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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of some stilbene-based analogues

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Abstract The phytoalexin 3,5,4′-trihydroxy-*trans*-stilbene (resveratrol) has attracted considerable attention from biologists and chemists due to its diverse biological properties. Owing to the biological importance of this compound, we have synthesized new stilbene-based analogues by using substituted benzyl chlorides and substituted aldehydes in a two-step reaction and evaluated their in vitro antioxidant, antibacterial and antifungal potential. Most of the compounds displayed moderate to significant radical scavenging activity. (*E*)-1-(3,4-difluorophenyl)-2-(4-fluorophenyl)ethene (**4c**) showed nearer equipotent antibacterial activity against *Staphylococcus aureus.* (*E*)-1,2-bis (4-fluorophenyl)ethene (**4a**), (*E*)-1-(3-fluorophenyl)-2-(4-fluorophenyl)ethene (**4b**), (*E*)-1-(2,4-dichlorophenyl)-2-(3,4-dichlorophenyl)ethene (**4f**), (*E*)-1-(2,4-dichlorophenyl)-2-(3-chlorophenyl)ethene (**4g**), (*E*)-1-(2,4-dichlorophenyl)-2-(4-fluorophenyl)ethene (**4j**) (*E*)-1-(4-fluorophenyl)-2-(3-chlorophenyl)ethene (**4l**) and (*E*)-1-(4-chlorophenyl)-2-(4-fluorophenyl)ethene (**4n**) inhibited the growth of *Penicillium chrysogenum.*

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Introduction

Stilbene-based compounds are largely present in nature and have attracted chemist and biologist, because of their wide range of biological activities (Hart, 1991; Burns *et al.*, 2002). Stilbene itself does not occur in nature, but hydroxylated stilbenes have been found in many medicinal plants. One such example is the *trans*-3,5,4′-trihydroxy stilbene (resveratrol), a phytoalexin present in grapes and plays a role in the prevention of coronary artery disease associated with red wine consumption. (Burns *et al.*, 2002; Soleas *et al.*, 1997; Zhou *et al.*, 2005; Pace-Asciak *et al.*, 1995).

Stilbene derivatives such as the 3,5,4′-trihydroxy-*trans*-stilbene and combretastatin A-4 are the plant microcomponents, and they exhibit a variety of biological activities including antineoplastic, chemopreventive, antioxidant and antiestrogenic (Simoni *et al.*, 2006; Griggs *et al.*, 2001; Mokni *et al.*, 2007; Cirla and Mann, 2003). Moran *et al.*, in 2009 have synthesized fluorinated stilbene analogues and evaluated against variety of cell lines, primarily the non-small lung carcinoma cell lines. They explained that (*E*)-3,5-difluoro-4′-acetoxy stilbene showed greater potency than that of 3,5,4′-trihydroxy-*trans*-stilbene. In the literature, several active stilbenes were identified, such as *cis*-3,5,4′-trimethoxy-3′-amino stilbene and *cis*-3,5,4′-trimethoxy-3′-hydroxy stilbene were found to induce HL60 apoptotic at nanomolar concentration ($IC_{50} = 30$ nm) (Roberti *et al.*, 2003).

3,5,4′-Tihydroxy-*trans*-stilbene displays anti-cyclooxygenase activity (Jang *et al.*, 1997; MacCarrone *et al.*, 1999; Szewczuk *et al.* 2004). Various potentially beneficial

health effects of resveratrol have been attributed to its intrinsic antioxidant capabilities (Knutson and Leeuwenburgh, 2008; Leifert and Abeywardena, 2008; Vingtdeux *et al*., 2008; Udenigwe *et al*., 2008). 3,5,4′-Trihydroxy-*trans*-stilbene however, has also been shown to act as prooxidant. This prooxidant effect is held likely to be responsible for cytotoxic, anti-proliferative and even pro-apoptotic effects of the compound (Ahmad *et al*., 2003; Lastra and Villegas, 2007).

One documented problem with resveratrol is its limited bioavailability owing to its metabolism in the liver. Studies carried out by Kang *et al*. (2009) have shown that circulating resveratrol has a serum half-life of 8–14 min because it is rapidly metabolized by sulfation and glucuronation.

To be useful as a chemotherapeutic, resveratrol must have greater bioavailability and a straightforward approach to increasing bioavailability involves finding analogues with comparable activity that lack the hydroxy groups of resveratrol which consequently cannot be sulfated or glucuronated. Thus, we present here such 14 stilbene-based analogues.

Experimental

Chemistry

All the chemicals used were procured from Sigma-Aldrich, SD Fine Chemicals and Rankem Chemicals, and purified using standard procedures wherever required. Melting points were recorded in open capillary tube on 'Superfit Melting Point Apparatus' and are uncorrected. IR spectra were recorded on KBr disk on the 'Nicolate IR' instrument and are reported in cm^{-1}. ^1H NMR spectra were recorded on a 'Bruker-300' instrument with tetramethylsilane (TMS) as the internal standard in $CDCl_3$ as a solvent. Stilbene analogues namely **4a** (Bevington *et al*., 1995), **4b** (Ager *et al*., 1972), **4e** and **4h** (Kvaran *et al*., 2000), **4f** (Bunce *et al*., 1990), **4i** (Traylor and Stewart, 1986), **4k** (Siegrist *et al*., 1969), **4l** (Gupta *et al*., 1984), **4m** (Murata *et al*., 2002) and **4n** (Prukala, 2006) were prepared according to literature.

General procedure for synthesis of benzyl(chloro)triphenylphosphorane (2)

A stirred solution of substituted benzyl chloride (**1**) (31.7 mmol) in acetonitrile (CH_3CN) (20 mL) was treated with triphenylphosphine (PPh_3) (8.57 g, 32.7 mmol) and the mixture was vigorously stirred with refluxing for 12 h and then evaporated. The crude product was purified by crystallization from chloroform/ethanol, affording 95% yield as a white solid.

General procedure for synthesis of 1-(substituted phenyl)-2-(substituted phenyl)ethene (4c, 4d, 4g and 4j)

Sodium hydride (72 mg, 3 mmol) was added in portions to a well stirred suspension of phosphonium chloride (**2**) (2 mmol) and aryl aldehyde (**3**) (2 mmol) in benzene (20 mL) at 0–5°C, and the mixture was allowed to warm to room temperature. After additional stirring for 16 h, excess sodium hydride was quenched by adding methanol (5 mL). Then chloroform (30 mL) and water was added. The organic and aqueous layers were separated. The aqueous layer contained the phosphonium oxide as an impurity and was discarded. The organic layer was dried over anhydrous $MgSO_4$, the solvent removed in vacuo, and the residue purified by preparative TLC using petroleum ether: ethyl acetate (7:3 v/v) as the eluent.

(E)-1-(3,4-difluorophenyl)-2-(4-fluorophenyl)ethene (4c)

White solid. Yield 37%. M. p. = 121–124°C. Anal. Calcd. for $C_{14}H_9F_3$: C, 71.79; H, 3.87; Found: C, 71.23; H, 3.55. FT-IR (KBr, cm^{-1}) ν_{max}: 3131, 1591, 1484, 1121, 995. ^1H NMR δ: 7.70-7.63 (m, 4H), 7.57 (m, 2H), 7.48 (d, 2H), 7.44 (m, 1H).

(E)-1-(2,4-difluorophenyl)-2-(4-fluorophenyl)ethene (4d)

White solid. Yield 38%. M. p. = 121–124°C. Anal. Calcd. for $C_{14}H_9F_3$: C, 71.79; H, 3.87; Found: C, 71.31; H, 3.41. FT-IR (KBr, cm^{-1}) ν_{max}: 3119, 1598, 1484, 1184, 995.

(E)-1-(2,4-dichlorophenyl)-2-(3-chlorophenyl)ethene (4g)

Yellowish white solid. Yield 35%. M. p. = 122–126°C. Anal. Calcd. for $C_{14}H_9Cl_3$: C, 59.30; H, 3.20; Found: C, 59.28; H, 3.29. FT-IR (KBr, cm^{-1}) ν_{max}: 3111, 1590, 1481, 995, 755 cm^{-1}.

(E)-1-(2,4-dichlorophenyl)-2-(4-fluorophenyl)ethene (4j)

White solid. Yield 40%. M. p. = 124–127°C. Anal. Calcd. for $C_{14}H_9Cl_2F$: C, 62.95; H, 3.40; Found: C, 62.53; H, 3.51. FT–IR (KBr, cm^{-1}) ν_{max}: 3055, 1591, 1471, 1120, 995, 755. ^1H NMR δ: 7.67–7.66 (m, 4H), 7.58–7.51 (m, 3H), 7.53 (d, J = 16.2 Hz, 1H), 7.59 (d, J = 16.2 Hz, 1H).

Biological activity

DPPH-free radical scavenging assay (Blois, 1958; Bondet et al., 1997)

The free radical scavenging ability of the test compounds were determined by using the DPPH-free radical

scavenging assay. An ethanolic solution of DPPH (33 mg in 1000 mL) (3 mL) was mixed with different concentration of each test compound (500–2500 μg/mL) (3 mL) and the absorbance of DPPH change at 517 nm was measured 30 min later. A reaction solution without DPPH was used as blank and DPPH solution as control. Ascorbic acid was used as standard.

Antibacterial assay (Norris et al., 1972; Rao and Venugopala, 2007)

The agar cup plate method was used for the assessment of in vitro antibacterial activity of the synthesized compounds against *Escherichia coli* and *Staph. aureus.* Nutrient agar plates were prepared by using pour plate technique and wells were prepared using a sterile cork borer. A 2% concentration of the synthesized compounds in dimethyl sulfoxide (DMSO) was used. A 2% solution of penicillin was used as the standard. A drug-free control was included and the values of zone of inhibition (mm) were determined after 24 h of static incubation at 37°C.

Antifungal assay (Shastri and Varudkar, 2009 Rivillas-Acevedo and Soriano-García, 2007)

The poison plate method was used for the assessment of in vitro antifungal activity of the synthesized compounds against *A. niger* and *P. chrysogenum*. Potato dextrose agar plates were prepared by using pour plate technique for each compound. A 2% concentration of the synthesized compounds in DMSO as a solvent was used. A 2% solution of griseofulvin was used as standard. A drug-free control was included and plates were observed for growth after 48 h of static incubation at 30°C.

Results and discussion

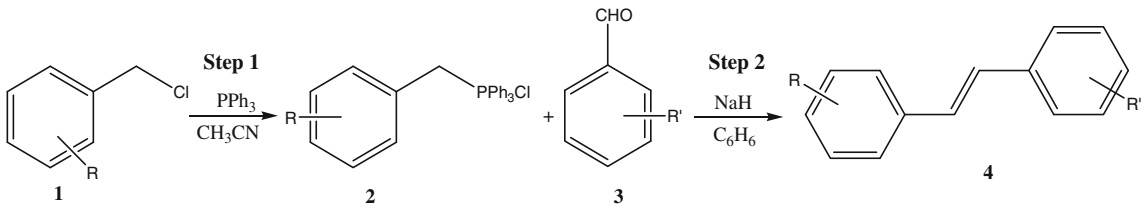
Chemistry

The synthesis of some of the stilbene analogues namely **4c**, **4d**, **4g** and **4j** were carried out by reacting substituted benzyl chlorides and substituted benzaldehydes in a two-step reaction as per Scheme 1 by a Wittig reaction. The products thus formed were *E* and *Z* isomers and were purified by preparative TLC. As discussed earlier in introduction, the aim of this work was to synthesize and evaluate stilbene analogues that lack hydroxyl groups of resveratrol; therefore, we have used fluorine, chlorine and methyl groups as substituents on the basis of the principle of bioisosterism in rational drug design.

Biological evaluation

Free radical scavenging activity

All synthesized stilbene analogues were tested for their in vitro antioxidant activity by using the 1,1-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$)-free radical scavenging assay; the method first employed by Blois in 1958. $DPPH^{\bullet}$ is a stable



R= 4-F; 2,4-Cl; 4-Me

R'= 4-F; 3-F; 3,4-F; 2,4-F; 2,4-Cl; 3,4-Cl; 3-Cl; 4-Cl; 4-Me; 4-F

4a, R= 4-F, R' = 4'-F
4b, R= 4-F, R' = 3'-F
4c, R= 4-F, R' = 3',4'-F
4d, R= 4-F, R' = 2',4'-F
4e, R= 2,4-Cl, R' = 2',4'-Cl
4f, R= 2,4-Cl, R' = 3',4'-Cl
4g, R= 2,4-Cl, R' = 3'-Cl
4h, R= 2,4-Cl, R' = 4'-Cl
4i, R= 4-Me, R' = 4'-Me
4j, R= 2,4-Cl, R' = 4'-F
4k, R= 2,4-Cl, R' = 4'-Me
4l, R= 4-F, R' = 3'-Cl
4m, R=4-F, R' = 4'-Me
4n, R=4-F, R' = 4'-Cl

Scheme 1 Synthesis of resveratrol analogues (**4a**–**4n**)

Table 1 % Radical scavenging activities of synthesized compounds (**4a–4n**)

Sl. no	Concentration (μg/mL)	Absorbance	RSA	SD
	2500	0.338	53.81	±0.3442
	1500	0.403	44.87	±0.3619
4a	1000	0.458	37.39	±0.9108
	500	0.474	35.16	±0.7238
	2500	0.369	49.52	±0.8543
	1500	0.387	47.06	±1.1197
4b	1000	0.423	42.13	±0.3619
	500	0.435	40.49	±0.3619
	2500	0.379	48.15	±0.7616
	1500	0.391	46.51	±0.4932
4c	1000	0.405	44.60	±0.7616
	500	0.410	43.91	±0.8321
	2500	0.347	52.53	±0.4104
	1500	0.363	50.34	±0.2736
4d	1000	0.380	48.02	±0.8321
	500	0.400	45.28	±1.8096
	2500	0.319	56.36	±0.7616
	1500	0.364	50.21	±0.3619
4e	1000	0.375	48.70	±0.9575
	500	0.405	44.60	±0.6839
	2500	0.307	58.00	±0.8321
	1500	0.335	54.17	±0.2736
4f	1000	0.372	49.11	±0.4738
	500	0.391	46.51	±0.7238
	2500	0.282	61.42	±1.0684
	1500	0.321	56.09	±0.3619
4g	1000	0.368	49.66	±0.3619
	500	0.404	44.73	±0.4104
	2500	0.386	47.20	±0.7238
	1500	0.397	45.69	±0.9477
4h	1000	0.413	43.50	±0.5472
	500	0.429	41.31	±2.1368
	2500	0.453	38.03	±0.4932
	1500	0.460	37.07	±0.8207
4i	1000	0.470	35.70	±0.6268
	500	0.476	34.88	±0.6268
	2500	0.444	39.26	±0.9575
	1500	0.455	37.76	±0.7616
4j	1000	0.460	37.07	±0.8970
	500	0.474	35.16	±0.3619
	2500	0.445	39.12	±0.8543
	1500	0.460	37.07	±0.3619
4k	1000	0.465	36.39	±1.1925
	500	0.477	34.75	±0.4104
	2500	0.440	39.81	±0.4932
	1500	0.455	37.76	±0.9864
4l	1000	0.471	35.57	±0.7238
	500	0.490	32.97	±0.4932
	2500	0.399	45.42	±2.1716
	1500	0.442	39.53	±1.0684
4m	1000	0.465	36.39	±0.4932
	500	0.472	35.43	±0.8543
	2500	0.398	45.55	±0.7616
	1500	0.427	41.59	±1.3049
4n	1000	0.433	40.77	±0.7108
	500	0.458	37.35	±1.2159
	50	0.020	94.69	±0.4738
	40	0.030	92.04	±0.3619
AA	30	0.050	86.74	±0.3619
	20	0.072	80.90	±0.3619

%RSA percentage radical scavenging activity

SD standard deviation

AA ascorbic acid

free radical that can accept an electron or a hydrogen radical to become a stable diamagnetic molecule. The radical scavenging potential of the synthesized compounds were determined by measuring the decrease in absorbance of $DPPH^{\bullet}$ (originally purple in colour) at 517 nm, representing the formation of its reduced form, 1,1-diphenyl-2-picryl-hydrazine, which is yellow in colour. All experiments were carried out in triplicate and repeated at least three times. Results are expressed as percentage radical scavenging activity and were calculated by the following formula:

$$\% \text{ Radical scavenging activity} = \frac{\text{Control} - \text{Sample}}{\text{Control}} \times 100$$

The activities of the synthesized compounds are shown in Table 1. The antioxidant activity of all synthesized stilbene analogues were evaluated at 10–50 times higher concentration of ascorbic acid (standard). Compounds **4a**, **4d**, **4e**, **4f** and **4g** showed %RSA > 50% radical scavenging activity, while compounds **4b**, **4c**, **4h**, **4m** and **4n** showed %RSA > 40% activity.

Antibacterial activity

The antibacterial activity of the synthesized stilbene analogues was determined by screening against *E. coli* and *Staph. aureus* bacterial species using the agar cup plate assay method. The antibacterial activities of the stilbene

Table 2 Antibacterial activity of compounds (**4a**–**4n**) against *Staph. aureus* and *E. coli*

Compound	*E. coli* (*mm*)	*S. aureus* (*mm*)
4a	−ve	24
4b	−ve	28
4c	−ve	36
4d	−ve	30
4e	−ve	24
4f	−ve	28
4g	−ve	26
4h	−ve	24
4i	−ve	20
4j	−ve	18
4k	−ve	12
4l	−ve	22
4m	−ve	−ve
4n	−ve	20
DMSO	−ve	−ve
Penicillin	17	40

−*ve* no antibacterial activity

mm Zone of inhibition in mm

Table 3 Antifungal activity of compounds against *Aspergillus niger* and *Penicillium chrysogenum*

Compound	*Aspergillus niger*	*Penicillium chrysogenum*
4a	+ve	−ve
4b	+ve	−ve
4c	+ve	+ve
4d	+ve	+ve
4e	+ve	+ve
4f	+ve	−ve
4g	+ve	−ve
4h	+ve	+ve
4i	+ve	+ve
4j	+ve	−ve
4k	+ve	+ve
4l	+ve	−ve
4m	+ve	+ve
4n	+ve	−ve
DMSO	+ve	+ve
Griseofulvin	−ve	−ve

+*ve* no antifungal activity observed

−*ve* antifungal activity observed

analogues are shown in Table 2. From the results, we can conclude that synthesized compounds had selectivity for *Staph. aureus* only. Compound **4c** showed equipotent antibacterial activity against *Staph. aureus* as compared to penicillin, while all other compounds showed moderate antibacterial activity against *Staph. aureus*.

Antifungal activity

The antifungal activity of the stilbene analogues was determined by screening against *A. niger* and *Penicillium chrysogenum* fungal species using the poison plate assay method and results are presented as the growth of organism observed or not. The antifungal activities of all synthesized stilbene analogues are shown in Table 3. All compounds showed negative antifungal activity against *A. niger*. Compounds **4a**, **4b**, **4f**, **4g**, **4j**, **4l** and **4n** inhibited the growth of *P. chrysogenum* and proved their antifungal potential.

Conclusion

The antioxidant activity was evaluated by DPPH-free radical scavenging assay and compounds showed moderate (%RSA > 40) to significant (%RSA > 50) radical scavenging activity.

All compounds showed negative antibacterial activity against *E. coli*. Compound **4c** showed nearly equipotent antibacterial activity against *S. aureus* as compared to penicillin, while all other compounds showed moderate to significant antibacterial activity against *S. aureus*. All compounds showed negative antifungal activity against *A. niger*. Compounds **4a**, **4b**, **4f**, **4g**, **4j**, **4l** and **4n** inhibited the growth of *P. chrysogenum*.

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