Mutual prodrugs of 4-biphenylacetic acid and phytophenolics as safer NSAIDs—Synthetic and spectral studies

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4-Biphenylacetic acid (4-BPA), the active metabolite of NSAID fenbufen has been modified using mutual prodrug approach. Number of 4-BPA derivatives have been synthesised as potential mutual prodrugs by the attachment of several phytophenols/alcohol as promoieties through ester linkage, directly as well as through spacers, with the objective of obtaining safer NSAIDs devoid of their ulcerogenic side effects. The structures of these derivatives have been established on the basis of spectral analysis.

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The gastrointestinal toxicity of the acidic nonsteroidal antiinflammatory drugs (NSAIDs) is one of the most challenging problems in medicinal chemistry, since these side effects are usually related to the intrinsic mechanism responsible for the desired activity. It is probably caused by combination of local irritation produced by the direct contact of the free carboxylic group of the NSAIDs and inhibition of the enzyme COX-1 responsible for gastric mucosal protection. Recent studies have revealed that local generation of various reactive oxygen species (ROS) may be playing a significant role in the formation of gastric mucosal lesions associated with NSAIDs therapy. Based on these results, it has been suggested that co-administration of antioxidants and NSAIDs in formulated dosage forms may possibly decrease the risk of NSAIDs induced gastrointestinal ulcerogenic side effects and a number of studies have been carried out in this direction. However, there are potential advantages in giving such coadministered drugs having complementary activities, in the form of a single chemical entity. Such agents are named as mutual prodrugs that are designed with improved physicochemical properties and release the parent drugs at the site of action.

4-Biphenylacetic acid (4-BPA) (1) is one of the active metabolites of NSAID fenbufen (2) which is twice as active as the parent drug. This agent has been introduced as an independent drug in the form of gel for local application in the symptomatic relief of articular inflammation and pain. However, it was observed that 4-BPA has severe gastrointestinal side effects on oral administration due to its direct local effect caused by free carboxylic group and therefore, therapeutic use of this potential NSAID by oral administration has not been extended. One promising approach to achieve this objective is the use of mutual prodrug concept. In this paper, we report the synthesis of mutual prodrugs of 4-BPA using naturally occurring phenolic antioxidants including thymol (3a), guaiacol (3b), eugenol (3c) as well as alcoholic compound menthol (3d) as promoieties. These phytoconstituents have been traditionally in use for their medicinal as well as flavouring properties and have well documented safety profiles. Study on physicochemical properties to assess their prodrug potential is underway.

Results and Discussion

Synthesis. Reaction of 4-biphenylacetyl chloride (4) with different phenolic/alcoholic compounds (3a-d) in dichloromethane at 0-5°C in the presence of triethylamine gave the corresponding esters (5a-d). For the preparation of ester prodrugs with spacers (6a-d), reaction of 4-BPA with an appropriate chloroacetyl phenol/alcohol was carried out in DMF at 90°C in the presence of sodium iodide and triethylamine. The sequence of steps of these reactions is shown in Scheme I. After processing the reaction mixtures, TLC showed the spots for the...
presence of starting materials also and efforts to obtain pure compounds by crystallization were unsuccessful. However, by the use of column chromatography, all the synthesized compounds were obtained in pure form (showing single spot on TLC). The chloroacetyl phenolic/alcoholic compounds (7a-d) required for the preparation of ester prodrugs with spacers were synthesized by the reaction of the appropriate phenolic/alcoholic compounds (3a-d) with chloroacetyl chloride (8). These derivatives were obtained in reasonable yield and their structures were confirmed by the use of IR, $^1$H NMR, $^{13}$C NMR and mass spectrometry (Table I).

Spectral Studies. The IR spectra of the simple ester derivatives (5a-d) of 4-BPA showed absorptions peaks at around 1740 and 1240 cm$^{-1}$ characteristic of C=O and C-O stretching of esters respectively. $^1$H NMR spectra showed two different multiplets in the aromatic region at 7.21-7.45 and 7.47-7.65 corresponding to 5 aromatic protons (2 protons of $p$-substituted aromatic ring overlapping the 3 aromatic protons of phenyl ring) and 4 aromatic protons (2 protons of $p$-substituted aromatic ring overlapping remaining 2 protons of the phenyl ring) of biphenyl respectively. The signals for methylene protons (Ar-CH$_2$) of the parent structure were observed in the range of δ3.57 (5d) and δ3.70 to δ3.93 (5a-c). Additionally, signals for the protons of the promoieties also appeared in the aromatic (5a-c) and aliphatic region (5d) respectively. In $^{13}$C NMR spectra, the signals for aromatic carbons had a spread from δ126-140 containing twelve peaks. Signals for other carbons of the parent structures were observed at about δ 41(Ar-CH$_2$) and 170 (COO). The mass spectra of simple esters of 4-BPA in general showed molecular ion peak with clearly discernible intensity for all of the compounds and showed similar fragmentation pattern and gave the fragment ion at m/z 194 as base peak. Other prominent peaks were observed at m/z 212, 195, 167 and 165. Cleavage next to C=O group of molecular ion (M$^+$) was responsible for the formation of two prominent fragments at m/z 195 and 167.

The IR spectra of the esters derivatives with spacers (6a-d) showed absorption peaks at 1780 and 1160 cm$^{-1}$ characteristic of C=O and C-O stretching of
<table>
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<tr>
<th>Compd</th>
<th>Yield (%)</th>
<th>m.p. °C</th>
<th>Spectral data</th>
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<tr>
<td>Thymol 4-biphenylacetate (5a)</td>
<td>39</td>
<td>52-54</td>
<td>IR(KBr): 2990 (C-H), 1750 (C=O), 1600 (C=C), 1240 (C-O), 740, 700 cm⁻¹; H NMR (CDCl₃): δ 1.06-1.08 (6H, d, J=6.8 Hz, 2xCH₃), 2.26 (3H, s, CH₃), 2.71-2.76 (1H, sept, J=6.8 Hz, CH₃), 3.90 (2H, s, CH₂), 6.79 (1H, s, Ar-H), 6.98-7.01 (1H, d, J=8.0 Hz, Ar-H), 7.13-7.16 (1H, d, J=8.0 Hz, Ar-H), 7.41-7.45 (2H, d, J=7.5 Hz, p-substituted Ar-H, overlapping 3H, Ar-H), 7.56-7.65 (2H, d, J=7.5 Hz, p-substituted Ar-H, overlapping 2H, Ar-H); C NMR (CDCl₃): δ 20.64 (Ar-CH₂), 22.97 (CH(CH₃)₂), 26.96 (CH₂CH₂), 41.29 (Ar-CH₂), 122.67-137.05 (Ar-carbons), 147.94 (COOC), 170.14 (COO); Mass (m/z): 344 (M⁺), 195, 194 (100%), 167, 165.</td>
</tr>
<tr>
<td>Guaiacol 4-biphenylacetate (5b)</td>
<td>40</td>
<td>50-52</td>
<td>IR (KBr): 3100, 2890 (C-H), 1750 (C=O), 1600 (C=C), 1250, 1110 (C-O), 740, 700 cm⁻¹; H NMR (CDCl₃): δ 3.74 (3H, s, OCH₃), 3.92 (2H, s, CH₂), 6.88-6.91 (2H, m, Ar-H), 7.00-7.14 (1H, m, Ar-H), 7.16-7.18 (1H, m, Ar-H), 7.32-7.45 (2H, d, J=8.0 Hz, p-substituted Ar-H, overlapping 3H, Ar-H), 7.54-7.60 (2H, d, J=8.0 Hz, p-substituted Ar-H, overlapping 2H, Ar-H); C NMR (CDCl₃): δ 40.56 (Ar-CH₂), 56.85 (OCH₃), 112.54-132.15 (Ar-carbons), 140.65 (COOC), 151.17 (CH₂OC), 169.41 (COO); Mass (m/z): 318 (M⁺), 195, 194 (100%), 168, 167.</td>
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<tr>
<td>Eugenol 4-biphenylacetate (5c)</td>
<td>24</td>
<td>40-42</td>
<td>IR (KBr): 2990 (C-H), 1760 (C=O), 1600 (C=C), 1120 (C-O), 760 cm⁻¹; H NMR (CDCl₃): δ 3.31-3.34 (2H, d, J=6.6 Hz, CH₂-CH=CH₂), 3.70 (2H, s, CH₂), 3.89 (3H, s, OCH₃), 5.03-5.09 (2H, m, CH₂CH=CH₂), 5.85-5.96 (1H, m, CH=CH₂), 6.70-6.73 (2H, m, m-Ar-H), 6.90 (1H, d, J=8.0 Hz, Ar-H), 7.26-7.43 (2H, d, J=8.0 Hz, p-substituted Ar-H overlapping 3H, Ar-H), 7.54-7.56 (2H, d, J=8.0 Hz, p-substituted Ar-H, overlapping 2H, Ar-H); C NMR (CDCl₃): δ 39.96 (Ar-CH₂), 40.12 (Ar-CH₂-CH=CH₂), 55.47 (OCH₃), 114.06 (CH₂=CH₂), 132.15 (CH=CH₂), 120.59-140.70 (Ar-carbons), 136.01 (COOC), 150.55 (CH₂OC), 169.93 (COO); Mass (m/z): 358 (M⁺), 195, 194 (100%), 167, 165, 164.</td>
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<td>Menthol 4-biphenylacetate (5d)</td>
<td>37</td>
<td>53-55</td>
<td>IR (KBr): 2990, 2900 (C-H), 1720 (C=O), 1600 (C=C), 1250, 1120 (C-O), 760 cm⁻¹; H NMR (CDCl₃): δ 0.70 (3H, d, J=6.8 Hz, CH₃), 0.82 (3H, d, J=7.1 Hz, CH₃), 0.90 (3H, d, J=6.5 Hz, CH₃), 0.90-1.05 (3H, m, CH₃ and CH), 1.29-1.31 (1H, m, CH), 1.61-1.64 (1H, m, CH), 1.67-1.73 (3H, m, CH₃ and CH), 1.94-1.96 (1H, m, CH), 3.57 (2H, s, CH₂), 4.59-4.68 (1H, m, CH), 7.21-7.38 (2H, d, J=8.1 Hz, p-substituted Ar-H overlapping 3H, Ar-H), 7.47-7.53 (2H, d, J=8.1 Hz, p-substituted Ar-H, overlapping 2H, Ar-H); C NMR (CDCl₃): δ 15.26-22.13 (3xCH₃), 23.66 (CH₂CH₂), 41.59 (Ar-CH₂), 74.54 (COOC), 127.19-129.66 (Ar-carbons), 170.55 (COO); Mass (m/z): 350 (M⁺), 212, 168, 167, 95, 95, 83 (100%).</td>
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<tr>
<td>Thymol (4-biphenylacetoxy)-acetate (6a)</td>
<td>56</td>
<td>88-90</td>
<td>IR (KBr): 2990 (C-H), 1780 (C=O), 1160 (C-O), 780 cm⁻¹; H NMR (CDCl₃): δ 1.15 (6H, d, J=6.8 Hz, 2xCH₃), 2.26 (3H, s, CH₃), 2.90-2.99 (1H, sept, J=6.4 Hz, CH₃), 3.76 (2H, s, Ar-CH₂), 4.67 (2H, s, OCH₃), 6.81 (1H, s, Ar-H), 6.99-7.03 (1H, d, J=7.8 Hz, Ar-H), 7.16-7.18 (1H, d, J=7.8 Hz, Ar-H), 7.27-7.41 (5H, m, Ar-H), 7.51-7.54 (4H, m, Ar-H); C NMR (CDCl₃): δ 20.74 (Ar-CH₂), 23.02 (CH₂CH₂), 27.01 (CH₂CH₂), 40.31 (Ar-CH₂), 60.99 (OCH₂OOC), 122.41-140.69 (Ar-carbons), 147.20 (COOC), 166.57 (CH₂COO), 170.96 (Ar-CH₂COO); Mass (m/z): 402 (M⁺), 253, 252, 194, 168, 167 (100%), 165.</td>
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<tr>
<td>Guaiacol (4-biphenylacetoxy)-acetate (6b)</td>
<td>51</td>
<td>75-76</td>
<td>IR (KBr): 3040 and 2990 (C-H), 1780 (C=O), 1600 (C-C), 1280, 1120 (C-O), 750 cm⁻¹; H NMR (CDCl₃): δ 3.62 (3H, s, OCH₃), 3.66 (2H, s, Ar-CH₂), 4.61 (2H, s, OCH₂), 6.79-6.84 (4H, m, Ar-H), 6.95-6.98 (1H, m, Ar-H), 7.04-7.09 (1H, m, Ar-H), 7.23-7.31 (2H, d, J=7.8 Hz, p-substituted Ar-H overlapping 3H, Ar-H), 7.23-7.46 (2H, d, J=7.8 Hz, p-substituted Ar-H overlapping 2H, Ar-H); C NMR (CDCl₃): δ 40.04 (Ar-CH₂), 55.56 (OCH₃), 60.55 (OCH₂OOC), 112.32-132.21 (Ar-carbons), 139.66 (COOC), 150.71 (CH₃OC), 165.73 (CH₂COO), 170.63 (Ar-CH₂COO); Mass (m/z): 376 (M⁺), 252, 194, 168, 167(100%), 165, 124.</td>
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<th>m.p. °C</th>
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<tr>
<td>Eugenol (4-biphenylacetoxy)-acetate (6e)</td>
<td>43</td>
<td>semi solid</td>
<td>IR (KBr): 3150 (C-H), 1780 (C=O), 1600 (C=C), 1280 (C-O), 820-780 cm⁻¹; ¹H NMR (CDCl₃): δ 3.35-3.37 (2H, d, J = 6.6 Hz, CH₂-CH=CH₂); 3.86 (3H, s, OCH₃); 3.87 (2H, s, Ar-CH₂); 4.94 (2H, s, OCH₂); 4.94-5.13 (2H, m, CH₂-CH=CH₂); 5.87-5.97 (1H, m, CH₂-CH=CH₂); 6.74-6.77 (2H, m, Ar-H); 6.94-6.97 (1H, d, J = 8.0 Hz, Ar-H); 7.35-7.45 (5H, m, Ar-H); 7.52-7.57 (4H, m, Ar-H); ¹³C NMR (CDCl₃): δ 36.46 (Ar-CH₂); 40.30 (CH₂-CH=CH₂); 55.60 (OCH₃); 60.55 (OCH₂COO); 116.25 (CH=CH₂); 120.56-140.59 (Ar-carbons); 132.35 (CH=CH₂); 137.14 (COOC); 150.55 (CH₃OC); 169.06 (CH₂COO); 170.66 (Ar-CH₂COO); Mass (m/z): 416 (M⁺), 167, 165, 164 (100%), 149.</td>
</tr>
<tr>
<td>Menthol (4-biphenylacetoxy)-acetate (6d)</td>
<td>59</td>
<td>semi solid</td>
<td>IR (KBr): 3000, 2980 (C-H), 1800 (C=O), 1150 (C-O), 810 (C=Cl) cm⁻¹; ¹H NMR (CDCl₃): δ 0.70 (3H, d, J = 6.5 Hz, CH₃); 0.82 (3H, d, J = 7.1 Hz, CH₃); 0.90 (3H, d, J = 6.5 Hz, CH₃); 0.90-1.05 (3H, m, CH₂ and CH₃); 1.29-1.31 (1H, m, CH); 1.51-1.61 (1H, m, CH); 1.67-1.73 (3H, m, CH₂ and CH₃); 1.94-1.96 (1H, m, CH); 4.59-4.66 (1H, m, CH); 3.76 (2H, s, Ar-CH₂); 4.60 (2H, s, OCH₂); 7.21-7.38 (2H, d, J = 8.0 Hz, p-substituted Ar-H overlapping 2H, Ar-H); ¹³C NMR (CDCl₃): δ 16.19-34.01 (menthol aliphatic carbons); 40.33 (Ar-CH₂); 61.13 (CH₂COO); 76.65 (COOC); 126.97-129.74 (Ar-carbons); 167.20 (CH₂COO); 170.19 (Ar-CH₂COO); Mass (m/z): 408 (M⁺), 270, 194 (100%), 167, 83.</td>
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<tr>
<td>Thymol chloroacetate (7a)</td>
<td>84</td>
<td>semi solid</td>
<td>IR (KBr): 3000, 2980 (C-H), 1800 (C=O), 1150 (C-O), 810 (C=Cl) cm⁻¹; ¹H NMR (CDCl₃): δ 1.26 (6H, d, J = 6.4 Hz, 2xCH₃); 2.36 (3H, m, CH₃); 2.99-3.06 (1H, sept, J = 6.4 Hz, CH₃); 4.25 (2H, s, CH₂); 5.85 (1H, s, Ar-H); 7.03-7.05 (1H, d, J = 7.8 Hz, Ar-H); 7.21-7.23 (1H, d, J = 7.8 Hz, Ar-H); ¹³C NMR (CDCl₃): 20.52 (Ar-CH₃); 22.80 (CH(СН(CH₃)); 26.01 (CH(CH₃)); 40.55 (CH₂); 122.09-136.65 (Ar-carbons); 147.33 (COOC), 165.95 (COO).</td>
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<tr>
<td>Guaiacol chloroacetate (7b)</td>
<td>84</td>
<td>46-48</td>
<td>IR (KBr): 3000, 2990 (C-H), 1780 (C=O), 1150 (C-O), 750 (C=Cl) cm⁻¹; ¹H NMR (CDCl₃): δ 3.62 (3H, s, OCH₃); 4.27 (2H, s, CH₂); 6.66-6.91 (2H, m, Ar-H); 6.99-7.02 (1H, Ar-H); 7.14-7.24 (1H, m, Ar-H); ¹³C NMR (CDCl₃): δ 40.65 (CH₂); 56.50 (OCH₃); 112.73-127.42 (Ar-carbons); 139.19 (COOC), 150.74 (CH₃OC), 165.47 (COO).</td>
</tr>
<tr>
<td>Eugenol chloroacetate (7c)</td>
<td>76</td>
<td>semi solid</td>
<td>IR (KBr): 2990 and 2810 (C-H), 1790 (C=O), 1150 (C-O), 730 (C=Cl) cm⁻¹; ¹H NMR (CDCl₃): δ 3.32 (2H, d, J = 6.2 Hz, CH₂-CH=CH₂); 3.72 (3H, s, OCH₃); 4.21 (2H, s, CH₂); 5.03-5.06 (2H, m, CH₂-CH=CH₂); 5.85-5.91 (1H, m, CH₂-CH=CH₂); 6.67-6.71 (2H, m, Ar-H); 6.86-6.89 (1H, d, J = 5.6 Hz, Ar-H); ¹³C NMR (CDCl₃): δ 39.67 (CH₂); 40.36 (CH₃CH₂); 115.91 (C=CH₂); 112.52-136.67 (Ar-carbons); 136.67 (CH=CH₂); 139.29 (COOC), 150.33 (CH₃OC), 165.26 (COO).</td>
</tr>
<tr>
<td>Menthol chloroacetate (7d)</td>
<td>89</td>
<td>34-36</td>
<td>IR (KBr): 2990 (C-H), 1750 (C=O), 1450 (C-H bend), 1200 (C-O), 760 (C=Cl) cm⁻¹; ¹H NMR (CDCl₃): δ 0.76 (3H, d, J = 6.9 Hz, CH₃); 0.89 (3H, s, OCH₃); 1.01 (3H, m, CH and CH₂); 1.01 (3H, m, CH and CH₂); 1.36-1.40 (1H, m, CH); 1.51-1.57 (1H, m, CH); 1.66-1.77 (2H, m, CH₂); 1.82-1.86 (1H, m, CH); 1.96-2.02 (1H, m, CH); 3.94 (2H, s, CH₂); 4.64-4.73 (1H, m, CH); ¹³C NMR (CDCl₃): δ 15.62-22.02 (3xCH₃); 26.21-46.92 (menthol aliphatic carbons); 41.22 (CH₂); 76.69 (COOC), 166.93 (COO).</td>
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</tbody>
</table>

Esters respectively. ¹H NMR spectra showed all the signals of protons of the biphenylacetic acid as well as of phenolic/alcoholic groups on similar pattern like simple esters. Additionally, it showed a signal at around 3.46 to 4.94 for -OCH₃. ¹³C NMR showed two signals at δ166 and 170 for Ar-CH₂COO, -OCH₂COO carbonyl carbons respectively. Signals of other carbons followed the pattern of simple esters. Mass spectra of these esters showed moderate molecular ion peaks, which underwent two different
fragmentation patterns to give m/z 194 (6d), 167 (6a and 6b) and 164 (6c) as base peaks. Other important peaks appeared at m/z 270, 253, 252, 195 and 165.

Experimental Section

General procedure. Melting points were taken in open capillary tubes on a Veego melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 882 IR spectrometer using KBr discs. Mass spectra were obtained on a VG micromass 7070F mass spectrometer. $^1$H NMR and $^{13}$C NMR were recorded on Brucker AC 300 F (300 MHz) equipment using TMS as internal standard and CDCl$_3$ as solvent. TLC was performed on glass plates coated with silica gel G, preactivated at 110°C for 5 min. Components were detected by iodine vapours.

4-BPA (1) was synthesized from biphenyl by performing Friedel-Crafts acylation, Willgerodt Kindler modified reaction and alkaline hydrolysis. A mixture of appropriate phenolic/alcoholic compound (10 mmole), triethylamine (11 mmole) and sodium bicarbonate (5 %, 3x50 mL) was added dropwise over a period of 1 hr. The reaction mixture was stirred overnight at room temperature, washed successively with HCI (5 %, 2x50 mL), sodium bicarbonate (5%, 2x50 mL) and finally with water (3x50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was evaporated under reduced pressure to obtain chloroacetyl derivative of appropriate phenol/alcohol. These derivatives were recrystallized from hexane-ethyl acetate (7b and d).

General method for the synthesis of esters of 4-BPA with spacer (6a-d). A mixture of 4-BPA (1) (10 mmole), appropriate 2-chloroacetate of phenol/alcohol (7a-d) (11 mmole), triethylamine (11 mmole) and sodium iodide (1 mmole) in 10 mL DMF was stirred at 90°C for 3 hr. The reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was washed successively with sodium thiosulphate (2%, 2x50 mL), HCI (5 %, 2x50 mL), sodium bicarbonate (5%, 2x50 mL) and finally with water (3x50 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to get solid residues, which were chromatographed on silica gel column using chloroform-ethyl acetate mixture as eluent. The final products were obtained as solids (5a and 5b) after recrystallization from ethyl acetate and petroleum ether, and as semi solids (5c and 5d).

Acknowledgement

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References