ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis of Stilbene-Based Resveratrol Analogs as Cytotoxic Agents.

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ABSTRACT

Several *trans* stilbenes and *cis* stilbenes with substitution on the olefinic bridge were synthesized and the chemical structures were confirmed by IR, 1H-NMR and mass spectral analysis. The chemical entities were screened for cytotoxic study against human tumor cell lines namely Molt4/C8, CEM and murine leukemia L1210 cell line. Among the tested compounds, results showed that the (*E*)-1,2,3-trimethoxy-5-(4-methylstyryl)benzene **(6h)** emerged as most antiproliferative agent with IC_{50}: 1.2 µM, 1.4 µM and 3.1 µM against L1210, Molt4/C8 and CEM respectively.

Keywords: Stilbene; cytotoxic; olefin

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ISSN: 0975-8585

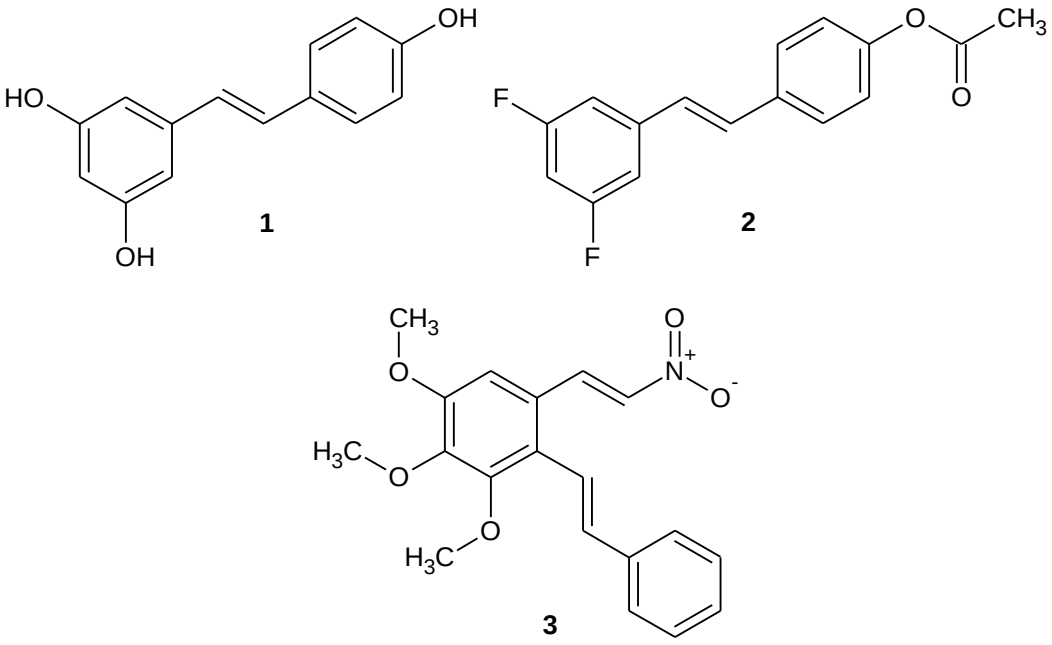
INTRODUCTION

Resveratrol, **1** (3,4',5-trihydroxy-*trans*-stilbene, **RSV**) is a polyphenolic stilbene classified as a phytoalexin produced by a wide variety of plants [1]. RSV is exclusively synthesized in the leaf epidermis and in the grape skins but not in the flesh [2]. RSV protect the cardiovascular system by a large number of mechanisms including defense against ischemic-reperfusion injury, promotion of vasorelaxation, protection & maintenance of intact endothelium, anti-atherosclerotic properties, inhibition of low-density lipoprotein oxidation, suppression of platelet aggregation & estrogen-like actions [3]. It can affect the processes underlying all three stages of carcinogenesis, involving tumor initiation, promotion & progression. RSV has anticarcinogenic effect and this appears to be closely associated with its anti-oxidant activity [4,5]. It inhibits cyclo-oxigenase [6], protein kinase C [7], BCl-2 phosphorelation [8], nuclear factor kappa β ($NF_{kβ}$) [6] and cell cycle regulators [9]. Lion *et al.,* in 2005 synthesized a novel family of monohydroxylated (*E*)-stilbenes and studied their ability to inhibit the growth and induce apoptosis in human tumor cell lines [10]. Heynekamp *et al.,* in 2006, synthesized various substituted *trans*-stilbenes including analogues of resveratrol, and proved that they inhibit the human tumor necrosis factor α-induced activation of transcription factor nuclear factor kappa-B [11].

Moran *et al.,* in 2009 synthesized fluorinated analogues of resveratrol **(2)** and assayed on a variety of cell lines, primarily the non-small lung carcinoma cell line DLKP-A [12]. Reddy et al., in 2011 designed and synthesized resveratrol-based nitrovinylstilbene **(3)** as antimitotic agents [13]. Karki et al., in 2011 synthesized some stilbene derivatives and screened them against human Molt4/C8, CEM and murine L1210 cell lines [14].

A potential effect of RSV as a trihydroxy stilbene and olefinic carbon scaffold has been the subject of modifications with the aim of generating novel RSV analogues with better anticancer activity.

Figure 1. Resveratrol and other related derivatives



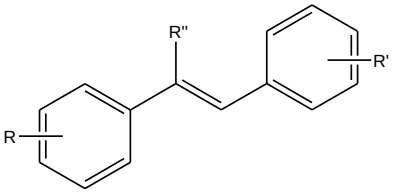
ISSN: 0975-8585

RESULTS AND DISCUSSION

Chemistry

Wittig reaction was carried out by using phosphonium chloride (**5**) with aryl aldehyde in benzene in the presence of sodium hydride. Excess of sodium hydride was quenched by addition of methanol and then were added chloroform and water. After evaporating, organic layer and residue was purified by column chromatography using 5% methanol in hexane as the eluent (**6a-k**) (Scheme 1, Table 1).

Table 1: Physicochemical property of synthesized derivatives



Code No	R	R'	R''	R_f	Mp (ºC)
6a	4-CH_3	3-NO_2	H	0.42	95-98
6b	4-CH_3	4-NO_2	H	0.46	148-150
6c	H	4-NO_2	H	0.45	120-123
6d	4-CH_3	2-NO_2	H	0.68	82-85
6e	4-Cl	2-NO_2	H	0.72	80-83
6f	4-Cl	3-NO_2	H	0.76	85-87
6g	4-Cl	4-NO_2	H	0.38	185-188
6h	4-CH_3	3,4,5-tri-OCH_3	H	0.48	115-120
6i	H	3,4,5-tri-OCH_3	H	0.70	95-98
6j	4-CH_3	3,4-di-OCH_3	H	0.52	105-108
6k	4-CH_3	4-Cl	H	0.58	96-98
8a	H	2-NO_2	COOH	0.60	185-188
8b	H	4-NO_2	COOH	0.72	200-203
8c	H	4-OH	COOH	0.40	210-213
8d	H	3,4-di-OCH_3	COOH	0.42	190-192
8e	H	3-NO_2	COOH	0.56	155-156
8f	H	3-OH-4-OCH_3	COOH	0.48	182-185

Table 2: Inhibitory effects of compounds on the proliferation of murine leukemia cells (L1210/0) and human T-lymphocyte cells (Molt4/C8, CEM/0)

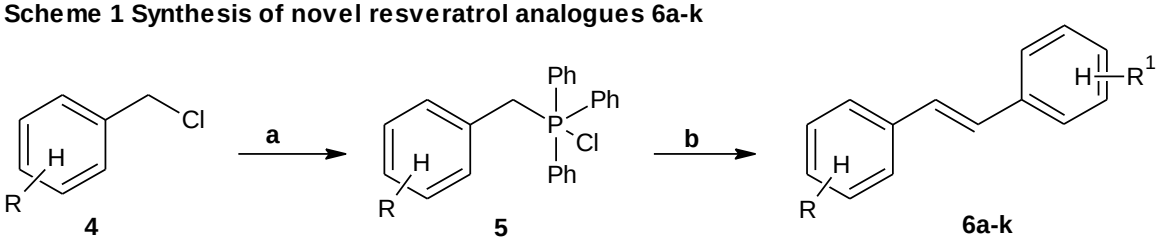
Compound	IC_{50}* (µM)		
	L1210/0	Molt4/C8	CEM/0
6a	≥500	>500	>500
6b	>500	478 ± 31	500
6c	>500	≥500	382 ± 54
6d	64 ± 13	45 ± 7	57 ± 1
6e	349 ± 16	182 ± 36	244 ± 3
6f	160 ± 61	195 ± 6	209 ± 18
6g	≥500	≥500	350 ± 28
6h	1.2 ± 0.5	1.4 ± 0.4	3.1 ± 0.6
6i	190 ± 3	51 ± 9	93 ± 1
6j	>500	>500	>500
6k	≥500	>500	>500
8a	368 ± 187	≥500	500
8b	200 ± 97	250 ± 22	255 ± 38
8c	172 ± 52	192 ± 15	198 ± 3
8d	187 ± 44	226 ± 14	236 ± 6
8e	185 ± 87	192 ± 10	254 ± 23
8f	NT	NT	NT
Melphalan	2.13 ± 0.02	3.24 ± 0.56	2.47 ± 0.21

NT - Not Tested

*50% inhibitory concentration.

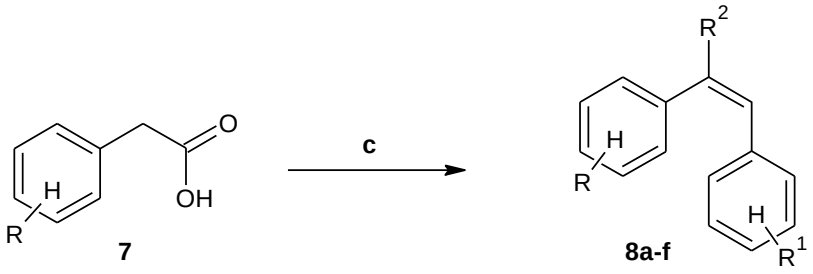
ISSN: 0975-8585

Scheme 1 Synthesis of novel resveratrol analogues 6a-k



a) CH_3CN, triphenyl phosphine; b) NaH, benzene, aryl aldehyde, 0-5 ^0C

Scheme 2 Synthesis of resveratrol analogues modified at olefinic carbon 8a-f



c) triethyl amine, acetic anhydride, aryl aldehyde, dil HCl

Several derivatives containing acidic functional groups were prepared. Base-catalyzed condition of phenyl acetic acid (**7**) with aryl aldehyde in the presence of triethylamine gave the carboxylic acid (**8a-f**) (Scheme 2, Table 1).

In Vitro Cytotoxic Activity

Fifteen *trans* stilbenes 6a-k and five *cis* stilbene 8a-f derivatives with substitution on the olefinic bridge carbon were evaluated for their antiproliferative activity against a panel of three different cell lines from human Molt4/C8 and CEM T-lymphocytes as well and murine leukemia L1210 using MTT assay and were compared with the reference compound melphalan. The results are presented in Table2.

For all the screened compounds, we can observe that the antiproliferative activity against Molt4/C8, CEM and L1210 cells are in general good to very mild activity. Among them derivatives **6h** showed antiproliferative activity with two fold higher IC50 values than that of melphalan against L1210 and Molt cells and displayed almost equipotent antiproliferative activity against CEM. Whereas for derivatives **6d** and **6i** exhibited moderate antiproliferative activity against Molt cells IC50 = 45 and 51 µM respectively. However structure-relationship in this series of resveratrol derivatives that possesses 3,4,5-trimethoxy moiety on one phenyl ring and 4-methyl substituent on another ring demonstrated that there was better antiproliferative activity against all three cell lines. This indicates that, replacement of methyl and 3,4,5-trimethoxy group may play a key role in the antiproliferative activity.

The cytotoxicity on tumor cell lines was evaluated by MTT assay and the results obtained for the different compounds are summarized in Table 2. This group of compounds includes 11 *trans* stilbenes (**6a-k**), 6 *cis* stilbene derivatives with substitution on the bridge connecting two phenyl rings (**8a-f**) (Table 1).

The *trans* stilbenes (**6a-k**) were poorly cytostatic except for **6h** (Table 2). The IC_{50} values ranged between 1.2 and ≥ 500 µM.

Regarding the *cis* stilbenes with substitutions on the olefinic bridge (Table 2), there was not much improvement in cytostatic activity. In separate experiments, a COOH group was introduced at the olefinic

carbon linkage, and this resulted in the formation of compounds **8a-f** (IC_{50} < 150 µg/ml). However, when the -COOH group of the compound was converted to a methyl ester, the cytostatic activity somewhat increased, and the N-methylamide derivatives were clearly less cytostatic (Karki et al., 2011).

CONCLUSION

Several *trans* stilbenes and *cis* stilbenes with substitution on the olefinic bridge were synthesized in an effort to obtain substances that could be more readily formulated. Derivative **6h** emerged as most cytostatic compound against all three cell lines evaluated.

EXPERIMENTAL

Chemistry

The solvents (AR grades) were obtained from Sd Fine Chem., Mumbai, and E. Merck, Mumbai. The reagents (puriss grade) were obtained from SRL, Mumbai. The melting points are taken in open capillary method and are uncorrected. FTIR spectra were recorded in KBr powder on a Jasco 430+ spectrophotometer by diffuse reflectance technique (Jasco, Japan). $^{1}H/^{13}C$ NMR spectra were measured in $CDCl_3$ and DMSO-d6 on a Bruker Ultraspec AMX 400 MHz spectrometer (Bruker, Germany). The reported chemical shifts were against that of TMS. Mass spectra were recorded in triple quadrapole LCMS-6410 from Agilent technologies (US).

General procedure A for the synthesis of Stilbenes (6a-k)

A stirred solution of arylmethyl chloride **4** (2.88 g, 31.7 mmol) in acetonitrile (20 ml) was treated with triphenylphosphine (8.57 g, 32.7 mmol) and the mixture was refluxed with stirring for 12 hrs and then evaporated. The crude product was purified by crystallization from chloroform and ether, affording 95 % yield (11. 7g) as a phosphonium chloride **5**. Sodium hydride (72 mg, 3 mmol) was added in portions to a well-stirred suspension of phosphonium chloride **5** (2 mmol) and aryl aldehyde (2 mmol) in benzene (20 mL) at 0-5 °C, and the mixture was allowed to warm up to room temperature. After an additional stirring for 16 hrs, excess sodium hydride was quenched by the addition of methanol (1 mL), after which 30 ml of chloroform and water was added. The organic and aqueous layers were then separated. Distilled of the organic layer, the residue was purified by preparative TLC using 5% methanol in hexane as the eluent.

(E)-1-(4-Methylstyryl)-3-nitrobenzene (6a):

Following general procedure A, compound **6a** was purified by column chromatography, eluting with hexane/methanol (95:5): 49% yield; IR (KBr) *v* 3086-3023, 2953-2853, 1527, 1480, 1351. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, s), 8.08 (d, *J* = 8 Hz, 1H), 7.78 (d, *J* = 8 Hz, 1H), 7.50 (t, *J* = 16 Hz, 1H), 7.44 (d, *J* = 8 Hz, 2H), 7.25-7.06 (md, *J* = 8 Hz, 4H), 2.37 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ; 148.79 (s), 139.42 (s), 138.61 (s), 133.54 (s), 132.09 (s), 131.74 (s), 129.56 (s), 126.77 (s), 125.12 (s), 121.78 (s), 120.77 (s), 29.68 (s), 21.28 (s). ESI MS: (m/z) 239 (M).

(E)-1-(4-Methylstyryl)-4-nitrobenzene (6b):

Following general procedure A, compound **6b** was purified by column chromatography, eluting with hexane/methanol (95:5): 60% yield; IR (KBr) *v* 3090-3021, 1593, 1517, 1342. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 12 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.26-7.07 (m, ar, 4H), 2.38 (s, 3H, CH_3). ESI MS (m/z) 239 (M)

(E)-1-nitro-4-styrylbenzene (6c):

Following general procedure A, compound **6c** was purified by column chromatography, eluting with hexane/methanol (95:5): 61% yield; IR (KBr) *v* 3103-3026, 2919-2847, 1593, 1510, 1345. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* =8 Hz, 2H), 7.57 (d, *J* = 6 Hz, 2H), 7.41 (t, *J* = 12 Hz, 2H), 7.36-7.32 (m, 1H), 7.29 (s, 1H), 7.17-7.14 (m, 1H).

(E)-1-(4-Methylstyryl)-2-nitrobenzene (6d):

Following general procedure A, compound **6d** was purified by column chromatography, eluting with hexane/methanol (95:5): 59% yield; IR (KBr) *v* 3082-3026, 2975-2854, 1519, 1346. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8 Hz, 1H), 7.41-7.37 (m, 2H), 7.31-7.29 (m, 1H), 6.98-6.93 (m, 4H), 6.85 (d, *J* = 8 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 2.27 (s, 3H, CH_3).

(E)-1-(4-chlorostyryl)-2-nitrobenzene (6e):

Following general procedure A, compound **6e** was purified by column chromatography, eluting with hexane/methanol (95:5): 66% yield; IR (KBr) *v* 3091-3029, 2960, 1524, 1493, 1355. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.12 (d, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.55-7.45 (td, *J* = 16, 8 Hz, 3H), 7.41 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 16 Hz, 1H), 7.12 (d, *J* = 16 Hz, 1H). ESI MS (m/z) 259 (M).

(E)-1-(4-chlorostyryl)-3-nitrobenzene (6f):

Following general procedure A, compound **6f** was purified by column chromatography, eluting with hexane/methanol (95:5): 61% yield; IR (KBr) *v* 3086-3033, 2958-2849, 1525, 1490, 1354. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.13 (d, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.56-7.46 (td, *J* = 16, 8 Hz, 3H), 7.38 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 16 Hz, 1H), 7.13 (d, *J* = 16 Hz, 1H). ESI MS (m/z) 259 (M).

(E)-1-(4-chlorostyryl)-4-nitrobenzene (6g):

Following general procedure A, compound **6g** was purified by column chromatography, eluting with hexane/methanol (95:5): 61% yield; IR (KBr) *v* 3106-3033, 2919-2848, 1591, 1507, 1339. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* =8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.24 (d, *J* = 16 Hz, 1H), 7.13 (d, *J* = 16 Hz, 1H).

(E)-1,2,3-trimethoxy-5-(4-methylstyryl)benzene (6h):

Following general procedure A, compound **6h** was purified by column chromatography, eluting with hexane/methanol (95:5): 51% yield; IR (KBr) *v* 3050, 2986-2826, 1584, 1510, 1335. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8 Hz, 2H), 7.18 (d, 2H, *J* = 8 Hz), 6.99 (s, 1H), 6.73 (s, 1H), 3.93 (s, 9H, $3OCH_3$), 2.36 (s, 3H, CH_3). ESI MS (m/z) 284 (M).

(E)-1-2-3-trimethoxy-5-styrylbenzene (6i):

Following general procedure A, compound **6j** was purified by column chromatography, eluting with hexane/methanol (95:5): 59% yield; IR (KBr) v 3059, 2994-2828, 1584, 1506, 1455, 1346, 1325. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8 Hz, 2H), 7.37 (t, J = 12 Hz, 2H), 7.28 (t, J = 12 Hz, 1H), 7.04 (d, 2H), 6.76 (s, 2H), 3.93 (s, 9H, $3OCH_3$).

(E)-1-2-dimethoxy-4-(4-methylstyryl)benzene (6j):

Following general procedure A, compound **6k** was purified by column chromatography, eluting with hexane/methanol (95:5): 59% yield; IR (KBr) v 3078-3003, 2958-2846, 1583, 1514, 1339. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8 Hz, 2H), 7.17 (d, J =8 Hz, 2H), 7.07-6.93 (m, 4H), 6.87 (d, J = 8 Hz, 1H), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3). ESI MS (m/z) (%) 254 (M).

(E)-1-chloro-4-(4-methylstyryl)benzene (6k):

Following general procedure A, compound **6l** was purified by column chromatography, eluting with hexane/methanol (95:5): 66% yield; IR (KBr) v 3052-3020, 2917-2852, 1588, 1562, 1479, 1383. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.41 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 1H), 7.29-7.16 (m, 4H), 7.10-7.06 (m, 1H), 7.00-6.96 (m, 1H), 2.36 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ; 139.48 (s), 138.02 (s), 134.63 (s), 134.07 (s), 130.09 (s), 129.83 (s), 129.47 (s), 127.26 (s), 126.58 (s), 126.22 (s), 124.62 (s), 29.69 (s), 21.25 (s). ESI MS (m/z) 228 (M-1).

General Procedure B for the Synthesis of olefinic substituted stilbenes (8a-f).

A mixture of aryl acetic acid **7** (2 mmol) aryl aldehyde (2 mmol) and triethylamine (0.5 mL) in acetic anhydride (5 mL) was heated under reflux for 12 hrs and poured into hot saturated sodium carbonate solution (50 mL) and left overnight. The mixture was extracted with ether (2 X 50 mL), the ether extracts were discarded, and the aqueous solution was acidified with dilute HCl, after which the precipitated product was filtered and dried.

(E)-3-(2-nitrophenyl)-2-phenyl-acrylicacid (8a):

Following general procedure B, compound **8a** was purified by recrystalization from ethyl acetate-hexane: 86% yield; IR (KBr) v 3200-2500, 1684, 1517, 1338. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.11 (d, J = 8 Hz, 1H), 7.39-7.30 (m, 2H), 7.26-7.24 (m, 3H), 7.16-7.15 (m, 2H), 6.95 (d, J = 8 Hz, 1H). ESI MS (m/z) 270 (M+1).

(E)-3-(4-nitrophenyl)-2-phenyl-acrylic acid (8b):

Following general procedure B, compound **8b** was purified by recrystalization from ethyl acetate-hexane: 88% yield; IR (KBr) v 3300-2700, 1683, 1617, 1591, 1516, 1344. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8 Hz, 2H), 7.95 (s, 1H), 7.41-7.27 (m, 3H), 7.22-7.20 (m, 4H). ESI MS (m/z) 270 (M+1).

(E)-3-(4-hydroxyphenyl)-2-phenyl-acrylic acid (8c):

Following general procedure B, compound **8c** was purified by recrystalization from ethyl acetate-hexane: 78% yield; IR (KBr) v 3300-2700, 1683, 1617, 1591, 1516, 1344. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 9.88 (s, 1H, OH), 7.67 (s, 1H), 7.42-7.36 (m, 3H), 7.17 (d, J = 8 Hz, 2H), 6.89 (d, J = 8Hz, 2H), 6.57 (d, J = 8 Hz, 2H). ESI MS (m/z) 240 (M).

(E)-3-(3,4-dimethoxyphenyl)-2-phenyl-acrylic acid (8d):

Following general procedure B, compound **8d** was purified by recrystalization from ethyl acetate-hexane: 82% yield; IR (KBr) v 3525, 3050, 2836-2971, 1669, 1595, 1514, 1422. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.44-7.26 (m, 6H), 6.88 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 6.43 (s, 1H), 3.85 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3). ESI MS (m/z) 284 (M).

(E)-3-(3-nitrophenyl)-2-phenyl-acrylic acid (8e):

Following general procedure B, compound **8e** was purified by recrystalization from ethyl acetate-hexane: 79% yield; IR (KBr) v 3305-2701, 1685, 1610, 1590, 1515, 1340. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.25 (s, br, COOH), 8.06 (s, 1H), 7.95 (d, J = 16 Hz, 2H), 7.41-7.33 (m, 5H), 7.22 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ; 172.24 (s), 148.17 (s), 139.38 (s), 136.01 (s), 134.88 (s), 134.05 (d), 129.44 (s), 129.19 (s), 129.06 (s), 128.76 (s), 126.93 (s), 125.19 (s), 123.76 (s), 122.91 (s). ESI MS (m/z) 292 (M+Na).

(E)-3-(3-hydroxy-4-methoxyphenyl)-2-phenyl-acrylic acid (8f):

Following general procedure B, compound **8f** was purified by recrystalization from ethyl acetate-hexane: 81% yield; IR (KBr) v 3518, 3037, 3000, 2942, 1674, 1366. ESI MS (m/z) 270 (M).

Cytostatic activity

The methodology for measuring the cytostatic activity in Molt 4/C8, CEM and L1210 assays has been published previously (15). In brief, varying concentrations of compounds were incubated at 37 °C with the cells for 72 h (human Molt 4/C8 or CEM T-lymphocytes) or 48 h (murine L1210 cells). After the incubation period, the cell number was counted by a coulter counter (Harpenden Herz, UK).

ACKNOWLEDGMENTS

We gratefully acknowledge the support for this research effort from All India Council for Technical Education (AICTE), New Delhi (Ref. No. 8023/BOR/RID/RPS-169/2008-09) for SSK. The cytotoxic activities were determined by financial support of the KU Leuven (GOA 10/014). We would also like to thank NMR facility, Indian Institute of Science, Bangalore for characterization of all compounds. We thank Lizette van Berckelaer for the cytostatic determinations.

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