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Synthesis, Characterization of Novel E-3- (Phenyl)-2-(Phenyl) Prop-2-Enoic Acid Derivatives

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ABSTRACT

A series of novel E-3- (phenyl)-2-(phenyl) prop-2-enoic acid derivatives (1a-1h and 2a-2e) have been synthesized by the base-catalyzed condensation of phenylacetic acids (1) with aryl aldehyde in the presence of triethylamine gave the series of E-3- (phenyl)-2-(phenyl) prop-2-enoic acid (1a-1h). Reaction of thionyl chloride with the E-3- (phenyl)-2-(phenyl) prop-2-enoic acid in benzene under refluxing gave the corresponding acid chlorides, which on subsequent reaction with appropriate amines, and (dialky1amino) ethanol gave compounds 2a-2e the yield of compound was found to be in the range of 60-85%.The synthesized compounds were characterized by their physiochemical properties like solubility, melting point, IR spectroscopy, ^{1}H NMR spectroscopy, Fab MASS and elemental analysis.

Keywords: Phenyl acetic acid, Amines, Thionyl chloride, Dialkylamino

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INTRODUCTION

The name stilbene (Figure 1) was derived from the Greek word *stilbos*, which means shining. Stilbene are chemically derivatives of trans 1,2- diphenylethylene.

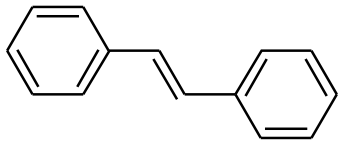

Figure 1: Stilbene

Stilbene based compounds are widely represented in nature and have become particular interest because of their wide range of biological activities[1]. Stilbene itself does not occur in nature, but its hydroxylated or methoxylated derivatives are abundantly found in nature. Some of these such as trans-resveratrol (Figure 2) [2], the cis-stilbene combrestatinA-4 (Figure 3) and stilbene based vitamin A analogue have shown unique potentialities for treatment of cancer[3, 4].

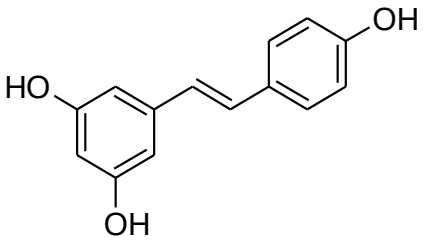

Figure 2: Trans –Resveratrol

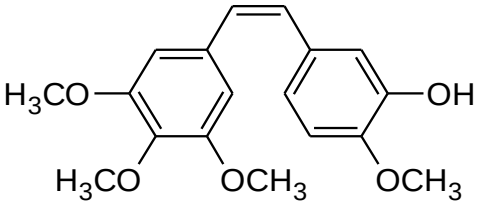

Figure 3: Combrestatin A-4

Stilbenes, such as resveratrol, piceatannol, and pinosylvin, are compounds found in numerous medicinal plants and food products [5-7]. 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[8]. In 1992, this compound was postulated to explain some of the cardioprotective effects of red wine (the so-called-French paradox) [9-11]. 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[12-15], cancer [6,7,13] and heart diseases[8, 16]. Recently, additional properties of resveratrol have been documented, such as radical scavenging, antioxidant activity [15, 17], neuroprotection [15, 18], antiviral activity [15, 19], antibacterial activity[20-22], antitubercular activity [23-25]. In 2007 Sinha *et a*[26], have been reported a mild and convenient one-pot two-step synthesis of hydroxystilbenes with trans selectivity developed through a modified Perkin reaction between benzaldehydes and phenyl acetic acids bearing 4- or 2-hydroxy substitution at the aromatic ring, in the presence of piperidine–methylimidazole and polyethylene glycol under microwave irradiation. In the present study of research for stilbene derivatives, we try to synthesize some

new methoxylated and hydroxylated stilbenes as well as other halogen containing stilbenes by the Base-catalyzed condensation of phenylacetic acids with aryl aldehyde in the presence of triethylamine gave the series of E-3- (phenyl)-2-(phenyl) prop-2-enoic acid. Reaction of thionyl chloride with the E-3- (phenyl)-2-(phenyl) prop-2-enoic acid in benzene under refluxing gave the corresponding acid chlorides, which on subsequent reaction with appropriate amines, and (dialky1amino)ethanol gave desired compounds. The title products reported were characterized on the basis of solubility, melting point, IR spectroscopy, ^{1}H NMR spectroscopy, Fab MASS and elemental analysis.

MATERIALS AND METHOD

Commercial reagents and solvents were procured from S.D Fine, Sigma Aldrich, Hi-Media, Merck, Loba Chemical (India). 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.

Chemistry:

Base-catalyzed condensation of phenylacetic acids (1) with aryl aldehyde in the presence of triethylamine gave the series of E-3- (phenyl)-2-(phenyl) prop-2-enoic acid (1a-1h). Reaction of thionyl chloride with the E-3- (phenyl)-2-(phenyl) prop-2-enoic acid (1a-1h). in benzene under refluxing gave the corresponding acid chlorides, which on subsequent reaction with appropriate amines, and (dialky1amino)ethanol gave compounds 2a-2e.The synthesized substituted cis-stilbene were characterized on the basis of the spectral and analytical studies.

General Methods:

The title compounds were prepared in following steps:

General procedure for the preparation of compounds (1a-1h)

In 250 ml round bottom flask, A solution of phenyl acetic acid (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.

General procedure for the preparation of compounds (2a-2e)

A mixture of carboxylic acid (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[27].

By adopting Scheme 1, similar type of procedures, and employing equimolar quantities of reactants, 13 compounds were synthesized. Physical data of synthesized compounds is given in Table 1. Synthetic pathway for preparation of compounds is shown in Scheme 1 (Figure 4).

Scheme-1

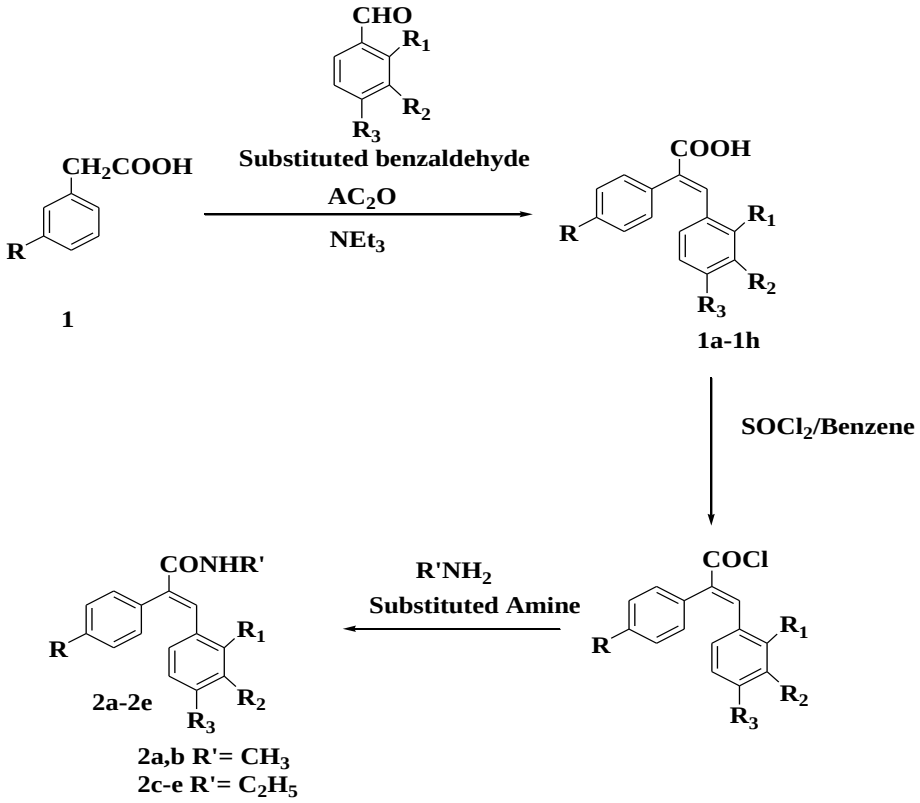

Figure 4: Synthetic pathway for preparation of compounds

RESULTS AND DISCUSSION

In present work focus was made manly on the synthesis of stilbene as the essential pharmacophore and investigation in combination with various substitutions in Ar and Ar' ring. To accomplish the synthesis of desired compounds, Scheme 1 presents a synthetic route of

conventional perkin reaction entails Base-catalyzed condensation of phenylacetic acids **(1)** with aryl aldehyde in the presence of triethylamine gave the series of E-3- (phenyl)-2-(phenyl) prop-2-enoic acid (1a-1h). Reaction of thionyl chloride with the E-3- (phenyl)-2-(phenyl) prop-2-enoic acid (1a-1h) in benzene under refluxing gave the corresponding acid chlorides, which on subsequent reaction with appropriate amines, and (dialky1amino)ethanol gave compounds 2a-2e.The synthesized substituted cis- stilbene were characterized on the basis of the spectral and analytical studies. The reaction was monitored by TLC. The IR spectra data of 1a-1h are revealed that the presence of C-H Str (Ar) peak at 3073-2986 cm^{-1}, 1610- 1590 cm^{-1} (C=C (Aliphatic)), 1707 cm^{-1} (C=O (Ar carboxylic)),~ 1520 cm^{-1} (N=O), 700-800 cm^{-1} (C-Cl (Ar)),~ 1100 cm^{-1}(C-F (Ar)) and for compound 2a-2e , ~1500 cm^{-1} (N-H amide) characteristically found. The ^{1}H NMR spectra data are revealed that δ: 6.94 (s, 1H, -COOH) in compound 1a-1h and δ: 6.02-6.35 (s, 1H,-NH) in compound 2a-2e characteristically found. The resonance peaks that appeared at δ: 7.19 –7.45 (m, 2H, Ar-H), δ: 7.67 – 7.68 (m, 3H, Ar'-H), could be assigned to the contribution of aromatic protons from stilbene moiety. The structures of the all compounds 1a-1h, 2a-2e were also confirmed by their element analysis and MASS spectral data. The spectral data of all compounds 1a-1h, 2a-2e were shown below that confirmed their structures.

Spectral data:

Table 1 Physical Data of E-3- (Phenyl)-2-(Phenyl) Prop-2-Enoic Acid Derivatives

Compound	R	R_1	R_2	R_3	Molecular formula	Molecular weight
1a	-H	-NO2	-H	-H	$C_{15}H_{11}O_4N$	269
1b	-H	-H	-H	-NO2	$C_{15}H_{11}O_4N$	269
1c	-H	-H	-H	-OH	$C_{15}H_{12}O_3$	240
1d	-H	-H	-OCH3	-OCH3	$C_{17}H_{16}O_4$	284
1e	-H	-H	-NO2	-H	$C_{15}H_{11}O_4N$	269
1f	-Cl	-H	-OCH3	-OCH3	$C_{17}H_{15}ClO$	318
1g	-F	-H	-H	-OCH3	$C_{16}H_{13}FO_3$	272
1h	-H	-H	-OH	-OCH3	$C_{16}H_{14}O_4$	270
2a	-CI	-H	-H	-OH	$C_{16}H_{14}ClNO_2$	287
2b	-OH	-H	-OCH3	-OCH3	$C_{18}H_{19}NO_4$	313
2c	-CI	-H	-H	-OH	$C_{17}H_{16}ClNO_2$	301
2d	-OH	-H	-OCH3	-OCH3	$C_{19}H_{21}NO_4$	327
2e	-OH	-H	-H	-OH	$C_{17}H_{17}NO_3$	283

(2E)-3-(2-Nitrophenyl)-2-Phenylprop-2-Enoic Acid (1a)

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.

(2E)-3-(4-Nitrophenyl)-2-Phenylprop-2-Enoic Acid (1b)

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.

(2E)-3-(4-Hydroxyphenyl)-2-Phenylprop-2-Enoic Acid (1c)

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.

(2E)-3-(4-Hydroxyphenyl)-2-Phenylprop-2-Enoic Acid (1d)

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.

(2E)-3-(3-Nitrophenyl)-2-Phenylprop-2-Enoic Acid (1e)

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.

(2E)-2-(4-Chlorophenyl)-3-(3,4-Dimethoxyphenyl)Prop-2-Enoic Acid(1f)

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.

(2E)-2-(4-Fluorophenyl)-3-(4-Methoxyphenyl)Prop-2-Enoic Acid (1g)

Pale yellow powder, yield 65%, mp 237-239^{0}C, 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.

(2E)-3-(3-Hydroxy-4-Methoxyphenyl)-2-Phenylprop-2-Enoic Acid (1h)

Yellowish green powder, yield 70%, mp 336-339^{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.

(2E)-2-(4-chlorophenyl)-3-(4-hydroxyphenyl)-N-methylprop-2-enamide (2a)

White crystalline powder, yield 65%, mp 349-352^{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.

(2E)-3-(3,4-Dimethoxyphenyl)-2-(4-Hydroxyphenyl)-N-Methylprop-2-Enamide(2b)

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.

(2E)-2-(4-Chlorophenyl)-N-Ethyl-3-(4-Hydroxyphenyl)Prop-2-Enamide (2c)

White crystalline powder, yield 68%, mp 361-363^{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.

(2E)-3-(3,4-Dimethoxyphenyl)- N-Ethyl-2-(4-Hydroxyphenyl)Prop-2-Enamide (2d)

Pale brown powder, yield 70%, mp 410-413^{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.

(2E)-N-Ethyl-2, 3-Bis(4-Hydroxyphenyl)Prop-2-Enamide (2e)

White crystalline powder, yield 64%, mp 430-432^{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.

CONCLUSION

The result of IR spectra and NMR spectra confirmed the structure of synthesized compound. The elemental analysis of **1a-1h** and **2a-2e** was in good agreement with those calculated values for the expected molecular formula. The mass spectrum illustrated the molecular ion peak found to be correct which will conform the structure of respective **1a-1h** and **2a-2e**. All the above spectral data supported the synthesis of compound **1a-1h** and **2a-2e.**

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