Int J Pharm Bio Sci 2013 July; 4(3): (P) 97 - 103

Research Article **Natural Chemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SYNTHESIS AND BIOLOGICAL EVALUATION OF *N*-(SUBSTITUTED CINNAMOYL)-*N'* (PYRIDIN-2-YL) PIPERAZINE AS ANTIOXIDANTS

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ABSTRACT

A series of novel cinnamamides (5a-5e) have been synthesized and tested for antioxidant activity using DPPH assay. Results revealed that compounds 5b and 5d shows excellent antioxidant activity as compared to standard. All the synthesized compounds were characterized by using IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral analysis.

KEYWORDS: **DPPH assay, Cinnamamides, Antioxidant, Synthesis.**

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INTRODUCTION

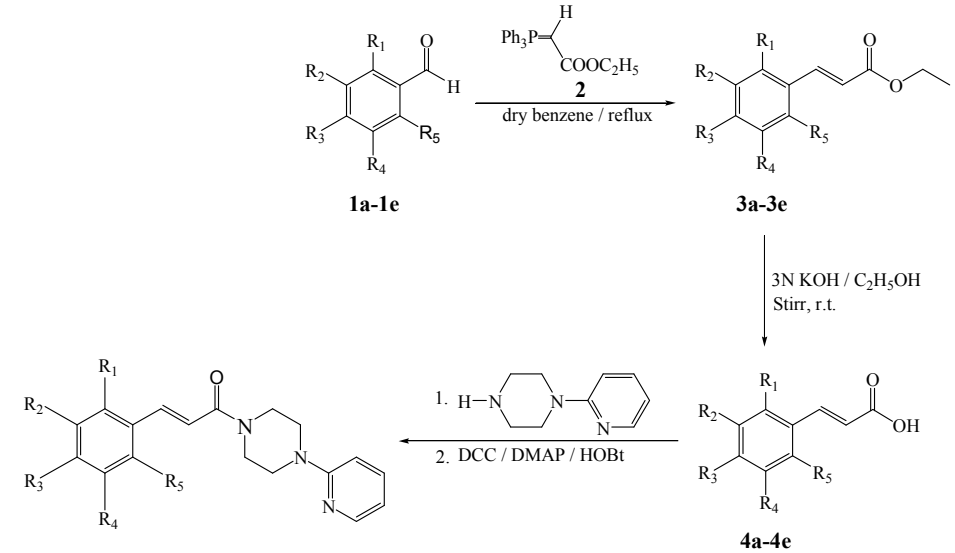
Several naturally occurring as well as synthetic cinnamamides are reported to possess broad spectrum of physiological function and biological activities and reported as Sedatives[1], CNS depressant[2], Local anesthetic[3], Antimycobacterial [4], Cytotoxicity [5] and Antioxidant [6]. Further the *N*-Feruloyl piperazine derivatives showed cytotoxic activity towards cancer cells and they have significant DNA binding activity[7]. After reviewing the literature, we found that natural and synthetic cinnamamides have various biological applications and methods of synthesis. So by taking this fact in consideration, the aim of this research article was to synthesize some novel *N*-(substituted cinnamoyl)-*N'*-(pyridine-2-yl)piperazine derivatives and to carry out their biological evaluation towards antioxidant activity.

MATERIALS AND METHODS

All reagents and solvents were used as obtained from the supplier or recryastallized/redistilled and dried as necessary. Melting points of the synthesized compounds were determined in open capillaries and are uncorrected. IR spectra were recorded on Shimadzu FT-IR spectrophotometer using KBr pellets in the region 4000-400 cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian mercury plus 300 MHz spectrophotometer in $CDCl_3$ as solvent and TMS as internal standard. The mass spectra were recorded on Varian Inc. 410 prostar binary LC with 500 MS IT. Column chromatography was performed on sd-Fine silica gel (60-120 and 200-400 mesh). TLC was performed on Fluka® silica gel plates (5-17µm, F_{254}). The mobile phase was ethyl acetate and n-hexane and detection was made using UV light and iodine vapors.

SCHEME 1

General route for the synthesis of N-(substituted cinnamoyl)-N'-(pyridine-2-yl)piperazine.



5a: R_1=R_2=R_3=R_4=R_5=H
5b: R_1=R_2=R_4=R_5=H, R_3= -OCH_3
5c: R_1=R_4=R_5=H, R_2=R_3= -OCH_3
5d: R_1=R_2=R_4=R_5=H, R_3= -NO_2
5e: R_1=R_2=R_4=R_5=H, R_3= -Cl

EXPERIMENTAL

CHEMISTRY

General procedure for the synthesis of compounds

Synthesis of triphenyl-α-ethoxycarbonylethylene phosphorane

Phosphorane 2 was prepared according to the reported procedure [8].

General procedure for the synthesis of cinnamates 3a-e

A solution of aromatic aldehydes (1a-1e) (10mmol) and phosphorane 2 (4 g, 10.3 mmol) in anhydrous benzene (20mL) was refluxed for 3-4 hrs. The solvent was removed in and the residue was purified by column chromatography over silica gel (hexane/ethyl acetate 8: 2) to yield cinnamates (3a-3e) as yellowish thick oil.

***(E)-Ethyl cinnamate 3a*[9].** Yield: 90 %; IR (KBr, cm^{-1}): 1712; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.33 t (*J*=7.0 Hz) 3H (-OCH_2-$C\underline{H}_3$), 4.26 q (*J*=7.0 Hz) 2H (-$OC\underline{H}_2$-CH_3), 6.44 d (*J*=16.1Hz) 1H $\underline{H}_A$, 7.35 -7.53 m 5H (5ArH), 7.68 d (*J*=15.9 Hz) 1H ($\underline{H}_B$); MS (ESI): 176.90 (M^{+1}).

***(E)-Ethyl 3-(4-methoxyphenyl) acrylate 3b*[10].** Yield: 91 %; IR (KBr, cm^{-1}): 1712; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.32 t (*J*= 7.2 Hz) 3H (-OCH_2-$C\underline{H}_3$), 3.83 s 3H (-$OC\underline{H}_3$), 4.24 q (*J*= 7.2 Hz) 2H (-$OC\underline{H}_2$-CH_3), 6.30 d (J= 15.7 Hz) 1H ($\underline{H}_A$), 6.89 d (J= 9.0 Hz) 2H ($\underline{H}_C$ and $\underline{H}_D$), 7.47 d (J= 8.6 Hz) 2H ($\underline{H}_E$ and $\underline{H}_F$), 7.63 d (J= 16.2 Hz) 1H ($\underline{H}_B$); MS (ESI): 207.00 (M +H) $^+$.

***(E)-Ethyl 3-(3,4-dimethoxyphenyl) acrylate 3c*[9].** Yield: 90 %; IR (KBr, cm^{-1}): 1705; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.34 t (*J*=7.2 Hz) 3H (-OCH_2 -$C\underline{H}_3$), 3.91 s 6H (2 X –$OC\underline{H}_3$), 4.26 q (*J*=7.2 Hz) 2H (-$OC\underline{H}_2$-CH_3), 6.31 d (*J*=15.7 Hz) 1H ($\underline{H}_A$), 6.87 d (*J*=8.1 Hz) 1H ($\underline{H}_C$), 7.05-7.12 m 2H (2ArH), 7.63 d (*J*=16.2 Hz) 1H ($\underline{H}_B$); MS (ESI): 237.05 (M +H) $^+$.

***(E)-Ethyl 3-(4-nitrophenyl) acrylate 3d*[9].** Yield: 92 %; IR (KBr, cm^{-1}): 1712, 1516; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.35 t (*J*=7.2 Hz) 3H (-OCH_2-$C\underline{H}_3$), 4.29 q (*J*=7.2 Hz) 2H (-$OC\underline{H}_2$-CH_3), 6.56 d (*J*=16.2 Hz) 1H ($\underline{H}_A$), 7.66-7.73 m 3H ($\underline{H}_B$ and 2ArH), 8.25 d (*J*=8.6 Hz) 2H ($\underline{H}_C$ and $\underline{H}_D$); MS (ESI): 222.00 (M +H) $^+$.

***(E)-Ethyl 3-(4-chlorophenyl) acrylate 3e*[9].** Yield: 90 %; IR (KBr, cm^{-1}): 1714; ^{1}H-NMR (300 MHz, $CDCl_3$): 1.33 t (*J*=7.2 Hz) 3H (-OCH_2-$C\underline{H}_3$), 4.26 q (*J*=7.2 Hz) 2H (-$OC\underline{H}_2$-CH_3), 6.40 d (*J*=15.7 Hz) 1H ($\underline{H}_A$), 7.36 d (*J*=1.9 Hz) 2H ($\underline{H}_C$ and $\underline{H}_D$), 7.45 d (*J*=8.6 Hz) 2H ($\underline{H}_E$ and $\underline{H}_F$), 7.63 d (*J*=15.8 Hz) 1H ($\underline{H}_B$); MS (ESI): 211.00 (M +H) $^+$.

General procedure for the synthesis of cinnamic acids 4a-e

Aqueous KOH (3N, 3 mL) was added to a solution of the appropriate cinnamate (3a-3e) (1 mmol) in ethanol (5 mL) and the mixture was stirred at rt for 6 hrs. The ethanol was removed yields residue then; water (5 ml) was added to it and acidified with ice-cold HCl (1: 1). The precipitated solid was filtered off, washed with water, dried and recryastallized from dichloromethane-hexane to provide cinnamic acids (4a-4j).

***Cinnamic acid 4a* [11].** White crystalline solid; Yield: 92 %; mp.: 133 ^{0}C, (lit. ^{11}.130-132 ^{0}C); IR (KBr, cm^{-1}): 2954, 1693; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.46 d (*J*=15.8 Hz) 1H ($\underline{H}_A$), 7.40-7.58 m 5H (5ArH), 7.81 d (*J*=15.8 Hz) 1H ($\underline{H}_B$); MS (ESI): 148.90 (M) $^+$.

***(E)-3-(4-methoxyphenyl) acrylic acid 4b* [12].** White crystalline solid; Yield: 88 %; mp.: 170 ^{0}C, (lit. ^{12}.170-173 ^{0}C); IR (KBr, cm^{-1}): 2954, 1693; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.84 s 3H (–$OC\underline{H}_3$), 6.46 d (*J*=15.8 Hz) 1H ($\underline{H}_A$), 7.40-7.58 m 4H (4ArH), 7.81 d (*J*=15.8 Hz) 1H ($\underline{H}_B$); MS (ESI): 178.06 (M) $^+$.

***(E)-3-(3, 4-dimethoxyphenyl) acrylic acid 4C* [13].** White crystalline solid; Yield: 90 %; mp.: 178 ^{0}C, (lit. ^{13}. 178-180 ^{0}C); IR (KBr, cm^{-1}): 2960, 1681; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.93 s 6H (2 X –$OC\underline{H}_3$), 6.32 d (*J*=16.2 Hz) 1H ($\underline{H}_A$), 6.88d (*J*=8.1 Hz) 1H ($\underline{H}_C$), 7.07-7.16 m 2H (2ArH), 7.73 d (*J*=15.7 Hz) 1H ($\underline{H}_B$); MS (ESI): 209.05 (M +H) $^+$.

(E)-3-(4-nitrophenyl) acrylic acid 4d [12]. Yellowish crystalline solid; Yield: 92 %; mp.: 289 ^{0}C, (lit. [12].285-287 ^{0}C); IR (KBr, cm^{-1}): 2965, 1695, 1529; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.57 d (*J*=16.3 Hz) 1H ($\underline{H}_A$), 7.69 d (*J*=8.1 Hz) 2H ($\underline{H}_E$ and $\underline{H}_F$), 8.03 d (*J*=8.6 Hz) 1H ($\underline{H}_B$), 8.27 d (*J*=8.6 Hz) 2H ($\underline{H}_C$ and $\underline{H}_D$); MS (ESI): 194.95 (M +H)$^+$.

(E)-3-(4-chlorophenyl) acrylic acid 4e [12]. White crystalline solid; Yield: 90 %; mp.: 248 ^{0}C, (lit. [12]. 245-247 ^{0}C); IR (KBr, cm^{-1}): 2965, 2920, 1693; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.42 d (*J*=16.2 Hz) 1H ($\underline{H}_A$), 7.38 d (*J*=8.1 Hz) 2H ($\underline{H}_C$ and $\underline{H}_D$), 7.48 d (*J*=8.1 Hz) 2H ($\underline{H}_E$ and $\underline{H}_F$), 7.71 d (*J*=15.7 Hz) 1H ($\underline{H}_B$); MS (ESI): 183.05 (M +H)$^+$.

General procedure for the synthesis of cinnamamides 5a-5e

To a solution of cinnamic acids (4a-4e) (1 mmol) in dichloromethane (10 ml), 1-(pyridin-2-yl) piperazine (2.1 mmol), HOBt (1.8 mmol) and DMAP (1.2 mmol) was added ones at 0 ^{0}C. Reaction mixture was stirred for 10 minutes. Then a solution of DCC (1.4 mmol) in dichloromethane was added toabove reaction mixture. Maintain the cooling for 2-3 hrs after addition of DCC with stirring and kept reaction mixture overnight at rt. Filter the reaction mixture (It separate DHU-Solid formed in the reaction mixture as byproduct).The reaction mixture was washed with 1N $KHSO_4$ and 10 % $NaHCO_3$ solution twice. Then whole dichloromethane layer was washed with brine water; and dried over Na_2SO_4. After removal of dichloromethane yields the cinnamamides (5a-5e) were obtained as white solids. All these cinnamamides were purified by recrystallization from dichloromethane: hexane.

(E)-3-phenyl-1-(4-(pyridin-2-yl)piperazin-1-yl)prop-2-en-1-one 5a. White crystalline solid; TLC: hexane/ethyl acetate (8:2, v/v); Yield: 92 %; mp.: 134-136 ^{0}C; IR (KBr, cm^{-1}): 3070, 1645, 1591; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.61-3.81 m 8H (2$\underline{H}_C$, 2$\underline{H}_{C'}$, 2$\underline{H}_D$ and 2$\underline{H}_{D'}$), 6.67 dd (*J*=4.8 Hz and 7.6 Hz) 1H ($\underline{H}_E$), 6.92 d (*J*= 15.2 Hz) 1H ($\underline{H}_A$), 7.37-7.56 m 7H ($\underline{H}_F$, $\underline{H}_G$ and 5ArH), 7.72 d (*J*= 15.2 Hz) 1H ($\underline{H}_B$), 8.21 d (*J*= 3.8 Hz) 1H ($\underline{H}_H$); ^{13}C-NMR (75 MHz, $CDCl_3$): 165.4, 158.8, 147.8, 142.9, 137.5, 135.0, 129.5, 128.6, 127.6, 116.7, 113.7, 107.0, 45.0; MS (ESI): 294.15 (M +H)$^+$.

(E)-3-(4-methoxyphenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl) prop-2-en-1-one 5b. White crystalline solid; Yield: 85 %; mp.: 148-150 ^{0}C; IR (KBr, cm^{-1}): 2995, 1651; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.57-3.79 m 11H (1 X –OC$\underline{H}_3$, 2$\underline{H}_C$, 2$\underline{H}_{C'}$, 2$\underline{H}_D$ and 2$\underline{H}_{D'}$), 6.63 dd (*J*=5.8 and 8.2 Hz) 1H ($\underline{H}_E$), 6.76 d (*J*= 15.8 Hz)1H ($\underline{H}_A$), 6.85-7.49 m 6H ($\underline{H}_F$, $\underline{H}_G$ and 4ArH), 7.65 d (*J*= 15.7 Hz) 1H ($\underline{H}_B$), 8.17 d (*J*= 3.3Hz) 1H ($\underline{H}_H$); MS (ESI): 324.25 (M +H)$^+$; ^{13}C-NMR (75 MHz, $CDCl_3$): 165.7, 158.8, 147.8, 142.6, 137.5, 129.2, 127.7, 114.2, 114.0, 113.6, 107.0, 55.2, 45.0.

(E)-3-(3,4-dimethoxyphenyl)-1-(4-(pyridin-2-yl) piperazin-1-yl) prop-2-en-1-one 5c. White crystalline solid; Yield: 90 %; mp.: 138-140 ^{0}C; IR (KBr, cm^{-1}): 3008, 1645; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.58-3.84 m 8H (2$\underline{H}_C$, 2$\underline{H}_{C'}$, 2$\underline{H}_D$ and 2$\underline{H}_{D'}$), 3.90 s 3H (1 X –OC$\underline{H}_3$), 3.93 s 3H (1 X –OC$\underline{H}_3$), 6.67 dd (*J*=3.9 and 8.1 Hz) 1H ($\underline{H}_E$), 6.80 d (*J*= 15.3 Hz) 1H ($\underline{H}_A$), 6.85-7.54 m 5H ($\underline{H}_F$, $\underline{H}_G$ and 3ArH), 7.68 d (*J*= 15.3 Hz) 1H ($\underline{H}_B$), 8.21 d (*J*= 3.8 Hz) 1H ($\underline{H}_H$); MS (ESI): 354.20 (M +H)$^+$; ^{13}C-NMR (75 MHz, $CDCl_3$): 165.6, 158.8, 150.4, 148.9, 147.8, 142.9, 137.5, 128.0, 121.7, 114.4, 113.6, 110.9, 109.7, 106.9, 55.7, 45.0.

(E)-3-(4-nitrophenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl)prop-2-en-1-one 5d. Yellow crystalline solid; Yield: 95 %; mp.: 218-220 ^{0}C; IR (KBr, cm^{-1}): 3113, 1649, 1514; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.65-3.84 m 8H (2$\underline{H}_C$, 2$\underline{H}_{C'}$, 2$\underline{H}_D$ and 2$\underline{H}_{D'}$), 6.69 dd (*J*=5.3 and 8.1 Hz) 1H ($\underline{H}_E$), 7.06 d (*J*= 15.7 Hz) 1H ($\underline{H}_A$), 7.53-7.70 m 4H ($\underline{H}_F$, $\underline{H}_G$, $\underline{H}_L$, and $\underline{H}_I$), 7.74 d (*J*= 15.8 Hz) 1H ($\underline{H}_B$), 8.21-8.26 m 3H ($\underline{H}_J$, $\underline{H}_K$, and $\underline{H}_H$); MS (ESI): 339.10 (M +H)$^+$; ^{13}C-NMR (75 MHz, $CDCl_3$): 164.5, 158.9, 148.0, 141.4, 140.2, 137.7, 128.3, 124.1, 121.2, 114.0, 107.2, 45.2.

(E)-3-(4-chlorophenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl)prop-2-en-1-one 5e. White crystalline solid; Yield: 90 %; mp.: 190-192 ^{0}C;

IR (KBr, cm^{-1}) : 3007, 1643; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.63-3.82 m 8H (2H_C, 2$H_{C'}$, 2H_D and 2$H_{D'}$), 6.68 dd (*J*=4.7 and 8.2 Hz) 1H (H_E), 6.90 d (*J*= 15.2 Hz) 1H (H_A), 7.46-7.54 m 4H (H_F, H_G, H_H, and H_I), 7.66 d (*J*= 15.2 Hz) 1H (H_B), 8.21 d (*J*= 3.9 Hz) 1H (H_L); MS (ESI): 328.10 $(M+H)^+$; ^{13}C-NMR (75 MHz, $CDCl_3$): 165.2, 158.8, 147.9, 141.6, 137.6, 135.4, 133.5, 128.9, 117.3, 113.8, 107.0, 45.0.

BILOGICAL ASSAY

Biological assay is used to evaluate the bioactivity of compounds which helps to establish structure activity relationship.

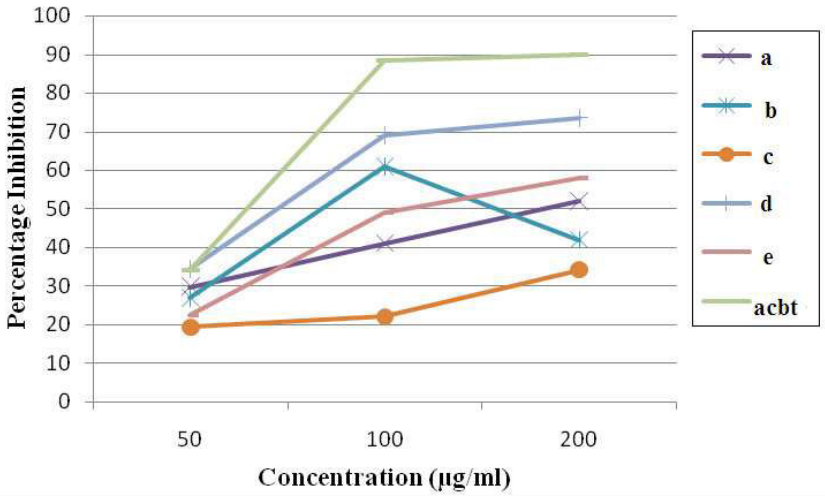
ANTIOXIDANT EVALUATION

The entire synthesized cinnamamides (5a-5e) were tested for their antioxidant properties using DPPH assay. The DPPH (2,2−diphenyl-1-picrylhydrazyl) radical scavenging activity of compounds (5a-5e) were analyzed at concentration of 50, 100, 200 µg/mL by using the method of Shimada [14] with certain modifications. In brief, a 0.8 ml of synthesized compound bearing specific concentration and 1 mL of freshly prepared 0.2 mM DPPH (Sigma) solution in methanol were mixed together to react for 30 min in dark. Blank samples contained methanol. The scavenged DPPH was then monitored by measuring the decrease in optical density at 517 nm. Percentage radical scavenging effect was defined as [O.D. Blank− O.D. Test / O.D. Blank] × 100. The decrease in optical density was measured on Instrument UV-mini 1240, Shimadzu, Japan. All the compounds showed the desired radical scavenging activity at all the three concentrations. Out of these cinnamamides, cinnamamides 5b and 5d showed excellent activity as compared to standard (Ascorbate). The results are summarized in Table 1.

Table 1
Antioxidant activity of synthesized cinnamamides 5a-5e.

5	Concentration (µg/ml)		
	Inhibition (%) ± 5		
	50	100	200
a	29.7	41.0	52.0
b	26.9	61.0	42.0
c	19.3	22.0	34.2
d	34.4	69.0	73.6
e	22.3	49.0	58.0
Ascorbate	34.0	88.5	90.0

Figure 1
% radical scavenging activity of the cinnamamides 5a-5e.



RESULTS AND DISCUSSION

CHEMISTRY

We synthesized the target title compounds according to the sequence of reaction as shown in scheme 1. The cinnamates (3a-3e) were obtained by the Wittig olefination of various aromatic aldehydes (1a-1e) with triphenyl-α-ethoxycarbonylethylene phosphorane (2) in refluxing benzene in just 3-4 hours in 90-92 % yields. Basic hydrolysis of 3a-3e using 3N KOH / C_2H_5OH at room temperature provides the cinnamic acids (4a-4e) in 88-92 % yield. These acids on coupling with 1-(pyridin-2-yl) piperazine inpresence of DCC / HOBt / DMAP provided the corresponding α, β-unsaturated amides (5a-5e) in 85-95% yield.

BIOLOGICAL EVALUATION

The antioxidant activity of the entire synthesized cinnamamides 5a-5e was carried out using DPPH assay. Ascorbate was used as standard. The results of the screening are summarized in table 1. From the results obtained, it was found that the compounds 5b and 5d showed significant antioxidant activity. The compound 5b has methoxy group and compound 5d has nitro group at C4 position of the aromatic ring which showed antioxidant activity which was nearly equal to that of the standard.

CONCLUSION

The objective of the present study was to synthesize the novel cinnamamides analogues and investigate their antioxidant activities with the hope of discovering new structural leads serving as antioxidant agents. The results of antioxidant screening revealed that two compounds were found to exhibit excellent degree of antioxidant activities using DPPH assay. In particular, compound 5b and 5d proved to be the most active member in this study.

ACKNOWLEDGEMENT

One of the author KRD thanks UGC-SAP for providing the financial assistance.

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