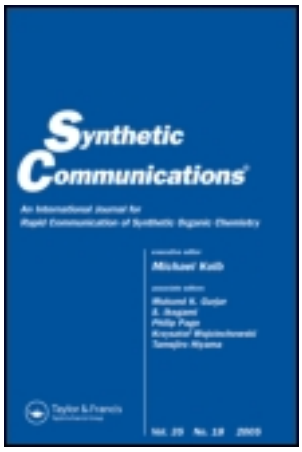

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Synthesis of a Piceatannol Analog: Replacement of Hydroxy Group with Amide Functionality

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ABSTRACT

Polyhydroxylated stilbene analogs of piceatannol are shown to possess protein-tyrosine kinase (PTK) inhibitory activity. We have developed a novel approach to introduce an amide moiety into the structure of piceatannol. The amido substituted stilbene derivative was synthesized in 10 steps with an overall yield of 30%.

Key Words: Protein-tyrosine kinase; Piceatannol; Stilbene derivatives; Amido group.

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INTRODUCTION

Protein-tyrosine kinases (PTKs) mediate important signaling events associated with cellular activation, differentiation, and mitogenesis. Highly potent and selective PTK inhibitors may serve as active drug substances with immunosuppressive, anti-inflammatory and anti-cancer activities.[1–4] Piceatannol analogs exhibit potent PTK inhibiting activity.[5–8] Although several syntheses of piceatannol and its analogs are known, these routes are found to proceed in moderate to low yields. In addition, instability of the phenolic stilbene derivative towards oxidation forming quinones made isolation of the product difficult.[9] This communication reports the synthesis of an amido-substituted stilbene derivative.

RESULTS AND DISCUSSION

Synthesis of an amido-substituted piceatannol was initiated following the synthetic (Sch. 1). 3,5-Dihydroxy benzoic acid (**1**) was converted into its benzyl ester (**2**) using benzyl bromide. The crystalline benzyl ester was reduced to the alcohol (**3**) with LAH. Conversion of the alcohol into its bromo derivative was achieved using phosphorus tribromide in anhydrous dichloromethane. The bromo derivative (**4**) thus obtained was treated with triethyl phosphite in the presence of tetrabutyl ammonium iodide to furnish the required phosphate ester (**5**). Compound (**7**) was obtained by condensing 5-formyl salicylic acid (**6**) with benzyl bromide in presence of anhydrous potassium carbonate in dimethylformamide. Condensation of compound (**5**) with compound (**7**) was accomplished in dimethylformamide in presence of potassium tertiary butoxide at room temperature to afford protected stilbene derivative (**8**). Compound (**10**) was prepared from *p*-amino benzoic acid (**9**) and EDC in *t*-BuOH. Compounds (**8**) and (**10**) were mixed together in presence of EDC in methylene chloride and refluxed for 18 hr. Usual workup gave compound (**11**) as a solid, which upon treatment with trifluroacetic acid for 1 hr at low temperature yielded the partially protected stilbene derivative (**12**). Finally, reaction of compound (**12**) with *N*-dimethyl aniline in dichloromethane at room temperature followed by anhydrous aluminum chloride treatment furnished the required stilbene analog (**13**) with an over all yield of 30%.

CONCLUSION

We have developed an efficient method for the introduction of an amido group into piceatannol. It is hoped that due to increased interest on PTK inhibitory activity shown by stilbene derivatives, the above synthetic methodology

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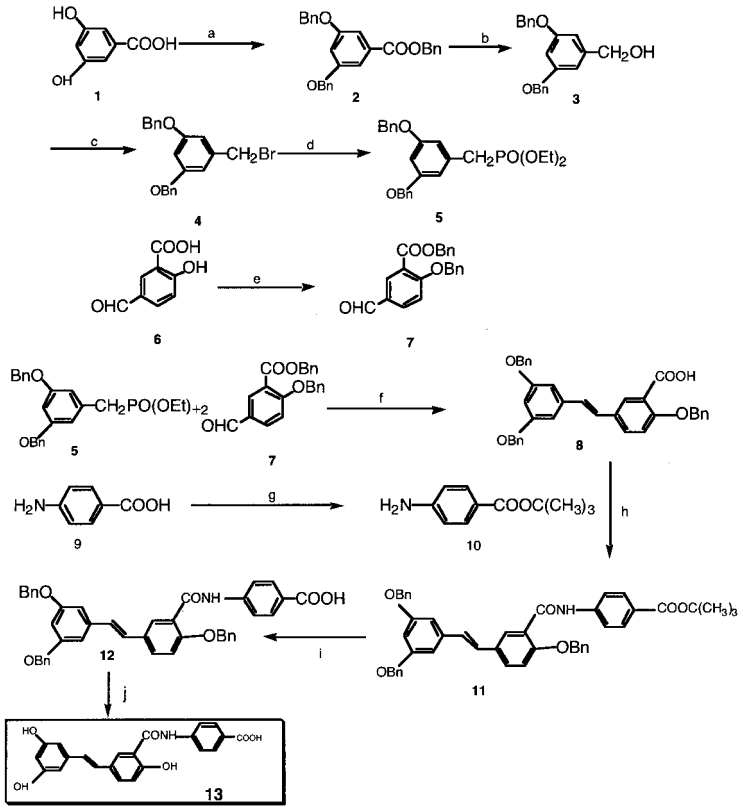

Scheme 1. Synthesis of piceatannol analog.

may be beneficial. It is envisioned that the amido-substituted piceatannol will be useful with properties of tyrosine kinase inhibiting immunoconjugates targeted against specific surface receptors on cancer cells.[10–12]

EXPERIMENTAL

All chemicals were purchased from Aldrich (Milwaukee, WI) and were used without further purification. Unless otherwise noted, each reaction vessel

was secured with a rubber septa, and the reaction was performed under nitrogen atmosphere. ^{1}H, ^{13}C NMR were obtained on a Varian Mercury 300 instrument at ambient temperature in either $CDCl_3$ or DMSO-d_6. Chemical shifts are reported as δ values in parts per million downfield from tetramethylsilane ($\delta = 0.0$ ppm) as an internal standard in the case of $CDCl_3$ or from the residual dimethylsufloxide signal ($\delta = 2.49$ ppm for ^{1}H NMR or $\delta = 39.7$ ppm for ^{13}C NMR). ^{31}P NMR were obtained using either of the above solvent and a capillary containing 0.1% phosphoric acid in water served as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FT-IR spectra were recorded on a Nicolet Protege 460 spectrometer. Mass spectra were performed either on a Hewlett Packard HP GC System 6890 Series or MALDI-TOF spectrometer (Model G2025A LD-TOF). Melting points were determined using a Melt John's apparatus and are uncorrected. Analytical thin-layer chromatography was done on Whatman silica 60 aluminum coated plates. Flash column chromatography was carried out with 230–400 mesh silica gel obtained from J. T. Baker Company.

Benzyl 3,5-dibenzyloxybenzoate (2). A mixture of 3,5-dihydroxylbenzoic acid (**1**) (3.08 g, 20 mmol), benzyl bromide (1.25 equiv., 8.9 mL, 75 mmol), and anhydrous potassium carbonate (16.6 g, 120 mmol) in anhydrous DMF (30 mL) was stirred and heated at 100°C under N_2 for 18 hr. After cooling, 150 mL of ethyl acetate was added and the inorganic salt was removed by filtration. The filtrate was successively washed with 10% NaOH (40 mL), H_2O (50 mL) and finally dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, leaving a yellow residue. Recrystallization from Et_2O–ethanol gave analytically pure product: yield 6.87 g (81%); Single spot in TLC (hexane/ethylacetate: 3 : 1); mp 50–52°C; IR (KBr) 3090, 3066, 3030, 2920, 2871, 1711, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.06 (s, 4H), 5.34 (s, 2H), 6.80 (s, 1H), 7.32 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 165.9, 159.6, 127.5, 108.5, 107.1, 70.3, 66.9, GC/MS: 424 (M^+), single peak, purity >98% by gas chromatography. Anal. calcd. for $C_{28}H_{24}O_4$: C: 79.22; H: 5.70; found; C: 79.33; H: 5.69.

3,5-Dibenzyloxybenzyl alcohol (3). The protected ester (**2**) (6.87 g, 16.2 mmol) in 60 mL anhydrous ether was added to a cold suspension of $LiAlH_4$ (1.23 g, 32.4 mmol) in anhydrous ether (100 mL) over a period of 40 min. The mixture was stirred at room temperature for 4 hr. The excess $LiAlH_4$ was decomposed by the treatment with methanol (2 mL), H_2O (4 mL), and 10% NaOH (5 mL). The inorganic salt was removed by filtration. The filtrate was dried over anhydrous $MgSO_4$. The solvent was evaporated by rotavap. Recrystallization from ethanol/water mixture gave the product as needle: yield 4.56 g (88%); mp 75–76°C (lit.,[7] m.p. 85°C); IR (KBr) 3288, 3032, 2859, 1596, 1451, 1291, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2H),

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5.04 (s, 4H), 6.55 (s, 1H), 6.62 (d, $J = 2.4$ Hz, 2H), 7.36 (m, 10H); [lit.,[7] ^{1}H NMR ($CDCl_3$), 200 MHz] δ 4.63 (s, 2H), 5.03 (s, 4H), 6.56 (t, 1H), 6.63 (d, $J = 2.0$ Hz, 2H), 7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 159.9, 143.3, 136.7, 128.5, 127.9, 127.4, 105.7, 101.2, 70.1, 65.3; GC/MS: 320 (M^+); single peak, purity >99% by gas chromatography. Anal. calcd. for $C_{21}H_{20}O_3$: C: 78.73; H: 6.29; found: C: 78.92; H: 6.28.

3,5-Dibenzyloxybenzyl bromide (4). Phosphorous tribromide (2.4 mL, 2.9 mmol) was added to a solution of benzyloxybenzyl alcohol (**3**) (4.13 g, 12.9 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0°C under N_2 and the reaction mixture was stirred for 2 hr at 0°C followed by 3 hr at room temperature. The mixture was poured into ice/water (200 mL) and the product was extracted with ether (6 × 50 mL). The combined ether layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude product as a yellow residue. Subsequent recrystallization from ethanol gave an analytically pure product: yield 2.2 g (42%); m.p. 77–79°C; IR (KBr) 3068, 3032, 2930, 2873, 1598, 1450, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.42 (s, 2H), 5.03 (s, 4H), 6.55 (s, 1H), 6.64 (d, $J = 2.4$ Hz, 2H), 7.35 (m, 10H); [lit.,[7] ^{1}H NMR ($CDCl_3$)] δ 4.41 (s, 2H), 5.02 (s, 4H), 6.55 (t, $J = 2.0$ Hz, 1H), 6.63 (d, $J = 2.0$ Hz, 2H), 7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 159.9, 139.6, 136.5, 128.5, 127.9, 127.5, 108.1, 102.1, 70.1, 33.6; GC/MS: 384 $(M + 1)^+$, 303 (M-HBr), 91 (Bn), single peak, purity >99% by gas chromatography. Anal. calcd. for $C_{21}H_{19}O_2Br$: C: 65.81; H: 5.00; found: C: 66.03; H: 5.06.

Diethyl[2,4-dibenzyloxybenzyl]phosphonate (5). Freshly distilled triethyl phosphite (1.4 mL, 1.5 mmol) was added to the benzyl bromide (**4**) (2.0 g. 5.2 mmol) in presence of catalytic amount (40 mg) of tetrabutylammonium iodide, and the reaction mixture was heated at 110–130°C for 18 hr. Excess triethyl phosphite was removed by vacuum distillation (0.2 mmHg), and the resultant mixture was heated at 50°C for 3 hr to obtain a yellowish syrup: yield 2.11 g (92%); IR (KBr) 3278, 3028, 2858, 1946, 1870, 1737, 1691, 1588, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, $J = 6.9$ Hz, 6H), 3.2 (d, $J = 21.6$ Hz, 2H), 3.97 (q, $J = 6.9$ Hz, 4H), 5.02 (s, 4H), 6.52 (m, 3H), 7.31 (m, 10H); [lit.,[7] ^{1}H NMR ($CDCl_3$)] δ 1.22 (t, $J = 7.4$ Hz, 6H), 3.10 (d, $J = 21.6$ Hz, 2H), 3.95 (q, $J = 7.4$ Hz, 4H), 5.05 (s, 4H), 6.54 (t, $J = 2.1$ Hz, 1H), 6.57 (d, $J = 2.1$ Hz, 2H), 7.38 (m, 10H)); ^{13}C NMR ($CDCl_3$) δ 159.7, 159.6, 136.6, 133.6, 133.5, 128.4, 127.8, 127.3, 108.9, 108.8, 100.8, 100.7, 69.9, 62.2, 62.1, 34.9, 33.1, 16.5, 16.4; ^{31}P NMR ($CDCl_3$) coupling with six protons gave septet peaks, decoupling with proton showed single peak (3.17 ppm); GC/MS: 440 (M^+), 349 (M-Bn), 91 (Bn); single peak, purity >99% by gas chromatography. Anal. calcd. for $C_{25}H_{29}O_5P$: C: 68.17; H: 6.64; found: C: 67.29; H: 6.80.

Benzyl 5-formyl-2-(benzyloxy) benzoate (7). To a well-stirred mixture of 5-formyl salicylic acid (**6**) (1.66 g, 10 mmol) in anhydrous DMF (15 mL),

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anhydrous potassium carbonate (5.53 g, 40 mmol), was added benzyl bromide (3 mL, 1.25 equiv., 25 mmol) under N_2. The resulting mixture was heated at 110°C for 20 hr. After cooling to 0°C, the mixture was poured into EtOAc (50 mL), and the precipitated inorganic salt was filtered. The organic layer was washed with 1 N KOH (15 mL), H_2O (15 mL) and dried over $MgSO_4$. The solvent was removed under vacuum. The residue was recrystallized from chloroform–hexane to yield a pale yellow solid: yield 2.94 g (85%); mp 90–92°C (lit.,[8] m.p. 80–85°C); IR (KBr) 3058, 3026, 2972, 2848, 2746, 1700, 1690, 1600, 1500, 1290 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.27 (s, 2H), 5.37 (s, 2H), 7.13 (d, $J = 8.7$ Hz, 1H), 7.33 (m, 10H), 7.97 (m, 1H), 8.36 (d, $J = 2.1$ Hz, 1H); (lit.,[8] ^1H NMR ($CDCl_3$) δ 5.26 (s, 2H), 5.36 (s, 2H), 7.14 (d, $J = 8.7$ Hz, 1H), 7.35 (m, 10H), 7.97 (dd, $J = 8.67$, 2.22 Hz, 1H), 8.34 (d, $J = 2.18$ Hz, 1H), 9.89 (s, 1H)); ^{13}C NMR ($CDCl_3$) δ 189.8, 162.4, 135.5, 135.3, 134.6, 134.2, 129.2, 128.6, 128.5, 128.3, 128.2, 128.1, 126.9, 113.6, 70.9, 67.2; MS: 346 $(M)^+$, 255 (M-Bn), 149 (M-2Bn), 91(Bn); single peak, purity >98% by gas chromatography. Anal. calcd. for $C_{22}H_{18}O_4$: C: 76.29; H: 5.24; found: C: 75.84; H: 5.33.

(*E*)-1(3′-Carboxy-4′-benzyloxy)phenyl-2-(3″,5″-dibenzyloxy)phenyl ethene (8). To phosphonate (**5**) (2.11 g, 4.8 mmol) in anhydrous DMF (20 mL) at 0°C under N_2 was added potassium *t*-butoxide (0.81 g, 7.2 mmol). The resulting yellow solution was stirred for 25 min, and then the aldehyde (**7**) (1.66 g, 4.8 mmol) in anhydrous DMF (5 mL) was added. The mixture was allowed to stir at room temperature for 4 hr. After this period, 10 N NaOH (5.0 mL) was added to the mixture and the contents were stirred for an additional hour. Finally, the reaction mixture was diluted with H_2O (100 mL) and acidified with 6 N HCl, extracted with CH_2Cl_2 (3 × 100 mL) and the organic layer was dried over anhydrous $MgSO_4$. Removal of solvent under vacuum resulted in a yellow liquid as crude product. Further purification was done using flash chromatography (hexanes–EtOAc: 5 : 1). Pooling of appropriate fractions, evaporation of the solvent, and further recrystallization from CH_2Cl_2–hexanes provided pure product: yield 1.3 g (50%); pale yellow solid; m.p. 156–158°C; (lit.,[8] 2″,5″ compound: m.p. 139–140°C); IR (KBr) 3278, 3028, 2858, 1946, 1870, 1737, 1691, 1588, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.07 (s, 4H), 5.31 (s, 2H), 6.57 (s, 1H), 6.75 (d, $J = 1.8$ Hz, 2H), 7.01 (s, 2H), 7.26 (m, 15H), 7.62 (d, $J = 7.2$ Hz, 1H), 8.35 (s, 1H); (lit.,[8] 2″,5″ compound); ^{13}C NMR ($CDCl_3$) δ 160.0, 138.8, 136.7, 132.7, 131.5, 129.1, 128.5, 127.9, 127.8, 127.4, 126.8, 113.4, 105.7, 101.8, 72.5, 70.1; MALDI-TOF MS: 543 (M + 1): purity >90%. Anal. calcd. for $C_{36}H_{30}O_5$: C: 79.68; H: 5.57; found: C: 78.63; H: 5.50. *t*-Butyl-4-aminobenzoate (**10**) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (3.815 g, 19.9 mmol) dissolved in dry *t*-butyl alcohol (60 mL, dried over anhydrous $MgSO_4$) was added to 4-amino benzoic acid (**9**) (2.5 g, 18.2 mmol) in

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t-butyl alcohol (60 mL). The reaction mixture was refluxed for 18 hr. The reaction mixture was cooled to 0°C and water (100 mL) was added. The resultant mixture was extracted with ether (4 × 100 mL) and the organic layer was separated from the aqueous layer. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated under vacuum to furnish a yellow solid as crude product. Additional purification was done by recrystallization from ethanol, which gave analytically pure product: yield 2.1 g (60%); m.p. 106–108°C; IR (KBr) 3416, 3355, 3232, 2981, 1691, 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (m, 9H), 6.61 (m, 2H), 7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 165.8, 150.2, 131.2, 121.6, 113.6, 79.9, 28.4; GC/MS: 193 $(M)^+$, 137 (M − *t*Bu), 120 (M − *t*Bu–NH_2) single peak, purity >98% by gas chromatography. Anal. calcd. for $C_{11}H_{15}O_2N$: C: 68.37; H: 7.82; N: 7.61; found: C: 67.88; H: 7.87; N: 7.16.

(*E*)-1-[3′-Benzamide(4″-*t*-butyl)benzoate)-4′-benzyloxy]phenyl-2-(3‴,5‴-dibenzyloxy)phenyl ethene (11). A stirred mixture of *trans*-1(3′-carboxy-4′-benzyloxy)phenyl-2-(3″,5″-dibenzyloxy)phenyl ethene (**8**) (1.084 g, 2 mmol), *t*-butyl-4-aminobenzoate (**10**) (0.386 g, 2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.422 g, 2.2 mmol) in $CHCl_3$ was refluxed for 18 hr. After cooling to 0°C, H_2O (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The organic layer was separated from the aqueous layer and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under vacuum gave crude product. The crude material was recrystallized from ether to furnish compound (**11**): yield 0.8 g (56%); TLC single spot (hexane/ethylacetate: 3 : 1); m.p. 168–170°C; IR (KBr) 3327, 3032, 2974, 2931, 1701, 1668, 1597, 1294, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (m, 9H), 5.09 (s, 4H), 5.25 (s, 2H), 6.57 (s, 1H), 6.77 (d, $J = 2.1$ Hz, 2H), 7.36 (m, 22H), 7.82 (d, $J = 8.4$ Hz, 1H), 8.49 (d, $J = 2.4$ Hz, 1H), 10.16 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 165.3, 159.9, 141.9, 139.1, 136.7, 131.4, 131.2, 130.5, 130.3, 129.3, 129.2, 128.7, 128.4, 127.9, 127.4, 118.7, 112.9, 105.7, 101.7, 80.7, 72.2, 70.1, 28.4, 28.3; MALDI (TOF)/MS: 717 $(M)^+$. Anal. calcd. for $C_{47}H_{46}O_6N$: C: 78.64; H: 6.04; N: 1.95; found: C: 77.90; H: 5.94; N: 1.94.

(*E*)-1-[3′-Benzamide(4″-carboxy)-4′-benzyloxy]phenyl-2-(3‴,5‴-dibenzyloxy)phenyl ethene (12). Freshly distilled trifluoroacetic acid (1 mL) precooled in an ice bath was added to *trans*-1-[3′-benzamide(4″-*t*-butyl)-benzoate)-4′-benzyloxy]phenyl-2-(3‴,5‴-dibenzyloxy)phenyl ethene (**11**) (0.717 g, 0.1 mmol) at 0°C, and the mixture was allowed to stir for 1 hr. The product was collected by filtration: yield 0.59 g (90%); m.p. >200°C; IR (KBr) 3335, 3064, 3033, 2879, 2674, 2546, 1784, 1686, 1593, 1163 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.13 (s, 4H), 5.27 (s, 2H), 6.59 (s, 1H), 6.91 (s, 2H), 7.43 (m, 24H), 10.56 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 166.9, 159.7, 142.9, 139.3, 137.1, 136.5, 130.4, 129.9, 128.5, 128.2, 127.9, 127.8, 125.4,

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118.7, 105.5, 69.4; MALDI(TOF)/MS: 661 $(M+1)^+$; purity >98%. Anal. calcd. for $C_{43}H_{38}O_6N$: C: 78.05; H: 5.33; N: 2.12; found: C: 77.77; H: 5.49; N: 2.24.

(*E*)-1-[3′-Benzamide(4″-carboxy)-4′-hydroxy]phenyl-2-(3‴,5‴-dihydroxy) phenyl ethene (13). Freshly distilled *N*,*N*′-dimethylaniline (0.94 mL, 7.4 mmol, 8 equiv.) was added to a solution of benzyl protected stilbene (**12**) (0.204 g, 0.31 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature under N_2. After 10 min, anhydrous $AlCl_3$ (0.53 g, 4 mmol) was added. The reaction was allowed to stir for 4 hr at room temperature. Subsequently the reaction mixture was cooled to 0°C, and was treated with H_2O (5 mL) and 1 M HCl (10 mL). The resulting mixture was extracted with EtOAc (6 × 10 mL). The ethyl acetate layer was separated from the aqueous layer and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent gave a residue. This residue was further purified using preparative thin layer chromatography technique using 3 : 1 $CHCl_3$–MeOH to give (**13**) as dark brown solid. Single band in PTLC: yield: 36 mg (30%); IR (KBr) 3448, 2983, 2254, 2127, 1658, 1250, 1050 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.01 (s, 1H), 6.31–6.30 (m, 2H), 6.37 (m, 1H), 6.50 (m, 1H), 6.83 (m, 1H), 7.29–7.27 (m, 1H) 7.72–7.70 (m, 2H), 7.85–7.80 (m, 3H), 9.08 (bs, 1H). GC/MS: 391 (M^+). HPLC Rt: 2.3 min, % purity: 85%. Anal. calcd. for $C_{22}H_{17}O_6N$: C: 67.51; H: 4.38; N: 3.58; found: C: 52.06; H: 3.92; N: 2.85* (*analysis low due to contamination of SiO_2 in the sample since the compound is extremely polar).

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