EXPERIMENTAL

Equipment and material

Melting points were determined on a Veego melting point apparatus and are uncorrected. For TLC, glass plates coated with silica gel G (E. Merck) were used. The TLC plates were activated at 110 °C for 30 min and visualized by exposure to iodine vapors. Silica gel G60 F aluminum sheets plates were used for final monitoring. Glass columns of appropriate sizes were used. Silica gel (60-120 mesh, BDH) was used as adsorbent. IR spectra were recorded on Perkin-Elmer 882 spectrometer using potassium bromide pellets. $^1$HNMR and $^{13}$CNMR spectra were recorded on 400 MHz Bruker AC 30 NMR spectrometer (Bruker, Switzerland), using CDCl$_3$ or DMSO-d$_6$ as solvents and tetramethylsilane as an internal standard at Regional Sophisticated Instrumentation Centre, Panjab University, Chandigarh. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN elemental analyzer. Mass spectra were performed on LC Waters Allianz 2695 Mass spectrometer with MS detector ESI, Software MassLynx 4.0 (Waters, USA) at 70eV using electron ionization (EI) source.

All solvents were freshly distilled and dried prior to use according to standard procedures. All chemicals were purchased from SD fine chemicals, Qualigen and Loba chemicals. Diclofenac was provided as a gift sample by B.M. pharmaceuticals, Chandigarh.

High pressure liquid chromatography (HPLC) separation was carried out using reverse phase HPLC C-18 column at isocratic mode. The Waters Associates fitted with pump (Model 510), injector (Model 6UK) detector (Lambda-Max Model 481 LC spectrophotometer), interfaced with Winchrom was used. The elution was carried out at ambient temperature (24 to 28 °C). Lichrosphere C-18 column (250 mm length x 4.6 mm diameter, E. Merck, India) was used for qualitative analysis. The samples were prepared by filtering the appropriately diluted extract through 0.45 μm filter before injection. Elution was carried out using methanol: water (80 : 20) at a flow rate of 1.0 mL/min and detection was done at 273 nm.
Chemistry

Synthesis of diclofenac-OCH₂COO-phytophenols/alcohol mutual prodrugs

Diclofenac-OCH₂COO-guaiacol; 2-Methoxyphenyl-2-[2-(2,6-dichlorophenyl amino)phenyl]ethanoyloxy ethanoate (146)

In a 250ml two neck flask, a mixture of guaiacol (129) (1.24g, 0.01 mol), TEA (1.01g, 1.4ml, 0.01 mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride (138) (1.12g, 0.8ml, 0.01mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1h, while maintaining the temperature constant during this period. The reaction mixture was stirred further for 5h, poured on crushed ice and then washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The resulting brown coloured solid product was recrystallized from petroleum ether and ethyl acetate to yield guaiacol chloroacetate (139) (1.61g, 80.5%), mp. 47-49 °C (46-48 °C) Rf 0.75 (pet ether : ethyl acetate :: 9 : 1). The reaction was repeated to obtain more quantity of the product required for further reactions.

Analysis

IR(KBr): 3050.3 (aromatic C-H st), 2947.0 (aliphatic C-H st), 2845.8 (C-H st of aromatic OCH₃), 1781.5 (C=0 st), 1501.7 (benzene ring C=C st), 1259.3 (asymm C-O-C st), 1142.4 (C-C(=0)-O st), 1024.2 (symm C-O-C st) cm⁻¹.

¹H NMR(CDCl₃): δ 3.62 (s, 3H, OCH₃), 4.27 (s, 2H, CH₂), 6.66-6.91 (m, 2H, Ar-H), 7.02 (dd, 1H, J=1.4 Hz and 7.8 Hz, Ar-H), 7.14-7.24 (m, 1H, Ar-H)

¹³C NMR (CDCl₃): δ 40.65 (CICH₂), 55.60 (OCH₃), 112.73-150.74 (Ar-carbons), 150.74 (ArC-OCH₃), 165.47 (C=O).
In a 250ml two neck flask, a mixture of guaiacol chloroacetate (139) (2.12g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol), sodium iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether : ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The resulting residue was recrystallized from petroleum ether and ethyl acetate to obtain diclofenac-OCH2COO-guaiacol (146) as white solid (2.31g, 50.2%), mp. 110-112 °C, Rf 0. 52 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3368.8 (N-H st), 3063.1 (aromatic C-H st), 2949.0 (aliphatic C-H st), 2843.6 (C-H st of aromatic OCH3), 1760.4 (C=O st), 1504.4 (benzene ring C=C st), 1262.6 (asymm C-O-C st), 1143.7 (C-C(=O)-O st), 1021.3 (symm C-O-C st), cm\(^{-1}\).

\(^1\)HNMR(CDC\(_3\)): \(\delta\) 3.81 (s, 3H, OCH3), 3.97 (s, 2H, Ar-CH2), 4.97 (s, 2H, OCH2) 6.56 (d, 1H, J = 8.0 Hz, Ar-H, diclofenac), 6.74 (s, 1H, NH, D\(_2\)O exchangeable), 6.90-6.99 (m, 4H, Ar-H, diclofenac, guaiacol), 7.04 (dd, 1H, J=1.7 Hz and 7.9 Hz, Ar-H, guaiacol), 7.11-7.15 (m, 1H, Ar-H, guaiacol), 7.28 (dd, 1H, J=1.4 Hz and 7.0 Hz, Ar-H, diclofenac), 7.33 (d, 2H, J =8.0 Hz, Ar-H, diclofenac).

\(^13\)CNMR (CDC\(_3\)): \(\delta\) 38.05 (Ar-CH2), 55.87 (OCH3), 60.99 (OCH2COO), 112.45-150.86 (Ar-carbons), 150.86 (ArC-OCH3), 165.73 (CH2COO), 171.41 (Ar-CH2COO).
LC-MS: m/z 460.06 [M]+.

**Calculated for** C$_{23}$H$_{19}$Cl$_2$NO$_5$: C, 60.01; H, 4.16; N, 3.04. *Found:* C, 60.11; H, 4.32; N, 3.08%.  

**Diclofenac-OCH$_2$COO-eugenol; 2-Methoxy-4-(2-propenyl)phenyl-2-[2(2,6-dichlorophenylamino)phenyl] ethanoyloxy ethanoate (147)**

In a 250ml two neck flask, a mixture of eugenol (130) (1.64g, 0.01 mol), TEA (1.01g, 1.4ml, 0.01 mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride (138) (1.12g, 0.8ml, 0.01 mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1h, and the temperature was maintained constant during this period. The reaction mixture was stirred further for 5h, poured on crushed ice and then washed with HCI (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain **eugenol chloroacetate (140)** as light brown semisolid product (1.81g, 75.4%), $R_f$ 0.76 (pet ether : ethyl acetate :: 9 : 1).$^{222}$

**Analysis**

IR(KBr): 3075.4 (aromatic C-H st), 2962.1 (aliphatic C-H st), 2844.1 (C-H st of aromatic OCH$_3$), 1778.7 (C=O st), 1508.2 (benzene ring C=C st), 1271.4 (asymm C-O-C st), 1145.0 (C-C(=O)-O st), 1032.9 (symm C-O-C st) cm$^{-1}$.

$^1$HNMR(CDC$_3$): δ 3.32 (d, 2H, $J = 6.2$ Hz, CH$_2$-CH=CH$_2$), 3.72 (s, 3H, OCH$_3$), 4.21 (s,2H, CH$_2$), 5.03-5.06 (m, 2H, CH$_2$-CH=CH$_2$), 5.85-5.91 (m, 1H, CH$_2$-CH=CH$_2$), 6.67-6.71 (m , 2H, Ar-H), 6.88 (d, 1H, $J = 7.6$ Hz, Ar-H).

$^{13}$CNMR (CDCl$_3$): δ 39.67 (ClCH$_2$), 40.36 (CH$_2$-CH=CH$_2$), 55.46 (OCH$_3$), 115.91 (CH=CH$_2$), 112.52-150.33 (Ar-carbons), 136.67 (CH=CH$_2$), 150.33 (ArC-OCH$_3$), 165.26 (C=O).

In a 250ml two neck flask, a mixture of eugenol chloroacetate (140) (2.40g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol), sodium
iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into a beaker containing finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether : ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The residue obtained was recrystallized from petroleum ether and ethyl acetate to obtain \textit{diclofenac-OCH}_2\textit{COO-eugenol} (147) as white solid (2.46g, 49.2%), mp. 72-73 °C, Rf 0. 64 (pet ether : ethyl acetate :: 8.0 : 2.0).

\textbf{Analysis}

\textbf{IR(KBr)}: 3363.8 (N-H st), 3066.5 (aromatic C-H st), 2964.7 (aliphatic C-H st), 1763.9 (C=O st), 2839.2 (C-H st of aromatic OCH$_3$), 1506.5 (benzene ring C=C st), 1271.1 (asym C-O-C st), 1141.3 (C-C(=O)-O st), 1058.1 (symm C-O-C st) cm$^{-1}$.

$^{1}$\textbf{HNMR (CDCl$_3$)}: \delta 3.36 (d, 2H, \textit{J} = 6.7 Hz, -CH$_2$-, eugenol), 3.79 (s, 3H, OCH$_3$) 3.96 (s, 2H, Ar-CH$_2$), 4. 96 (s, 2H, OCH$_2$), 5.06-5.12 (m, 2H, =CH$_2$, eugenol) 5.90-5.97 (m, 1H, -CH=, eugenol), 6.55 (d , 1H, \textit{J} = 8.0 Hz, Ar-H, diclofenac), 6.73-6.77 (m, 3H, NH, D$_2$O exchangeable, Ar-H, diclofenac), 6.94-6.99 (m, 3H, Ar-H, eugenol), 7.10-7.14 (m, 1H, Ar-H, diclofenac), 7.25 (dd, 1H, \textit{J} = 1.4 Hz and 7.5 Hz, Ar-H, diclofenac), 7.32 (d, 2H, \textit{J} = 8.0 Hz, Ar-H, diclofenac)

$^{13}$\textbf{CNMR (CDCl$_3$)}: \delta 38.05 (Ar-CH$_2$), 40.10 (CH$_2$-CH=CH$_2$), 55.85 (OCH$_3$), 61.01 (OCH$_2$COO), 112.76 (CH=CH$_2$), 116.28 - 150.63 (Ar-carbons), 136.97 (CH=CH$_2$), 150.63 (ArC-OCH$_3$), 165.86 (CH$_2$COO), 171.42 (Ar-CH$_2$COO).

\textbf{LC-MS}: \textit{m/z} 500.11 [M]$^+$.
Calculated for $\text{C}_{26}\text{H}_{23}\text{Cl}_{2}\text{NO}_{5}$: C, 62.41; H, 4.63; N, 2.80. Found: C, 62.34; H, 4.65; N, 2.95%.

Diclofenac-OCH$_2$COO-thymol; 2-Isopropyl-5-methylphenyl-2-[2(2,6-dichlorophenylamino) phenyl] ethanoyloxy ethanoate (148)

In a 250ml two neck flask, a mixture of thymol (131) (1.50g, 0.01mol), TEA (1.01 g, 1.4ml, 0.01mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride (138) (1.12g, 0.8ml, 0.01mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1h, while maintaining the temperature constant during this period. The reaction mixture was stirred further for 5h, poured on crushed ice and then washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain thymol chloroacetate (141) as light brown coloured semisolid product (1.95g, 86.2%), Rf 0.72 (pet ether : ethyl acetate :: 9 : 1).222

Analysis

IR(KBr): 3025.7 (aromatic C-H st), 2965.1 (aliphatic C-H st), 1775.5 (C=O st), 1505.0 (benzene ring C=C st), 1153.3 (C-C(=0)-0 st) cm$^{-1}$.

$^1$HNMR(CDC$_3$): $\delta$ 1.26 (d, 6H, $J = 6.4$ Hz, 2 X CH$_3$), 2.36 (s, 3H, Ar-CH$_3$), 3.04 (sept, 1H, $J = 6.4$ Hz, CH), 4.25 (s, 2H, CH$_2$), 6.85 (s,1H, Ar-H,), 7.04 (d,1H, $J = 7.8$ Hz, Ar-H), 7.22 (d,1H, $J = 7.8$ Hz, Ar-H).

$^{13}$CNMR (CDC$_3$): $\delta$ 20.52 (Ar-CH$_3$), 22.80 (CH(CH$_3$)$_2$), 26.61 (CH(CH$_3$)$_2$), 40.55 (ClCH$_2$), 122.09-136.65 (Ar-carbons), 165.95 (C=O).

In a 250ml two neck flask, a mixture of thymol chloroacetate (141) (2.26g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol), sodium iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature The reaction mixture was poured into finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was
washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether: ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure and the residue was recrystallized from petroleum ether and ethyl acetate to obtain diclofenac-OCH2COO-thymol as white solid (148) (2.11g, 43.5%), mp. 63-65 °C, Rf 0.73 (pet ether: ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3364.0 (N-H), 3043.2 (aromatic C-H st), 2954.9 (aliphatic C-H st), 1761.0 (C=O st), 1503.6 (benzene ring C=C st), 1140.9 (C-C(=O)-O st) cm⁻¹.

1HNMR(CDCl₃): δ 1.15 (d, 6H, J = 6.9, 2CH₃), 2.29 (s, 3H, Ar-CH₃), 2.93 (sept, 1H, J = 6.9, CH), 3.97 (s, 2H, OCH₂), 4.93 (s, 2H, OCH₂) 6.55 (d, 1H, J = 8.0 Hz, Ar-H, diclofenac), 6.74 (s, 1H, NH, D₂O exchangeable), 6.81 (s, 1H, Ar-H, thymol), 6.94-7.0 (m, 2H, Ar-H, diclofenac), 7.02 (d, 1H, J = 7.9 Hz, Ar-H, thymol), 7.11-7.15 (m, 1H, Ar-H, diclofenac), 7.18 (d, 1H, J=7.9 Hz, Ar-H, thymol), 7.27 (dd, 1H, J = 1.4 Hz and 7.6 Hz, Ar-H, diclofenac), 7.33 (d, 2H, J = 8.0Hz, Ar-H, diclofenac).

13CNMR (CDCl₃): δ 20.83 (Ar-CH₃), 23.06, (CH(CH₃)₂), 27.05 (CH(CH₃)₂), 38.04 (Ar-CH₂), 61.27 (OCH₂COO), 118.52-147.20 (Ar-carbons), 166.44 (CH₂COO), 171.61 (Ar-CH₂COO).

LC-MS: m/z 486.14 [M]+

Calculated for C₂₆H₂₅Cl₂NO₄: C, 64.20; H, 5.18; N, 2.88. Found: C, 64.45; H, 5.23; N, 2.69%.
Diclofenac-OCH₂COO-vanillin; 4-Formyl-2-methoxyphenyl-2-[2(2,6-
dichlorophenylamino)phenyl]ethanoyloxy ethanoate (149)

In a 250ml two neck flask, a mixture of vanillin (132) (1.52g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride (138) (1.12g, 0.8ml, 0.01mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1h, while maintaining the temperature constant during this period. The reaction mixture was stirred further for 5h, poured on crushed ice and then washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain vanillin chloroacetate (142) as pale yellow coloured solid product which was recrystallized from petroleum ether and ethyl acetate (1.82g, 79.8%), mp. 82-84 °C, Rf 0.33 (pet ether : ethyl acetate :: 9 : 1).

Analysis

IR(KBr): 3035.2 (aromatic C-H st), 2956.7 (aliphatic C-H st), 2847.8 (C-H st of aromatic OCH₃), 1766.1 (C=O st), 1696.9 (C=O st aldehyde), 1505.3 (benzene ring C=C st), 1280.1 (asymm C-O-C st), 1149.9 (C-C(=O)-O st), 1032.8 (symm C-O-C st) cm⁻¹.

¹HNMR(CDCl₃): δ3.93 (s, 3H, OCH₃), 4.39 (s, 2H, -CH₂), 7.27-7.29 (m, 1H, ArH), 7.50-7.53 (m, 2H, Ar-H), 9.98 (s, 1H, CHO)

¹³CNMR (CDCl₃): δ 40.52 (ClCH₂), 56.19 (OCH₃), 110.98-151.68 (Ar-carbons), 151.68 (Ar-C-OCH₃), 164.89 (C=O), 190.96 (CHO)

Calculated for C₁₀H₉ClO₄: C, 52.53; H, 3.97. Found: C, 52.64; H, 3.99%.

In a 250ml two neck flask, a mixture of vanillin chloroacetate (142) (2.28g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol), sodium iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into finely crushed ice with stirring...
and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether : ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure and the residue was recrystallized from petroleum ether and ethyl acetate to obtain dinclofenac-OCH$_2$COO-vanillin as white solid (149) (2.87g, 58.9%), mp. 68-70 °C, R$_f$ 0.24 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis
IR(KBr): 3365.7 (N-H st), 3064.7 (aromatic C-H st), 2923.8 (aliphatic C-H st), 2832.3 (C-H st of aromatic OCH$_3$), 1779.4 (C=O st), 1752.4 (C=O st), 1699.9 (C=O st aldehyde), 1503.5 (benzene ring C=C st), 1275.6 (asymm C-O-C st), 1144.2 (C-C(=O)-O st), 1032.4 (symm C-O-C st) cm$^{-1}$.

$^1$HNMR($CDCl_3$): $\delta$ 3.91 (s, 3H, OCH$_3$), 4.00 (s, 2H, Ar-CH$_2$), 5.01 (s, 2H, OCH$_2$), 6.58 (d, 1H, $J$ =8.0 Hz, Ar-H, diclofenac), 6.72 (s, 1H, NH, D$_2$O exchangeable), 6.96-7.02 (m, 2H, Ar-H, diclofenac) 7.13-7.17 (m, 1H, Ar-H, diclofenac) 7.23-7.30 (m, 2H, Ar-H, diclofenac, vanillin), 7.35 (d, 2H, $J$ = 8.0 Hz, Ar-H, diclofenac), 7.47-7.50 (m, 2H, Ar-H, vanillin), 9.97 (s, 1H, CHO).

$^{13}$CNMR ($CDCl_3$): $\delta$ 37.99 (Ar-CH$_2$), 56.15 (OCH$_3$), 60.85 (OCH$_2$COO), 110.85-151.71 (Ar-carbons), 151.71 (ArC-OCH$_3$), 165.13 (CH$_2$COO), 171.40 (Ar-CH$_2$COO), 190.99 (CHO).

LC-MS: $m/z$ 488.07 [M]$^+$

Calculated for C$_{24}$H$_{19}$Cl$_2$NO$_6$: C, 59.03; H, 3.92; N, 2.87. Found: C, 59.18; H, 3.99; N, 2.78%.
Diclofenac-OCH$_2$COO-sesamol; 3,4-(Methylenedioxy)phenyl-2-[2(2,6-dichlorophenylamino)phenyl]ethanoyloxy ethanoate (150)

In a 250ml two neck flask, a mixture of sesamol (133) (1.38g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride (138) (1.12g, 0.8ml, 0.01mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1h and the temperature was maintained constant during this period. The reaction mixture was stirred further for 5h, poured on crushed ice and then washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain sesamol chloroacetate (143) as buff coloured solid product which was recrystallized from petroleum ether and ethyl acetate (1.83g, 85.5%), mp. 46-48 °C, R$_f$ 0.29 (pet ether : ethyl acetate :: 7 : 3).

Analysis

IR(KBr): 3033.9 (aromatic C-H st), 2911.8 (aliphatic C-H st), 1767.3 (C=O st), 1483.4 (benzene ring C=C st), 1154.3 (C-C(=O)-O st) cm$^{-1}$.

$^1$HNMR(CDC$_3$): $\delta$ 4.30 (s, 2H, -CH$_2$), 6.02 (s, 2H, OCH$_2$O), 6.59 (dd, 1H, $J = 2.4$ Hz and 8.4 Hz, Ar-H), 6.66 (d, 1H, $J = 2.4$ Hz, Ar-H), 6.81 (d, 1H, $J = 8.4$, Ar-H).

$^{13}$CNMR (CDC$_3$): $\delta$ 40.83 (Cl/CH$_2$), 101.86 (OCH$_2$O), 103.30-148.13 (Ar-carbons), 166.21 (C=O).

Calculated for C$_9$H$_7$CIO$_4$: C, 50.37; H, 3.29. Found: C, 50.45; H, 3.43%.

In a 250ml two neck flask, a mixture of sesamol chloroacetate (143) (2.14g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol), sodium iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium
hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The resulting semisolid residue was chromatographed on silica gel column using petroleum ether : ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure and residue was recrystallized from petroleum ether and ethyl acetate to obtain diclofenac-OCH2COO-sesamol (150) as buff coloured solid (2.53g, 53.4%), mp. 80-82 °C, Rf 0.29 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3367.4 (N-H st), 3051.2 (aromatic C-H st), 2942.7 (aliphatic C-H st), 1753.0 (C=O st), 1498.8 (benzene ring C=C st), 1131.4 (C-C(=O)-O st) cm⁻¹.

¹H NMR (CDCl₃): δ 4.02 (s, 2H, Ar-CH₂), 4.92 (s, 2H, OCH₂COO), 5.98 (s, 2H, OCH₂), 6.56 (dd, 1H, J = 2.4 Hz and 8.4 Hz, Ar-H, sesamol), 6.62 (d, 1H, J = 8.0 Hz, Ar-H, diclofenac), 6.64 (d, 1H, J = 2.3 Hz, Ar-H, sesamol), 6.78 (d, 1H, J = 8.4 Hz, Ar-H, sesamol), 6.78-6.79 (NH, D₂O exchangeable), 6.99-7.03 (m, 2H, Ar-H, diclofenac), 7.16-7.20 (m, 1H, Ar-H, diclofenac), 7.32 (dd, 1H, J=1.4 Hz and 7.5 Hz, Ar-H, diclofenac), 7.37 (d, 2H, J=8.0, Ar-H, diclofenac).

¹³C NMR (CDCl₃): δ 38.02 (Ar-CH₂), 61.24 (OCH₂COO), 101.86 (OCH₂O), 103.43-148.07 (Ar-carbons), 166.43 (CH₂COO), 171.56 (Ar-CH₂COO).

LC-MS: m/z 474.03[M]⁺.

Calculated for C₂₃H₁₇Cl₂N₀₆: C, 58.24; H, 3.61; N, 2.95. Found: C, 58.44; H, 3.75; N, 2.75%.

Diclofenac-OCH₂COO-umbelliferone; 2-Oxo-2H-chromen-7-y-2-[2(2,6-dichlorophenylamino)phenyl]ethanol oxy ethanoate (151)

In a 250ml two neck flask, a mixture of umbelliferone (134) (1.62g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride (138) (1.12g,
0.8ml, 0.01mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1h and the temperature was maintained constant during this period. The reaction mixture was stirred further for 5h, poured on crushed ice and then washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure and the resulting solid product was recrystallized from petroleum ether and ethyl acetate to obtain umbelliferone chloroacetate (144) (1.98 g, 83.2%), mp. 160-162 °C (163-164 °C)\textsuperscript{252}, R\textsubscript{f} 0.24 (pet ether : ethyl acetate :: 7 : 3).

Analysis

IR(KBr): 3023.7 (aromatic C-H st), 2946.3 (aliphatic C-H st), 1770.9 (C=O st ketone), 1735.5 (OO st), 1165.7 (C-C(=0)-O st) cm\textsuperscript{-1}.

\textsuperscript{1}HNMR(CDCl\textsubscript{3}): \( \delta \) 4.35 (s, 2H, -CH\textsubscript{2}), 6.42 (d, 1H, \( J = 9.6 \), H of lactone ring), 7.10 (dd, 1H, \( J = 8.5 \text{ Hz and } 2.2 \text{ Hz, Ar-H} \)), 7.17 (d, 1H, \( J = 2.2 \), Ar-H), 7.53 (d, 1H, \( J = 8.5 \), Ar-H), 7.71 (d, 1H, \( J = 9.6 \text{ Hz, H of lactone ring} \)).

\textsuperscript{13}CNMR (CDCl\textsubscript{3}): \( \delta \) 40.80 (ClCH\textsubscript{2}), 110.23 (Ar-CH=CH-), 116.60-154.73 (Ar-carbons), 142.77 (Ar-CH=CH-), 160.20 (C=O, umbelliferone), 165.37 (C=O).

Calculated for \( C_{11}H_{7}ClO_4 \): C, 55.37; H, 2.96. Found: C, 55.45; H, 3.19%.

In a 250ml two neck flask, a mixture of umbelliferone chloroacetate (144) (2.38 g, 0.01mol), diclofenac (38) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol), sodium iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into a beaker containing finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The semisolid residue was chromatographed on silica gel column using petroleum ether : ethyl acetate
mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The resulting solid residue was recrystallized from petroleum ether and ethyl acetate to obtain **diclofenac-OCH₂COO-umbelliferone (151)** as white solid (2.78g, 55.8 %), mp. 139-140 °C, Rf 0.19 (pet ether : ethyl acetate :: 7 : 3).

**Analysis**

**IR(KBr):** 3351.8 (N-H st), 3061.2 (aromatic C-H st), 2952.4 (aliphatic C-H st), 1776.6 (C=O st ketone), 1733.2 (C=O st), 1506.0 (benzene ring C=C st), 1140.5 (C-C(=O)-O st) cm⁻¹.

**¹HNMR(CDCI₃):** δ 3.98 (s, 2H, Ar-CH₂), 4.93 (s, 2H, OCH₂), 6.40 (d, 1H, J = 9.6 Hz, H of lactone ring, umbelliferone), 6.56 (d, 1H, J=8.0 Hz, Ar-H, diclofenac), 6.65 (s, 1H, NH, D₂O exchangeable), 6.95-7.03 (m, 3H, Ar-H, diclofenac, umbelliferone) 7.09 (d, 1H, J = 2.2, Ar-H, umbelliferone), 7.11-7.14 (m, 1H, Ar-H, diclofenac), 7.27 (dd, 1H, J=1.4 Hz and 7.5 Hz, Ar-H, diclofenac), 7.33 (d, 2H, J =8.0 , Ar-H, diclofenac), 7.46 (d, 1H, J =8.5 Hz, Ar-H, umbelliferone), 7.67 (d, 1H, J =9.6 Hz, H of lactone ring, umbelliferone)

**¹³CNMR (CDCI₃):** δ 37.96 (Ar-CH₂), 61.00 (OCH₂COO), 110.14 (Ar-CH=CH-), 116.40-154.59 (Ar-carbons), 142.75 (Ar-CH=CH-), 160.20 (C=O, umbelliferone), 165.52 (CH₂COO), 171.52 (Ar-CH₂COO).

**LC-MS:** m/z 498.04[M⁺].

**Calculated for** C₂₅H₁₇Cl₂NO₆: C, 60.26; H, 3.44; N, 2.81. Found: C, 60.40; H, 3.58; N, 2.67%.

**Diclofenac-OCH₂COO-menthol; 2-isopropyl-5-methyl-cyclohexyl-2-[2(2,6-dichlorophenylamino)phenyl]ethanoyloxy ethanoate (152)**

In a 250ml two neck flask, a mixture of menthol (135) (1.50g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and chloroform (25ml) was cooled in an ice salt mixture to -10 °C. To this reaction mixture, chloroacetyl chloride(138) (1.12g, 0.8ml,
0.01 mol) in chloroform (25ml) was added drop wise with constant stirring over a period of 1 h, while maintaining the temperature constant during this period. The reaction mixture was stirred further for 5 h, poured on crushed ice and then washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The light brown solid product was recrystallized from petroleum ether and ethyl acetate to yield menthol chloroacetate (145) (1.61 g, 80.5%), mp. 35-37 °C (34-36 °C)222, Rf 0.75 (pet ether : ethyl acetate :: 9 : 1).

Analysis

IR(KBr): 2961.0 (aliphatic C-H st), 1750.0 (C=O st), 1196.2 (C-C(=0)-O st) cm⁻¹.

¹HNMR(CDC₃): δ 0.76 (d, 3H, J = 7.0 Hz, CH₃), 0.85(d, 3H, J=5.9 Hz, CH₃), 0.92 (d,3H, J=7.0 Hz, CH₃), 1.01 (m, 3H, CH₂ and CH), 1.36-1.40 (m,1H, CH), 1.51-1.57 (m, 1H, CH), 1.66-1.77(m, 2H, CH₂), 1.82-1.86 (m, 1H, CH), 1.96-2.02 (m, 1H, CH), 3.94 (s, 2H, CH₂), 4.64- 4.73 (1H, m, CH)

¹³CNMR (CDC₃): δ 16.26 (CH₃), 20.66 (OCOCH₃), 21.18 (CH(CH₃)₂), 21.94 (CH(CH₃)₂), 22.02 (CH₂), 26.23 (CH), 31.30 (CH), 34.21 (CH₂), 40.87 (CH₂), 46.92 (CH), 166.93 (C=O).

In a 250ml two neck flask, a mixture of menthol chloroacetate (145) (2.12g, 0.01mol), diclofenac (2.96g, 0.01mol), TEA (1.01 g, 1.4ml, 0.01mol), sodium iodide (1.5g, 0.01mol) and DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured on finely crushed ice contained in a beaker with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether : ethyl acetate mixture as eluent. The fractions were combined and the solvent
was removed under reduced pressure. The residue obtained was recrystallized from petroleum ether and ethyl acetate to yield **diclofenac-OCH$_2$COO-menthol** (152) as white solid (2.22g, 45.2%), mp. 68-70 °C, Rf 0.78 (pet ether : ethyl acetate :: 8.0 : 2.0).

**Analysis**

IR(KBr): 3369.6 (N-H st), 2954.4 (aliphatic C-H st), 1742.9 (C=O st), 1152.7 (C-C(=0)-0 st) cm$^{-1}$.

$^1$H NMR(CDC$_3$): δ 0.73 (d, 3H, $J$ = 7.0 Hz, CH$_3$), 0.77-0.91 (m, 8H, 2CH$_3$, 2CH), 0.96-1.05 (m, 1H, CH), 1.20-1.28 (m, 1H, CH), 1.41-1.46 (m, 1H, CH), 1.58-1.66 (m, 2H, 2CH), 1.77-1.81 (m, 1H, CH), 1.92-1.97 (m, 1H, CH), 3.92 (s, 1H, Ar-CH$_2$), 4.65 (s, 1H, OCH$_2$), 4.70-4.77 (m, 1H, CH), 6.55 (d, 1H, $J$ = 8.0 Hz, Ar-H, diclofenac), 6.79 (s, 1H, NH, D$_2$O exchangeable), 6.94-7.00 (m, 2H, Ar-H, diclofenac), 7.11-7.15 (m, 1H, Ar-H, diclofenac), 7.25 (dd, 1H, $J$ = 1.4 and 7.5, Ar-H, diclofenac), 7.33 (d, 2H, $J$ = 8.0, Ar-H, diclofenac)

$^{13}$C NMR (CDC$_3$): δ 16.31 (CH$_3$), 20.76 (CH(CH$_3$)$_2$), 22.00 (CH(CH$_3$)$_2$), 23.41 (CH$_2$), 26.25 (CH), 31.42 (CH), 34.14 (CH$_2$), 38.21 (Ar-CH$_2$), 40.61 (CH$_2$), 46.82 (CH), 61.53 (Ar-CH$_2$), 75.86 (CH), 118.55-142.89 (Ar-carbons), 167.16 (CH$_2$COO), 171.52 (Ar-CH$_2$COO).

**LC-MS:** $m/z$ 492.12[M]$^+$.  
Calculated for C$_{26}$H$_{33}$Cl$_2$NO$_4$: C, 63.42; H, 6.35; N, 2.84. Found: C, 63.21; H, 6.46; N, 2.96%.

**Synthesis of diclofenac-OCH$_2$CH$_2$CH$_2$O-phytophens mutual prodrugs**

Diclofenac-OCH$_2$CH$_2$CH$_2$O-guaiacol; 3-(2-Methoxyphenyl)oxypropyl-[2-(2, 6-dichlorophenylamino)phenyl]acetate (160)

In a 250ml two neck flask, a mixture of guaiacol (129) (1.24g, 0.01mol), and 1-bromo-3-chloropropane (153) (10.0ml) in ethyl methyl ketone (25ml), containing anhydrous potassium carbonate (5.0g) was refluxed on an oil bath,
with stirring for 8h. The reaction mixture was filtered, and the residue was washed with ethyl methyl ketone. The combined organic layer was evaporated and the semisolid residue obtained was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure to yield guaiacol ether, chloropropoxyguaiacol (154) as light brown coloured semisolid product (1.70g, 85.0%), Rf 0.73 (pet ether : ethyl acetate :: 8.0 : 2.0). 253

Analysis

IR(KBr): 3065.8 (aromatic C-H st), 2957.3 (aliphatic C-H st), 2836.6 (C-H st of aromatic OCH₃), 1503.9 (benzene ring C=C st), 1253.6 (asymm C-O-C st), 1028.9 (symm C-O-C st) cm⁻¹.

¹HNMR(CDCl₃): δ 2.27 (quin, 2H, J = 6.2 Hz, Cl-CH₂-CH₂-CH₂OAr), 3.77 (t, 2H, J = 6.3 Hz, Cl-CH₂-CH₂-CH₂OAr), 3.85 (s, 3H, OCH₃), 4.15 (t, 2H, J = 6.0 Hz, CH₂-CH₂-CH₂OAr), 6.86-6.92 (m, 4H, Ar-H).

¹³CNMR (CDCl₃): δ 32.09 (Cl-CH₂-CH₂-CH₂OAr), 41.46 (Cl-CH₂-CH₂-CH₂OAr), 55.59 (OCH₃), 65.36 (Cl-CH₂-CH₂-CH₂OAr), 111.74-149.39 (Ar-carbons), 149.39 (Ar-C-OCH₃).

In a 250ml two neck flask, a mixture of chloropropoxyguaiacol (154) (2.00g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01 g, 1.4ml, 0.01mol) and sodium iodide (1.5g, 0.01 mol) in DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured on finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The resulting semisolid residue was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed.
under reduced pressure to obtain diclofenac-OCH₂CH₂CH₂O-guaiacol (160) as a white solid substance (1.86g, 40.4%), mp. 66-68 °C, Rf 0.67 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis
IR(KBr): 3328.2 (N-H st), 3063.9 (aromatic C-H st), 2930.0 (aliphatic C-H st), 2836.9 (C-H st of aromatic OCH₃), 1719.4 (C=O st), 1507.1 (benzene ring C=C st), 1255.0 (asymm C-O-C st), 1123.8 (C-C(=O)-O st), 1019.9 (symm C-O-C st) cm⁻¹.

¹HNMR(CDCl₃): δ 2.16 (quin, 2H, J = 6.2 Hz, -CH₂-CH₂-CH₂OAr), 3.79 (s, 2H, Ar-CH₂), 3.80 (s, 3H, OCH₃), 4.04 (t, 2H, J = 6.2 Hz, -CH₂-CH₂-CH₂OAr), 4.35 (t, 2H, J = 6.2 Hz, -CH₂-CH₂-CH₂OAr), 6.53 (d, 1H, J = 8.0 Hz, Ar-H, diclofenac), 6.78-6.94 (m, 7H, guaiacol, diclofenac, NH, D₂O exchangeable), 7.06-7.10 (m, 1H, Ar-H, diclofenac), 7.18 dd, 1H J=1.4 and 7.2 Hz, Ar-H, diclofenac), 7.29 (d, 2H, J=8.0, Ar-H, diclofenac).

¹³CNMR (CDCl₃): δ 28.53 (CH₂-CH₂-CH₂), 38.05 (Ar-CH₂COO), 55.74 (OCH₃), 62.28 (CH₂-CH₂-CH₂OAr), 65.40 (CH₂-CH₂-CH₂OAr), 111.82-149.74 (Ar-carbons), 149.74 (ArC-OCH₃), 172.26 (Ar-CH₂COO).

LC-MS: m/z 460.19 [M⁺].

Calculated for C₂₄H₂₃Cl₂N₂O₄: C, 62.62; H, 5.04; N, 3.04. Found: C, 62.51; H, 4.99; N, 3.17%.

Diclofenac-OCH₂CH₂CH₂O-eugenol;3-[(2-Methoxy-4-(2-propenyl)phenyl)oxypropyl]-2-(2,6-dichlorophenylamino)phenylacetate (161)

In a 250ml two neck flask, a mixture of eugenol (130) (1.64g, 0.01mol), and 1-bromo-3-chloropropane (153) (10.0ml) in ethyl methyl ketone (25ml), containing anhydrous potassium carbonate (5.0g) was refluxed on an oil bath, with stirring for 8h. The reaction mixture was filtered, and the residue was washed with ethyl methyl ketone. The combined organic layer was evaporated...
and the resulting residue obtained was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure to yield chloropropoxyeugenol (155) as semisolid product (2.0 g, 83.3%), Rf 0.30 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3075.2 (aromatic C-H st), 2960.1 (aliphatic C-H st), 2835.6 (C-H st of aromatic OCH3), 1512.3 (benzene ring C=C st), 1262.5 (asymmetric C-O-C st), 1034.5 (symmetric C-O-C st) cm⁻¹.

¹H NMR(CDC1₃): δ 2.28 (quin, 2H, J = 6.2 Hz, Cl-CH₂-CH₂-CH₂OAr), 3.38 (d, 2H, J = 6.7 Hz, CH₂-CH=CH₂), 3.79 (t, 2H, J = 6.3 Hz, Cl-CH₂-CH₂-CH₂OAr), 3.87 (s, 3H, OCH₃), 4.15 (t, 2H, J = 6.0 Hz, Cl-CH₂-CH₂-CH₂OAr), 5.10-5.16 (m, 2H, CH₂-CH=CH₂), 5.96-6.04 (m, 1H, CH₂-CH=CH₂), 6.74-6.77 (m 2H, Ar-H), 6.88 (d, 1H, J = 6.9 Hz, Ar-H).

¹³C NMR (CDCl₃): δ 32.18 (Cl-CH₂-CH₂-CH₂OAr), 39.61 (CH₂-CH=CH₂), 41.49 (Cl-CH₂-CH₂-CH₂OAr), 55.63 (OCH₃), 65.65 (Cl-CH₂-CH₂-CH₂OAr), 112.28 (CH=CH₂), 113.74-149.38 (Ar-carbons), 137.43 (CH=CH₂), 149.38 (ArC-OCH₃).

In a 250ml two neck flask, a mixture of chloropropoxyeugenol (155) (2.40g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and sodium iodide (1.5g, 0.01mol) in DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3x50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The resulting semisolid residue was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed.
under reduced pressure to obtain diclofenac-\textit{OCH}_2\textit{CH}_2\textit{CH}_2\textit{O}-eugenol (161) as light brown semisolid product (1.79g, 35.8%), \( R_f \) 0.58 (pet ether : ethyl acetate :: 8.0 : 2.0).

**Analysis**

\textbf{IR(KBr):} 3326.2 (N-H st), 3073.8 (aromatic C-H st), 2929.8 (aliphatic C-H st), 2835.8 (C-H st of aromatic OCH$_3$), 1722.6 (C=O st), 1510.1 (benzene ring C=C st), 1260.3 (asymm C-O-C st), 1144.4 (C-C(=O)-O st), 1039.1 (symm C-O-C st) cm$^{-1}$.

\textbf{\textsuperscript{1}HNMR(CDC$_3$):} \( \delta \) 2.16 (quin, 2H, \( J = 6.2 \) Hz, -CH$_2$-CH$_2$-CH$_2$OAr), 3.30 (d, 2H, \( J = 6.7 \) Hz, CH$_2$-CH=CH$_2$), 3.80 (s, 5H, Ar-CH$_2$ OCH$_3$), 4.04 (t, 2H, \( J = 6.2 \) Hz, -CH$_2$CH$_2$CH$_2$OAr), 4.35 (t, 2H, \( J = 6.3 \) Hz, -CH$_2$CH$_2$CH$_2$OAr), 5.03-5.08 (m, 2H, CH$_2$-CH=CH$_2$), 5.93-5.94 (m, 1H, -CH$_2$-CH=CH$_2$), 6.52 (d, 1H, \( J = 8.0 \), Ar-H, diclofenac), 6.64-6.68 (m, 2H, Ar-H, eugenol), 6.74 (d, 1H, \( J = 8.0 \), Ar-H, eugenol), 6.90-6.96 (m, 3H, NH,D$_2$O exchangeable, Ar-H, diclofenac), 7.07-7.12 (m, 1H, Ar-H, diclofenac), 7.19 (dd, 1H, \( J = 1.3 \) and 7.5 Hz, Ar-H, diclofenac), 7.30 (2H, d, \( J = 8.0 \), Ar-H, diclofenac).

\textbf{\textsuperscript{13}CNMR (CDC$_3$):} \( \delta \) 28.65 (CH$_2$-CH$_2$-CH$_2$OAr), 38.61 (Ar-CH$_2$), 39.83 (-CH$_2$-CH=CH$_2$), 55.86 (OCH$_3$), 62.40 (-CH$_2$-CH$_2$-CH$_2$OAr), 65.71 (CH$_2$-CH$_2$-CH$_2$OAr), 112.39 (CH=CH$_2$), 113.63-149.49 (Ar-carbons), 137.79 (CH=CH$_2$), 149.49 (ArC-OCH$_3$), 172.38(Ar-CH$_2$COO).

\textbf{LC-MS:} \( m/z \) 500.12 [M$^+$].

**Diclofenac-\textit{OCH}_2\textit{CH}_2\textit{CH}_2\textit{O}-\textit{thymol};3-(2-Isopropyl-5-methylphenyl)oxypropyl-[2-(2,6-dichlorophenylamino)phenyl]acetate (162)**

In a 250ml two neck flask, a mixture of thymol (131) (1.50g, 0.01mol), and 1-bromo-3-chloropropane (153) (10.0ml) in ethyl methyl ketone (25ml), containing anhydrous potassium carbonate (5.0g) was refluxed on an oil bath, with stirring for 8h. The reaction mixture was filtered, and the residue was washed with ethyl methyl ketone. The combined organic layer was combined and solvent was evaporated under reduced pressure. The semisolid residue obtained
was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure to yield chloropropoxythymol (156) as light brown semisolid product (1.89g, 83.6%), Rf 0.83 (pet ether : ethyl acetate :: 8.0 : 2.0).

**Analysis**

IR(KBr): 3045.8 (aromatic C-H st), 2961.6 (aliphatic C-H st), 1505.1 (benzene ring C=C st), 1256.4 (asymm C-O-C st), 1044.7 (symm C-O-C st) cm⁻¹.

¹HNMR(CDCl₃): δ 1.19 (d, 6H, J = 6.9 Hz, 2 X CH₃), 2.26 (quin, 2H, J = 6.1 Hz, CH₂-CH₂-CH₂OAr), 2.32 (s, 3H, Ar-CH₃), 2.36 (sept, 1H, J = 6.9 Hz, CH), 3.78 (t, 2H, J = 6.4 Hz, Cl-CH₂-CH₂-CH₂OAr), 4.10 (t, 2H, J = 5.7 Hz, Cl-CH₂-CH₂-OAr), 6.67 (s, 1H, Ar-H), 6.75 (d, 1H, J = 7.6 Hz, Ar-H), 7.09 (d, 1H, J = 7.6, Ar-H).

¹³CNMR (CDCl₃): δ 21.38 (Ar-CH₃), 22.82 (CH(CH₃)₂), 26.64 (CH(CH₃)₂), 32.56 (Cl-CH₂-CH₂-CH₂), 41.79 (Cl-CH₂-CH₂-CH₂), 64.14 (Cl-CH₂-CH₂-CH₂OAr), 112.23-155.69 (Ar-carbons).

In a 250ml two neck flask, a mixture of chloropropoxythymol (156) (2.00g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01 g, 1.4ml, 0.01mol) and sodium iodide (1.5g, 0.01mol) in DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured on finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. The semisolid residue was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure to obtain diclofenac-OCH₂CH₂CH₂O-thymol (162) as light brown

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coloured semisolid product (2.06g, 42.4%), Rf 0.79 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3364.0 (N-H st), 3063.9 (aromatic C-H st), 2926.3 (aliphatic C-H st), 1758.6 (C=O st), 1507.6 (benzene ring C=C st), 1243.6 (asymm C-O-C st), 1153.9 (C-C(=O)-O st), 1087.1 (symm C-O-C st) cm⁻¹.

¹HNMR(CDCl₃): δ 1.18 (d, 6H, J = 6.96 Hz, 2 X CH₃), 2.13 (quin, 2H, J = 6.2 Hz, CH₂-CH₂-CH₂OAr), 2.29 (s, 3H, Ar-CH₃), 3.26 (sept, 1H, J = 6.9 Hz, CH), 3.80 (s, 2H, Ar-CH₂), 3.97 (t, 2H, J = 6.0 Hz, CH₂-CH₂-CH₂OAr), 4.36 (t, 2H, J = 6.4 Hz, -CH₂-CH₂-CH₂OAr), 6.54 (d, 1H, J = 8.0 Hz, Ar-H, diclofenac), 6.59 (s, 1H, Ar-H, thymol), 6.72 (d, 1H, J = 7.6 Hz, Ar-H, thymol), 6.91 (t, 2H, J = 8.0 Hz, Ar-H, diclofenac), 6.96 (s, 1H, NH, D₂O exchangeable), 7.06-7.12 (m, 2H, Ar-H, diclofenac, thymol), 7.19 (dd, 1H, J = 1.24 and 7.5 Hz, Ar-H, diclofenac), 7.29 (d, 2H, J = 8.0 Hz, Ar-H, diclofenac).

¹³CNMR (CDCl₃): δ 21.35 (Ar-CH₃), 22.78 (CH(CH₃)₂), 26.54 (CH(CH₃)₂), 28.79 (CH₂-CH₂-CH₂OAr), 38.59 (Ar-CH₂), 62.41 (-CH₂CH₂CH₂OAr), 63.94 (-CH₂-CH₂-CH₂OAr), 112.04-155.66 (Ar-carbons), 172.34 (Ar-CH₂COO).

LC-MS: m/z 486.13 [M]⁺.

Diclofenac-OCH₂CH₂CH₂O-vanillin; 3-(4-Formyl-2-methoxyphenyl) oxypropyl-[2-(2,6-dichlorophenylamino)phenyl]acetate (163)

In a 250ml two neck flask, a mixture of vanillin (132) (1.52g, 0.01mol), and 1-bromo-3-chloropropane (153) (10.0ml) in ethyl methyl ketone (25ml), containing anhydrous potassium carbonate (5.0g) was refluxed on an oil bath, with stirring for 8h. The reaction mixture was filtered, and the residue was washed with ethyl methyl ketone. The combined organic layer was evaporated and the semisolid residue obtained was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure to yield vanillin.
ether, chloropropoxyvanillin (157) as pale yellow coloured solid product which was recrystallized from petroleum ether and ethyl acetate (1.83 g, 80.3%), mp. 82-84 °C, Rf 0.38 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3054.6 (aromatic C-H st), 2956.9 (aliphatic C-H st), 2852.1 (C-H st of aromatic OCH3), 1683.1 (C=O st aldehyde), 1511.5 (benzene ring C=C st), 1271.7 (asymmetric C-O-C st), 1030.0 (symmetric C-O-C st) cm⁻¹.

¹HNMR(CDCI₃): δ 2.33 (quin, 2H, J = 6.1 Hz, CH₂-CH₂-CH₂OAr), 3.78 (t, H, J = 6.2 Hz, Cl-CH₂-CH₂-CH₂OAr), 3.92 (s, 3H, OCH₃), 4.26 (t, H, J = 6.0 Hz, CH₂-CH₂-CH₂OAr), 7.01 (d, 1H, J = 8.1 Hz, Ar-H), 7.42 (d, 1H, J = 1.8 Hz, Ar-H), 7.45 (dd, 1H, J = 8.1 and 1.8 Hz, Ar-H), 9.86 (s, 1H, CHO).

¹³CNMR (CDCl₃): δ 31.98 (CH₂-CH₂-CH₂), 41.40 (Cl-CH₂-CH₂-CH₂OAr), 56.06 (OCH₃), 65.54 (Cl-CH₂-CH₂-CH₂OAr), 109.38-153.78 (Ar-carbons), 153.78 (ArC-OCH₃), 191.00 (CHO).

Calculated for C₁₁H₁₃ClO₃: C, 57.78; H, 5.73. Found: C, 57.89; H, 5.87%.

In a 250ml two neck flask, a mixture of chloropropoxyvanillin (157) (2.28g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and sodium iodide (1.5g, 0.01mol) in DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured into finely crushed ice with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether: ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The white solid substance was recrystallized from
petroleum ether and ethyl acetate to obtain diclofenac-OCH₂CH₂CH₂O-vanillin (163) (1.91g, 39.1%), mp. 94-96 °C, Rf 0. 24 (pet ether : ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3355.9 (N-H st), 3075.1 (aromatic C-H st), 2943.0 (aliphatic C-H st), 2832.0 (C-H st of aromatic OCH₃), 1734.6 (C=O st), 1677.6 (C=O st aldehyde), 1506.1 (benzene ring C=C st), 1263.1 (asymm C-O-C st), 1135.6 (C-C(=O)-O st), 1034.6 (symm C-O-C st) cm⁻¹.

¹HNMR(CDCI₃) : δ 2.23 (quin, 2H, J = 6.1 Hz, CH₂-CH₂-CH₂OAr), 3.83 (s, 2H, Ar-CH₂), 3.88 (s, 3H, OCH₃), 4.13 (t, 2H, J = 6.1 Hz, -CH₂-CH₂-CH₂OAr), 4.39 (t, 2H, J = 6.1 Hz, -CH₂-CH₂-CH₂OAr), 6.53 (d, 1H, J =7.9 Hz, Ar-H, diclofenac), 6.85-6.87 (m, 2H, NH, D₂O exchangeable, Ar-H, vanillin), 6.94 (t, 2H, J =8.1 Hz, Ar-H, diclofenac) 7.08-7.11 (m, 1H, Ar-H, diclofenac), 7.21 (dd, 1H, J =1.1 and 7.5 Hz, Ar-H, diclofenac), 7.30 (d, 2H, J = 8.0 Hz, Ar-H, diclofenac), 7.34 -7.36 (m, 2H, Ar-H, vanillin), 9.97 (s, 1H, CHO).

¹³CNMR (CDCI₃): δ 28.26 (CH₂-CH₂-CH₂OAr), 38.38 (Ar-CH₂), 55.73 (OCH₃), 61.95 (-CH₂-CH₂-CH₂OAr), 65.43 (-CH₂-CH₂-CH₂OAr), 109.11-153.50 (Ar-carbons), 153.50 (ArC-OCH₃), 172.17 (Ar-CH₂COO), 190.72 (CHO).

LC-MS: m/z 488.11[M]+.

Calculated for C₂₅H₂₃Cl₂NO₅: C, 61.48; H, 4.75; N, 2.87. Found: C, 61.65; H, 4.71; N, 2.88%.

Diclofenac-OCH₂CH₂CH₂O-sesamol; 3-[3,4-(Methylenedioxy)phenyl]oxypropyl-[2-(2,6-dichlorophenylamino)phenyl]acetate (164)

In a 250ml two neck flask, a mixture of sesamol (133) (1.38g, 0.01mol), and 1-bromo-3-chloropropane (153) (10.0ml) in ethyl methyl ketone (25ml), containing anhydrous potassium carbonate (5.0g) was refluxed on an oil bath, with stirring for 8h. The reaction mixture was filtered, and the residue was washed with ethyl methyl ketone. The combined organic layer was evaporated and the semisolid residue obtained was chromatographed on silica gel column
using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The buff coloured solid product was recrystallized from petroleum ether and ethyl acetate to yield chloropropoxysesamol (158) (1.81g, 84.6%), mp. 44-46 °C, Rf 0.82 (pet ether: ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3054.0 (aromatic C-H st), 2927.5 (aliphatic C-H st), 1495.0 (benzene ring C=C st), 1249.4 (asymmetric C-O-C st), 1035.4 (symmetric C-O-C st) cm⁻¹.

¹H NMR(CDCl₃): δ 2.16 (quin, 2H, J = 6.1 Hz, -CH₂-CH₂-CH₂OAr), 3.69 (t, 2H, J = 6.3 Hz, Cl-CH₂-CH₂-CH₂OAr), 3.98 (t, 2H, J = 5.9 Hz, -CH₂-CH₂-CH₂OAr), 5.86 (s, 2H, -OCH₂O-), 6.30 (dd, 1H, J = 8.4 and 2.5 Hz, Ar-H), 6.47 (d, 1H, J = 2.5 Hz, Ar-H), 6.67 (d, 1H, J = 8.4 Hz, Ar-H).

¹³C NMR (CDCl₃): δ 32.19 (Cl-CH₂-CH₂-CH₂OAr), 41.48 (Cl-CH₂-CH₂-CH₂OAr), 65.13 (Cl-CH₂-CH₂-CH₂OAr), 101.08 (OCH₂O), 105.57-154.13 (Ar-carbons).

Calculated for C₁₀H₁₁ClO₃: C, 55.96; H, 5.17. Found: C, 55.87; H, 5.12%.

In a 250ml two neck flask, a mixture of chloropropoxysesamol (158) (2.14g, 0.01mol), diclofenac (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and sodium iodide (1.5g, 0.01mol) in DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured on a finely crushed ice contained in a beaker, with stirring and extracted with chloroform (4 x 25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The buff coloured solid substance was recrystallized...
from petroleum ether and ethyl acetate to obtain diclofenac-OCH$_2$CH$_2$CH$_2$O-
sesamol (164) (1.96g, 41.4%), mp. 117-119 °C, R$_f$ 0.70 (pet ether: ethyl acetate :: 8.0 : 2.0).

Analysis

IR(KBr): 3364.0 (N-H st), 3031.9 (aromatic C-H st), 2965.2 (aliphatic C-H st),
1724.8 (C—O st), 1504.3 (benzene ring C=C st), 1249.9 (asymm C-O-C st),
1154.6 (C-C(=O)-O st), 1016.6 (symm C-O-C st) cm$^{-1}$.

$^1$HNMR(CDC$_3$):
\[
\begin{align*}
&\delta 2.10 (quin, 2H, J = 6.2 Hz, CH$_2$-CH$_2$-CH$_2$OAr), 3.81 (s, 2H, Ar-CH$_2$), \\
&3.92 (t, 2H, J = 6.0 Hz, CH$_2$-CH$_2$-CH$_2$OAr), 4.33 (t, 2H, J = 6.1 Hz, \\
&CH$_2$-CH$_2$-CH$_2$OAr), 5.90 (s, 2H, -OCH$_2$-), 6.26 (dd, 1H, J = 2.5 and 8.5 Hz, Ar-H, \\
&sesamol), 6.44 (d, 1H, J = 2.5 Hz, Ar-H, sesamol), 6.54 (d, 1H, J = 8.0 Hz Ar-H, \\
diclofenac), 6.66 (d, 1H, J = 8.5 Hz, Ar-H, sesamol), 6.89 (s, 1H, NH, D$_2$O exchangeable), \\
&6.92-6.99 (m, 2H, Ar-H, diclofenac), 7.22 (dd, 1H, J = 1.4 and 7.5 Hz, Ar-H, diclofenac), \\
&7.33 (d, 2H, J = 8.0 Hz, Ar-H, diclofenac).
\end{align*}
\]

$^{13}$CNMR (CDC$_3$):
\[
\begin{align*}
&\delta 28.67 (CH$_2$-CH$_2$-CH$_2$OAr), 38.68 (Ar-CH$_2$), \\
&62.30 (CH$_2$-CH$_2$-CH$_2$OAr), 65.20 (CH$_2$-CH$_2$-CH$_2$OAr), 98.14 (OCH$_2$O), \\
&101.16-154.24 (Ar-carbons), 172.38 (Ar-CH$_2$COO).
\end{align*}
\]

LC-MS: m/z 474.19[M]$^+$. Calculated for C$_24$H$_{21}$Cl$_2$NO$_5$: C, 60.77; H, 4.46; N, 2.95. Found: C, 60.87; H, 4.48; N, 2.99%.

Diclofenac-OCH$_2$CH$_2$CH$_2$O-umbelliferone; 3-(2-Oxo-2H-chromen-7-yl)
oxypropyl-[2-(2,6-dichlorophenylamino)phenyl]acetate (165)

In a 250ml two neck flask, a mixture of umbelliferone (134) (1.62g, 0.01mol), and
1-bromo-3-chloropropane (153) (10.0ml) in ethyl methyl ketone (25ml),
containing anhydrous potassium carbonate (5.0g) was refluxed on an oil bath,
with stirring for 8h. The reaction mixture was filtered, and the residue was
washed with ethyl methyl ketone. The combined organic layer was evaporated and the semisolid residue obtained was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure. The white solid product was recrystallized from petroleum ether and ethyl acetate to yield **chloropropoxyumbelliferone (159)** (1.96g, 82.4%), mp. 105-106°C (105-108°C), $R_f$ 0.26 (pet ether : ethyl acetate :: 8.0 : 2.0)

**Analysis**

IR(KBr): 3068.2 (aromatic C-H st), 2951.9 (aliphatic C-H st), 1711.1 (C=O st ketone), 1508.6 (benzene ring C=C st), 1238.4 (asymm C-O-C st), 1022.5 (symmetric C-O-C st) cm$^{-1}$.

$^1$HNMR(CDC$_3$): $\delta$ 2.28 (quin,2H, J = 6.1 Hz, Cl-CH$_2$-CH$_2$-C=OAr), 3.76 (t, 3H, J = 6.2 Hz, Cl-CH$_2$-CH$_2$-CH$_2$OAr), 4.18 (t, 2H, J = 5.8 Hz, Cl-CH$_2$-CH$_2$-C=OAr), 6.25 (d, 1H, J = 9.4, H of lactone ring), 6.81-6.86 (m, 2H, Ar-H), 7.38 (d, 1H, J = 8.6, Ar-H), 7.65 (d, 1H, J = 9.4, H of lactone ring).

$^{13}$CNMR (CDC$_3$): $\delta$ 31.90 (CH$_2$-CH$_2$- CH$_2$), 41.21 (CH$_2$-CH$_2$- CH$_2$), 64.85 (Cl-CH$_2$-CH$_2$-CH$_2$), 112.73 (Ar-CH=CH-), 113.22-161.16 (Ar-carbons), 142.77 (Ar-CH=CH-), 161.89 (C=O).

**Calculated for** C$_{12}$H$_{11}$ClO$_3$: C, 60.39; H, 4.65. **Found:** C, 60.57; H, 4.57%.

In a 250ml two neck flask, a mixture of chloropropoxyumbelliferone (159) (2.38g, 0.01mol), diclofenac (33) (2.96g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and sodium iodide (1.5g, 0.01mol) in DMF (25ml) was stirred overnight at room temperature. The reaction mixture was poured on finely crushed ice with stirring and extracted with chloroform (4x25ml). The combined organic layer was washed with sodium thiosulphate (2%, 3 x 50ml), HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed.
under reduced pressure to obtain semisolid residue, which was chromatographed on silica gel column using petroleum ether and ethyl acetate mixture as eluent. The fractions were combined and the solvent was removed under reduced pressure to diclofenac-\text{-OCH}_2\text{CH}_2\text{CH}_2\text{O-umbelliferone (165) as white solid substance which was recrystallized from petroleum ether and ethyl acetate (2.23g, 44.8%), mp. 92-94 °C, Rf 0. 22 (pet ether: ethyl acetate: 8.0: 2.0).

Analysis

\text{IR(KBr): 3360.0 (N-H st), 3064.3 (aromatic C-H st), 2941.6 (aliphatic C-H st), 1735.8 (C=O st), 1504.7 (benzene ring C=C st), 1228.9 (asymm C-O-C st), 1114.5 (C-C(=O)-O st), 1040.6 (symm C-O-C st) cm}^{-1}.

\text{\textsuperscript{1}HNMR(CDC}3\text{)}: \delta 2.18 (quin, 2H, J = 6.1 Hz, CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}OAr), 3.82 (s, 2H, Ar-CH\textsubscript{2}), 4.02 (t, 2H, J = 6.0 Hz, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}OAr), 4.36 (t, 2H, J = 6.1 Hz, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}OAr), 6.23 (d, 1H, J = 9.4 Hz, Ar-H, umbelliferone), 6.52 (d, 1H, J=8.0 Hz, diclofenac), 6.72-6.82 (m, 3H, NH, D\textsubscript{2}O exchangeable, Ar-H, diclofenac), 6.91-6.98(m, 2H, Ar-H, umbelliferone) 7.09-7.13 (m, 1H, Ar-H, diclofenac), 7.21 (dd, 1H, J = 1.40 and 7.5 Hz, Ar-H, diclofenac), 7.30-7.32 (m, 3H, Ar-H, diclofenac, umbelliferone) 7.59 (d, 1H, J =9.4, Ar-H, umbelliferone).

\text{\textsuperscript{13}CNMR (CDCl}\textsubscript{3}): \delta 28.38 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}OAr), 38.62 (Ar-CH\textsubscript{2}), 61.91 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}OAr), 64.89 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}OAr), 112.63 (Ar-CH=CH\textsubscript{2}), 112.92-161.19 (Ar-carbons), 142.68 (Ar-CH=CH\textsubscript{2}), 161.88 (C=O, umbelliferone), 172.29 (Ar-CH\textsubscript{2}COO).

LC-MS: 498.08 [M]\textsuperscript{+}

\text{Calculated for C}_{26}H_{21}Cl_{2}NO_{5}: C, 62.66; H, 4.25; N, 2.81. Found: C, 62.45; H, 4.12; N, 2.76%.
Synthesis of antioxidant prodrugs

Guaiacol acetate; 2-Methoxyphenyl ethanoate (167)

In a 250ml two neck flask fitted with a dropping funnel and guard tube, guaiacol (129) (1.24g, 0.01 mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01 mol) was added slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The semisolid product formed was extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give guaiacol acetate (167) as a brown semisolid product (1.12g, 74.6%), \( R_f 0.67 \) (chloroform: methanol :: 9.9 : 0.1). 

Analysis

IR(KBr): 3070.1 (aromatic C-H st), 2945.5 (aliphatic C-H st), 2841.9 (C-H st of aromatic OCH\(_3\)), 1764.7 (C=O st), 1501.0 (benzene ring C=C st), 1258.9 (asymm C-O-C st), 1172.1 (C-C(=O)-O st), 1023.7 (symm C-O-C st) cm\(^{-1}\).

\(^1\)HNMR(CDC\(_3\)): 2.28 (s, 3H, OCOCH\(_3\)), 3.78 (s, 3H, OCH\(_3\)), 6.89-6.94 (m, 2H, Ar-H), 7.00-7.03 (m, 1H, Ar-H), 7.14-7.19 (m, 1H, Ar-H)

\(^13\)CNMR (CDC\(_3\)): 20.51 (OCOCH\(_3\)), 55.65 (OCH\(_3\)), 112.29-151.01 (Ar-carbons), 168.93 (OCOCH\(_3\)).

Eugenol acetate; 2-Methoxy-4-(2-propenyl)phenyl ethanoate (168)

In a 250ml two neck flask fitted with a dropping funnel and guard tube, eugenol (130) (1.24g, 0.01 mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01 mol) was added slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The semisolid product formed was
extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain eugenol acetate (168) as a brown semisolid product (1.45g, 70.3%), Rf 0.69, (chloroform : methanol:: 9.9 : 0.1).256

Analysis

IR(KBr): 3072.6 (aromatic C-H st), 2937.9 (aliphatic C-H st), 2842.6 (C-H st of aromatic OCH3), 1764.8 (C=O st), 1509.2 (benzene ring C=C st), 1272.6 (asymm C-O-C st), 1150.8 (C-C(=O)-O st), 1033.7 (symm C-O-C st) cm\(^{-1}\).

\(^1\)HNMRC(CDC\(_3\)): \(\delta\) 2.28 (s, 3H, OCOCH\(_3\)), 3.35 (d, 2H, \(J = 6.7\) Hz, CH\(_2\)-CH=CH\(_2\)), 3.79 (s, 3H, OCH\(_3\)), 5.05-5.12 (m, 2H, CH\(_2\)-CH=CH\(_2\)), 5.89-5.99 (m, 1H, CH\(_2\)-CH=CH\(_2\)), 6.73-6.78 (m, 2H, Ar-H), 6.93 (d, 1H, \(J = 8.0\) Hz, Ar-H).

\(^13\)CNMR (CDC\(_3\)): \(\delta\) 20.60 (OCOC\(_3\)), 40.03 (CH\(_2\)-CH=CH\(_2\)), 55.71 (OCH\(_3\)), 112.63(CH=CH\(_2\)), 116.10-150.81 (Ar-carbons), 137.92 (CH=CH\(_2\)), 150.81 (ArC-OCH\(_3\)), 169.16 (OCOCH\(_3\)).

Thymol acetate; 2-Isopropyl-5-methylphenyl ethanoate (169)

In a 250ml two neck flask fitted with a dropping funnel and guard tube, thymol (131) (1.24g, 0.01mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01mol) was added slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8 h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The semisolid product formed was extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give thymol acetate (169) as a brown semisolid product (1.49g, 77.6%), R, 0.80 (chloroform: methanol:: 9.9 : 0.1).257
Analysis

IR(KBr): 3027.5 (aromatic C-H st), 2964.6 (aliphatic C-H st), 1762.7 (C=O st), 1505.9 (benzene ring C=C st), 1208.1 (asymm C-O-C st), 1150.1 (C-C(=O)-O st), 1088.1 (symm C-O-C st) cm⁻¹.

¹H NMR (CDCl₃): δ 1.18 (d, 6H, J = 6.9 Hz, 2 × CH₃), 2.29 (s, 3H, OCOCH₃), 2.30 (s, 3H, Ar-CH₃), 2.96 (sept, 1H, J = 6.9 Hz, CH), 6.79 (s, 1H, Ar-H), 6.99-7.02 (m, 1Hz, Ar-H), 7.17-7.20 (m, 1Hz, Ar-H).

¹³C NMR (CDCl₃): δ 20.80 (OCOCH₃), 20.91 (Ar-CH₃), 23.03 (CH(CH₃)₂), 27.14 (CH(CH₃)₂), 122.74-147.88 (Ar-carbons), 169.75 (OCOCH₃).

Vanillin acetate, 4-Formyl-2-methoxyphenyl ethanoate (170)

In a 250ml two neck flask fitted with a dropping funnel and guard tube, vanillin (132) (1.52g, 0.01 mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01 mol) was added slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8 h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The semisolid product formed was extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give vanillin acetate (170) as white solid product which was recrystallized from chloroform and methanol (1.41g, 78.3%), mp. 74°C, Rᵣ 0.42 (chloroform : methanol:: 9.9 : 0.1).

Analysis

IR(KBr): 3073.6 (aromatic C-H st), 2941.6 (aliphatic C-H st), 2847.4 (C-H st of aromatic OCH₃), 1767.1 (C=O st), 1697.0 (C=O st aldehyde), 1503.9 (benzene ring C=C st), 1275.4 (asymm C-O-C st), 1151.0 (C-C(=O)-O st), 1026.0 (symm C-O-C st) cm⁻¹.
\[1^1\text{HNMR} (\text{CDCl}_3)\]: \(\delta\) 2.33 (s, 3H, OCOCH\(_3\)), 3.89 (s, 3H, OCH\(_3\)), 7.20 (d, 1H, \(J = 7.9\) Hz, Ar-H), 7.45-7.49 (m, 2H, Ar-H), 9.92 (s, 1H, CHO).

\[1^3\text{CNMR} (\text{CDCl}_3)\]: \(\delta\) 20.55 (OCOCH\(_3\)), 56.00 (OCH\(_3\)), 110.80-151.89 (Ar-carbons), 151.89 (ArC-OCH\(_3\)), 168.29 (OCOCH\(_3\)), 191.01 (CHO).

**Sesamol acetate; 3,4-(Methylenedioxy)phenyl ethanoate (171)**

In a 250ml two neck flask fitted with a dropping funnel and guard tube, sesamol (133) (1.38g, 0.01 mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01mol) was added slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8 h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The semisolid product formed was extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5\%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain **sesamol acetate (171)** as a brown semisolid product (1.31 g, 72.8\%), \(R_f\) 0.71 (chloroform : methanol:: 9.9 : 0.1).\(^{259}\)

**Analysis**

IR(KBr): 3081.7 (aromatic C-H st), 2987.4 (aliphatic C-H st), 1760.8 (C=O st), 1486.7 (benzene ring C=C st), 1211.7 (asymm C-O-C st), 1121.4 (C-C(=O)-O st), 1035.2 (symm C-O-C st) cm\(^{-1}\).

\[1^1\text{HNMR} (\text{CDCl}_3)\]: \(\delta\) 2.24 (s, 3H, OCOCH\(_3\)), 5.93 (s, 2H, OCH\(_2\)O), 6.50 (dd, 1H, \(J = 2.4\) and 8.4 Hz, Ar-H), 6.58 (d, 1H, J = 2.3 Hz, Ar-H), 6.74 (d, 1H, J = 8.4 Hz, Ar-H).

\[1^3\text{CNMR} (\text{CDCl}_3)\]: \(\delta\) 20.84 (OCOCH\(_3\)), 101.62 (OCH\(_2\)O), 103.62-147.89 (Ar-carbons), 169.73 (OCOCH\(_3\)).
Umbelliferone acetate; 2-Oxo-2H-chromen-7-yl ethanoate (172)
In a 250ml two neck flask fitted with a dropping funnel and guard tube, umbelliferone (134) (1.62g, 0.01 mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01mol) was added slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8 h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The product obtained was extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give a white solid product as umbelliferone acetate (172) which was recrystallized from chloroform and methanol (1.68g, 79.4%), mp. 142-144°C, Rf 0.29 (chloroform: methanol:: 9.9 : 0.1).

Analysis
IR(KBr): 3079.3 (aromatic C-H st), 2943.7 (aliphatic C-H st), 1745.1 (C=O st), 1505.7 (benzene ring C=C st), 1268.4 (asymm C-O-C st), 1120.9 (C-C(=0)-0 st), 1010.2 (symm C-O-C st) cm\(^{-1}\).

\(^1\)HNMR(CDC\(_3\)): \(\delta\) 2.34 (s, 3H, OCOCH\(_3\)), 6.39 (d, 1H, \(J = 9.5\), Ar-H ), 7.05 (dd, 1H, \(J = 8.4\) and 2.2 Hz, Ar-H ), 7.11 (d, 1H, \(J = 2.2\), Ar-H), 7.48 (d, 1H, \(J = 8.4\), Ar-H) 7.69 (d, 1H, \(J = 9.5\), Ar-H).

\(^1\)3CNMR (CDCl\(_3\)): \(\delta\) 21.14 (OCOCH\(_3\)), 110.48 (Ar-CH=CH-), 116.48-160.35 (Ar-carbons), 142.87 (Ar-CH=CH-), 160.35 (C=O, umbelliferone) 168.73 (OCOCH\(_3\)).

Menthol acetate; 2-Isopropyl-5-methylcyclohexyl ethanoate (173)
In a 250ml two neck flask fitted with a dropping funnel and guard tube, menthol (135) (1.56g, 0.01mol), pyridine (2-3 ml) and dried dichloromethane (25 ml) was taken. To this reaction mixture, acetyl chloride (166) (0.79g, 0.01mol) was added

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slowly over a period of 10 min with stirring using magnetic stirrer. The reaction mixture was further stirred for 8 h at room temperature, poured into ice cold water (100 ml) and allowed to stand for 1 h. The semisolid product formed was extracted with dichloromethane (100 ml). The organic layer was washed with water (2 x 50 ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine (2 x 10 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain **menthol acetate (173)**, a brown semisolid product (1.50g, 75.8%), Rf 0.81 (chloroform : methanol:: 9.9 : 0.1).

### Analysis

**IR(KBr):** 2952.7 (aliphatic C-H st), 1735.6 (C=0 st), 1244.4 (asymm C-O-C st), 1026.1 (symm C-O-C st) cm⁻¹.

**¹HNMR(CDCI₃):** δ 0.76 (d, 3H, J = 7.0 Hz, CH₃), 0.85-1.08 (m, 9H, 2CH₃, 3CH), 1.33-1.39 (m, 1H, CH), 1.47-1.49 (m, 1H, CH), 1.64-1.70 (m, 2H, 2CH), 1.85-1.90 (m, 1H, CH), 1.97-2.03 (m, 4H, 3H, OCOCH₃, 1CH), 4.64-4.71 (m, 1H, CH).

**¹³CNMR (CDCI₃):** δ 16.29 (CH₃), 20.66 (OCOCH₃), 21.18 (CH(CH₃)₂), 21.94 (CH(CH₃)₂), 23.42 (CH₂), 26.23 (CH), 31.30 (CH), 34.21 (CH₂), 40.87 (CH₂), 46.94 (CH), 170.46 (OCOCH₃).

### Attempts to prepare diclofenac-antioxidant prodrugs without spacer

In a 100ml round bottom flask, diclofenac (33) (2.96g, 0.01 mol) was dissolved in dried chloroform. To this solution distilled thionyl chloride (3g, 2ml, 0.025mol) was added drop wise and the reaction mixture was stirred at room temperature for 24h. The excess of thionyl chloride was removed by distillation under reduced pressure and the sticky residue obtained was suspended in dichloromethane. The solvent was removed under reduced pressure. The procedure was repeated several times to remove unreacted thionyl chloride to obtain expected diclofenac acid chloride (2.48g, 89.0%), Rf 0.34 (CHCl₃ : methanol:: 9.8 : 0.2). The product was used for further reactions without purification.
In a 250 ml two neck flask, a mixture of guaiacol (129) (1.24g, 0.01mol), TEA (1.01g, 1.4ml, 0.01mol) and CH₂Cl₂ (25ml) was cooled in an ice salt mixture to -10°C and to the reaction mixture, a solution of expected diclofenac acid chloride in CH₂Cl₂ (25ml) was added drop wise with constant stirring over a period of 1h and the temperature was maintained constant during addition. The reaction mixture was stirred overnight at room temperature, washed with HCl (5%, 3 x 50ml), sodium hydroxide (5%, 3 x 50ml) and finally with brine solution (2 x 25ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain a solid product, which was recrystallized from methanol (2.04g, 73.4%), mp. 122-124 °C (124-125 °C)\textsuperscript{35}, R\textsubscript{f} 0.34 (CHCl\textsubscript{3} : methanol :: 9.8 : 0.2). The product so obtained was characterized on the basis of spectral data and was found to be 1-(2,6-dichlorophenyloxindole) (174). The above route was tried with all other phytophenols/alcohol. The product so obtained was found to be oxindole in all the cases and attempts to obtain the expected compound were without success.

**Analysis**

IR(KBr): 3056.3 (aromatic C-H st), 2914.4 (aliphatic C-H st), 1731.9 (C=O st), 1489.1 (benzene ring C=C st), 1458.0 (3° nitrogen), 749.0 (C-Cl bend) cm\textsuperscript{-1}.

\textsuperscript{1}HNMR(CDC\textsubscript{3}): \(\delta\) 3.78 (s, 2H, Ar-CH\textsubscript{2}), 6.40 (d, 1H, \(J=7.7\) Hz, Ar-H), 7.09 (t, 1H, \(J=7.3\) Hz Ar-H), 7.20 (t, 1H, \(J=7.3\), Ar-H), 7.33-7.40 (m, 2H, Ar-H), 7.51 (d, 2H, \(J=8.0\) Hz, Ar-H).

\textsuperscript{13}CNMR (CDCl\textsubscript{3}): \(\delta\) 35.72 (Ar-CH\textsubscript{2}), 109.12-143.26 (Ar-carbons), 173.64 (Ar-CH\textsubscript{2}CON).
Pharmacological activity evaluation

Animals: Wistar rats (150-200g) of both sexes and laca mice (male, 25-35g) procured from Central Animal House, Panjab University, Chandigarh, India were used. Animals were housed under standard laboratory conditions, allowed free access to food and water until used and fasted 24 h prior to studies.

Experimental conditions: Unless otherwise stated, the following conditions were employed in all experiments. The test compounds were suspended in 0.5% carboxymethylcellulose (CMC) and administered per orally (p.o). Control animals were given the corresponding amount of vehicle (0.5%, CMC). The test drugs were administered on molar equivalent basis of diclofenac.

Antiinflammatory activity: Antiinflammatory activity was determined by using carrageenan induced rat paw edema model. Rats were divided into different groups and the drugs were administered to each group. Acute edema was induced in left hind paw of rats by injecting freshly prepared solution of carrageenan (Type IV, 0.1ml, 1%) under plantar region of left hind paw. In the right paw, saline (1ml, 0.9%) was injected, which served as control for comparison. The increase in paw volume was measured by using plethysmometer (water displacement, UGO BASILE, Italy) at 2 and 4h after carrageenan challenge. Percentage change in paw volume was calculated and expressed as the amount of inflammation.244

Analgesic activity: Analgesic was determined by using abdominal writhing assay. Mice were divided into different groups containing 6 animals in each group. Writhing response was elicited by intraperitoneal (i.p) injection of freshly prepared acetic acid solution (1%, 10ml/kg, i.p.). The number of writhes due to acetic acid was expressed as antinociceptive response. The number of writhes per animal was counted during a 20 min period. Writhings were counted 3 min after the injection of acetic acid solution.245

\[
\% \text{ Inhibition} = \left\{1 - \frac{N_t}{N_c}\right\} \times 100
\]

where, \(N_c\) – number of writhes in control group and
\(N_t\) – number of writhes in drug treated group
Antiulcer activity: The fasted animals (rats) were divided into different groups containing 6 animals in each group. Animals were treated with diclofenac (75mg/kg, p.o.), equimolar doses of diclofenac antioxidant mutual prodrugs and their physical mixture. Animals were sacrificed 12h after the treatment. The stomach was removed, opened along greater curvature, washed with saline and observed for the ulcers.\(^{246}\) The ulcers were scored as

0  - Normal colored stomach  
0.5 - Red coloration  
1.0 - Spot ulcers  
1.5 - Hemorrhagic streaks  
2.0 - Ulcers > 3 but < 5  
3.0 - Ulcers > 5  

Statistical Analysis: Results were expressed as mean±SEM. Significance of the difference of the responses to treatment group in comparison to control group was determined by one-way analysis of variance (ANOVA) followed by Dunnet's t-test. \(p<0.05\) was considered significant.

Physicochemical properties evaluation
The synthesized derivatives were studied for their physicochemical properties including solubility, partition coefficient, chemical stability, and enzymatic hydrolysis, to assess their prodrug potential.

Preparation of standard plots of diclofenac antioxidant mutual prodrugs
A standard stock solution of diclofenac antioxidant mutual prodrugs was prepared by dissolving appropriate amount of compound in 50 ml methanol. Standard plot for HPLC analysis was prepared by injecting in triplicate a constant volume of 10 \(\mu\)l of serially diluted concentrations and AUC was measured.
Aqueous solubility

Solubility of diclofenac-OCH$_2$COO-phytophenols/alcohol mutual prodrugs (146-152), and diclofenac-OCH$_2$CH$_2$CH$_2$O-phytophenols mutual prodrugs (160-165) was determined by HPLC in 0.05 M phosphate buffer of pH 7.4 at 25 °C using water bath shaker. Excess amount of each compound was added to 2.0 mL of buffer in screw capped test tubes and suspension vortexed for 10 min and shaken for 24 h at 25°C in water bath shaker. Solutions were filtered through 0.45μ membrane filter in a warm test tube and after appropriate dilution in same buffer, 10 μL was injected in triplicate and AUC was measured. The concentration of each compound was calculated from the standard plot obtained on same day under similar conditions.

Partition coefficient (P)

The apparent partition coefficients (P) of diclofenac antioxidant mutual prodrugs were determined in octanol buffer system at 25 °C using 0.05 M phosphate buffer of pH 7.4 as aqueous phase. Concentration was determined by HPLC to afford rapid evaluation and better reliability. Partition coefficients for diclofenac antioxidant mutual prodrugs were determined in octanol / phosphate buffer (pH 7.4) system, using shake-flask method.

Octanol and phosphate buffers were mutually saturated by shaking overnight. The system was left undisturbed for half an hour and the layers were separated. Saturated solutions of the compounds were prepared in octanol (2 ml). Phosphate buffer (5 ml) was added to the solutions in conical flasks. The sealed flasks were kept for shaking in a water bath shaker maintained at 25 ± 2 °C for 8h. Octanol layer was removed and appropriately diluted. The amount of drug partitioned into buffer layer and octanol layer was analyzed through HPLC by injecting 10 μL from each layer. Partition coefficient was calculated by following formula and values were reported as log $P$:

\[
\text{Partition coefficient (P)} = \frac{\text{AUC octanol}}{\text{AUC buffer}} \times \text{dilution factor}
\]
Chemical stability

The chemical stability of diclofenac antioxidant mutual prodrugs in isotonic phosphate buffer (pH 7.4) and in HCl buffer (pH 2.0) was studied at 37 °C. At appropriate intervals, samples were withdrawn and analysed by HPLC for appearance of diclofenac. Pseudo-first order rate constants (k) and half-lives (t₁/₂) were determined.

\[ k_{\text{obs}} = \text{slope} \times 2.303 \]
\[ t_{1/2} = \frac{0.693}{k_{\text{obs}}} \]

Enzymatic hydrolysis

The hydrolysis of diclofenac antioxidant mutual prodrugs was studied in 80 % human plasma at pH 7.4. The reaction was initiated by adding 20-50 μl of the stock solution of the derivative in acetonitrile in to 2-5 ml of preheated plasma solution. The solution was kept in water bath at 37 °C and samples of 100-250 μl were withdrawn at appropriate time intervals and added to 1000-5000 μl of cold acetonitrile or methanol in order to deproteinise the plasma. After immediate mixing and centrifugation for 5 min at 7000 rpm, 20 μl of the clear supernatant was analyzed by HPLC for appearance of diclofenac. The values of rate constant (k) and half-live (t₁/₂) were determined.