Research Article

Synthesis of Cinnamanilide Derivatives and Their Antioxidant and Antimicrobial Activity

Satish Balasaheb Nimse,1 Dilipkumar Pal,2 Avijit Mazumder,3 and Rupa Mazumder3

1Institute for Applied Chemistry and Department of Chemistry, Hallym University, Chuncheon 24252, Republic of Korea
2Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh 495009, India
3Department of Pharmaceutical Technology, Noida Institute of Engineering and Technology, Greater Noida 201306, India

Correspondence should be addressed to Satish Balasaheb Nimse; satishnimse@hallym.ac.kr

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The amide derivatives of cinnamic acid were synthesized and their antimicrobial and antioxidant activities were investigated. The investigation of antimicrobial potentials of the compounds demonstrated a strong activity against 21 bacterial strains comprising Gram-positive and Gram-negative bacteria. Compounds 2a, 2b, and 3b showed strong antimicrobial activity against all microorganisms with the pMIC value ranging from 2.45 to 3.68. Compounds 2a, 3a, and 3b demonstrated strong antioxidant activity with % inhibition of the DPPH radical of 51% (±1.14), 41% (±1.01), and 50% (±1.23), respectively. These findings indicate that the amide derivatives of the cinnamic acid possess strong antibacterial and antioxidant activities.

1. Introduction

Discovery of simple organic compounds with the antimicrobial and antioxidant activities is of growing concern in the food industries for their preservative properties [1, 2]. Preservation of industrial food containing polyunsaturated fatty acids (eicosapentaenoic (20:5ω-3) acid) has been a subject of growing interest, because of their importance in human nutrition. ω-3-Polyunsaturated fatty acids have several health benefits in cardiovascular disease, immune disorders, inflammation, allergies, and diabetes [3]. Therefore, the development of the antimicrobial compounds that can act as food preservatives by inhibiting the growth of bacteria or fungi, including mold, is very important [4].

Apart from the bacterial deterioration, the radical associated oxidation of fatty acids is one of the most important reactions leading to a degeneration of food [5, 6]. Several compounds with the antioxidant activity have been used to slow down the radical associated oxidative reactions. Antioxidants are molecules that inhibit or quench free radical reactions and delay or inhibit the cellular damage [7, 8]. The butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tertiary butylhydroquinone (TBHQ) have been used commonly as food antioxidants. However, some of these molecules are known to possess toxic and carcinogenic side effects in animal models [9]. Therefore, the demand has increased because of questions about the long-term safety and negative consumer perception of the commonly used synthetic antioxidants BHT and BHA. The discovery of compounds that can show both antimicrobial and antioxidant activities with no toxic effects on health is highly awaited.

Due to its common occurrence in plants and its low toxicity [10, 11], cinnamic acid has been evaluated as an antioxidant compound [12, 13]. Moreover, the cinnamic acid derivatives are reported to possess better antimicrobial activity than cinnamic acid itself [14, 15]. In the present paper the synthesis, antimicrobial, and antioxidant activities of the amide derivatives of cinnamic acid are presented.

2. Materials and Methods

All chemicals, solvents, and biochemical reagents were of analytical grade and purchased from commercial sources. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) was purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). UV-Vis spectra were obtained on a Perkin-Elmer 554 double beam spectrophotometer. The final products were characterized by 1H
and $^{13}$C NMR (JEOL FX-90Q FT NMR, 300 MHz) and mass spectrometry (JEOL JMS 600 Mass Spectrometer).

2.1. General Procedure for the Synthesis of Compounds 2a–2g and 3a–3b. Compounds 2a–2d and 3a–3b (Scheme 1) were synthesized by slight modification of the typical procedure adopted for various cinnamic acid derivatives [16, 17]. To a stirred solution containing aniline derivatives or amine derivatives (25 mmol), K$_2$CO$_3$ (4.15 g, 30 mmol), and tetrahydrofuran (5 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min and then at RT for 3 hours. The solution was concentrated under vacuum and then poured on ice cold water with stirring. The precipitated product was washed with water and dried in an oven at 100 °C. The final compounds were then obtained by crystallization from ethanol.

For the synthesis of compounds 2e–2g, to a stirred solution of respective aniline derivatives (30 mmol) in diethyl ether (30 mL), the cinnamyl chloride (4.10 g, 20 mmol) dissolved in diethyl ether (5 mL) was added dropwise at 0°C. The mixture was stirred at 0°C for 30 min and then at RT for 3 hours. After completion of reaction the solvent was concentrated and then added to 100 mL of dichloromethane. The solution was washed 3 times with 1 N HCl and 2 times with 1 N NaHCO$_3$. The separated organic layer was dried over MgSO$_4$ and solvent was evaporated completely to obtain a residue. The final compounds were obtained by crystallization from ethanol.

(2a) N-Phenylicinnamamide. 75.55% yield, $^1$H NMR (CDCl$_3$, 300 MHz, 298 K) δ (ppm): 9.74 (s, 1H, -OH), 7.57 (m, 10H, Ar-H), 7.50 (d, 1H, $J = 15.6$ Hz, CH=CH), 6.72 (d, 1H, $J = 15.6$ Hz, CH=CH). $^{13}$C NMR (300 MHz, CDCl$_3$): 163.66 (C=O), 140.32 (Ar=CH=CH), 139.16, 134.86, 129.42, 128.90, 128.11, 127.52, 122.31 (Ar), 121.62 (CH=CH=C=O), JEOl JMS 600, El$^+$ mode: $m/z = 223.2089$ [M]$^+$, 224.2087 [M + H]$^+$. (2b) N-(2-Hydroxyphenyl)cinnamamide. 50.76%, $^1$H NMR (d$_6$-DMSO, 300 MHz, 298 K) δ (ppm): 10.03 (bs, 1H, -OH), 9.52, (s, 1H, -OH), 7.96 (d, 1H, $J = 15.6$ Hz, CH=CH), 7.38–7.65 (m, 6H, Ar-H), 7.18 (d, 1H, $J = 15.6$ Hz, CH=CH), 6.90–6.96 (dt, 2H, Ar-H), 6.81 (t, 1H, Ar-H). $^{13}$C NMR (d$_6$-DMSO, 300 MHz, 298 K): 164.9 (C=O), 142.9 (HO-Ar), 135.5, 130.2, 129.5, 128.5, 128.3, 127.3, 125.1, 123.3, 122.5, 116.2 (Ar), 119.5 (CH=CH=C=O), JEOl JMS 600, El$^+$ mode: $m/z = 257.2134$ [M]$^+$, 258.7136 [M + H]$^+$. (2c) N-(4-Chlorophenyl)cinnamamide. 76.65% yield, $^1$H NMR (CDCl$_3$, 300 MHz, 298 K) δ (ppm): 7.76 (d, 1H, $J = 15.6$ Hz, CH=CH), 7.62–7.60 (m, 4H, Ar-H), 7.52 (d, 2H, Ar-H), 7.41–7.39 (m, 3H, Ar-H), 7.33 (br, 1H, -NH), 6.58 (d, $J = 15.6$ Hz, CH=CH). $^{13}$C NMR (300 MHz, CDCl$_3$): 164.0 (C=O), 142.9 (Ar=CH=CH), 136.6, 134.5 (Ar), 130.2 (Cl-Ar-c), 129.1, 129.04, 128.9, 121.2 (Ar-C), 120.4 (CH=CH=C=O), JEOl JMS 600, El$^+$ mode: $m/z = 257.2134$ [M]$^+$, 258.7136 [M + H]$^+$. (2d) N-(4-Bromophenyl)cinnamamide. 70.45% yield, $^1$H NMR (CDCl$_3$, 300 MHz, 298 K) δ (ppm): 7.79 (d, 1H, $J = 15.6$ Hz, CH=CH), 7.57–7.54 (m, 4H, Ar-H), 7.49 (d, 2H, Ar-H), 7.43–7.34 (m, 3H, Ar-H), 7.34 (br, 1H, -NH), 6.55 (d, 1H, $J = 15.6$ Hz, CH=CH). $^{13}$C NMR (300 MHz, CDCl$_3$): 164.3 (C=O), 141.0 (Ar=CH=CH), 138.0, 132.2, 130.1, 129.5, 128.1 (Ar), 121.5 (Ar-C), 119.7 (CH=CH=C=O). JEOl JMS 600, El$^+$ mode: $m/z = 302.1662$ [M]$^+$, 303.1664 [M + H]$^+$. (2e) N-(3-Nitrophenyl)cinnamamide. 70.34% yield, $^1$H NMR (CDCl$_3$, 300 MHz, 298 K) δ (ppm): 10.61 (br, 1H, -NH), 8.92 (1H, d, $J = 7.8$ Hz, Ar-H), 8.22 (1H, d, $J = 8.4$ Hz, Ar-H), 7.75 (d, 1H, $J = 15.6$ Hz, CH=CH), 7.64–7.70 (t, 1H, Ar-H), 7.56–7.59 (dd, 2H, Ar-H), 7.39–7.41 (m, 3H, Ar-H), 7.17–7.20 (t, 1H, Ar-H), 6.58 (d, 1H, $J = 15.6$ Hz, CH=CH). $^{13}$C NMR (d$_6$-DMSO, 300 MHz): 164.9 (C=O), 144.2 (NO$_2$-Ar), 136.9 (Ar=CH=CH), 136.4, 135.8, 134.8, 130.9, 129.5, 128.7, 126.3, 126.3, 122.8 (Ar), 121.6 (CH=CH=C=O). JEOl JMS 600, El$^+$ mode: $m/z = 268.2617$ [M]$^+$. (2f) N-(3-Nitrophenyl)cinnamamide. 72.95% yield, $^1$H NMR (d$_6$-DMSO, 300 MHz, 298 K) δ (ppm): 10.68 (br, 1H, -NH), 8.77 (1H, s, Ar-H), 8.02 (d, 1H, $J = 7.8$ Hz, Ar-H), 7.89 (d, 7.8Hz, Ar-H).
Table 1: Antimicrobial activity of compounds 2a–2g and 3a-3b.

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<th>2b</th>
<th>2c</th>
<th>2d</th>
<th>2e</th>
<th>2f</th>
<th>2g</th>
<th>3a</th>
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<td>3.11</td>
<td>2.58</td>
<td>2.83</td>
<td>2.53</td>
<td>3.13</td>
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<td>3.38</td>
<td>3.11</td>
<td>2.58</td>
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<td>2.53</td>
<td>3.13</td>
<td>2.53</td>
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<td><em>Bacillus pumilus 82</em></td>
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<td>3.38</td>
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<td><em>Bacillus subtilis ATCC 6633</em></td>
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<td>3.68</td>
<td>3.71</td>
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</table>

* No antimicrobial activity was observed in the concentration range of 5–800 µg/mL.

1H, J = 7.8 Hz, Ar-H), 7.44–7.72 (m, 7H, Ar-H, CH=CH), 6.82 (d, 1H, J = 15.6 Hz, CH=CH), 13C NMR (d6-DMSO, 300 MHz): 164.6 (C-O), 148.5 (NO2-Ar), 141.6 (Ar=CH=CH), 140.9, 135.0, 130.4, 129.4, 128.3, 125.6, 122.1, 113.9 (Ar), JMS600, EI mode: m/z = 268.2615 [M]+.

(2g) N-(4-Nitrophenyl)cinnamamide. 68.23% yield, 1H NMR (d6-DMSO, 300 MHz, 298 K) δ (ppm): 10.90 (s, 1H, -NH), 8.22 (d, 2H, J = 8.7 Hz, Ar-H), 7.93 (d, 2H, J = 7.8 Hz, Ar-H), 7.69–7.43 (m, 6H, Ar-H, CH=CH), 6.85 (d, 1H, J = 15.0 Hz, CH=CH), 13C NMR (d6-DMSO, 300 MHz): 164.9 (C-O), 146.1 (NO2-Ar), 142.8, 142.4 (Ar), 142.2 (Ar=CH=CH), 135.0, 129.5, 128.5, 127.1, 119.6 (Ar-C), JMS600, EI mode: m/z = 268.2615 [M]+, 269.2657 [M + H]+.

(3a) N,N-Dimethylcinnamamide. 73.34% yield, 1H NMR (CDCl3, 300 MHz, 298 K) δ (ppm): 7.66–7.71 (d, 1H, J = 15.6 Hz, CH=CH), 7.53 (d, 2H, J = 7.8 Hz, Ar-H), 7.35 (m, 3H, Ar-H), 6.68 (d, 1H, J = 15.0 Hz, CH=CH), 3.12 (s, 6H, -CH3), 13C NMR (300 MHz, CDCl3): 167.0 (C-O), 142.9 (Ar=CH=CH), 135.5, 129.8, 129.0, 128.0 (Ar), 117.3 (Ar=CH=CH-C), 37.0 (CH3), JMS600, EI mode: m/z = 175.0993 [M]+, 176.1403 [M + H]+.

(3b) N,N-Diethylcinnamamide. 76.85% yield, 1H NMR (CDCl3, 300 MHz, 298 K) δ (ppm): 7.73, 7.1 (d, 1H, J = 15.9 Hz, CH=CH), 7.55 (m, 2H, J = 7.8 Hz, Ar-H), 7.39 (m, 3H, Ar-H), 6.85 (d, 1H, J = 15.0 Hz, CH=CH), 3.40–3.50 (m, 4H, CH2), 1.25 (m, 6H, CH3). 13C NMR (300 MHz, CDCl3): 165.7 (C-O), 142.3 (Ar=CH=CH), 135.5, 129.4, 128.7, 127.7 (Ar), 117.7 (CH=CH=C), 42.3 (CH2=CH2), 31.2 (-CH3), JMS600, EI mode: m/z = 203.2913 [M]+, 204.2732 [M + H]+.

2.2. Antimicrobial Activity. The antimicrobial activity of the synthesized compounds was tested in vitro against twenty-one microorganisms. Stock solutions (1 mg/mL) of synthesized compounds 2a–2g and 3a–3b were prepared by dissolving each compound in dimethyl sulfoxide. Calculated volumes of stock solutions were dispensed in series of McCartney bottles previously containing calculated volumes of sterile cooled molten nutrient agar media (40–45 °C) to prepare the volume of 30 mL each with dilutions of 5, 10, 25, 50, 100, 200, and 400 µg/mL. These sterile nutrient agar media solutions were poured into Petri plates and allowed to solidify. These plates were kept in the refrigerator at 4°C for 24 h to allow the uniform diffusion of the compounds throughout the nutrient agar medium. Before spot inoculation, plates were kept at 37°C for 2 h. One loop full (loop diameter: 3 mm) of an overnight grown peptone water culture of each microorganism was inoculated, and the location of the inoculation was marked by the checkerboard technique. The spot inoculated plates were incubated at 37°C for 24 h and the minimum inhibitory concentration (MIC, mM) values were obtained. The calculated pMIC (−log10 MIC) values are presented in Table 1. Experiments were done in triplicate, and the results were presented as mean values of the three measurements.
2.3. Antioxidant Activity. The antioxidant activity of the synthesized compounds (2a–2g, 3a-3b) was evaluated using the DPPH free radical scavenging assay [18]. The 200 µL of test sample solution (1 mg/mL) was added to 4 mL of 100 µM methanolic DPPH. The solution was allowed to incubate for 20 minutes at 25°C, and the absorbance was measured at 517 nm. Ascorbic acid (1 mg/mL) was used as reference standard. A blank was prepared without adding the standard or test compound. The lower absorbance of the reaction mixture indicates higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated using the following equation:

\[
\text{% inhibition} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100, \tag{1}
\]

where \(A_{\text{control}}\) is the absorbance of the DPPH alone and \(A_{\text{sample}}\) is the absorbance of DPPH in the presence of compounds 2a–2g, 3a-3b. All determinations were performed in triplicate (\(n = 3\)). The results are presented in Figure 1.

3. Results and Discussions

3.1. The Synthesis. The amide derivatives of cinnamic acid 2a–2g and 3a-3b were synthesized to study the effect of amide nitrogen substituents on the antimicrobial activity. As shown in Scheme 1, the reaction of cinnamoyl chloride with corresponding aromatic or aliphatic amines gave compounds 2a–2g and 3a-3b. All compounds were obtained in good yield, purified by recrystallization, and characterized by \(^1\)H NMR, \(^{13}\)C NMR, and mass spectrometry.

3.2. Antimicrobial Activity. The pMIC (– log(MIC)) values of compounds 2a–2g, 3a-3b are presented in Table 1. Except compound 2d, all compounds showed a good antibacterial activity against Gram-negative compared to Gram-positive bacterial strains. Compound 2b showed strong antimicrobial activity against all microorganisms with the pMIC values ranging from 2.78 to 3.68. However, compound 2d demonstrated little (pMIC = 2.58) or no antibacterial activity in the tested concentration domain. Similarly, compound 3a also showed very poor or no antimicrobial activity against the tested microorganisms. Therefore, compounds 2d and 3a were considered as poor antimicrobial compounds. Compounds 2c, 2e–2g showed the highest antimicrobial activity against E. coli LT37 with the pMIC of 4.03–4.43. Moreover, compounds 2e and 2f demonstrated strong activity against Vibrio cholerae 85 and Staphylococcus aureus ML267, respectively.

Compound 2a demonstrated strongest activity against E. coli LT37, Salmonella TyphiTy2, Vibrio cholerae 85, and Bacillus subtilis ATCC 6633 with the pMIC value of 3.95. Compound 2b showed strong activity against all microorganisms except for Shigella dysenteriae 1, Shigella sonnei 1, and Staphylococcus aureus ML267 with the lowest pMIC value of 2.78. Compound 2c did not show any antibacterial activity against Shigella sonnei 1 and Bacillus pumilus 82. Compound 3b showed the strongest activity against E. coli LT37 and Shigella boydii DI3629 with the pMIC of 3.85.

3.3. Antioxidant Activity. DPPH radical scavenging is considered as a good in vitro model and is widely used to assess antioxidant efficacy [19, 20]. The DPPH free radical scavenging assay was employed to evaluate the antioxidant activity of the synthesized compounds. The DPPH radical scavenging activity of compounds 2a–2g, 3a-3b (50 µg/mL) was compared with that of ascorbic acid at the same concentration. As presented in Figure 1, the results of antioxidant screenings were expressed as % of inhibition of the DPPH radical.

From the results of the microbiological studies, it is evident that substituents on the amide nitrogen of cinnamamide derivatives 2a–2g and 3a-3b play a critical role in their antimicrobial activities. Derivatives 2a–2g and 3a-3b were obtained from primary amines (aniline derivatives) and secondary amines, respectively. It is important to notice that compound 2b, which contains p-hydroxyphenyl substituent on the amide nitrogen, showed a significant increase in the antimicrobial activity as compared to compound 2a, which contains only phenyl group. Compound 2c containing p-chlorophenyl substituent on the amide nitrogen showed strong activity as compared to compound 2d, which contains p-bromophenyl substitution on the amide nitrogen. Among the compounds containing the nitrophenyl substituents on the amide nitrogen, compound 2e showed strong activity as compared to compounds 2f and 2g. The m-nitrophenyl substituent in compound 2e endows it with a strong antibacterial activity as compared to the o-nitrophenyl and p-nitrophenyl substituents in compounds 2f and 2g, respectively. It is also important to notice that the aromatic substituents on the amide nitrogen allow overall strong activity as compared to the aliphatic substituents. The presence of bulky ethyl groups on the amide nitrogen of compound 3b allows it to demonstrate strong activity as compared to compound 3b containing methyl groups.
31% (±0.97), and 30% (±1.02), respectively. The results clearly indicate the electron donating groups on the amide nitrogen (3a-3b) play an important role in scavenging the free radicals. Moreover, compound 2a, which contains phenyl group on amide nitrogen, demonstrates almost similar radical scavenging activity to that of compounds 3a, 3b, which contain dimethyl and diethyl substituents on amide nitrogen, respectively.

However, the electron withdrawing substituents such as p-chloro, p-bromo, and o-nitro, m-nitro, and p-nitro on phenyl ring in compounds 2c, 2d, and 2e-2g, respectively, significantly decrease radical scavenging activity. The results obtained in this study are in line with other findings [21].

4. Conclusion

Most of the amide derivatives of cinnamic acid mentioned in this showed moderate-to-high antibacterial and antioxidant activities. The investigation of antimicrobial potentials of the compounds demonstrated a strong activity against 21 bacterial strains comprising Gram-positive and Gram-negative bacteria. Compounds 2a, 2b, and 3b showed strong antimicrobial activity against all microorganisms with the MIC value ranging from 2.45 to 3.68. Compounds 2a, 3a, and 3b demonstrated strong antioxidant activity. These findings encourage the synthesis of new amide derivatives of cinnamic acid. These findings indicate that the amide derivatives of the cinnamic acid afford strong antibacterial and antioxidant activities.

Conflict of Interests

All authors declare that there is no conflict of interests.

Acknowledgment

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References

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