IJPSR (2013), Vol. 4, Issue 5 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 January, 2013; received in revised form, 21 April, 2013; accepted, 29 April, 2013

SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF NOVEL SUBSTITUTED CIS-STILBENE DERIVATIVES

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Keywords:

Cis-stilbene, Carrageenan- induced, Anti-inflammatory activity

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ABSTRACT: In the present study, novel derivatives of substituted cis-stilbene were prepared from benzyl (chloro) triphenyl phosphorane, substituted phenyl acetic acid and In vivo anti-inflammatory activity was evaluated by carrageenan- induced rat paw edema assay model. The newly synthesized compounds were characterized by IR, ^{1}H NMR and Mass analyses. The results revealed that all the test compounds protected the rats from carrageenan induced inflammation and the test compounds showed a significant anti-inflammatory activity against the control group. Among the compounds tested 1i, 1l, 1o, 2c, 2d, 2h, 3b and 3d showed better anti-inflammatory activity and 2f, 3c showed moderate activity.

INTRODUCTION: Inflammation is a defensive but exaggerated local tissue reaction in response to exogenous or endogenous insult. Cyclooxygenase (COX) and 5-lipoxygenase (5-LO) are enzymes which catalyze the rate-limiting steps in the biosynthesis of prostaglandins and leukotrienes from arachidonic acid. A large number of non-steroidal anti-inflammatory drugs (NSAIDs) are available clinically to treat inflammatory disorders. The most important mechanism of anti-inflammatory action of NSAIDs is considered to be primarily by inhibition of prostaglandin synthesis. The principal side effects associated with chronic use of non-selective NSAIDs are gastrointestinal irritation, bleeding and formation of life threatening gastrointestinal ulcer.

QUICK RESPONSE CODE

IJPSR: ICV (2011)- 5.07

Article can be accessed online on: www.ijpsr.com

In addition, there is evidence to suggest that leukotriene promotes gastric ulceration, which limits the therapeutic utilization of these drugs [1-3]. Therefore, there is a need to develop new compounds. Stilbenes are chemically derivatives of trans 1, 2- diphenylethylene. Natural (*E*)-stilbenes, hydroxylated in two to five positions. Stilbenes, such as resveratrol, piceatannol, and pinosylvin, are compounds found in numerous medicinal plants and food products [4-6].

The natural stilbene most relevant and more described in the literature is resveratrol, which was first isolated from Chinese and Japanese medicinal plants in 1963 [7]. In 1992, this compound was postulated to explain some of the cardioprotective effects of red wine (the so-called-French paradox) [8-10]. Since then, dozens of studies have indicated that resveratrol plays an important role in preventing or slowing the progression of many diseases and illnesses, such as inflammation [11-14], cancer [5, 6, 12, 37-39] and heart diseases [7, 15].

Recently, additional properties of resveratrol have been documented, such as radical scavenging, antioxidant activity [14, 16], neuroprotection [14, 17], antiviral activity [14, 18], antibacterial activity [19-21], antitubercular activity [22-24]. Suitable substituted *cis*-stilbene derivatives are characterized by potent inhibitory activity on COX-2, quite similarly with that observed for a variety of vicinal diarylheterocycles, among which important anti-inflammatory drugs, like celecoxib and valdecoxib, are found [25].

In the last class of drugs, the central five member ring may be of very different nature, either heterocyclic or carbocyclic [26-27]; while the nature of substitutents on the two benzene rings is believed to be responsible for COX-2 selectivity by insertion into the secondary pocket of the enzyme, with the p-sulfonamido and pmethylsulfonyl groups playing a key role[28]. Accordingly, we have now designed and synthesized 30 new cis stilbene derivative that among them some contains prop-2-enoic acid which could play some peculiar role in the interaction with COX enzymes.

EXPERIMENTAL: Commercial reagents and solvents were procured from S.D fine chemicals (India) and were used without purification. The purity of all the synthesized compounds were checked by thin layer chromatography on silica gel G as a stationary phase and different solvent systems as a mobile phase using iodine vapors as a detecting agent The melting points were determined by open capillary method using jindal melting point apparatus and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Bruker Alpha FTIR Spectrophotometer. Proton NMR spectra were done on Bruker Avance II 400 NMR Spectrometer using tetramethyl silane as internal standard. Mass spectra of the compounds were carried out on JOEL SX 102/DA- 600 Mass spectrometer using fast atom bombardment (FAB) technique in positive ion mode. All the compounds have been screened in-vivo for their anti-inflammatory activity.

1. **Chemistry:** A series of P-(substituted phenyl) - 2 (substituted phenyl) Ethene has been synthesized. Substituted benzyl chloride reacted with the phosphonium chloride salt give the P substituted benzyl (chloro) triphenyl phosporane **(1)** which on further reaction with substituted benzaldehyde yielded the corresponding 1a–1q. Base-catalyzed condensation of phenylacetic acids **(2)** with aryl aldehyde in the presence of triethylamine gave the series of E-3- (phenyl)-2-(phenyl) prop-2-enoic acid (2a-2h). Reaction of thionyl chloride with the E-3- (phenyl)-2-(phenyl) prop-2-enoic acid **(2)** in benzene under refluxing gave the corresponding acid chlorides, which on subsequent reaction with appropriate amines, and (dialky1amino)ethanol gave compounds 3a-3e.The synthesized substituted cis- stilbene were characterized on the basis of the spectral and analytical studies.

2. **General Methods**: The title compounds were prepared in following steps:

a. **Procedure for preparation of benzyl (chloro) triphenyl phosphorane (1):** In 250ml round bottom flask, a solution of benzyl chloride (20.25g, 0.16 mol) and PPh_3 (41.5g, 0.17 mol) in CH_3CN (100 ml) was stirred for 12 hr under reflux. The reaction mixture was concentrated by evaporation to give a residue. The crude product 1, was purified by crystallization from $CHCl_3$ / Et_2O, affording 95% yield (58.3 g) as a white solid: mp 324-326 ^oC [29].

b. **General procedure for synthesis of compound (1a-1q):** A well-stirred suspension of phosphonium chloride salt (2 m mol) and aryl aldehyde (2 m mol) in benzene (20 ml) was prepared and Sodium hydride (72.0 mg, 3 m mol) was added under 0-5 ^0C and the mixture were allowed to come to room temperature. After the additional stirring for 16 hr, excess sodium hydride was quenched by the addition of methanol (1 ml). Solvent from the reaction mixture were evaporated at reduced pressure. Residue was extracted with 30 ml mixture of chloroform and water; separate the organic and aqueous layer. Aqueous layer contains the phosphonium oxide as an impurity Distilled off the organic layer and residue was purified by preparative column chromatography using 5% EtOH in hexane as the eluent or by recrystalization with ethanol.

c. **General procedure for the preparation of compounds (2a-2h):** In 250 ml round bottom flask, A solution of phenyl acetic acid 2 (2m.mol), substituted benzaldehydes (2m.mol) and tri ethyl amine (0.5ml) in acetic anhydride

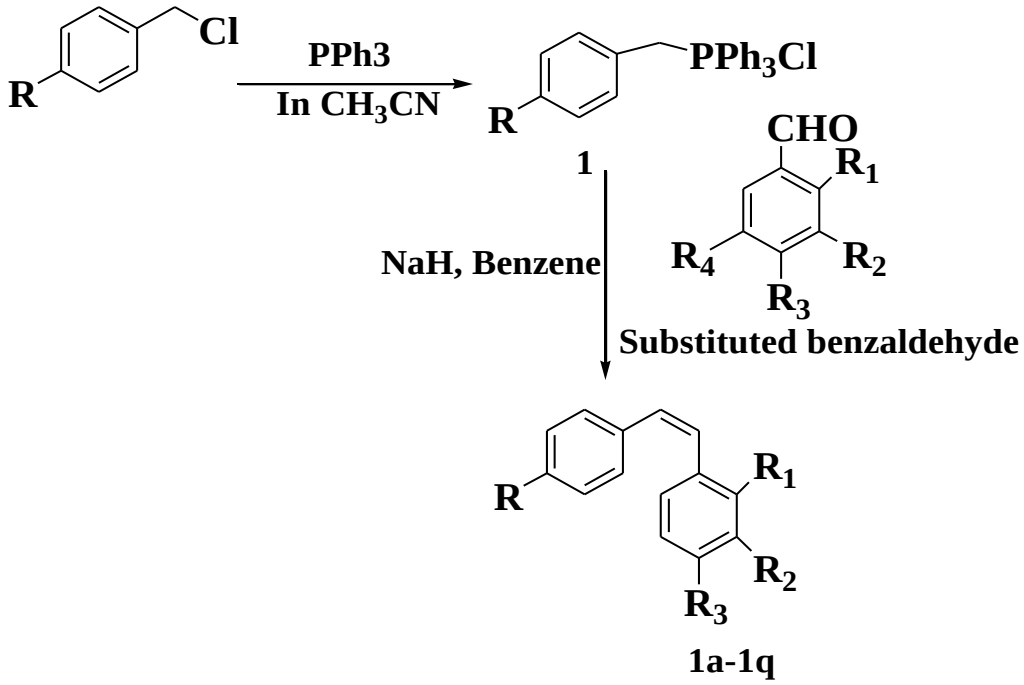
(5ml) was heated at reflux for 12 hr. after refluxing mixture was poured in to hot saturated sodium carbonate solution (50ml) and left over night. The mixture was extracted with ether (2 X50ml), and the ether extracts were discarded, the aqueous solution was acidified with dilute HCl, and the precipitated product was filtered and dried. Recrystalization from EtOAc – Hexane give pure product.

d. **General procedure for the preparation of compounds (3a-3e):** A mixture of carboxylic acid 3 (0.5 m mol) and thionyl chloride (1 ml) in benzene (10 ml) was refluxed for 6 h. The excess thionyl chloride and benzene were removed at reduced pressure, and the residue was kept under vacuum for 30 min. It was subsequently mixed with aqueous methylamine solution (40%, 5 ml) and kept at room temperature for 2 h. The precipitated product was filtered, washed sequentially with 2% NaOH solution and water, and then dried. An analytical sample was prepared by recrystallization from EtOAc: Hexane[30]. By adopting similar type of procedures, and employing equimolar quantities of reactants, 30 compounds were synthesized. Physical data of synthesized compounds is given in **Table 1**. Synthetic pathway for preparation of compounds is shown in **Scheme 1 and 2**.

TABLE 1 PHYSICAL DATA OF SUBSTITUTED CIS-STILBENE DERIVATIVE

Compound	R	R_1	R_2	R_3	Molecular formula	Molecular weight
1a	-CH3	-H	-NO2	-H	$C_{15}H_{13}O_2N$	239
1b	-H	-H	-NO2	-H	$C_{14}H_{11}O_2N$	225
1c	-CH3	-H	-H	-NO2	$C_{15}H_{13}O_2N$	239
1d	-H	-H	-OCH3	-H	$C_{15}H_{14}O$	210
1e	-Cl	-H	-H	-OCH3	$C_{15}H_{13}ClO$	244
1f	-F	-H	-H	-OH	$C_{14}H_{11}FO$	214
1g	-CH3	-H	-H	-Cl	$C_{15}H_{13}Cl$	228
1h	-OH	-H	-Cl	-Cl	$C_{14}H_{10}Cl_2O$	265
1i	-OH	-H	-OCH3	-OCH3	$C_{16}H_{16}O3$	256
1j	-OH	-H	-F	-F	$C_{14}H_{10}F_2O$	232
1k	-OH	-H	-OH	-OCH3	$C_{16}H_{16}O_3$	256
1l	-OH	-H	-OCH3	-OH	$C_{15}H_{14}O_3$	242
1m	-CH3	-H	-Cl	-Cl	$C_{15}H_{12}Cl_2$	263
1n	-Cl	-H	-OCH3	-OCH3	$C_{16}H_{15}ClO_2$	274
1o	-Cl	-H	-OH	-OCH3	$C_{15}H_{13}ClO_2$	260
1p	-CH3	-H	-F	-F	$C_{15}H_{12}F_2$	230
1q	-Cl	-H	-OC2H5	-OH	$C_{16}H_{15}ClO_2$	274
2a	-H	-NO2	-H	-H	$C_{15}H_{11}O_4N$	269
2b	-H	-H	-H	-NO2	$C_{15}H_{11}O_4N$	269
2c	-H	-H	-H	-OH	$C_{15}H_{12}O_3$	240
2d	-H	-H	-OCH3	-OCH3	$C_{17}H_{16}O_4$	284
2e	-H	-H	-NO2	-H	$C_{15}H_{11}O_4N$	269
2f	-Cl	-H	-OCH3	-OCH3	$C_{17}H_{15}ClO$	318
2g	-F	-H	-H	-OCH3	$C_{16}H_{13}FO_3$	272
2h	-H	-H	-OH	-OCH3	$C_{16}H_{14}O_4$	270
3a	-CI	-H	-H	-OH	$C_{16}H_{14}ClNO_2$	287
3b	-OH	-H	-OCH3	-OCH3	$C_{18}H_{19}NO_4$	313
3c	-CI	-H	-H	-OH	$C_{17}H_{16}ClNO_2$	301
3d	-OH	-H	-OCH3	-OCH3	$C_{19}H_{21}NO_4$	327
3e	-OH	-H	-H	-OH	$C_{17}H_{17}NO_3$	283

SCHEME-1



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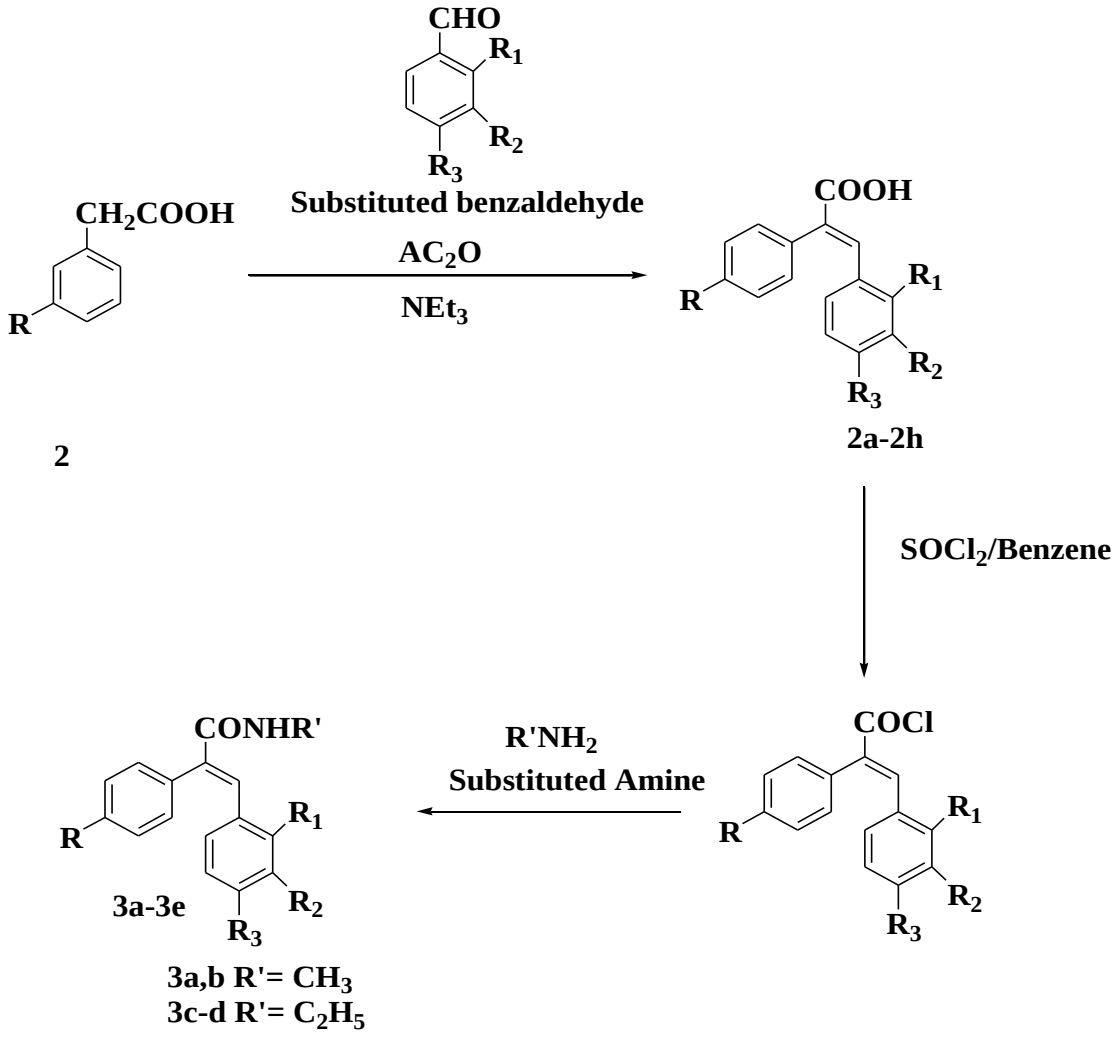

3. **Spectral data:**

i. **1-[(Z)-2-(4-Methylphenyl)Ethenyl]-3-Nitrobenzene (1a):** Light yellow Powder, yield 60%, mp 95-98 ^{0}C, R_f Value 0.42, IR (KBr, cm^{-1}): 3026 (C-H Str (Ar)), 2822(C-H (Aliphatic)), 1604(C=C (Aliphatic)), 1524 (N=O), 850 (C-N (Ar nitro)). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.41 (s, 3H, -CH3), 6.49 – 6.59 (m, 2H, CH=CH), 7.24 (s, 3H, -CH3), 7.54 – 7.59 (m, 2H, Ar'-H), 7.71 –8.34 (m, 1H, Ar'-H). MS, m/z (%): 239 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.26; H, 5.39; N, 5.23.

ii. **1-Nitro-3-[(Z)-2-Phenylethenyl] Benzene (1b):** White powder, yield 65%, mp 85-88^{0}C, R_f Value 0.50, IR (KBr, cm^{-1}): 2944 (C-H Str (Ar)), 2830 (C-H (Aliphatic)), 1606 (C=C (Aliphatic)), 1523 (N=O), 850 (C-N (Ar nitro)). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.51 – 6.60 (m, 2H, CH=CH), 7.15 – 7.21 (ddt, 1H, Ar-H), 7.24 – 7.32 (m, 3H, Ar-H), 7.55 – 7.60 (dt, 1H, Ar'-H), 7.71 – 8.35 (t, 1H, Ar'-H).MS, m/z (%): 225 $[M+H]^+$ (100%). Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92; N, 6.22. Found: C, 75.04; H, 4.71; N, 6.43.

iii. *1*-**Methyl-4-[(Z)-2-(4-Nitrophenyl)Ethenyl] Benzene(1c):** White powder, yield 70%, mp 148-150^{0}C, R_f Value 0.46, IR (KBr, cm^{-1}): 3028 (C-H Str (Ar)), 2924(C-H (Aliphatic)), 1604 (C=C (Aliphatic)), 1523(N=O),850 (C-N (Ar- nitro)). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.41 (s, 3H, -CH3), 6.51 – 6.56-6.65 (dt, 1H, CH-CH), 7.24 (s, 3H, Ar-H), 7.69 - 8.45 (m, 2H, Ar'-H). MS, m/z (%): 239 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.02; H, 5.24; N, 5.42.

iv. **1-Methoxy-3-[(Z)-2-Phenylethenyl] Benzene (1d):** Light Green powder, yield 75%, mp 66-68^{0}C, R_f Value 0.53, IR (KBr, cm^{-1}): 3083 (C-H Str (Ar)), 3033(C-H (Aliphatic)), 1597(C=C (Aliphatic)), 2832 (-OCH_3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.86 – 3.89 (s, 3H, -CH3), 6.49 – 6.57 (m, 2H, CH=CH), 6.83 –6.97 (dt, 1H, Ar'-H), 7.09 – 7.13 (t, 1H, Ar'-H), 7.24 – 7.33 (m, 2H, Ar-H), 7.33 – 7.44 (m, 4H, Ar-H). MS, m/z (%): 210 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71.Found: C, 85.09; H, 6.31.

v. **1-Chloro-4-[(Z)-2-(4-Methoxyphenyl) Ethenyl]Benzene (1e):** Pale Yellow powder, yield 60%, mp 109-110C, Rf Value 0.48, IR (KBr, cm^{-1}): 3028 (C-H Str (Ar)), 2962 (C-H (Aliphatic)), 1593 (C=C (Aliphatic)), 2839 (-OCH3 Ar), 758 (C-Cl (Ar) mono). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.88 (s, 3H-CH3), 6.43 – 6.48 (m, 1H, CH=CH), 7.21 – 7.23 (dt, 1H Ar'-H), 7.43 – 7.48 (m, 2H, Ar'-H), 7.56 – 7.58 (m, 1H, Ar-H). MS, m/z (%): 244 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{13}ClO$: C, 73.62; H, 5.35. Found: C, 73.19; H, 5.11.

vi. **4-[(Z)-2-(4-Fluorophenyl)Ethenyl]Phenol(1f):** Pale Yellow powder, yield 75%, mp 145-147^{0}C, R_f Value 0.63, IR (KBr, cm^{-1}): 1704 (C=C (Aliphatic)), 3351 (-OH), 1015 (C-F (Ar) mono). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 4.74 (s, 1H,-OH), 6.47 – 6.48 (s, 4H, -CH=CH), 6.72 – 6.77 (m, 2H), 7.39 – 7.43 (d, 3H, Ar'-H), 7.53 – 7.66 (m, 6H, Ar-H). MS, m/z (%): 214 $[M+H]^+$ (100%). Anal. Calcd. for $C_{14}H_{11}FO$: C, 78.49; H, 5.18. Found:C, 78.21; H, 5.71

vii. **1-Chloro-4-[(Z)-2-(4-Methylphenyl)Ethenyl] Benzene (1g):** White Crystalline powder, yield 65%, mp 87-880C, Rf Value 0.62, IR (KBr, cm^{-1}): 3027 (C-H Str (Ar)), 2923 (C-H (Aliphatic)), 1603 (C=C (Aliphatic)),727 (C-Cl (Ar) mono).. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.48 (t, 2H, -CH3), 6.47 (d, 1H, -CH=CH), 7.31 – 7.34 (m, 2H, Ar'-H), 7.41 – 7.43 (m, 1H, Ar'-H), 7.53 – 7.58 (m, 1H, Ar-H).MS, m/z (%): 228 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{13}Cl$: C, 78.77; H, 5.73. Found: C, 78.39; H, 5.20.

viii. **4-[(Z)-2-(3,4-Dichlorophenyl)Ethenyl]Phenol (1h):** Pale yellow powder, yield 67%, mp 217-219^{0}C, R_f Value 0.48, IR (KBr, cm^{-1}): 3032 (C-H Str (Ar)), 2869 (C-H (Aliphatic)), 1694 (C=C (Aliphatic)), 821 (C-Cl (Ar) Poly), 3445 (-OH). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 4.68 (s, 1H, Ar-OH), 6.36 – 6.40 (d, 2H, CH=CH), 6.63 – 6.65 (m, 2H, Ar-H), 7.25 – 7.31 (m, 5H, Ar'-H).MS, m/z (%): 264 $[M+H]^+$ (100%). Anal.

Calcd. for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80. Found: C, 63.31; H, 3.69.

ix. **4-[(Z)-2-(3,4-Dimethoxyphenyl)Ethenyl] Phenol(1i):** Light brown powder, yield 70%, mp 224-226^{0}C, R_f Value 0.49, IR (KBr, cm^{-1}): 2962(C-H Str (Ar)), 2836 (C-H (Aliphatic)), 1595 (C=C (Aliphatic)), 2939 (-OCH_3 Ar). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.84 – 3.86 (d, 6H, -CH3), 4.79 (s, 1H, Ar- OH), 6.37 – 6.38 (d, 2H, CH=CH), 7.04 (d, 1H, Ar'-H), 7.21(d, 2H, Ar'-H), 7.30 – 7.31 (m, 2H, Ar-H).MS, m/z (%): 253 $[M+H]^+$ (100%). Anal. Calcd. for $C_{16}H_{16}O3$: C, 74.98; H, 6.29. Found: C, 74.77; H, 6.18.

x. **4-[(Z)-2-(3,4-Difluorophenyl)Ethenyl]Phenol (1j):** Pale yellow green powder, yield 75%, mp 158-160^{0}C, R_f Value 0.41, IR (KBr, cm^{-1}): 3032 (C-H Str (Ar)), 1599 (C=C (Aliphatic)), 1264 (C-F (Ar) Poly). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 4.75 (s, 1H, Ar- OH),), 6.35 – 6.40 (m, 2H, CH=CH), 6.63 – 6.65 (m, 2H, Ar-H), 7.02 – 7.09 (m, 2H, Ar'-H), 7.28 – 7.30 (m, 2H, Ar-H).MS, m/z (%): 231 $[M+H]^+$ (100%). Anal. Calcd. for $C_{14}H_{10}F_2O$: C, 72.41; H, 4.34. Found: C, 72.34; H, 4.10.

xi. *2*-**Ethoxy-4-[(Z)-2-(4-Hydroxyphenyl) Ethenyl]Phenol(1k):** White crystalline powder, yield 65%, mp 301-303^{0}C, R_f Value 0.53, IR (KBr, cm^{-1}): 3060 (C-H Str (Ar)), 1599 (C=C (Aliphatic)), 1747(C-O), 2966 (-OCH_3 Ar). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.95 (t, 3H,-CH_3), 4.13 (q, 2H,—OC_2H_5), 4.71 (s, 1H, Ar- OH), 5.79 (s, 1H, Ar'- OH), 6.32 – 6.38 (m, 2H, CH=CH), 6.63 – 6.65 (m, 2H, Ar-H), 6.77 (dd, 1H, Ar'-H), 7.02 – 7.05 (m, 2H, Ar'-H), 7.28 – 7.33 (m, 2H, Ar-H). MS, m/z (%): 256 $[M+H]^+$ (100%). Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.81; H, 6.12

xii. **5-[(Z)-2-(4-Hydroxyphenyl)Ethenyl]-2-Methoxyphenol(1l):** White crystalline powder, yield 65%, mp 290-293^{0}C, R_f Value 0.56, IR (KBr, cm^{-1}): 3031 (C-H Str (Ar)), 2982 (C-H (Aliphatic)), 1644.52 (C=C (Aliphatic)), 2932 (-OCH_3 Ar), 3429 (-OH). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.85 (s, 3H, -OCH_3), 4.84 (s, 1H, Ar- OH), 5.75 (s, 1H, Ar'- OH), 6.32 – 6.36 (m, 2H, CH=CH), 6.63 – 6.65 (m, 2H, Ar-H), 7.30-7.32 (dd, 2H, Ar-H). MS, m/z (%): 243 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.73.

xiii. **1,2-Dichloro-4-[(Z)-2-(4-Methylphenyl) Ethenyl]Benzene (1m):** White powder, yield 70%, mp 129-131^{0}C, R_f Value 0.57, IR (KBr, cm^{-1}): 3029 (C-H Str (Ar)), 2868 (C-H (Aliphatic)), 1591 (C=C (Aliphatic)), 819 (C-Cl (Ar) Poly). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.41 (s, 3H, -CH_3)6.39 – 6.44 (m, 2H, CH=CH), 7.24 (ddd, 1H, Ar'-H), 7.28 – 7.35 (m, 2H, Ar-H). MS, m/z (%): 263 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{12}Cl_2$: C, C, 68.46; H, 4.60. Found: C, 68.24; H, 4.49.

xiv. **4-[(Z)-2-(4-chlorophenyl)ethenyl]-1,2-di methoxybenzene(1n):** Brown powder, yield 70%, mp 155-157^{0}C, R_f Value 0.48, IR (KBr, cm^{-1}): 3027 (C-H Str (Ar)), 2839 (C-H (Aliphatic)), 1593 (C=C (Aliphatic)), 2962 (-OCH_3 Ar), 758(C-Cl (Ar) mono). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.85 (d, 6H, -CH_3), 6.41 (d, 2H, CH=CH), 7.11 – 7.12 (m, 1H, Ar'-H), 7.21 (d, 1H, Ar'-H), 7.30 (d, 1H, Ar'-H), 7.34 – 7.30 (m, 2H, Ar-H). MS, m/z (%): 273 $[M+H]^+$ (100%). Anal. Calcd. for $C_{16}H_{15}ClO_2$: C, 69.95; H, 5.50. Found: C, 69.87; H, 5.34.

xv. **5-[(Z)-2-(4-Chlorophenyl)Ethenyl]-2-Methoxy phenol(1o):** Yellowish Green powder, yield 75%, mp 220-222^{0}C, R_f Value 0.49, IR (KBr, cm^{-1}): 3027 (C-H Str (Ar)), 2841 (C-H (Aliphatic)), 1680 (C=C (Aliphatic)), 2957 (-OCH_3 Ar), 761 (C-Cl (Ar) mono). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.85 (s, 3H, -CH_3), 5.75 (s, 1H, Ar'-OH), 6.35 – 6.39 (m, 2H, CH=CH), 7.07 (d, 2H, Ar'-H), 7.34-7.50 (m, 2H, Ar-H). MS, m/z (%): 261 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03.Found:C, 68.94; H, 4.98.

xvi. **1,2-Difluoro-4-[(Z)-2-(4-Methylphenyl) Ethenyl]Benzene(1p):** Pale Yellow powder, yield 80%, mp 70-74^{0}C, R_f Value 0.46, IR (KBr, cm^{-1}): 3030 (C-H Str (Ar)), 1593 (C=C (Aliphatic)), 1601(C=C (Aliphatic)), 1206 (C-F (Ar) Poly). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.41 (s, 3H, -CH_3) 6.37-6.43 (d, 2H, CH=CH), 7.05 – 7.09 (m, 3H, Ar'-H), 7.23 – 7.29 (m, 1H, Ar-H). MS, m/z (%): 2232 $[M+H]^+$

(100%). Anal. Calcd. for $C_{15}H_{12}F_2$: C, 78.24; H, 5.25. Found:C, 78.10; H, 5.41.

xvii. **4-[(Z)-2-(4-Chlorophenyl)Ethenyl]-2-Ethoxy phenol(1q):** White crystalline powder, yield 75%, mp 232-235^{0}C, R_f Value 0.53, IR (KBr, cm^{-1}): 3963 (C-H Str (Ar)), 2838 (C-H (Aliphatic)), 1592 (C=C (Aliphatic)), 1507(C=O Ar), 1026 (C-Cl (Ar) mono), 3383 (-OH). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.83 (t, 3H, -CH_3), 4.13 (q, 2H,-OC_2H_5), 5.81 (s, 1H, Ar'- OH), 6.36 (s, 2H, CH=CH), 6.83 – 6.84 (m, 1H, Ar'-H), 7.48 – 7.50 (m, 2H, Ar-H).MS, m/z (%): 274 $[M+H]^+$ (100%). Anal. Calcd. for $C_{16}H_{15}ClO_2$: C, 69.95; H, 5.50. Found: C, 69.87; H, 5.44.

xviii. **(2E)-3-(2-Nitrophenyl)-2-Phenylprop-2-Enoic Acid (2a):** Light brown Powder, yield 62%, mp 185-188^{0}C, R_f Value 0.60, IR (KBr, cm^{-1}): 3073 (C-H Str (Ar)), 2930(C-H (Aliphatic)), 1707 (C=O (Ar carboxylic)), 1522(N=O), 1104(C-O(Carboxylic), 933 (C-N (Ar- nitro)). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.94 (s, 1H, -COOH), 7.29 –7.51 (m, 2H Ar-H), 7.81 – 7.89 (m, 3H, Ar'-H), 8.21 – 8.22 (dd, 1H, Ar'-H). MS, m/z (%): 270 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.19; H, 4.05; N, 5.87.

xix. **(2E)-3-(4-Nitrophenyl)-2-Phenylprop-2-Enoic Acid (2b):** Light yellow Powder, yield 63%, mp 200-203^{0}C, R_f Value 0.72, IR (KBr, cm^{-1}): 3072 (C-H Str (Ar)), 1709 (C=O (Ar carboxylic)), 1609 (C=C (Aliphatic)), 1521 (N=O), 1104(C-O(Carboxylic), 934 (C-N (Ar-nitro)). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.87 (s, 1H, -COOH), 7.19 –7.45 (m, 2H, Ar-H), 7.67 – 7.68 (m, 3H, Ar'-H), 7.69 (s, 1H, -CH) 8.41 – 8.43 (m, 2H, Ar'-H).MS, m/z (%): 270 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12; N, 5.20.Found: C, 66.82; H, 4.56; N, 5.09.

xx. **(2E)-3-(4-Hydroxyphenyl)-2-Phenylprop-2-Enoic Acid (2c):** White to off white powder, yield 70%, mp 210-213^{0}C, R_f Value 0.40, IR (KBr, cm^{-1}): 3025 (C-H Str (Ar)), 2824 (C-H (Aliphatic)), 1594 (C=C (Aliphatic)), 1687 (C=O (Ar carboxylic)), 3418 (-OH).^{1}H NMR (400 MHz, $CDCl_3$, ppm): 4.79 (s, 1H,-OH),6.69 – 6.71 (m, 2H, Ar'-H), 6.93(s, 1H,-COOH), 7.25 – 7.27 (dt, 2H, Ar-H), 7.31 – 7.40 (m, 3H, Ar-H), 7.48 – 7.51 (t, 2H, Ar'-H)..MS, m/z (%): 240 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.80; H, 5.11.

xxi. **(2E)-3-(4-Hydroxyphenyl)-2-Phenylprop-2-Enoic Acid (2d):** Light brown Powder, yield 50%, mp 190-192^{0}C, R_f Value 0.42, IR (KBr, cm^{-1}): 3018 (C-H Str (Ar)), 1703 (C=O (Ar carboxylic)), 1111(C-O (Carboxylic), 2625 (-OCH_3 Ar). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.82 – 3.88 (d, 6H, -OCH3), 6.87 (s, 1H, -COOH), 7.11 – 7.12 (dd, 1H, Ar-H), 7.17 – 7.33 (m, 1H, Ar-H), 7.42 – 7.44 (m, 2H, Ar-H), 7.54 – 7.57 (t, 1H, Ar'-H). MS, m/z (%): 284 $[M+H]^+$ (100%). Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.67; H, 6.03.

xxii. **(2E)-3-(3-Nitrophenyl)-2-Phenylprop-2-Enoic Acid (2e):** Light brown Powder, yield 70%, mp 155-156^{0}C, R_f Value 0.56, IR (KBr, cm^{-1}): 2986 (C-H Str (Ar)), 1717 (C=O (Ar carboxylic)), 1044 (C-O (Carboxylic), 1527(N=O),849C-N (Ar- nitro)), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 6.87 (s, 1H, -COOH), 7.19 – 7.21 (dt, 2H, Ar-H), 7.30 – 7.44 (t, 2H, Ar-H), 7.62 –7.75 (m, 2H, Ar'-H), 8.08 – 8.14 (dt, 1H, Ar'-H), 8.19 – 8.22 (m, 2H, Ar'-H). MS, m/z (%): 268 $[M+H]^+$ (100%). Anal. Calcd. for $C_{15}H_{11}O_4$ N: C, 66.91; H, 4.12; N, 5.20. Found:C, 66.87; H, 4.33; N, 5.51.

xxiii. **(2E)-2-(4-Chlorophenyl)-3-(3,4-Dimethoxy phenyl)Prop-2-Enoic Acid(2f):** Brown Powder, yield 71%, mp 313-316^{0}C, R_f Value 0.76, IR (KBr, cm^{-1}): 2989 (C-H Str (Ar)), 1703 (C=O (Ar carboxylic)), 1161(C-O (Carboxylic), 2629 (-OCH_3 Ar), 760(C-Cl (Ar) mono). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.84 – 3.86 (d, 6H, -CH3), 6.87 (s, 1H, -COOH), 7.08 – 7.13 (m, 3H, Ar'-H), 7.20 – 7.26 (m, 1H, Ar'-H), 7.38 – 7.40 (m, 2H, Ar-H), 7.64 (m, 1H,C=CH). MS, m/z (%): 319 $[M+H]^+$ (100%). Anal. Calcd. for $C_{17}H_{15}ClO$: C, 64.06; H, 4.74. Found: C, 64.11; H, 4.21.

xxiv. **(2E)-2-(4-Fluorophenyl)-3-(4-Methoxyphenyl) Prop-2-Enoic Acid (2g):** Pale yellow powder, yield 65%, mp 237-

239^0C, R_f Value 0.73, IR (KBr, cm^{-1}): 3024(C-H Str (Ar)), 1596 (C=C (Aliphatic)), 1706 (C=O (Ar carboxylic)), 1160(C-O (Carboxylic), 2842 (-OCH_3 Ar), 1017 (C-F (Ar) mono). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 3.95 (s, 3H, -CH3), 7.02 (s, 1H, -OH), 7.28 – 7.32 (m, 6H, Ar'-H), 7.47 – 7.53 (m, 2H), 7.62 – 7.63 (m, 1H, -C=CH).MS, m/z (%): 274 $[M+H]^+$ (100%). Anal. Calcd. for $C_{16}H_{13}FO_3$: C, 70.58; H, 4.81.Found:C, 70.15; H, 4.79.

xxv. **(2E)-3-(3-Hydroxy-4-Methoxyphenyl)-2-Phenylprop-2-Enoic Acid (2h):** Yellowish green powder, yield 70%, mp $336\text{-}339^0$C, R_f Value 0.52, IR (KBr, cm-1): 3029 (C-H Str (Ar)), 2836 (C-H (Aliphatic)), 1595 (C=C (Aliphatic)), 1686(C=O(Ar carboxylic)), 1158 (C-O (Carboxylic), 2962 (-OCH_3 Ar), 3398 (-OH).^{1}H NMR (400 MHz, CDCl3, ppm): 3.85 (s, 3H, pAr' OCH_3), 5.26 (s, 1H, Ar'- OH), 6.83-6.85(m, 2H, Ar'-H), 7.31 – 7.46 (m, 2H, Ar-H). MS, m/z (%): 272 [M+H]+ (100%). Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.23; H, 5.09.

xxvi. **(2E)-2-(4-chlorophenyl)-3-(4-hydroxy phenyl)-N-methylprop-2-enamide (3a):** White crystalline powder, yield 65%, mp $349\text{-}352^0$C, R_f Value 0.71, IR (KBr, cm^{-1}): 3032 (C-H Str (Ar)), 2868 (C-H (Aliphatic)), 1591(C=C (Aliphatic)), 1694(C=O (Ar amide)), 1591 (N-H amide), 1052 (C-Cl (Ar) mono), 3389 (-OH). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.68 (s, 3H, -CH_3), 4.70 (s, 1H, Ar'- OH), 6.37 (s, 1H,-NH), 6.63 – 6.65 (m, 2H, Ar'-H), 6.89 – 6.90 (m, 1H,-C=CH), 7.22 – 7.27 (m, 2H, Ar'-H), 7.37 – 7.42 (m, 2H, Ar-H).MS, m/z (%): 288 $[M+H]^+$ (100%). Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.65; H, 4.71; N, 4.73.

xxvii. **(2E)-3-(3,4-Dimethoxyphenyl)-2-(4-Hydroxyphenyl)-N-Methylprop-2-Enamide(3b):** Brown powder, yield 60%, mp 399-4020C, R_f Value 0.74, IR (KBr, cm-1): 2945 (C-H Str (Ar)), 2835 (C-H (Aliphatic)), 1598 (C=C (Aliphatic)), 1677 (C=O (Ar amide)), 1512 (N-H amide), 3368 (-OH). ^{1}H NMR (400 MHz, CDCl3, ppm): 3.85 (d, 6H, -CH3), 4.67 (s, 1H, Ar- OH), 6.35 (s, 1H,-NH), 6.92 – 6.94 (m, 2H, Ar'-H), 7.14 – 7.23 (m, 3H, Ar-H).MS, m/z (%): 310 [M+H]+ (100%). Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found:C, 69.03; H, 6.02; N, 4.18.

xxviii. **(2E)-2-(4-Chlorophenyl)-N-Ethyl-3-(4-Hydroxyphenyl)Prop-2-Enamide (3c):** White crystalline powder, yield 68%, mp $361\text{-}363^0$C, R_f Value 0.73, IR (KBr, cm-1): 3042 (C-H Str (Ar)), 1644 (C=C (Aliphatic)), 1701 (C=O (Ar amide)), 1591(N-H amide), 2986 (-OCH_3 Ar), 1038 (C-Cl (Ar) mono),3399 (-OH). ^{1}H NMR (400 MHz, CDCl3, ppm): 3.32 (q, 1H, - C_2H_5), 4.84 (s, 1H, Ar- OH), 6.02 (s, 1H,-NH), 6.63-6.65 (d, 2H, Ar'-H), 7.13-7.15 (d, 2H, Ar-H), MS, m/z (%): 300 [M+H]+ (100%). Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64.Found:C, 67.52; H, 5.11; N, 4.75.

xxix. **(2E)-3-(3,4-Dimethoxyphenyl)- N-Ethyl-2-(4-Hydroxyphenyl)Prop-2-Enamide (3d):** Pale brown powder, yield 70%, mp $410\text{-}413^0$C, R_f Value 0.77, IR (KBr, cm-1): 3030 (C-H Str (Ar)), 2837 (C-H (Aliphatic)), 1960 (C=C(Ar)), 1592 (C=C (Aliphatic)), 1658 (C=O (Ar amide)), 1503(N-H amide), 3390 (-OH). ^{1}H NMR (400 MHz, CDCl3, ppm): 3.27-3.34 (dq, 2H, - C_2H_5), 3.85 (d, 6H,-Ar'-OCH_3), 4.86 (s, 1H, Ar- OH), 6.13 (s, 1H, -NH), 6.98(q, 1H, Ar'-H), 7.16 – 7.24 (m, 4H, Ar-H). MS, m/z (%): 338 [M+H]+ (100%). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.62; H, 6.52; N, 4.19.

xxx. **(2E)-N-Ethyl-2,3-Bis(4-Hydroxyphenyl) Prop-2-Enamide (3e):** White crystalline powder, yield 64%, mp $430\text{-}432^0$C, R_f Value 0.75, IR (KBr, cm-1): 3031 (C-H Str (Ar)), 2959 (C-H (Aliphatic)), 1594 (C=C (Aliphatic)), 1504(N-H amide), 3426 (-OH). ^{1}H NMR (400 MHz, CDCl3, ppm): 3.32 (q, 1H, - C_2H_5), 4.83 (s, 2H, Ar, Ar'- OH), 6.08 (s, 1H , -NH), 6.63 – 6.65 (m, 2H Ar'-H), 6.75 –7.24 (m, 1H, Ar-H).MS, m/z (%): 286 [M+H]+ (100%). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 5.89; N, 5.03.

Biological Activity:

1. **Animals:** Healthy Albino mice of either sex weighing between 20 and 25 g were used for acute toxicity studies. Healthy male albino adult rats weighing between 150 and 200 g were used for anti-inflammatory activities. Animal ethical clearance was obtained from Ethics Committee (1429/PO/a/11/CPCSEA) of Sagar Institute of Research & technology-Pharmacy, Bhopal, India

   Animals were housed in polypropylene cages an air-conditioned area at 25 ± 20C in 12 hrs light dark cycle on normal food standard rat pellet diet, (Hindustan Lever Ltd., Mumbai, India) and water ad libitum.

2. **Drug Formulation:** The drug formulations for all synthesized compounds were prepared from corresponding dose with sodium carboxymethyl cellulose.

3. **Acute Toxicity:** The acute toxicity test was carried out according to OECD guidelines[31] to establish the effective dose of the test compounds. After obtaining ethical clearance from Ethics Committee of Sagar Institute of Research & technology-Pharmacy, Bhopal, India. Albino mice of either sex weighing between 20 and 25 g were divided into six groups of 6 animals each. Animals were starved for 24 h with water ad libitum prior to test. On the day of the experiment, animals were administered with different compounds to different groups in an increasing dose of 10, 20, 100, 200, 1000 and 2000 mg/kg body weight orally.

   The animals were then observed continuously for 3 h for general behavioral, neurological, autonomic profiles and then every 30 min for next 3 h and finally for next 24 h or till death. From preliminary toxicity studies, it was observed that animals were found to be safe up to a maximum dose of 1000 mg/ kg body weight. But there were few changes in the behavioral response like alertness, touch response, and restlessness. Therefore, 1/10th of the maximum tolerated dose, i.e. 100 mg/kg body weight (b.w.) was chosen for the studies

4. **Anti-Inflammatory Activity:** *In vivo* anti-inflammatory activity was evaluated by carrageenan- induced rat paw edema assay model[32] for the compounds listed in Table 1. The Male or female albino rat with a body weight between 150 to 200 g were used. Animals were divided into 30 groups of 6 animals each weighed and numbered. They were starved overnight with water ad libitum prior to the day of experiment. Control group received 1 ml of 0.5% sodium carboxymethyl cellulose (sodium CMC), standard group received 20 mg/kg diclofenac and test groups received 100 mg/kg of synthesized compounds 1a-1q, 2a-2h and 3a-3e orally.

   The initial paw volume of each rat was taken with the help of volume displacement method by plethysmometer. Edema was induced by subcutaneous injection of 0.05 ml of 1% solution of carrageenan in sterile distilled water in all mice into the plantar side of the left hind paw of all groups. The paw edema volume of each group was measured in interval of 0.5 hr, 1hr, 2hr, 3hr, 4hr, with the help of plethysmometer. Paw edema volume was compared with vehicle control group and the percent inhibition of edema was calculated by formula.

% inhibition of edema

$= [(V_t\text{-}V_0)\ \text{Control}\text{-}(V_t\text{-}V_0)\ \text{Test}]/\ (V_t\text{-}V_0)\ \text{Control X } 100$

Where; V_t = Paw volume after carrageenan injection at time, V_0 = Paw volume before carrageenan injection at 0 time

5. **Statistical Analysis:** The statistical analysis was performed by using Graph pad prism software version 4.03. The level of significance was calculated by one-way ANOVA followed by Dunnet's multiple comparison test. According to this test, there was a significant difference between the drug treated groups and control at the level of $P<0.05$. Results, expressed as Mean ± SEM were evaluated using the student t-test. Values of $P < 0.05$ were considered statistically significant [33-34].

RESULT AND DISCUSSION: The role of test compounds (1a-1q, 2a-2h and 3a-3e) on carrageenan induced acute inflammation model was evaluated at concentrations of 100 mg/kg. In carrageenan administered animals the severe swelling was reached at 0.5 h and the swelling was maintained until the third hour. The diclofenac sodium treated groups decreased paw edema significantly throughout the period of study. The swelling was completely reduced during the fourth hour in diclofenac treated rats.

However, the animals treated with test compounds (100 mg/kg) showed considerable inhibition on swelling as compared to carrageenan administered animals. The results revealed that all the test compounds protected the rats from carrageenan induced inflammation and the test compounds showed a significant anti-inflammatory activity against the control group. Among the compounds tested 1i, 1l, 1o, 2c, 2d, 2h, 3b and 3d showed better anti-inflammatory activity and 2f, 3c showed moderate activity.

Carrageenan-induced paw edema as an in vivo model of inflammation has been frequently used to assess the anti-edematous effects, which is known to be sensitive to cycloxygenase (COX) inhibitors and has been used to evaluate the effects of NSAID. Development of edema in the paw of the rat after the injection of carrageenan involves three phases by several inflammatory mediators released in an ordinary sequence. An initial phase during the first 1.5 h is caused by the release of histamine and serotonin, the second phase is mediated by bradykinin-like substances from 1.5 to 2.5 h. The treatment with the COX-1 inhibitor could reduce the first and second phases of paw edema [35].

Finally, COX-2 is up-regulated only in the third phase, the mediator of which is suspected to be prostaglandins, proteases and lysosymes occur from 2.5 to 6 h after carrageenan injection [36]. The results of our in vivo study (Tables 2-4) indicated that the test compounds were able to effectively inhibit edema in the third phase, suggesting that test compounds inhibited cyclo oxygenase pathway of inflammation.

TABLE 2: PERCENTAGE INHIBITION OF TEST COMPOUNDS 1A-1Q (100 MG/KG) AGAINST CARRAGEENAN-INDUCED PAW EDEMA IN RATS

Treatment	Normal Paw Volume (Mean±SEM)	Rat paw volume (Mean ±SEM) in time (hr)					
		0.5 Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	% edema inhibition
Control	0.46±0.12	0.81±0.11	0.79±0.18	0.79±0.08	0.78±0.06	0.78±0.04	-
1a	0.48±0.11	0.79±0.12	0.77±0.12	0.74±0.04	0.70±0.22	0.68±0.015	37.50
1b	0.47±0.32	0.77±0.19	0.75±0.21	0.75±0.14	0.73±0.23	0.72±0.08	16.67
1c	0.50±0.11	0.78±0.13	0.76±0.34	0.73±0.16	0.72±0.01	0.71±0.04	30.00
1d	0.48±0.42	0.78±0.14	0.72±0.02	0.69±0.17	0.67±0.01	0.64±0.25	46.67
1e	0.49±0.31	0.76±0.112	0.74±0.04	0.68±0.11	0.65±0.05	0.63±0.34	53.33
1f	0.48±0.52	0.79±0.05	0.75±0.09	0.72±0.12	0.68±0.09	0.65±0.42	43.33
1g	0.49±0.01	0.77±0.04	0.74±0.62	0.71±0.14	0.69±0.03	0.67±0.23	40.00
1h	0.50±0.04	0.80±0.05	0.77±0.063	0.74±0.15	0.71±0.39	0.69±0.22	36.67
1i	0.46±0.09	0.78±0.06	0.71±0.16	0.66±0.41	0.57±0.36	0.53±0.05	**76.67***
1j	0.47±0.19	0.77±0.03	0.74±0.18	0.72±0.23	0.69±0.23	0.69±0.04	26.67
1k	0.48±0.03	0.77±0.02	0.75±0.19	0.73±0.24	0.69±0.38	0.68±0.08	33.33
1l	0.50±0.02	0.80±0.24	0.75±0.04	0.69±0.22	0.63±0.08	0.54±0.09	**86.67***
1m	0.51±0.03	0.82±0.31	0.77±0.05	0.72±0.20	0.69±0.11	0.62±0.44	63.33
1n	0.50±0.05	0.76±0.26	0.71±0.07	0.65±0.31	0.60±0.17	0.58±0.32	73.33
1o	0.51±0.7	0.77±0.25	0.75±0.08	0.7±0.06	0.64±0.18	0.58±0.31	**76.67***
1p	0.46±0.02	0.77±0.22	0.75±0.11	0.72±0.05	0.7±0.17	0.68±0.01	26.67
1q	0.47±0.03	0.79±0.31	0.76±0.53	0.73±0.03	0.69±0.07	0.64±0.09	43.33
Diclofenac Sodium	0.48±0.02	0.78±0.04	0.7±0.08	0.64±0.06	0.55±0.06	0.5±0.02	**93.3***

* P< 0.05 against control at the fourth hour. Values are expressed as mean± SEM, n=6 rats in each group.

TABLE 3: PERCENTAGE INHIBITION OF TEST COMPOUNDS 2A-2H (100 MG/KG) AGAINST CARRAGEENAN-INDUCED PAW EDEMA IN RATS

Treatment	Normal Paw Volume (Mean±SEM)	Rat paw volume (Mean ±SEM) in time (hr)					
		0.5 Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	% edema inhibition
Control	0.46±0.12	0.81±0.11	0.79±0.18	0.79±0.08	0.78±0.06	0.78±0.04	-
2a	0.49±0.22	0.80±0.04	0.78±0.06	0.72±0.07	0.69±0.06	0.69±0.09	37.50
2b	0.50±0.04	0.80±0.03	0.77±0.05	0.76±0.06	0.73±0.08	0.71±0.17	30.00
2c	0.48±0.06	0.79±0.02	0.68±0.06	0.60±0.11	0.55±0.13	0.53±0.02	**83.33***
2d	0.48±0.21	0.78±0.09	0.70±0.12	0.61±0.12	0.57±0.16	0.54±0.02	**80.00***
2e	0.50±0.01	0.81±0.27	0.76±0.11	0.71±0.08	0.68±0.12	0.65±0.05	50.00
2f	0.51±0.11	0.82±0.11	0.73±0.19	0.69±0.13	0.64±0.11	0.62±0.12	63.33
2g	0.50±0.23	0.79±0.12	0.74±0.05	0.71±0.12	0.70±0.03	0.69±0.32	36.67
2h	0.46±0.25	0.77±0.09	0.69±0.04	0.62±0.33	0.53±0.04	0.50±0.04	**86.67***
Diclofenac Sodium	0.48±0.02	0.78±0.04	0.70±0.08	0.64±0.06	0.55±0.06	0.5±0.02	**93.3***

* P< 0.05 against control at the fourth hour. Values are expressed as mean± SEM, n=6 rats in each group.

TABLE 4: PERCENTAGE INHIBITION OF TEST COMPOUNDS 3A-3E (100 MG/KG) AGAINST CARRAGEENAN-INDUCED PAW EDEMA IN RATS

Treatment	Normal Paw Volume (Mean±SEM)	Rat paw volume (Mean ±SEM) in time (hr)					
		0.5 Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	% edema inhibition
Control	0.46±0.12	0.81±0.11	0.79±0.18	0.79±0.08	0.78±0.06	0.78±0.04	-
3a	0.51±0.02	0.81±0.13	0.75±0.21	0.71±0.04	0.66±0.05	0.65±0.05	53.33
3b	0.51±0.03	0.80±0.14	0.72±0.07	0.64±0.13	0.58±0.11	0.55±0.06	**86.67***
3c	0.49±0.02	0.78±0.09	0.71±0.24	0.68±0.11	0.40±0.16	0.61±0.23	60.00
3d	0.48±0.26	0.76±0.11	0.69±0.02	0.62±0.14	0.56±0.17	0.51±0.22	**90.00***
3e	0.5±0.31	0.77±0.12	0.71±0.15	0.67±0.08	0.64±0.21	0.63±0.31	56.67
Diclofenac Sodium	0.48±0.02	0.78±0.04	0.70±0.08	0.64±0.06	0.55±0.06	0.5±0.02	**93.3***

* P< 0.05 against control at the fourth hour. Values are expressed as mean± SEM, n=6 rats in each group.

CONCLUSION: In conclusion, we have designed and synthesized a series of novel substituted cis-stilbene derivatives. These novel compounds were evaluated for In vivo anti-inflammatory activity against carrageenan- induced rat paw edema assay model. Substituted cis-stilbene gives significant anti-inflammatory. All synthesized compounds are confirmed by FT-IR, ^{1}H NMR and Mass analysis. We believe the insights gained in this study would be useful for the development of potential drug candidate derived from cis-stilbene in the development of novel anti-inflammatory agent.

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How to cite this article:
Jain N, Singhal S and Jain SK: Synthesis, characterization and Anti-inflammatory activity of Novel substituted Cis-Stilbene derivatives. *Int J Pharm Sci Res* 2013; 4(5); 1982-1993.