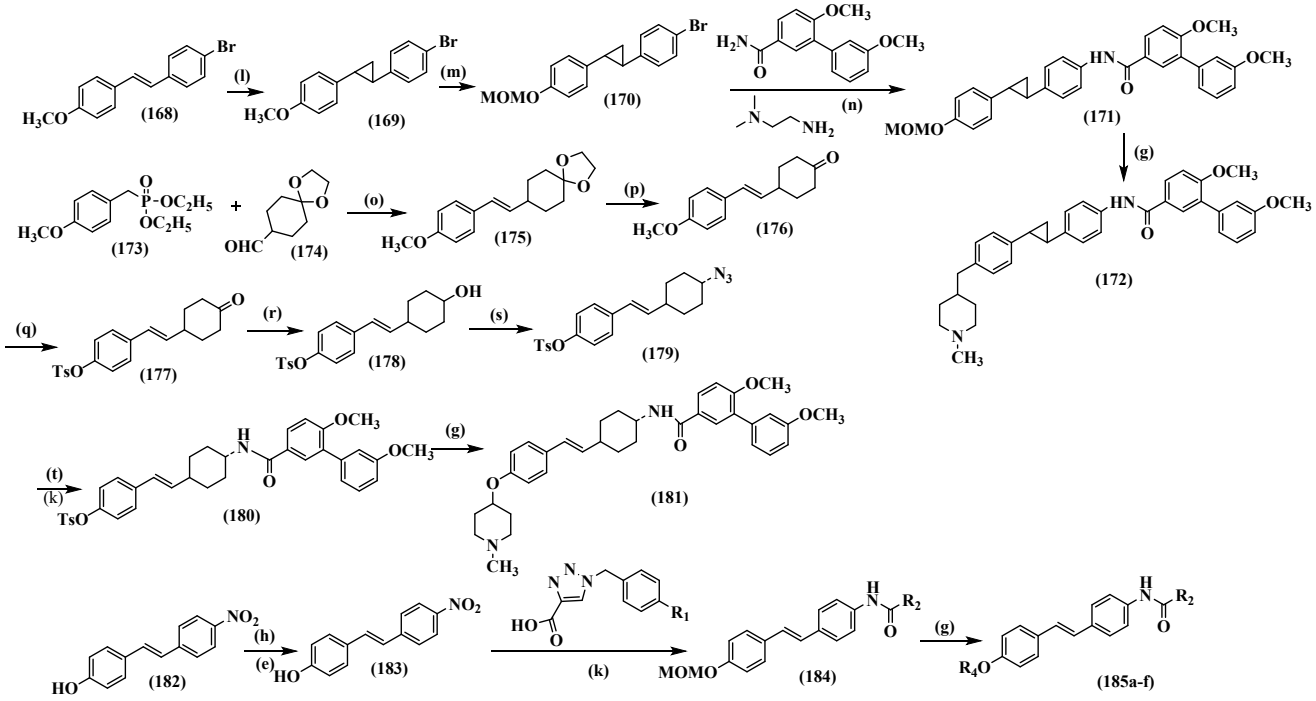


SCHEME 26 Synthesis of stilbene derivatives. Reagents and conditions: (a) Ac_2O, DIPEA, room temperature, 80 ˚C; (b) DMF, EDCI, HOBut, R_1R_2NH, TEA, room temperature; (c) CH_3OH, $NH_2OH.HCl$, KOH, room temperature; (d) THF, TEA, methyl chloroformate, $NaBH_4$, CH_3OH, 5-30 ˚C; (e) DCM, PCC, room temperature; (f) CH_3OH, R_1R_2-NH, $NaBH_4$, room temperature

Katherine *et al*. synthesized stilbene analogous and evaluated their cytotoxicity activity. First, the reaction of vinyl triflate **153** and 4-hydroxyphenylboronic acid yielded **154**. Then, with **154**, *N*-methyl-4-piperidinol was coupled. Following that, intermediate **155** was combined with acid chloride to produce **156**. Then, hydrogenation of compound **156** yielded the saturated derivative **157**. On the other hand, tetralone **158** was first converted to vinyl triflate and then immediately combined with 4-nitrophenylboronic acid to form **160**. After, the nitro group in **161** was reduced to the corresponding aniline, and the aniline reacted with acid chloride in procedure **162**. Next, hydrogenation of **162** resulted in saturated compound **163**. Afterword, triethanolamine was added to a mixture of styrene **164** to produce **165a**,**b**. Compounds **166a**,**b** and **167** were prepared following the same procedure for **162** and **161**, respectively. Besides, the cyclopropane

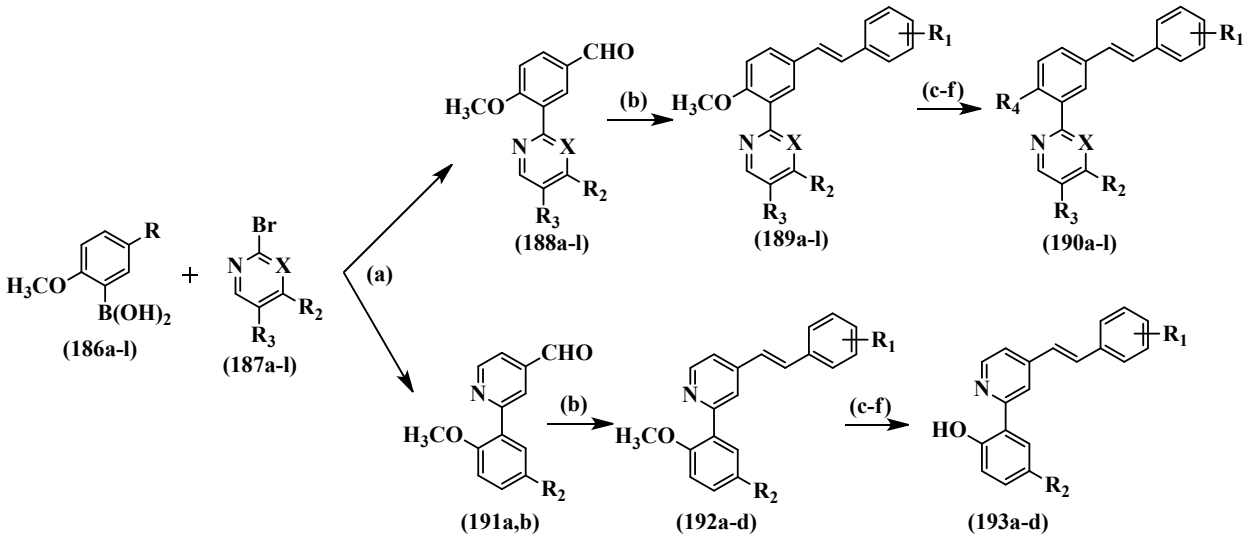
analogues were created by cyclopropanation of stilbene **168**. After demethylating **169**, a methoxymethyl group was added to the resulting phenol. According to the formula, aryl bromide **170** was amidated with amide to form **171**. After removing the methoxymethyl ether, the corresponding phenol was combined with *N*-methyl-4-piperidinol to yield **172**. Next, the saturated analogue was created through a reaction between phosphonate **173** and aldehyde **174**, yielding **175**. After that, the ketal on **175** was removed, the resulting ketone **176** was subjected to a deprotection protocol to yield **177**. Then, **177** was used to make compound **178**. The alcohol was activated with methanesulfonyl chloride, and the resulting mesylate was displaced to form azide **179**. Removal of the toluenesulfonate ester and coupling of the resulting phenol with *N*-methyl-4-piperidinol completed the preparation of **181**. Compound **183** was produced by **182**. Then, compound **184** reduced with hydrogen and ammonium chloride and it was added to the solution of **183** to produce compounds **185a-d** (Scheme **29**).





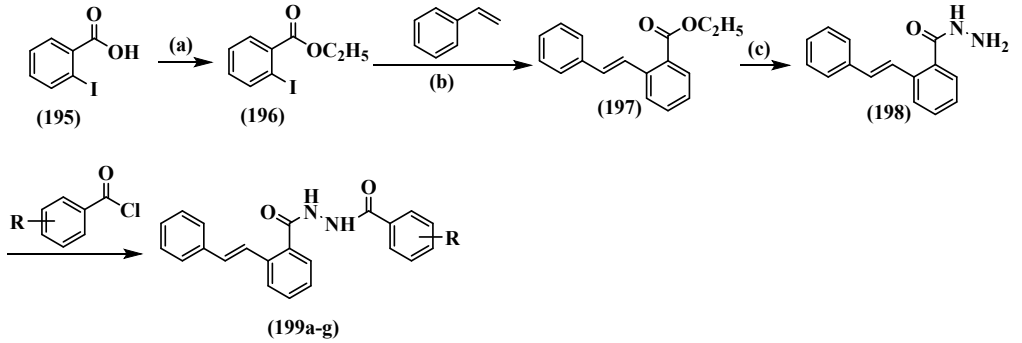
SCHEME 29 Synthesis of stilbene analogous. Reagents and conditions: (a) $Pd(dppf)Cl_2$, K_2CO_3, 4-hydroxyphenylboronic acid, DMF, H_2O, 130 ˚C, 30 min, MW; (b) TMAD, Bu_3P, benzene, 0 to 70 ˚C; (c) TFA, DCM, (ii) TEA, DCM, room temperature; (d) H_2 (g), Pd/C, C_2H_5OH, room temperature; (e) MOMCI, DIPEA, DCM, room temperature; (f) (i) NaHMDS, $PhNTf_2$, THF, -78 ˚C, 1.5 h, (ii) $Pd(dppf)Cl_2$, K_2CO_3, 4-hydroxyphenylboronic acid, DMF, H_2O, 130 ˚C, 30 min, MW; (g) (i) HCl, CH_3OH, reflux, (ii) 1-methylpiperidin-4-ol, TMAD, Bu_3P, Benzene, 0 to 70 ˚C; (h) (i) Fe (reduced by H_2), NH_4CI H_2O/C_2H_5OH, refluxed, 2 h, (ii) 3',6-dimethoxy-[1,1'-biphenyl]-3-carbonyl chloride, TEA, DCM, room temperature; (i) H_2 (g), Pd/C, C_2H_5OH, room temperature; (j) Pd(OAc), triethanolamine 100 ˚C; (k) (h) Fe, NH_4CI, C_2H_5OH/H_2O, refluxed, 2 h (ii) EDCI, DIPEA, DCM, room temperature; (l) DCM, TFA, C_2H_5Zn, 0 ˚C, room temperature; (m) (i) BBr_3, DCM, 0 ˚C, 2h, (ii) MOMCl, DIPEA, DCM, room temperature, 3 h; (n) CuI, K_2CO_3, 1,4-dioxan, 100 ˚C; (o) NaHMDS, THF, 0 ˚C, room temperature; (p) HCl, CH_3OH, 90 ˚C, 1 h; (i) NaOH, C_2H_5OH, TMAD, Bu_3P, benzene, 0-70 ˚C, (ii) 10, TMAD, Bu_3P; (q) (i) BBr_3, DCM, 0 ˚C, 2h, (ii) TsCl, K_2CO_3, THF/H_2O 0 ˚C, room temperature; (r) L-selectrie, THF, 0 ˚C, room temperature; (s) (i) MsCl, Pry. DCM, 0 ˚C, room temperature, (ii) *n*-Bu_4NH_3, DMF, 100 ˚C; (t) $ZnHCO_2NH_4$, CH_3OH, room temperature

Duan *et al.* designed stilbene derivatives as LSD1 inhibitors and evaluated their cytotoxicity activity. Boronic acid first reacted with numerous substituted 2-bromopyrimidine or 2-bromopyridine to give compounds **188a-l** and **191a,b**. Then, **188a-l** and **191a**,**b** with different substituted diethyl benzylphosphonate reacted to yield the stilbene compounds. Next, demethylation and reduction of these compounds, followed by reactions with BBr_3 and hydroxylamine, afforded amidoxime compounds **190a-l** and **193a-d** (Scheme **30**).



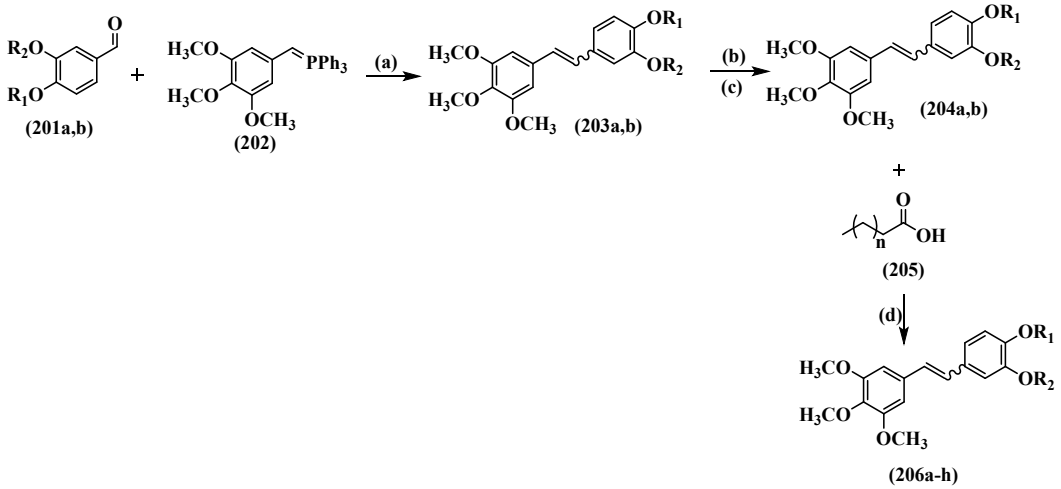
SCHEME 30 Synthesis of stilbene derivatives. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, toluene, C_2H_5OH, 95 ˚C, 4-6 h; (b) substituted diethyl benzylphosphonate, *t*-BuOK, dry DMF, 0 ˚C, room temperature, 0.5-3 h; (c) BBr_3, dry DCM, -35 ˚C, room temperature, overnight; (d) $NH_2OH.HCl$, TEA, CH_3OH, refluxed, 6 h; (e) Ethyl acetate, $SnCl_2$, C_2H_5OH, refluxed, 3-6 h; (f) BBr_3, dry DCM, TEA, -35 ˚C, room temperature, overnight

Iqbal *et al.* synthesized *E*-stilbene hydrazides and tested their cytotoxicity activity. 2-Iodobenzoic acid **195** produced ester **196** and the resulting ester was coupled with styrene to give *E*-**197**. Accordingly, the ester of compound **197** was changed to *E*-stilbene hydrazide **198** by treating it with hydrazine hydrate. Finally, compounds **199a-g** were accomplished from hydrazide **198** by condensation with a diversity of acid chloride (Scheme **31**).



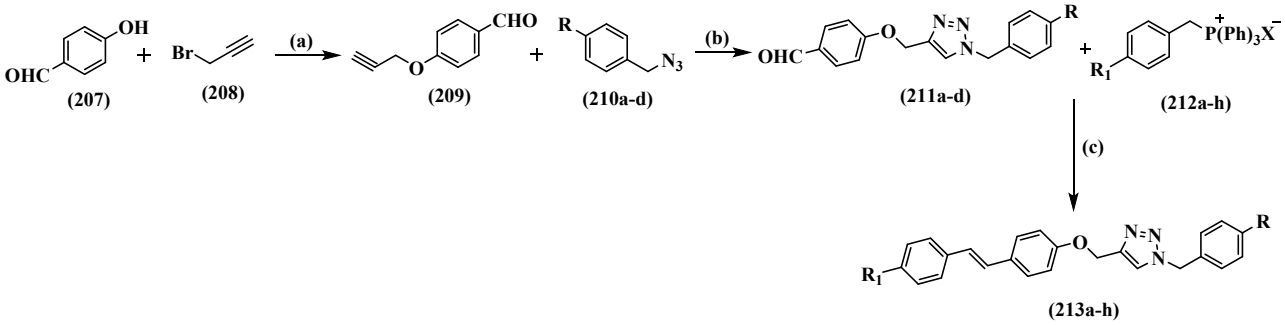
SCHEME 31 Synthesis of *E*-isomer stilbene hydrazides. Reagents and conditions: (a) C_2H_5OH/H^+, H_2SO_4; (b) $Pd(OAc)_2$, PPh_3, TEA; (c) $NH_2NH_2.H_2O$, C_2H_5OH

Wong *et al.* synthesized stilbene long-chain fatty acid conjugates and assessed their cytotoxicity activity. Reaction between compounds **201** and **202** afford *E/Z*-**203a**,**b**. Then, compounds *E/Z*-**203a**,**b** with suitable reagents yielded *E/Z*-**204a,b**. After that, compounds *E/Z*-**204a**,**b** reacted with carboxylic acid. Finally, compounds **206a-h** were produced from acid and a mixture of *E/Z*-**204a,b** (Scheme **32**).



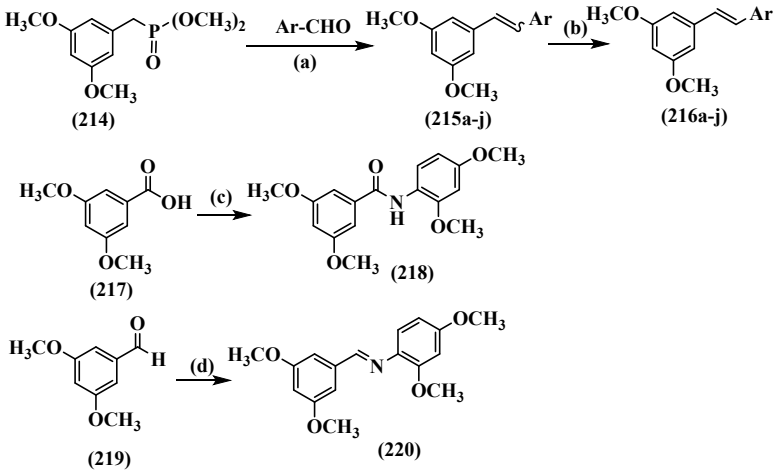
SCHEME 32 Synthesis of stilbene long-chain fatty acid conjugates. Reagents and conditions: (a) *n*-BuLi, THF, 0 ˚C; (b) TBAF, THF, N_2 gas, 0 ˚C, 4 h; (c) R-CO_2H, DCC, DMAP, DCM, MW, room temperature, 12 min; (d) Stearic acid, oleic acid, linoleic acid, DCC, DMAP, DCM ,100 W, 25 ˚C

Das *et al.* synthesized and tested stilbene linked 1,2,3-triazoles against six cell lines. First, the reaction between **207** and **208** led to compound **209**. Then, compounds **211a-d** obtained by **209** and **210a-d**. Finally, *E*-**213a-h** were obtained by reaction between the respective **211a-d** and **212a-h** (Scheme **33**).



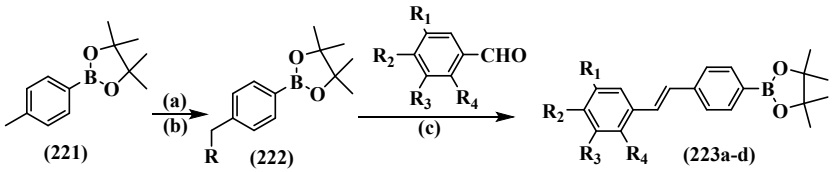
SCHEME 33 Synthesis of stilbene linked 1,2,3-triazoles. Reagents and conditions: (a) K_2CO_3, 25 °C, dry DMF, 10 h; (b) Cat.Cu, $CuSO_4.5H_2O$, sodium ascorbate, *tert*-butanol, 35 °C, 5 h; (c) Benzene, NaH, 0-5 °C, 16 h, 28 °C

Kim *et al*. synthesized *E*-stilbene analogues and evaluated their inhibitory activity on human CYP1A1, CYP1A2, and CYP1B1. The reaction of aromatic aldehydes with phosphonate **214** yielded *E*/*Z*-**215a-j**. Then, *E*/*Z*-**215a-j** were converted to *E*-**216a-j**. On the other side, compound **217** was converted to amide **218**. Finally, the imine analogue **220** was prepared by **219** and 2,4-dimethoxyaniline (Scheme **34**).



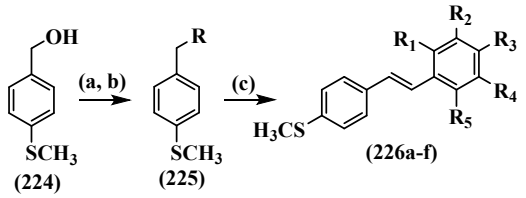
SCHEME 34 Synthesis of *E*-isomer stilbene derivatives. Reagents and conditions: (a) Ar-CHO, cat.18-crown-6, KOH, DCM; (b) Cat. I_2, heptane, refluxed; (c) CCl_3CN, Ph_3P, DCM, room temperature, 2,4-dimethoxyaniline, TEA; (d) Toluene, refluxed

Das *et al.* synthesized pinacolyl boronate-substituted stilbenes and tested lipogenic inhibitors. Compound **222** was prepared from compound **221**. Next, the resulting compound reacted with aldehyde in the presence of a base to obtain compound **223a-d** (Scheme **35**).



SCHEME 35 Synthesis of pinacolyl boronate-substituted stilbenes. Reagents and conditions: (a) NBS, AIBN, CCl_4, reflux, 12 h; (b) PPh_3Br, CH_3CN, 90 °C, 6 h; (c) *t*-BuONa, DMF, room temperature

Mikstacka *et al.* synthesized *E*-resveratrol analogues and evaluated their inhibitory activity on some CYPs. 4-Methylthiobenzyl alcohol **224** was converted to **225** by the corresponding reagents. Finally, analogues **226a-f** were prepared via the reaction of **225** with benzaldehydes (Scheme **36**).

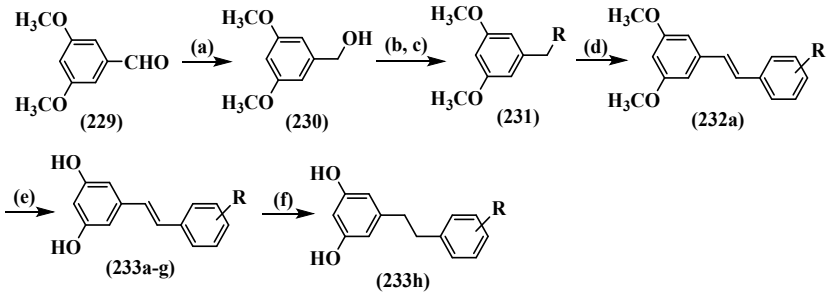


SCHEME 36 Synthesis of the *E*-resveratrol analogues. Reagents and conditions: (a) $SOCl_2$, toluene, 0.5 h, room temperature ;(b) $P(OC_2H_5)_3$, 130 °C, 2 h ; (c) (R_1-R_5)PhCHO, NaH, DMF, 0 °C to room temperature, 2 h

Lu *et al*. synthesized resveratrol derivatives and tested their Aß-aggregation inhibitory activity.

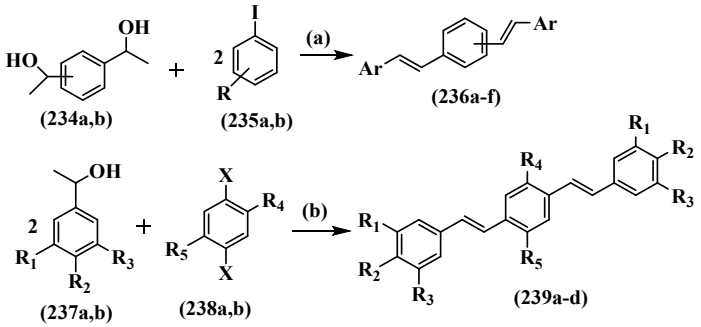
First, **230** was obtained by reducing **229** with sodium borohydride. Then, in the presence of pyridine, this compound reacted with phosphorus tribromide to produce bromo derivatives,

which were then converted into diethyl 3,5-dimethoxybenzylphosphonate. Next, compound **232a** was synthesized by olefination of compound **231** with various substituted benzaldehydes. After that, demethylation of **232a** with boron tribromide yielded the target compounds **233a-g**. Subsequently, compound **233h** was obtained from compound **233a** (Scheme **37**).



SCHEME 37 Synthesis of resveratrol derivatives. Reagents and conditions: (a) $NaBH_4$, CH_3OH; (b) PBr_3, pyridine, 0 ˚C; (c) triethyl phosphite, 120 ˚C; (d) CH_3ONa, 0 ˚C, room temperature, 12 h; (e) BBr_3, DCM, -20 ˚C, 2 h; room temperature, 4 h; (f) Pd/C, H_2, room temperature, 12 h

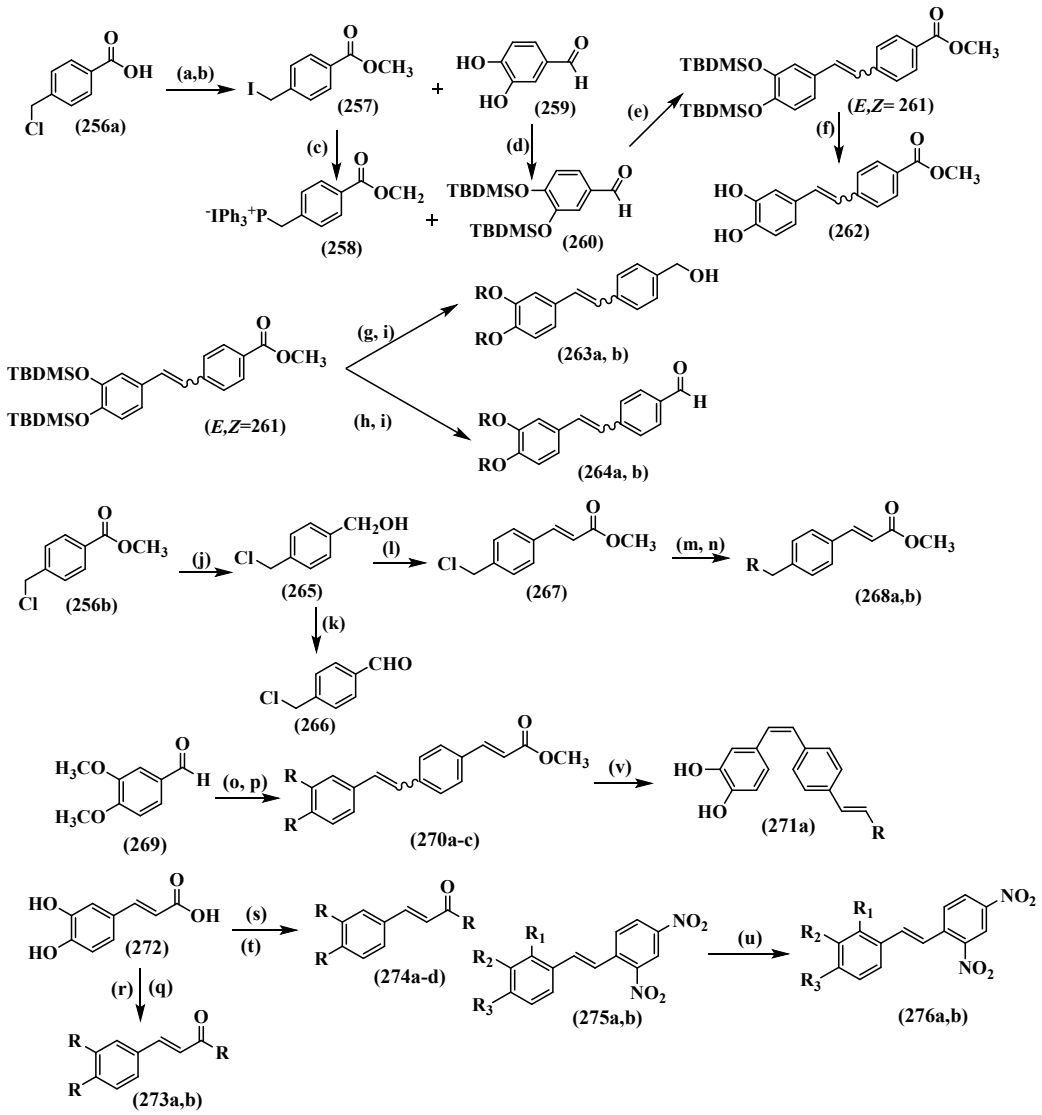
Andhare *et al.* designed *E*-distyrylbenzenes and tested them against Alzheimer's disease. A mixture of compounds **234a**/**b** with compounds **235a**/**b** reacted to give the target distyrylbenzenes **236a-f**. In addition, hydroxylated distyrylbenzenes **239a-d** were produced by the reaction of secondary benzyl alcohols **237a**,**b** and **238a**,**b** (Scheme **38**).



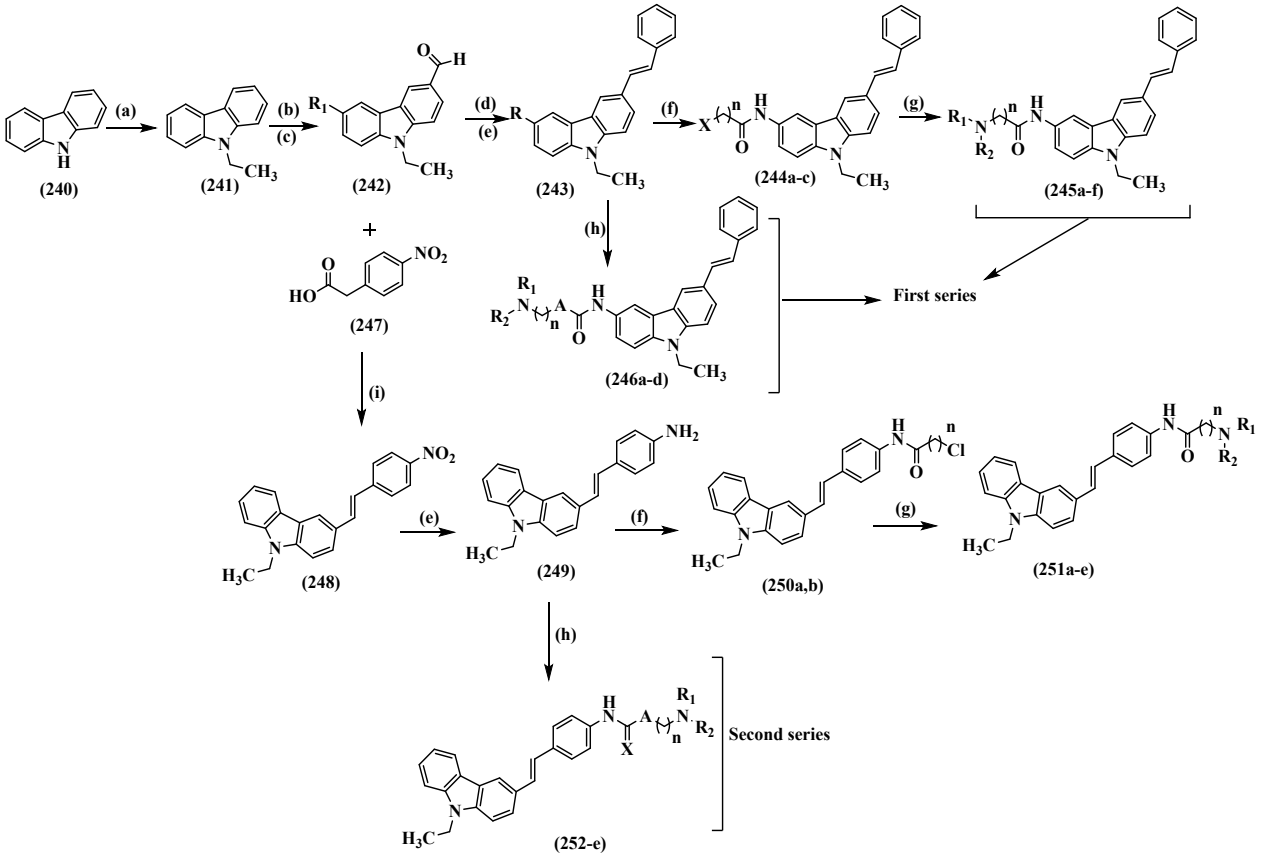
SCHEME 38 Synthesis of *E*-distyrylbenzenes derivatives. Reagents and conditions: (a) $Pd(dba)_2$, PCy_3, HCOONa, piperidine, LiCl, [hmim]Br, MW; (b) $Pd(dba)_2$, PCy_3, piperidine, sodium formate, LiCl, [hmim]Br, MW, 150 ˚C

Patel *et al*. designed carbazole-stilbene hybrids and tested their anti-alzheimer activity. *N*-ethylcarbazole **241** was produced by ethylation of carbazole **240**. Next, mono-formylation of *N*-ethylcarbazole **241** produced **242**. The nitro derivative was obtained by reacting **242** with nitric acid. Then, produced intermediate reacted with benzyltriphenylphosphonium bromide to produce a mixture of *E/Z*-isomers. By performing the reaction with catalytic amounts of iodine, an amine intermediate was offered by the reduction of the nitro group. Then, it was converted to *E*-**243**. The reaction of the amine intermediate with the acid chloride resulted in the amide intermediates **244a-c**. Next, it was linked with alicyclic amines to provide the compounds **245a-e**. The designed **246a-f** was obtained by reacting the **243** with *p*-nitrophenyl chloroformate. The *E*-**248** was obtained by reacting **242** with 4-nitrophenylacetic acid **247**. The desired amine intermediate **249** was obtained by reducing the nitro group of compound **248** with stannous chloride. Similar to compounds **245a-e**, derivatives **251a-e** have been synthesized. The reaction of intermediate amine **249** with *p*-nitrophenyl chloroformate yielded **250a,b**, which were then treated with aminoalkylamines to yield the designed urea derivatives **251a-e**. Similarly, the designed thiourea derivatives **252a-f** were obtained by reacting the amine intermediate **249** with thiocarbonyldiimidazole (Scheme **39**).

Jung *et al*. synthesized stilbene derivatives and tested their inhibitor activity against protein tyrosine phosphatase 1B (PTP1B). Compound **257** was produced by **256a** and NaI. Compounds **258** and **260** were produced by compounds **257** and **259** in the presence of PPh_3 and tert-butyldimethylsilyl chloride, respectively. The reaction of the protected aromatic aldehyde **260** with the compounds **258** gave the *E*/Z-stilbene derivative **261**. Compound **262** was produced by **261**. Further, reduction of ester moiety of *E*-**261** provided **263** and **264a**,**b**. On the other hand, compounds **265** and **266** produced by **256b**. Compound **267** was produced by **265** and **266** in the presence of $NaOCH_3$. Compounds **266** and **267** prepared **268**. Compound **268** with the aromatic aldehyde **269** afforded olefin compounds **270a-c.** Similarly, demethylation of *Z*-**270c** provided **271a**. Compound **273** was produced by **272**. Derivatives **274a-d** was also produced by compound **272**. Compounds **274a-d** are produced using **273**. Similarly, demethylation of stilbenes **275a-c** by the boron tribromide afforded stilbene derivatives **276a-c** (Scheme **40**).



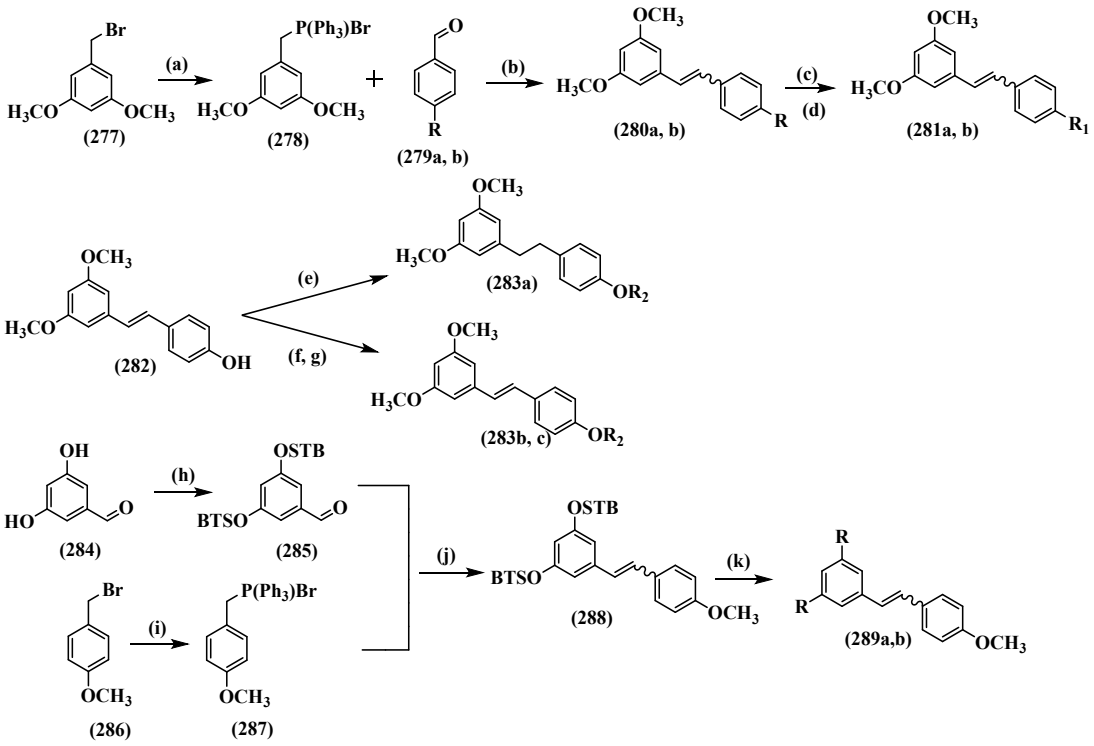
SCHEME 40 Synthesis of stilbene derivatives. Reagents and conditions: (a) $(CH_3)_2SO_4$, K_2CO_3, acetone; (b) NaI, dry acetone, refluxed; (c) PPh_3, dry ether, refluxed; (d) *Tert*-Butyldimethylsilyl chloride, imidazole, DMF, 25 ˚C; (e) NaH/THF, 0 ˚C; (f-h) THF, 0-25 ˚C, 1 h; (i) Diisobutylaluminium hydride, tert-butyldimethylsilyl ethers, *tetra-n*-butylammonium fluoride DCM, -78 ˚C; (j) Diisobutylaluminium hydride, -78˚C, DCM, N_2; (k) Pyridinium chlorochromate, 0 ˚C, DCM, N_2; (l) Trimethyl phosphate, $NaOCH_3$, CH_3OH; (m) NaI, N_2, acetone, refluxed; (n) Thiamine pyrophosphate, $NaOCH_3$, CH_3OH; (o) *n*-BuLi, THF, 0 ˚C, 12 h; (p) Boron tribromide, DCM, 0 ˚C; (q) CH_2N_2, $(C_2H_5)_2O$, 0 ˚C; (r) LiOH, THF/H_2O, room temperature; (s) Hydroxybenzotriazole, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, amine, DCM, room temperature; (t) Boron tribromide, DCM, 0 ˚C; (u) Boron tribromide, DCM, 0 ˚C, 2 h; (v) demethylation



SCHEME 39 Synthesis of carbazole-stilbene hybrids. Reagents and conditions: (a) C_2H_5Br, NaOH, DMSO, room temperature; (b) $POCl_3$, DMF, $CHCl_3$; (c) HNO_3, AcOH; (d) (i) benzyltriphenylphosphonium bromide, LiOH, IPA, reflux, (ii) I_2, toluene, reflux; (e) $SnCl_2$, THF, CH_3OH, refluxed; (f) acid chloride, K_2CO_3, acetone; (g) NHR_1R_2, THF, reflux; (h) pnitrophenyl chloroformate, TEA, DCM:THF, 0 ˚C to room temperature, pyrrolidine/piperidine/aminoalkylamines, room temperature; (i) Piperidine, MW

Mizuno *et al*. studied pterostilbene analogues on peroxisome proliferator-activated receptor α (PPARα) activation. Compound **278** was produced by **277**. Next, the reaction of phosphonium salt **278** with aromatic aldehydes **279** produced a mixture of *E/Z*-**280**. Then, nitro derivative **280a** was treated with sodium dithionite to yield compound **281a**. In the next step, hydrolysis of esters **280b** afforded acid **281b**. Compound **282** produced compounds **283a-c** with the corresponding reagents. Finally, reaction between **284**, **286**, PPh_3, and toluene produced **285**

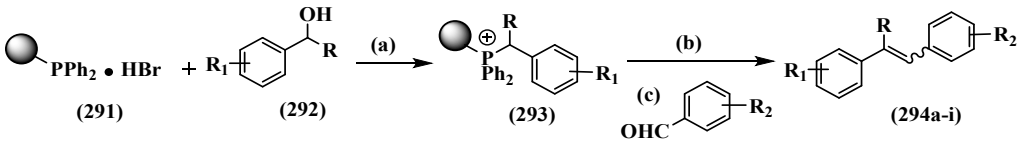
and **287**. The reaction between aldehyde **285** and phosphonium salt **287** produced **288**. Finally, this compound afforded *E/Z*-**289a,b** (Scheme **41**).



SCHEME 41 Synthesis of stilbene derivatives. Reagents and Conditions: (a) PPh_3, toluene, refluxed, overnight; (b) *n*-BuLi, THF, -78 ˚C, room temperature, overnight; (c) $Na_2S_2O_4$, acetone/H_2O, 50 ˚C. (d) NaOH, CH_3OH, refluxed, 4 days; (e) Pd/C, CH_3OH, overnight; (f) DMAP, DIEA, CH_3CN, dibenzyl phosphite, CCl_4, -10 ˚C, room temperature, 12 h; (g) $BrSi(CH)_3$, DCM 0 ˚C, room temperature, 2 h; (h) TBDMSCl, DIEA, DMF, 18 h, room temperature; (i) PPh_3, toluene, refluxed, overnight; (j) *n*-BuLi, THF, 15 ˚C, room temperature, 12 h; (k) TBAF, THF, 15 min

Kang *et al*. synthesized resveratrol analogues and reported their inhibitory activity against COX-1, COX-2, and NF-κB.

To produce **293**, a phosphine-substituted polystyrene resin **291** was used to form a phosphonium ion with various substituted benzylic alcohols **292**. Next, the resveratrol analogues **294a-i** were formed by deprotonation of **293** and then reaction with various substituted benzaldehydes (Scheme **42**).



SCHEME 42 Solid-phase synthesis of resveratrol analogues. Reagents and conditions: (a) CH_3Cl, 65 ˚C,8h; (b) NaH