EQUIPMENT AND MATERIALS

Equipment

Infrared spectra were recorded on a Perkin-Elmer 882 infrared spectrophotometer using potassium bromide discs. Mass spectra were obtained on a VG Micromass 7070F mass spectrometer and for ultraviolet spectra, Perkin-Elmer Lambda 15 UV/VIS spectrophotometer was used. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Varian EM 390 NMR (90 MHz) spectrometer and Bruker AC 300F (300 MHz) equipment using tetramethylsilane as internal standard and CDCl$_3$ and DMSO-d$_6$ as solvents.

Melting points reported are uncorrected. Microanalysis was performed on Perkin-Elmer 2400 CHN elemental analyser. High performance liquid chromatography was performed with a Waters equipment consisting of two M501 pumps controlled by automated gradient controller 680, a Waters 484 tunable detector, Waters 746 data module and a 20 μl Rheodyne loop injection valve.

Readings of pH were carried out on a Control Dynamics pH meter. High precision thermostatic water baths fitted with contact thermometers supplied by Jumo (West Germany) and shaking water bath Haake SWB 20 were used for kinetic studies. Block thermostat BT 3 Grant, 20-140 °C was used.
Thin layer chromatography was performed on glass plates coated with silica gel G, preactivated at 110 °C for 50 min. Components were detected by iodine vapours. The solvents used for crystallisation were distilled. Removal of the solvents was carried out with an Eyela Rotary Vacuum Evaporator NE-1.

Materials

Reagents used for the preparation of buffer solutions were of analytical reagent grade. Various amines required for the synthesis of substituted 2-chloroacetamides, chloroacetyl chloride, 2-chloroacetamide and methyl chloroacetate were purchased from Fluka AG and used as received. Fresh triple distilled water from all glass apparatus was employed in the preparation of all the solutions.

Human plasma was procured from the blood bank of Post Graduate Institute of Medical Education and Research, Chandigarh. Sections of liver, required for the preparation of liver homogenate, were obtained from Albino rats (porton strain) kept in Central Animal House, Panjab University, Chandigarh.
2-Methoxynaphthalene (98)

Dimethyl sulphate (31.5 g, 0.25 mol) was added dropwise to an ice-cooled solution of 2-naphthol (36.0 g, 0.25 mol) and sodium hydroxide (10.5 g, 0.26 mol) in water (150 ml) with stirring. After complete addition, the mixture was warmed for 1 h at 75 °C and then kept for cooling. The residue thus separated was filtered, washed with sodium hydroxide solution (10% , 100 ml) and then with water till free from alkali. Recrystallisation of this product from methanol yielded 2-methoxynaphthalene (30.4 g, 76.9%) as white crystals, mp 72 °C (lit 72 °C)\(^9\).\(^9\)

\[\text{IR (KBr)} : 3055, 3006, 2963, 2937, 2838, 1621, 1595, 1258 (C-O-C), 1216, 1169, 1028 (C-O-C), 837, 814, 742 \text{ cm}^{-1}.\]

\[\text{\(^1\)H-NMR (CDCl}_3\) : \delta 3.9 (3H, s, OCH}_3\), 7.1-8.0 (7H, m, ArH).\]

\[\text{MASS (m/z)} : 158 (M^+), 143 (M^+ - CH}_3\), 128 (M^+ - CH}_2\text{O), 127, 115.\]

2-Acetyl-6-methoxynaphthalene (99)

Anhydrous aluminium chloride (43 g, 0.32 mol) was dissolved in dry nitrobenzene (200 ml) with stirring in a three-necked flask. Finely powdered 2-methoxynaphthalene (98) (39.5 g, 0.25 mol) was added to this solution and the mixture was kept in an ice-water slush. Redistilled acetyl chloride (25 g, 0.32 mol) was added dropwise, while...
maintaining the temperature between 10.5 and 13.0 °C by adjusting the stirring and addition rates. After complete addition, the mixture was further stirred for 2 h in an ice bath, kept at room temperature for 24 h, cooled in an ice bath and poured with stirring into a beaker containing crushed ice (200 g). Hydrochloric acid (100 ml) was added with stirring and to the resulting two phase mixture, chloroform (50 ml) was added. Organic layer was separated, washed with water (3 X 100 ml) and steam distilled to remove nitrobenzene. The residue was cooled and after decanting water, the solid organic matter was dissolved in chloroform (50 ml). The chloroform layer was dried over anhydrous magnesium sulphate and solvent was removed on a rotary evaporator. The solid residue thus obtained was distilled under vacuum and fraction boiling at about 185-200 °C (10 mm) was collected. This yellow solid distillate (38 g) was recrystallised from methanol (75 ml) to obtain white crystalline 2-acetyl-6-methoxynaphthalene (20.3 g, 40.6%), mp 106-108 °C (lit 106.5-108 °C101, 104-105 °C149)

IR (KBr) : 3067, 2971, 2936. 2849, 1674 (C=O), 1621, 1599, 1479, 1277 (C-O-C), 1202, 1019 (C-O-C), 861, 819 cm⁻¹.  

$^1$H-NMR (CDCl₃) : $\delta$ 2.7 (3H, s, COCH₃), 4.0 (3H, s, OCH₃), 7.2- 7.4 (2H, m, ArH), 7.7-8.2 (3H, m, ArH), 8.5 (1H, m, ArH).

$^{13}$C-NMR (CDCl₃) : $\delta$ 26.28 (COCH₃), 55.16 (OCH₃), 105.59
4-(6-Methoxy-2-naphthylthioacetyl)-morpholine (100)

A mixture of 2-acetyl-6-methoxynaphthalene (30 g, 0.15 mol), morpholine (30 g) and sulphur (13.5 g) was refluxed at 140 °C for 18 h. The hot mixture was poured into ethanol (60 ml) and left overnight. Solid residue thus obtained was filtered, washed with cold ethanol (2 x 25 ml) to afford crude product (33 g, 73%), which was utilised as such for the next step. A small amount of this product was chromatographed on silica gel using chloroform-petroleum ether as eluant. The product obtained was crystallised from ethanol to get 4-(6-methoxy-2-naphthylthioacetyl)-morpholine for analysis. Mp 134 °C (lit 134-135 °C).107

IR (KBr) : 3058, 2985, 2930, 2848, 1496, 1265 (C-O-C), 1106, 1030 (C-O-C), 854, 815 cm⁻¹.

¹H-NMR (CDCl₃): δ 3.3-3.9 (6H, m, ArCH₂C(S)N(CH₂CH₂)₂O), 3.9 (3H, s, OCH₃), 4.3-4.6 (4H, m, N(CH₂CH₂)₂O), 7.2-7.8 (6H, m, ArH).

MASS (m/z) : 301 (M⁺), 214, 185, 171, 157, 149, 83 (100%).

6-Methoxy-2-naphthylacetic acid, 6-MNA (48)

A mixture of 4-(6-methoxy-2-naphthylthioacetyl)-morpholine (30.1 g, 0.1 mol), aqueous sodium hydroxide
solution (50%, 110 ml) and ethyl alcohol (70% v/v, 560 ml) was refluxed for 8 h. The alcohol was evaporated, water (500 ml) was added and the resulting solution was filtered. The filtrate was cooled, acidified with hydrochloric acid, the precipitate formed was filtered, washed thoroughly with water and recrystallised from methanol to obtain 6-methoxy-2-naphthylacetic acid (16.5 g, 76.5%), mp 172-173 °C (lit 175 °C105, 170 °C107).

IR (KBr) : 3000 (br, OH), 1698 (C=O) , 1270 (C-O-C) , 1223, 1028 (C-O-C), 848, 814 cm⁻¹.

¹H-NMR (DMSO-d₆) : 6 3.7 (2H, s, ArCH₂) , 3.9 (3H, s, OCH₃) , 7.0-7.8 (6H, m, ArH).

MASS (m/z) : 216 (M⁺), 171 (100%), 156, 140, 128.

Alternatively, 6-MNA was prepared by refluxing a mixture of 4-(6-methoxy-2-naphthylthioacetyl)-morpholine (9.03 g, 0.03 mol), glacial acetic acid (36 ml) and hydrochloric acid (45 ml) for 24 h. The solvent was evaporated, water (30 ml) was added, the dark solid product was separated by filtration and dissolved in aqueous sodium carbonate solution (2 N, 100 ml). The resulting solution was filtered and acidified with hydrochloric acid. The precipitate formed was filtered, washed and recrystallised from ethanol-water mixture to afford 6-hydroxy-2-naphthylacetic acid (4.2 g, 69.3%), mp 210 °C (lit 210 °C)107.
The mixture of 6-hydroxy-2-naphthylacetic acid (3.03 g, 0.015 mol), potassium carbonate (16 g) and dimethyl sulphate (19 g) in acetone (150 ml) was refluxed for 8 h. The solvent was removed under reduced pressure, water (50 ml) was added and the mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with water (3 x 50 ml), dried over anhydrous sodium sulphate and the solvent was evaporated. The residue obtained was recrystallised from methanol to afford methyl 6-methoxy-2-naphthylacetate (102) (2.85 g, 82.6%), mp 75 °C (lit 73-74 °C)\textsuperscript{107}.

The ester 102 (2.30 g, 0.01 mol) was refluxed with ethanolic potassium hydroxide (50 ml) for 2 h. Alcohol was evaporated under reduced pressure, the residue was dissolved into water and filtered. The filtrate was cooled, acidified with hydrochloric acid, the precipitate formed was filtered, washed with water and recrystallised from methanol to yield 6-methoxy-2-naphthylacetic acid (1.90 g, 88.0%), mp 173 °C. The product was identified with the help of mixed melting point and IR spectrum.

**PREPARATION OF GLYCOLAMIDE ESTER PRODRUGS OF 6-METHOXY-2-NAPHTHYLACETIC ACID**

**Synthesis of 2-chloroacetamides**

A number of 2-chloroacetamides, used in the preparation of various glycolamide ester prodrugs of 6-MNA, were synthesised by the following methods.

\textsuperscript{136}
General method 'a',\textsuperscript{110}

To a mixture of the respective amine (0.1 mol), aqueous sodium hydroxide solution (20%, 25 ml) and 1,2-dichloroethane (40 ml), chloroacetyl chloride (13.5 g, 0.12 mol) was added at -10 to -15 °C during 45 min with stirring. The temperature was allowed to rise to 10 °C, aqueous layer was separated and washed with 1,2-dichloroethane (2 X 20 ml). The organic layers were combined, washed successively with hydrochloric acid (5%, 50 ml), aqueous sodium bicarbonate (5%, 50 ml) and water (3 X 25 ml) and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure. The solid compounds were recrystallised from petroleum ether (60-80 °C), whereas liquid chloroacetamides were used for the next step as such. Various chloroacetamides prepared are given in Table 25.

General method 'b',\textsuperscript{111}

To a solution of methyl chloroacetate (23.8 g, 0.22 mol) in methanol (25 ml) cooled to -2 °C was added with stirring, the respective amine (0.2 mol) in methanol (35 ml) over a long period during which the temperature was maintained at -2 to 2 °C. The reaction mixture was stored overnight in the refrigerator and the resulting colourless solution was evaporated to a constant weight, first at water pump pressure and then at 0.5 mm to obtain colourless viscous 2-chloroacetamides (Table 25). The structures of various 2-chloroacetamides synthesised were confirmed using $^1$H-NMR and IR Spectra.
Table 25: List of 2-chloroacetamides prepared for the synthesis of glycolamide ester prodrugs of 6-MNA

\[
\text{Cl-CH}_2\text{CON}_2\text{H}_2
\]

(113)

<table>
<thead>
<tr>
<th>Compound</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Method of preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>114</td>
<td>H</td>
<td>CH(_3)</td>
<td>70.2</td>
<td>39</td>
<td>a</td>
</tr>
<tr>
<td>115</td>
<td>H</td>
<td>CH(_2)CH(_3)</td>
<td>65.8</td>
<td>Liquid</td>
<td>a</td>
</tr>
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<td>116</td>
<td>H</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>77.5</td>
<td>Liquid</td>
<td>a</td>
</tr>
<tr>
<td>117</td>
<td>H</td>
<td>CH(CH(_3))(_2)</td>
<td>73.8</td>
<td>62</td>
<td>a</td>
</tr>
<tr>
<td>118</td>
<td>H</td>
<td>CH(_2)CH(_2)CH(_2)CH(_3)</td>
<td>80.8</td>
<td>Liquid</td>
<td>a</td>
</tr>
<tr>
<td>119</td>
<td>H</td>
<td>CH(CH(_3))(_2)CH(_2)CH(_3)</td>
<td>78.6</td>
<td>45</td>
<td>a</td>
</tr>
<tr>
<td>120</td>
<td>H</td>
<td>C(CH(_3))(_3)</td>
<td>60.6</td>
<td>84-85</td>
<td>a</td>
</tr>
<tr>
<td>121</td>
<td>H</td>
<td></td>
<td>87.7</td>
<td>109-110</td>
<td>a</td>
</tr>
<tr>
<td>122</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>51.9</td>
<td></td>
<td>a</td>
</tr>
<tr>
<td>123</td>
<td>CH(_2)CH(_3)</td>
<td>CH(_2)CH(_3)</td>
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<td>Liquid</td>
<td>a</td>
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<td>CH(_2)CH(_2)CH(_3)</td>
<td>CH(_2)CH(_2)CH(_3)</td>
<td>70.1</td>
<td>Liquid</td>
<td>a</td>
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<tr>
<td>125</td>
<td>CH(CH(_3))(_2)</td>
<td>CH(CH(_3))(_2)</td>
<td>66.7</td>
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<td>a</td>
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<tr>
<td>126</td>
<td>CH(_2)CH=CH(_2)</td>
<td>CH(_2)CH=CH(_2)</td>
<td>87.6</td>
<td>Liquid</td>
<td>a</td>
</tr>
<tr>
<td>127</td>
<td></td>
<td></td>
<td>50.3</td>
<td>114-115</td>
<td>a</td>
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<td>128</td>
<td>(NR(_1)R(_2))</td>
<td>N</td>
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<td>Liquid</td>
<td>a</td>
</tr>
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<td>129</td>
<td>(NR(_1)R(_2))</td>
<td>O</td>
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<td>Liquid</td>
<td>a</td>
</tr>
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<td>CH(_3)</td>
<td>CH(_2)CH(_2)OH</td>
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<td>Liquid</td>
<td>b</td>
</tr>
<tr>
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<td>CH(_2)CH(_3)</td>
<td>CH(_2)CH(_2)OH</td>
<td>90.6</td>
<td>Liquid</td>
<td>b</td>
</tr>
<tr>
<td>132</td>
<td>CH(_2)CH(_2)OH</td>
<td>CH(_2)CH(_2)OH</td>
<td>96.4</td>
<td>Liquid</td>
<td>b</td>
</tr>
</tbody>
</table>
Carbamoylmethyl 6-methoxy-2-naphthylacetate (133)

A mixture of 6-methoxy-2-naphthylacetic acid (2.16 g, 0.01 mol), N,N-dimethylformamide (DMF) (10 ml), triethylamine (1.12 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and 2-chloroacetamide (1.02 g, 0.011 mol) was stirred at 80-90 °C for 3 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate layer was washed successively with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The organic layer was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure. The solid residue obtained was recrystallised from ethyl acetate-hexane to afford white crystals of carbamoylmethyl 6-methoxy-2-naphthylacetate (1.9 g, 69.6%), mp 157-159 °C.


UV (CH₃CN) : Amax 230.2 nm log ε 4.89

IR (KBr) : 3383 (NH), 3185 (NH), 1730 (C=O), 1664 (C=O), 1630, 1271 (C-O-C), 1215, 1140, 1028 (C-O-C), 850, 817 cm⁻¹.

¹H-NMR (CDCl₃) : δ 3.87 (3H, s, OCH₃) 3.88 (2H, s, ArCH₂), 4.49 (2H, s, COOCH₂CO), 7.09-7.18 (2H, m, ArH), 7.21 (1H, br, C=N⁻H), 7.36-7.40 (1H, m, ArH), 7.44 (1H, br, C=N⁻H), 7.68-7.73 (3H, m, ArH).
$^{13}$C-NMR (CDCl$_3$) : δ 40.14 (ArCH$_2$), 55.05 (OCH$_3$), 62.33 (COOCH$_2$CO), 105.53 (C-5), 118.72 (C-7), 126.72, 127.70, 128.04 and 128.88 (C-1, C-3, C-4 and C-8), 128.45, 129.01 and 133.26 (C-2, C-9 and C-10), 157.28 (C-6), 169.17 (CON), 170.75 (COO).

**MASS** (m/z) : 273 (M$^+$), 255, 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

**N-Methylcarbamoylmethyl 6-methoxy-2-naphthylacetate (134)**

A mixture of 6-MNA (2.16 g, 0.01 mol) in DMF (10 ml), triethylamine (1.12 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and 2-chloro-N-methylacetamide (1.18 g, 0.011 mol) was stirred at 90 °C for 3 h, poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined extracts were washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). After drying over anhydrous sodium sulphate, the ethyl acetate was removed under reduced pressure and the residue obtained was recrystallised from ethyl acetate-hexane mixture to yield white crystalline **N-methylcarbamoylmethyl 6-methoxy-2-naphthylacetate** (1.8 g, 62.7%), mp 120-121 °C.

**Anal** : Found C, 66.39; H, 5.96; N, 4.92. C$_{16}$H$_{17}$NO$_4$ requires C, 66.88; H, 5.97; N, 4.88.

**UV** (CH$_3$CN) : λ$_{max}$ 230.7 nm log ε 4.92
IR (KBr) : 3270 (NH), 3093, 2841, 1730 (C=O), 1660 (C=O),
1562 (amide-II band), 1264 (C-O-C), 1215, 1141, 1030 (C-O-C), 849, 817 cm⁻¹.

¹H-NMR (CDCl₃) : δ 2.59-2.61 (3H, d, J = 4.9 Hz, NHCH₃), 3.83
(2H, s, ArCH₂), 3.91 (3H, s, OCH₃), 4.57 (2H, s, COOCH₂CO),
5.82 (1H, br, CONH, exchanged with D₂O), 7.11-7.18 (2H, m,
ArH), 7.34-7.39 (1H, m, ArH), 7.66-7.75 (3H, m, ArH).

¹³C-NMR (CDCl₃) : δ 25.68 (NHCH₃), 41.18 (ArCH₂), 55.32
(OCH₃), 62.99 (COOCH₂CO), 105.67 (C-5), 119.40 (C-7),
127.43, 127.50, 127.82 and 129.10 (C-1, C-3, C-4 and C-8),
128.39, 128.90 and 133.77 (C-2, C-9 and C-10), 157.93 (C-6),
167.55 (CON), 170.00 (COO).

MASS (m/z) : 287 (M⁺), 199, 198 (100%), 183, 171, 170, 156,
155, 141, 140, 139, 128.

**N-Ethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (135)**

A mixture of 6-MNA (2.16 g, 0.01 mol), DMF (10 ml),
triethylamine (1.12 g, 0.011 mol), sodium iodide (0.15 g,
0.001 mol) and 2-chloro-N-ethylacetamide (1.34 g, 0.11 mol)
was stirred at 80-90 °C for 3 h. The reaction mixture was
poured in water (50 ml) and extracted with ethyl acetate
(3 X 50 ml). The combined ethyl acetate layer was washed
successively with aqueous sodium thiosulphate (2%, 50 ml),
aqueous sodium bicarbonate (2%, 50 ml) and water
(3 X 50 ml), dried over anhydrous sodium sulphate and the
solvent was removed under reduced pressure. The solid
residue obtained was recrystallised from ethyl acetate-hexane mixture to afford white crystals of \textit{N-ethylcarbamoylmethyl 6-methoxy-2-naphthylacetate} (2.1 g, 69.8\%), mp 110-111 °C.

\textbf{Anal}: Found C, 67.54; H, 6.33; N, 4.59. C\textsubscript{17}H\textsubscript{19}NO\textsubscript{4} requires C, 67.76; H, 6.36; N, 4.65.

\textbf{UV} (CH\textsubscript{3}CN): \(\lambda\) max 230.2 nm \(\log \epsilon\) 4.92

\textbf{IR} (KBr): 3250 (NH), 3073, 1731 (C=O), 1650 (C=O), 1569 (amide-II band), 1265 (C-O-C), 1214, 1143, 1029 (C-O-C), 850, 816 cm\textsuperscript{-1}.

\textbf{\textsuperscript{1}H-NMR} (CDCl\textsubscript{3}): \(\delta\) 0.78-0.83 (3H, t, \(J = 7.3\) Hz, NHCH\textsubscript{2}CH\textsubscript{3}), 3.01-3.11 (2H, m, NHCH\textsubscript{2}), 3.83 (2H, s, ArCH\textsubscript{2}), 3.91 (3H, s, OCH\textsubscript{3}), 4.57 (2H, s, COOCH\textsubscript{2}CO), 5.66 (1H, br, CONH, exchanged with D\textsubscript{2}O), 7.11-7.18 (2H, m, ArH), 7.35-7.39 (1H, m, ArH), 7.67-7.75 (3H, m, ArH).

\textbf{\textsuperscript{13}C-NMR} (CDCl\textsubscript{3}): \(\delta\) 14.22 (NHCH\textsubscript{2}CH\textsubscript{3}), 33.84 (NHCH\textsubscript{2}), 41.27 (ArCH\textsubscript{2}), 55.32 (OCH\textsubscript{3}), 62.86 (COOCH\textsubscript{2}CO), 105.62 (C-5), 119.42 (C-7), 127.50, 127.50, 127.83 and 129.08 (C-1, C-3, C-4 and C-8), 128.47, 128.89 and 133.77 (C-2, C-9 and C-10), 157.93 (C-6), 166.72 (CON), 169.88 (COO).

\textbf{MASS} (m/z): 301 (M\textsuperscript{+}), 199, 198 (100\%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

\textit{N-Propylcarbamoylmethyl 6-methoxy-2-naphthylacetate} (136)

6-methoxy-2-naphthylacetic acid (2.16 g, 0.01 mol) and 2-chloro-\textit{N}-propylacetamide (1.49 g, 0.011 mol) were
dissolved in DMF (10 ml). Sodium iodide (0.15 g, 0.001 mol) and triethylamine (1.12 g, 0.011 mol) were added and the mixture was stirred at 80-90 °C for 3 h. After addition of water (50 ml), the reaction mixture was extracted with ethyl acetate (3 X 50 ml). The combined extracts were washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue obtained was recrystallised from ethyl acetate to give white crystalline \(N\)-\textit{propylcarbamoylmethyl} 6-methoxy-2-naphthylacetate (1.78 g, 56.5%), mp 119-121 °C.

\textbf{Anal}: Found C, 68.24; H, 6.79; N, 4.41. \(\text{C}_{18}\text{H}_{21}\text{N}_{04}\) requires C, 68.54; H, 6.71; N, 4.44.

\textbf{UV} (CH\(_3\)CN) : \(\lambda_{\text{max}}\) 230.1 nm \(\log\epsilon\) 4.94

\textbf{IR} (KBr) : 3254 (NH), 3086, 1730 (C=O), 1651 (C=O), 1562 (amide-II band), 1265 (C-O-C), 1215, 1143, 1031 (C-O-C), 850, 816 cm\(^{-1}\).

\textbf{\(^{1}\text{H-NMR}\)} (CDCl\(_3\)) : \(\delta\) 0.62-0.68 (3H, t, \(J = 7.3\) Hz, NHCH\(_2\)CH\(_2\)CH\(_3\)), 1.07-1.20 (2H, sex, \(J = 7.3\) Hz, NHCH\(_2\)CH\(_2\)CH\(_3\)), 2.92-3.00 (2H, m, NHCH\(_2\)), 3.84 (2H, s, ArCH\(_2\)), 3.92 (3H, s, OCH\(_3\)), 4.57 (2H, s, COOCH\(_2\)CO), 5.61 (1H, br, CONH, exchanged with D\(_2\)O), 7.12-7.19 (2H, m, ArH), 7.36-7.40 (1H, m, ArH), 7.68-7.75 (3H, m, ArH).

\textbf{\(^{13}\text{C-NMR}\)} (CDCl\(_3\)) : \(\delta\) 11.02 (NHCH\(_2\)CH\(_2\)CH\(_3\)), 22.30 (NHCH\(_2\)CH\(_2\)), 40.62 (NHCH\(_2\)), 41.34 (ArCH\(_2\)), 55.34 (OCH\(_3\)), 62.88 (COOCH\(_2\)CO), 105.61 (C-5), 119.44 (C-7), 127.51, 127.51,
127.81 and 129.10 (C-1, C-3, C-4 and C-8), 128.48, 128.92 and 133.80 (C-2, C-9 and C-10), 157.96 (C-6), 166.82 (CON), 169.83 (COO).

**MASS** (m/z) : 315 (M⁺), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

*N-Isopropylcarbamoylmethyl 6-methoxy-2-naphthylacetate* (137)

To a solution of 6-MNA (2.16 g, 0.01 mol) in DMF (10 ml), triethylamine (1.12 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and 2-chloro-N-isopropylacetamide (1.49 g, 0.011 mol) were added. The mixture was stirred at 85-90 °C for 3 h, poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with aqueous solution of sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 x 50 ml). After drying over anhydrous sodium sulphate, the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate-hexane mixture to yield *N-isopropylcarbamoylmethyl 6-methoxy-2-naphthylacetate* (1.88 g, 59.7%), mp 113-114 °C.

**Anal** : Found C, 68.36; H, 6.76; N, 4.44. C₁₈H₂₁NO₄ requires C, 68.54; H, 6.71; N, 4.44.

**UV** (CH₃CN) : \( \lambda_{\text{max}} 230.3 \) nm \( \log \varepsilon 4.9 \)

**IR** (KBr) : 3239 (NH), 3068, 1733 (C=O), 1651 (C=O), 1561 (amide-II band), 1263 (C-O-C), 1216, 1139, 1029 (C-O-C), 848, 816 cm⁻¹.

144
**$^1$H-NMR** (CDCl$_3$) : $\delta$ 0.77-0.80 (6H, d, $J = 6.6$ Hz, NHCH(CH$_3$)$_2$), 3.83-3.93 (1H, m, NHCH), 3.84 (2H, s, ArCH$_2$), 3.90 (3H, s, OCH$_3$), 4.54 (2H, s, COOCH$_2$CO), 5.45 (1H, br, CONH, exchanged with D$_2$O), 7.12-7.19 (2H, m, ArH), 7.37-7.40 (1H, m, ArH), 7.68-7.75 (3H, m, ArH).

**$^{13}$C-NMR** (CDCl$_3$) : $\delta$ 22.15 (NHCH(CH$_3$)$_2$), 40.78 (NHCH), 41.33 (ArCH$_2$), 55.32 (OCH$_3$), 62.77 (COOCH$_2$CO), 105.61 (C-5), 119.44 (C-7), 127.54, 127.54, 127.83 and 129.10 (C-1, C-3, C-4 and C-8), 128.53, 128.91 and 133.79 (C-2, C-9 and C-10), 157.94 (C-6), 165.90 (CON), 169.76 (COO).

**MASS** (m/z) : 315 (M$^+$), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

*N-Butylcarbamoylmethyl 6-methoxy-2-naphthylacetate (138)*

A mixture of 6-MNA (2.16 g, 0.01 mol), DMF (10 ml), triethylamine (1.12 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and N-butyl-2-chloroacetamide (1.64 g, 0.011 mol) was stirred at 85-90 °C for 3 h. The mixture was poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The ethyl acetate layer was washed successively with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to obtain a solid residue, which was recrystallised from ethyl acetate-hexane mixture to afford *N-butylcarbamoylmethyl 6-methoxy-2-naphthylacetate* (1.98 g, 60.2%), mp 110-111 °C.
Anal : Found C, 69.05; H, 7.13; N, 4.26. C_{19}H_{23}NO_{4} requires C, 69.28; H, 7.04; N, 4.25.

UV (CH$_3$CN) : A$_{\text{max}}$ 230.2 nm log $\varepsilon$ 4.97

IR (KBr) : 3251 (NH), 3087, 1730 (C=O), 1649 (C=O), 1571 (amide-II band), 1267 (C-O-C), 1214, 1144, 1029 (C-O-C), 850, 816 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$) : $\delta$ 0.72-0.75 (3H, t, J = 6.7 Hz, NHCH$_2$CH$_2$CH$_2$CH$_3$), 1.00-1.10 (4H, m, NHCH$_2$CH$_2$CH$_2$CH$_3$), 2.95-3.02 (2H, m, NHCH$_2$), 3.82 (2H, s, ArCH$_2$), 3.89 (3H, s, OCH$_3$), 4.56 (2H, s, COOCH$_2$CO), 5.67 (1H, br, CONH, exchanged with D$_2$O), 7.11-7.17 (2H, m, ArH), 7.35-7.38 (1H, m, ArH), 7.66-7.73 (3H, m, ArH).

$^{13}$C-NMR (CDCl$_3$) : $\delta$ 13.57 (NHCH$_2$CH$_2$CH$_2$CH$_3$), 19.78 (NHCH$_2$CH$_2$CH$_2$), 31.07 (NHCH$_2$CH$_2$), 38.70 (NHCH$_2$), 41.27 (ArCH$_2$), 55.28 (OCH$_3$), 62.82 (COOCH$_2$CO), 105.62 (C-5), 119.41 (C-7), 127.49, 127.49, 127.80 and 129.08 (C-1, C-3, C-4 and C-8), 128.51, 128.90 and 133.76 (C-2, C-9 and C-10), 157.93 (C-6), 166.77 (CON), 169.87 (COO).

MASS (m/z) : 329 (M$^+$), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

$N$-sec-Butylcarbamoylmethyl 6-methoxy-2-naphthylacetate (139)

6-MNA (1.08 g, 0.005 mol) and $N$-sec-butyl-2-chloroacetamide (0.82 g, 0.0055 mol) were dissolved in DMF (10 ml). Sodium iodide (0.075 g, 0.0005 mol) and
triethylamine (0.56 g, 0.0055 mol) were added, and the mixture was stirred at 85-90 °C for 3 h. After addition of water (50 ml), the reaction mixture was extracted with ethyl acetate (3 X 50 ml). The combined extracts were washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue obtained was recrystallised from ethyl acetate-hexane to give white crystals of N-sec-butyl-carbamoylmethyl 6-methoxy-2-naphthylacetate (0.83 g, 50.5%), mp 95-96 °C.

Anal: Found C, 69.01; H, 7.15; N, 4.17. C_{19}H_{23}NO_{4} requires C, 69.28; H, 7.04; N, 4.25.

UV (CH3CN): \( \lambda_{\text{max}} \) 230.3 nm \( \log \epsilon \) 4.91

IR (KBr): 3287 (NH), 3089, 1749 (C=O), 1655 (C=O), 1559 (amide-II band), 1265 (C-O-C), 1231, 1132, 1052, 1027 (C-O-C), 853, 812 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\)): \( \delta \) 0.55-0.65 (3H, t, \( J = 7.2 \) Hz, NHCH\((\text{CH}_3)\text{CH}_2\text{CH}_3\)), 0.74-0.77 (3H, d, \( J = 6.7 \) Hz, NHCH\((\text{CH}_3)\text{CH}_2\text{CH}_3\)), 0.86-1.21 (2H, m, NHCH\((\text{CH}_3)\text{CH}_2\text{CH}_3\)), 3.63-3.83 (1H, m, NHCH), 3.84 (2H, s, ArCH\(_2\)), 3.91 (3H, s, OCH\(_3\)), 4.55 (2H, s, COOCH\(_2\)CO), 5.35 (1H, br, CONH, exchanged with D\(_2\)O), 7.12-7.19 (2H, m, ArH), 7.36-7.40 (1H, m, ArH), 7.67-7.73 (3H, m, ArH).

\(^1\)C-NMR (CDCl\(_3\)): \( \delta \) 9.99 (NHCH\((\text{CH}_3)\text{CH}_2\text{CH}_3\)), 19.90 (NHCH\((\text{CH}_3)\text{CH}_2\text{CH}_3\)), 29.05 (NHCH\((\text{CH}_3)\text{CH}_2\text{CH}_3\)), 41.38 (ArCH\(_2\)),
45.99 (NHCH), 55.33 (OCH₃), 62.78 (COOCH₂CO), 105.60 (C-5), 119.43 (C-7), 127.55, 127.55, 127.81 and 129.09 (C-1, C-3, C-4 and C-8), 128.56, 128.94 and 133.81 (C-2, C-9 and C-10), 157.96 (C-6), 166.13 (CON), 169.74 (COO).

MASS (m/z) : 329 (M⁺), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

N-tert-Butylcarbamoylmethyl 6-methoxy-2-naphthylacetate (140)

To a solution of 6-MNA (2.16 g, 0.01 mol) in DMF (10 ml), triethylamine (1.12 g, 0.011), sodium iodide (0.15 g, 0.001 mol) and N-tert-butyl-2-chloroacetamide (1.64 g, 0.011 mol) were added. The mixture was stirred at 90 °C for 3 h, poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 x 50 ml). The organic layer was dried over anhydrous sodium sulphate, the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate-hexane mixture to get N-tert-butylcarbamoylmethyl 6-methoxy-2-naphthylacetate (1.97 g, 59.9%), mp 91 °C.


UV (CH₃CN) : λ max 230.3 nm. log ε 4.91

IR (KBr) : 3310 (NH), 3086, 2843, 1749 (C=O), 1661 (C=O), 1558 (amide-II band), 1263 (C-O-C), 1228, 1155, 1032 (C-O-C), 846, 821 cm⁻¹.
\(^1\text{H-}{\text{NMR}}\) (CDCl\(_3\)) : \(\delta\) 1.10 (9H, s, NHC(CH\(_3\))\(_3\)), 3.80 (2H, s, ArCH\(_2\)), 3.86 (3H, s, OCH\(_3\)), 4.46 (2H, s, COOCH\(_2\)CO), 5.60 (1H, br, CONH, exchanged with D\(_2\)O), 7.08-7.16 (2H, m, ArH), 7.33-7.37 (1H, m, ArH), 7.63-7.71 (3H, m, ArH).

\(^{13}\text{C-NMR}\) (CDCl\(_3\)) : \(\delta\) 28.15 (NHC(CH\(_3\))\(_3\)), 40.95 (ArCH\(_2\)), 50.82 (NHC), 55.00 (OCH\(_3\)), 62.90 (COOCH\(_2\)CO), 105.40 (C-5), 119.03 (C-7), 127.22, 127.36, 127.59 and 128.84 (C-1, C-3, C-4 and C-8), 128.29, 128.69 and 133.54 (C-2, C-9 and C-10), 157.60 (C-6), 165.74 (CON), 169.68 (COO).

**MASS** (m/z) : 329 (M\(^+\)), 199, 198 (100%), 171, 170, 156, 155, 141, 140, 139, 128.

\(N\text{-Cyclohexylcarbamoylmethyl 6-methoxy-2-naphthylacetate (141)}\)

A mixture of 6-MNA (1.62 g, 0.0075 mol), DMF (10 ml), triethylamine (0.84 g, 0.0083 mol), sodium iodide (0.112 g, 0.00075 mol) and 2-chloro-\(N\text{-cyclohexylacetamide (1.45 g, 0.0082 mol)}\) was stirred at 80-90 °C for 3 h. The mixture was poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The ethyl acetate layer was successively washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The organic layer was dried over anhydrous sodium sulphate and solvent was evaporated under reduced pressure to get a solid residue, which was recrystallised from ethyl acetate to afford white crystalline \(N\text{-cyclohexylcarbamoylmethyl 6-methoxy-2-naphthylacetate (1.61 g, 60.3%)}\), mp 121-122 °C.
Anal: Found C, 70.44; H, 7.21; N, 3.90. C_{21}H_{25}NO_{4} requires C, 70.96; H, 7.09; N, 3.94.

UV (CH$_3$CN): $\lambda_{\text{max}}$ 230.2 nm \ log $\epsilon$ 4.96

IR (KBr): 3293 (NH), 3091, 1738 (C=O), 1652 (C=O), 1560 (amide-II band), 1264 (C-O-C), 1220, 1160, 1027 (C-O-C), 855, 818 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$): $\delta$ 0.35-1.65 (10H, m, NHCH$_2$CH$_2$), 3.53-3.58 (1H, m, NHCH$_2$CH$_2$), 3.85 (2H, s, ArCH$_2$), 3.92 (3H, s, OCH$_3$), 4.55 (2H, s, COOCH$_2$CO), 5.28-5.31 (1H, br d, $J$ = 7.6 Hz, CONH), 7.14-7.29 (2H, m, ArH), 7.37-7.43 (1H, m, ArH), 7.70-7.77 (3H, m, ArH).

$^{13}$C-NMR (CDCl$_3$): $\delta$ 24.58 (NHCH$_2$CH$_2$), 25.12 (NHCH$_2$CH$_2$), 32.43 (NHCH$_2$CH$_2$), 41.47 (ArCH$_2$), 47.29 (NHCH$_2$CH$_2$), 55.36 (OCH$_3$), 62.70 (COOCH$_2$CO), 105.59 (C-5), 119.49 (C-7), 127.62, 127.62, 127.82 and 129.18 (C-1, C-3, C-4 and C-8), 128.63, 128.98 and 133.87 (C-2, C-9 and C-10), 158.03 (C-6), 165.76 (CON), 169.64 (COO).

Mass (m/z): 355 ($M^+$), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.
N,N-Dimethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (142)

A mixture of 6-MNA (2.16 g, 0.01 mol), DMF (10 ml), N,N-dimethyl-2-chloroacetamide (1.34 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and triethylamine (1.12 g, 0.011 mol) was stirred at 90 °C for 3 h. The mixture was poured in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate layer was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was recrystallised from ethyl acetate-hexane mixture to afford N,N-dimethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (1.96 g, 65.2%), mp 116-117 °C.

Anal: Found C, 67.46; H, 6.31; N, 4.24. C_{17}H_{19}NO_{4} requires C, 67.76; H, 6.36; N, 4.65.

UV (CH_3CN): \lambda_{max} 230.1 nm \ log \varepsilon 4.88

IR (KBr): 1744 (C=O), 1654 (C=O), 1259 (C-O-C), 1223, 1143, 1053, 1023 (C-O-C), 858, 823 cm^{-1}.

^{1}H-NMR (CDCl_3): \delta 2.89 (3H, s, C=\text{N-CH}_3), 2.94 (3H, s, C=\text{N-CH}_3), 3.89 (3H, s, O\text{CH}_3), 3.90 (2H, s, Ar\text{CH}_2), 4.72 (2H, s, COO\text{CH}_2\text{CO}), 7.10-7.26 (2H, m, Ar\text{H}), 7.42-7.44 (1H, m, Ar\text{H}), 7.66-7.71 (3H, m, Ar\text{H}).

^{13}C-NMR (CDCl_3): \delta 35.57 (C=\text{N-CH}_3), 35.78 (C=\text{N-CH}_3), 40.85
(ArCH₂), 55.28 (OCH₃), 61.65 (COOCH₂CO), 105.65 (C-5), 118.91 (C-7), 127.06, 127.99, 128.01, and 129.19 (C-1, C-3, C-4 and C-8), 128.89, 128.92 and 133.64 (C-2, C-9 and C-10), 157.63 (C-6), 166.26 (CON), 171.42 (COO).

**MASS (m/z)**: 301 (M⁺), 199, 198 (100%), 171, 170, 155, 141, 140, 139, 128.

**N,N-Diethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (143)**

6-MNA (2.16 g, 0.01 mol) was taken in DMF (10 ml). After the addition of 2-chloro-N,N-diethylacetamide (1.64 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and triethylamine (1.12 g, 0.011 mol), the mixture was heated with stirring at 90 °C for 3 h. The mixture was taken in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate extract was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The organic layer, after drying with anhydrous sodium sulphate, was evaporated under reduced pressure and the residue was purified by passing through a silica column to get **N,N-diethylcarbamoylmethyl 6-methoxy-2-naphthylacetate** (2.4 g, 72.9%).

**Anal**: Found C, 68.96; H, 7.05; N, 4.11. C₁₉H₂₃NO₄ requires C, 69.28; H, 7.04; N, 4.25.

**UV (CH₃CN)**: λmax 230.2 nm log ε 4.82

**IR (KBr)**: 1735 (C=O), 1671 (C=O), 1269 (C-O-C), 1221, 1140, 1029 (C-O-C), 853, 811 cm⁻¹.
$^1$H-NMR (CDCl$_3$): $\delta$ 1.07-1.11 (3H, t, $J = 7.1$Hz, CH$_2$CH$_3$), 1.10-1.15 (3H, t, $J = 7.1$Hz, CH$_2$CH$_3$), 3.10-3.18 (2H, q, $J = 7.1$Hz, CH$_2$CH$_3$), 3.33-3.39 (2H, q, $J = 7.1$Hz, CH$_2$CH$_3$), 3.86 (3H, s, OCH$_3$), 3.87 (2H, s, ArCH$_2$), 4.70 (2H, s, COOCH$_2$CO), 7.08-7.13 (2H, m, ArH), 7.38-7.42 (1H, m, ArH), 7.64-7.69 (3H, m, ArH).

$^{13}$C-NMR (CDCl$_3$): $\delta$ 12.77 (C-N), 13.94 (C-N), 40.41 (C-N), 40.67 (C-N), 40.88 (ArCH$_2$), 55.14 (OCH$_3$), 61.50 (COOCH$_2$CO), 105.54 (C-5), 118.76 (C-7), 126.96, 127.88, 127.93 and 129.08 (C-1, C-3, C-4 and C-8), 128.71, 128.78 and 133.53 (C-2, C-9 and C-10), 157.50 (C-6), 165.48 (CON), 171.39 (COO).

MASS (m/z): 329 (M$^+$), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 128.

$N,N$-Dipropylcarbamoylmethyl 6-methoxy-2-naphthylacetate (144)

6-MNA (1.62 g, 0.0075 mol) was dissolved in DMF (10 ml) and to the above solution, 2-chloro-$N,N$-dipropylacetamide (1.47 g, 0.0082 mol), sodium iodide (0.113 g, 0.00075 mol) and triethylamine (0.84 g, 0.0082 mol) were added. The reaction mixture was heated for 3 h at 153
85 °C with stirring, poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate layer was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2% , 50 ml) and water (3 X 50 ml). The washed organic layer was dried over anhydrous sodium sulphate, the solvent was removed under reduced pressure and the residue obtained was recrystallised from ethyl acetate-hexane mixture to yield white crystals of N,N-dipropylcarbamoylmethyl 6-methoxy-2-naphthylacetate (1.98 g, 73.9%), mp 68-69 °C.

**Anal:** Found C, 70.18; H, 7.35; N, 3.91. C_{21}H_{27}NO_{4} requires C, 70.56; H, 7.62; N, 3.92.

**UV (CH₃CN):** $\lambda_{\text{max}}$ 230.2 nm, log $\varepsilon$ 4.97

**IR (KBr):** 1735 (C=O), 1666 (C=O), 1459, 1295, 1267 (C-O-C), 1221, 1128, 1059, 1021 (C-O-C), 847, 816 cm⁻¹.

**$^1$H-NMR (CDCl₃):** $\delta$ 0.85-0.91 (6H, t, $J=7.3$ Hz, C$_{2}$H$_{5}$), 1.50-1.61 (4H, m, C$_{3}$H$_{7}$), 3.03-3.09 (3H, s, ArH), 4.73 (2H, s, COOCH$_{2}$CO), 7.10-7.14 (2H, m, ArH), 7.40-7.43 (1H, m, ArH), 7.66-7.71 (3H, m, ArH).

**$^{13}$C-NMR (CDCl₃):** $\delta$ 11.15 (C$_{2}$H$_{5}$), 11.32 (C$_{3}$H$_{7}$).
(C=\text{N} \text{CH}_2 \text{CH}_2 \text{CH}_3), 20.78 (C=\text{N} \text{CH}_2 \text{CH}_2 \text{CH}_3), 21.98 (C=\text{N} \text{CH}_2 \text{CH}_2 \text{CH}_3),
40.82 (\text{ArCH}_2), 47.74 (C=\text{N} \text{CH}_2 \text{CH}_2 \text{CH}_3), 48.48 (C=\text{N} \text{CH}_2 \text{CH}_2 \text{CH}_3),
55.25 (\text{OCH}_3), 61.65 (\text{COOCH}_2 \text{CO}), 105.62 (\text{C}-5), 118.87 (\text{C}-7),
127.08, 127.99, 128.02 and 129.18 (\text{C}-1, \text{C}-3, \text{C}-4 and \text{C}-8),
128.89 128.92 and 133.62 (\text{C}-2, \text{C}-9 and \text{C}-10), 157.60 (\text{C}-6),
165.91 (\text{CON}), 171.48 (\text{COO}).

**MASS (m/z)** : 357 (M$^+$), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

**N,N-Diisopropylcarbamoylmethyl 6-methoxy-2-naphthylacetate (145)**

A mixture of 6-MNA (1.62 g, 0.0075 mol), DMF (10 ml), triethylamine (0.84 g, 0.0082 mol), sodium iodide (0.113 g, 0.00075 mol) and 2-chloro-N,N-diisopropylacetamide (1.47 g, 0.0082 mol) was stirred for 3 h at 90 °C. The reaction mixture was poured in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The ethyl acetate layer was washed successively with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The washed organic layer was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure and the solid residue obtained was recrystallised from ethyl acetate-hexane mixture to afford **N,N-diisopropylcarbamoylmethyl 6-methoxy-2-naphthylacetate** as white crystals (2.19 g, 81.8%), mp 130-131 °C.
Anal: Found C, 70.26; H, 7.60; N, 3.97. C_{21}H_{27}NO_{4} requires C, 70.56; H, 7.62; N, 3.92.

UV (CH_{3}CN): \lambda_{\text{max}} 230.0 \text{ nm} \quad \log \varepsilon 4.88

IR (KBr): 1734 (C=O), 1664 (C=O), 1453, 1291, 1265 (C-O-C), 1220, 1132, 1042, 1019 (C-O-C), 847, 814 cm^{-1}.

^{1}H-NMR (CDCl_{3}): \delta 1.16-1.19 (6H, d, J = 7.0 \text{ Hz}, C=\text{N}CH(CH_{3})_{2}), 1.38-1.41 (6H, d, J = 7.0 \text{ Hz}, C=\text{N}CH(CH_{3})_{2}), 3.40-3.55 (1H, sept, J = 7.0 \text{ Hz}, C=\text{N}CH(CH_{3})_{2}), 3.60-3.75 (1H, sept, J = 7.0 \text{ Hz}, C=\text{N}CH(CH_{3})_{2}), 3.89 (3H, s, OCH_{3}), 3.91 (2H, s, ArCH_{2}), 4.68 (2H, s, COOCH_{2}CO), 7.10-7.14 (2H, m, ArH), 7.39-7.43 (1H, m, ArH), 7.66-7.71 (3H, m, ArH).

^{13}C-NMR (CDCl_{3}): \delta 20.49 (C=\text{N}CH(CH_{3})_{2}), 20.71 (C=\text{N}CH(CH_{3})_{2}), 40.84 (ArCH_{2}), 46.08 (C=\text{N}CH(CH_{3})_{2}), 47.58 (C=\text{N}CH(CH_{3})_{2}), 55.25 (OCH_{3}), 62.66 (COOCH_{2}CO), 105.61 (C-5), 118.88 (C-7), 127.02, 128.03, 128.93, 129.17 and 133.62 (C-2, C-9, C-10, C-1, C-3, C-4 and C-8), 157.59 (C-6), 164.68 (CON), 171.43 (COO).

MASS (m/z): 357 (M^{+}), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.
N,N-Diallylcarbamoylmethyl 6-methoxy-2-naphthylacetate (146)

6-MNA (2.16 g, 0.01 mol) was dissolved in DMF (10 ml) and to this solution, 2-chloro-N,N-diallylacetamide (1.92 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and triethylamine (1.12 g, 0.011 mol) were added. The reaction mixture was heated for 3 h at 90 °C with stirring, poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate layer was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 x 50 ml). The organic layer was dried over anhydrous sodium sulphate, the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate-hexane mixture to yield N,N-diallylcarbamoylmethyl 6-methoxy-2-naphthylacetate as white crystals (2.2 g, 62.3%), mp 70-72 °C.

Anal. Found C, 71.14; H, 6.25; N, 4.16. C_{21}H_{23}NO_{4} requires C, 71.37; H, 6.56; N, 3.96.

UV (CH_{3}CN) : λ max 230.3 nm log ε 4.91

IR (KBr) : 3086, 3059, 3017, 1738 (C=O), 1675 (C=O), 1637, 1476, 1454, 1410, 1301, 1264 (C-O-C), 1220, 1132, 1017 (C-O-C), 844, 812 cm^{-1}.

{^1}H-NMR (CDCl_{3}) : δ 3.74-3.77 (2H, d, J = 6.0 Hz, C=\text{N}\left(\text{CH}_{2}\text{CH=CH}_{2}\right)), 3.88 (3H, s, OCH_{3}), 3.89 (2H, s, ArCH_{2}), 3.97-4.00 (2H, d, J = 6Hz, C=\text{N}\left(\text{CH}_{2}\text{CH=CH}_{2}\right)), 4.72 (2H, s, \text{CH}_{2}\text{CH=CH}_{2})
COOCH₂CO), 5.10-5.22 (4H, m, N(CH₂CH=CH₂)₂), 5.66-5.78 (2H, m, N(CH₂CH=CH₂)₂), 7.09-7.14 (2H, m, ArH), 7.39-7.43 (1H, m, ArH), 7.66-7.71 (3H, m, ArH).

¹³C-NMR (CDCl₃) : δ 40.78 (ArCH₂), 48.14 (C=NCH₂CH=CH₂), 48.33 (C=NCH₂CH=CH₂), 55.24 (OCH₃), 61.61 (COOCH₂CO) 105.62 (C-5), 117.24 (C=NCH₂CH=CH₂), 117.88 (C=NCH₂CH=CH₂) 118.89 (C-7), 127.05, 127.99, 127.99 and 129.17 (C-1, C-3, C-4 and C-8), 128.79, 128.90 and 133.63 (C-2, C-9 and C-10), 131.99 (C=NCH₂CH=CH₂), 132.54 (C=NCH₂CH=CH₂), 157.60 (C-6), 166.43 (CON), 171.40 (COO).

MASS (m/z) : 353 (M⁺), 199, 198 (100%), 183, 171, 170, 156, 155, 141, 140, 139, 128.

N,N-Dicyclohexylcarbamoylmethyl 6-methoxy-2-naphthylacetate (147)

A mixture of 6-MNA (2.16 g, 0.01 mol), 2-chloro-N,N-dicyclohexylacetamide (2.83 g, 0.011 mol), triethylamine (1.12 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and DMF (10 ml) was stirred for 3 h at 90 °C. This reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate layer was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The organic layer was dried over anhydrous sodium sulphate
and solvent was removed under reduced pressure. The residue on recrystallisation with ethanol gave

\[ N,N\text{-dicyclohexylcarbamoylmethyl 6-methoxy-2-naphthylacetate} \]

as white crystals (3.36 g, 76.9%), mp 115-116 °C.

**Anal:** Found C, 73.70; H, 8.18; N, 3.03. \( C_{27}H_{35}NO_4 \) requires C, 74.11; H, 8.06; N, 3.20.

**UV (CH\(_3\)CN):** \( \lambda_{\text{max}} 230.6 \text{ nm} \), log \( \varepsilon \) 4.83

**IR (KBr):** 2936, 1762 (C=O), 1666 (C=O), 1448, 1263 (C-O-C), 1164, 1032 (C-O-C), 860, 815 cm\(^{-1}\).

**\(^1\)H-NMR (CDCl\(_3\))**: \( \delta \) 1.0-1.85 (20H, \( m\), NCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 2.35-2.55 (1H, \( m\), C=\(\text{N}\)), 3.10-3.23 (1H, \( m\), OCH\(_3\)), 3.88 (3H, s, OCH\(_3\)), 3.90 (2H, s, ArCH\(_2\)), 4.69 (2H, s, COOCH\(_2\)CO), 7.08-7.14 (2H, \( m\), ArH), 7.39-7.43 (1H, \( m\), ArH), 7.65-7.70 (3H, \( m\), ArH).

**\(^{13}\)C-NMR (CDCl\(_3\))**: \( \delta \) 25.24 (C=\(\text{N}\))
25.86 (C=N), 26.52 (C=N)

29.91 (C=N), 31.16 (C=N)

40.87 (ArCH₂), 55.22 (OCH₃), 56.17 (C=N), 56.83 (C=N), 62.75 (COOCH₂CO), 105.59 (C-5), 118.85 (C-7), 127.00, 127.96, 128.01 and 129.14 (C-1, C-3, C-4 and C-8), 128.93, 128.93 and 133.60 (C-2, C-9 and C-10), 157.57 (C-6), 164.89 (CON), 171.38 (COO).

**MASS (m/z)**: 257, 222, 200, 198, 176, 171, 141, 140, 132, 128, 98, 94, 85, 83 (100%).

**1-Pyrrolidinylcarbonylmethyl 6-methoxy-2-naphthylacetate (148)**

A mixture of 6-MNA (2.16 g, 0.01 mol), 1-(2-chloroacetyl) pyrrolidine (1.62 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol), triethylamine (1.12 g, 0.011 mol) and DMF (10 ml) was stirred at 90 °C for 3 h. This reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate
extract was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The ethyl acetate layer was dried over anhydrous sodium sulphate and solvent was evaporated under reduced pressure. The residue thus obtained was recrystallised from ethyl acetate-hexane mixture to afford white crystals of 1-Pyrrolidinylcarbonylmethyl 6-methoxy-2-naphthylacetate (2.33 g, 71.3%), mp 113 °C.

Anal: Found C, 69.16; H, 6.39; N, 4.68. C_{19}H_{21}NO_{4} requires C, 69.70; H, 6.47; N, 4.28.

UV (CH$_3$CN): A$_{\text{max}}$ 230.1 nm log ε 4.94

IR (KBr): 1755 (C=O), 1652 (C=O), 1454, 1333, 1265 (C=O-C), 1184, 1159, 1028 (C=O-C), 853, 814 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$): δ 1.75-1.85 (2H, q, J = 6.8 Hz, C$^\text{N}\text{CH}_2\text{CH}_2$)

1.85-1.95 (2H, q, J = 6.8 Hz, C$^\text{N}\text{CH}_2\text{CH}_2$), 3.26-3.32 (2H, t, J = 6.8 Hz, C$^\text{N}\text{CH}_2\text{CH}_2$)

3.45-3.50 (2H, t, J = 6.8 Hz, C$^\text{N}\text{CH}_2\text{CH}_2$)

3.89 (3H, s, OCH$_3$), 3.90 (2H, s, ArCH$_2$), 4.63 (2H, s, COOCH$_2$CO), 7.10-7.14 (2H, m, ArH), 7.40-7.44 (1H, m, ArH), 7.66-7.71 (3H, m, ArH).

$^{13}$C NMR (CDCl$_3$): δ 23.87 (C$^\text{N}\text{CH}_2\text{CH}_2$), 26.08 (C$^\text{N}\text{CH}_2\text{CH}_2$)

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40.84 (ArCH₂), 45.21 (C≡N\(\text{CH₂CH₂}\)), 45.98 (C≡N\(\text{CH₂CH₂}\)),
55.29 (OCH₃), 62.26 (COOCH₂CO) 105.64 (C-5), 118.91 (C-7),
127.07, 128.02, 128.02 and 129.20 (C-1, C-3, C-4 and C-8),
128.90, 128.90 and 133.64 (C-2, C-9 and C-10), 157.63 (C-6),
164.86 (CON), 171.45 (COO).

**MASS (m/z)**: 327 (M⁺), 199, 198 (100%), 183, 171, 170, 156,
155, 141, 140, 139, 128.

**Morpholinocarbonylmethyl 6-methoxy-2-naphthylacetate (149)**

6-MNA (2.16 g, 0.01 mol) was dissolved in DMF (10 ml) and to this solution, 4-(2-chloroacetyl) morpholine (1.8 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol) and triethylamine (1.12 g, 0.011 mol) were added. The reaction mixture was heated for 3 h at 90 °C with stirring, poured into water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate extract was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (3 X 50 ml). The organic layer was dried over anhydrous sodium sulphate, solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate-hexane mixture to afford **morpholinocarbonylmethyl 6-methoxy-2-naphthylacetate** as white crystals (2.35 g, 68.5%), mp 114-115 °C.

**Anal**: Found C, 66.23; H, 5.98; N, 4.12. C₁₉H₂₁NO₅ requires C, 66.46; H, 6.16; N, 4.08.
UV (CH$_3$CN) : λ$_{\text{max}}$ 230.3 nm \[ \log \varepsilon 4.92 \]

IR (KBr) : 1749 (C=O), 1658 (C=O), 1464, 1265 (C-O-C), 1151, 1111, 1029 (C-O-C), 847, 816 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$) : δ 3.22-3.35 (2H, m, C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 3.50-3.65 (4H, m, C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 3.65-3.75 (2H, m, C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 3.89 (3H, s, OCH$_3$), 3.89 (2H, s, ArCH$_2$), 4.70 (2H, s, COOCH$_2$CO), 7.10-7.15 (2H, m, ArH), 7.38-7.43 (1H, m, ArH), 7.67-7.72 (3H, m, ArH).

$^{13}$C-NMR (CDCl$_3$) : δ 40.85 (ArCH$_2$), 42.13 (C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 44.96 (C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 55.27 (OCH$_3$), 61.58 (COOCH$_2$CO), 66.23 (C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 66.66 (C=N\(\begin{array}{c} \text{CH}_2\text{CH}_2\text{O} \end{array}\)), 105.63 (C-5), 119.00 (C-7), 127.10, 127.93, 127.93 and 129.14 (C-1, C-3, C-4 and C-8), 128.65, 128.89 and 133.65 (C-2, C-9 and C-10), 157.66 (C-6), 165.02 (CON), 171.29 (COO).

MASS (m/z) : 343 (M$^+$), 199, 198 (100%), 183, 171, 170, 156, 155, 140, 139, 128.

$N$-Methyl-$N$-$\beta$-hydroxyethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (150)

A mixture of 6-MNA (2.16 g, 0.01 mol), 2-chloro-$N$-methyl-$N$-$\beta$-hydroxyethylacetamide (1.67 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol), triethylamine (1.12 g, 0.011 mol) and DMF (10 ml) was stirred at 80°C for 4 h. The
reaction mixture was poured in water (50 ml) and extracted with ethyl acetate (4 X 50 ml). The combined ethyl acetate extract was washed with aqueous sodium thiosulphate (2%, 25 ml), aqueous sodium bicarbonate (2%, 25 ml) and water (2 X 25 ml), dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure. The residue thus obtained was recrystallised from ethyl acetate-hexane mixture to afford *N*-methyl-*N*-β-hydroxyethyl-carbamoylmethyl 6-methoxy-2-naphthylacetate as white crystals (1.66 g, 50.2%), mp 103-104 °C.

**Anal**: Found C, 64.77; H, 6.38; N, 4.27. C_{18}H_{21}NO_{5} requires C, 65.24; H, 6.39; N, 4.23.

**UV** (CH₃CN) : λ max 230.5 nm log ε 4.87

**IR** (KBr) : 3395 (OH), 1746 (C=O), 1652 (C=O), 1268 (C-O-C), 1201, 1148, 1116, 1055, 1029 (C-O-C), 856, 824 cm⁻¹.

**¹H-NMR** (CDCl₃ + DMSO-d₆) : δ 2.94 and 3.03 (3H, s and s, N(CH₃)CH₂CH₂OH)*, 3.31-3.34 and 3.46-3.50 (2H, t and t, J = 5.1 Hz, N(CH₃)CH₂CH₂OH)*, 3.64-3.68 (2H, m, N(CH₃)CH₂CH₂OH), 3.87 and 3.88 (2H, s and s, ArCH₂)*, 3.90 (3H, s, OCH₃), 4.76 and 4.89 (2H, s and s, COOCH₂CO)*, 7.08-7.13 (2H, m, ArH), 7.37-7.41 (1H, m, ArH), 7.66-7.71 (3H, m, ArH).

**¹³C-NMR** (CDCl₃ + DMSO-d₆) : δ 32.79 and 34.78 (N(CH₃)CH₂CH₂OH)*, 40.12 (ArCH₂), 50.26 and 50.37 (N(CH₃)CH₂CH₂OH)*, 54.73 (OCH₃) 58.04 and 59.02

* two peaks because of hindered rotation (see discussion)
(N(CH₃)CH₂CH₂OH)*, 61.27 and 61.34 (COOCH₂CO)*, 105.13 (C-5), 118.40 (C-7), 126.39, 127.36, 127.68 and 128.55 (C-1, C-3, C-4 and C-8), 128.20, 128.67 and 132.97 (C-2, C-9 and C-10), 157.02 (C-6), 165.85 and 166.30 (CON)*, 170.59 (COO).

MASS (m/z) : 331 (M⁺), 216, 198, 171(100%), 156, 155, 141, 140, 139, 128.

N-Ethyl-N-ß-hydroxyethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (151)

A mixture of 6-MNA (2.16 g, 0.01 mol), 2-chloro-N-ethyl-N-ß-hydroxyethylacetamide (1.82 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol), triethylamine (1.12 g, 0.011 mol) and DMF (10 ml) was stirred at 80 °C for 4 h. The mixture was poured in water (50 ml) and extracted with ethyl acetate (4 X 50 ml). The combined ethyl acetate extract was washed with aqueous sodium thiosulphate (2%, 50 ml), aqueous sodium bicarbonate (2%, 50 ml) and water (2 X 50 ml), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue obtained was recrystallised from ethyl acetate-hexane mixture to afford N-ethyl-N-ß-hydroxyethylcarbamoylmethyl 6-methoxy-2-naphthylacetate as white crystals (1.51 g, 43.8%), mp 104-105 °C.

Anal : Found C, 65.77; H, 6.62; N, 3.91. C₁₉H₂₃NO₅ requires C, 66.07; H, 6.71; N, 4.05.

UV (CH₃CN) : ʎ max 230.5 nm log ε 4.87

IR (KBr) : 3424 (OH), 1745 (C=O), 1647 (C=O), 1484, 1266 (C-O-C), 1202, 1147, 1121, 1057, 1027 (C-O-C), 864, 820 cm⁻¹.

* two peaks because of hindered rotation (see discussion)
$^1$H-NMR (CDCl$_3$) : $\delta$ 1.09-1.14 and 1.16-1.21 (3H, t and t, $J$ = 7.1 Hz and 7.1 Hz, N(CH$_2$CH$_3$)CH$_2$CH$_2$OH)*, 3.28-3.5 (4H, m, N(CH$_2$CH$_3$)CH$_2$CH$_2$OH), 3.64-3.7 (2H, m, N(CH$_2$CH$_3$)CH$_2$CH$_2$OH), 3.87 and 3.88 (2H, s and s, ArCH$_2$)*, 3.89 (3H, s, OCH$_3$), 4.78 and 4.89 (2H, s and s, COOCH$_2$CO)*, 7.09-7.12 (2H, m, ArH), 7.38-7.41 (1H, m, ArH), 7.64-7.70 (3H, m, ArH).

$^1$H-NMR (CDCl$_3$ + D$_2$O) : 1.08-1.14 and 1.15-1.22 (3H, t and t, $J$ = 7.1 Hz and 7.1 Hz, N(CH$_2$CH$_3$)CH$_2$CH$_2$OD)*, 3.26-3.32 and 3.35-3.44 (2H, q and q, $J$ = 7.1 Hz and 7.1 Hz, N(CH$_2$CH$_3$)CH$_2$CH$_2$OD)*, 3.27-3.31 and 3.46-3.50 (2H, t and t, $J$ = 5.3 Hz and 5.3 Hz, N(CH$_2$CH$_3$)CH$_2$CH$_2$OD)*, 3.64-3.68 and 3.70-3.74 (2H, t and t, $J$ = 5.3 Hz and 5.3 Hz, N(CH$_2$CH$_3$)CH$_2$CH$_2$OD)*.

$^{13}$C-NMR (CDCl$_3$) : $\delta$ 12.20 and 13.31 (N(CH$_2$CH$_3$)CH$_2$CH$_2$OH)*, 40.16 (ArCH$_2$), 40.24 and 42.10 (N(CH$_2$CH$_3$)CH$_2$CH$_2$OH)*, 48.25 and 49.50 (N(CH$_2$CH$_3$)CH$_2$CH$_2$OH)*, 54.74 (OCH$_3$), 58.84 and 59.47 (N(CH$_2$CH$_3$)CH$_2$CH$_2$OH)*, 61.09 and 61.41 (COOCH$_2$CO)*, 105.11 (C-5), 118.39 (C-7), 126.42, 127.38, 127.56 and 127.64 (C-1, C-3, C-4 and C-8), 128.24, 128.57 and 133.00 (C-2, C-9 and C-10), 157.04 (C-6), 165.81 and 165.90 (CON)*, 170.69 (COO).

MASS (m/z) : 345 (M$^+$), 216, 199 , 198(100%), 171, 170, 156, 155, 140, 139, 128.

* two peaks because of hindered rotation (see discussion)
N,N-Di-β-hydroxyethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (152)

A mixture of 6-MNA (2.16 g, 0.01 mol), 2-chloro-N,N-di-β-hydroxyethylacetamide (2.0 g, 0.011 mol), sodium iodide (0.15 g, 0.001 mol), triethylamine (1.12 g, 0.011 mol) and DMF (10 ml) was heated at 90 °C for 3 h. The reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (4 X 50 ml). The combined ethyl acetate extract was washed with aqueous sodium thiosulphate (2%, 25 ml), aqueous sodium bicarbonate (2%, 25 ml) and water (2 X 25 ml). After drying over anhydrous sodium sulphate, the solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate-hexane mixture to obtain N,N-di-β-hydroxyethylcarbamoylmethyl 6-methoxy-2-naphthylacetate as white crystals (1.98 g, 54.8%), mp 109-110 °C.

Anal : Found C, 62.61; H, 6.42; N, 3.60. C_{19}H_{23}NO_{6} requires C, 63.14; H, 6.41; N, 3.88.

UV (CH_{3}CN) : λ max 230.6 nm log ε 4.89

IR (KBr) : 3357(OH), 3260 (OH), 1738 (C=O), 1633 (C=O), 1249, 1224, 1058, 1025 (C-O-C), 854, 818 cm^{-1}.

^{1}H-NMR (CDCl_{3} + DMSO-d_{6}) : δ 3.35-3.39 (2H, t, J = 5.1 Hz, C=OCH_{2}CH_{2}OH ), 3.42-3.46 (2H, t, J = 5.4 Hz, C=OCH_{2}CH_{2}OH ), 3.62-3.67 (4H, m, C=OCH_{2}CH_{2}OH), 3.84 (2H, s, ArCH_{2}), 3.88
(3H, s, OCH₃), 4.4-4.7 (1H, br, C=NC₃H₂OH), 4.7-5.0 (1H, br, C=NC₃H₂OH), 4.89 (2H, s, COOCH₂CO), 7.06-7.10 (2H, m, ArH), 7.35-7.38 (1H, m, ArH), 7.64-7.72 (3H, m, ArH).

¹H-NMR (CDCl₃ + DMSO-d₆ + D₂O) : δ 3.67-3.71 (2H, t, J = 5.2 Hz, C=NC₃H₂OD), 3.72-3.77 (2H, t, J = 5.2 Hz, C=NC₃H₂OD), hydroxy protons exchanged and remaining signals as above.

¹³C-NMR (CDCl₃ + DMSO-d₆) : δ 40.12 (ArCH₂), 49.01 (C=NC₃H₂OH), 50.06 (C=NC₃H₂OH), 54.72 (OCH₃), 58.83 (C=NC₃H₂OH), 59.16 (C=NC₃H₂OH), 61.38 (COOCH₂CO), 105.09 (C-5), 118.38 (C-7), 126.36, 127.34, 127.65 and 128.65 (C-1, C-3, C-4 and C-8), 128.18, 128.62 and 132.94 (C-2, C-9 and C-10), 157.00 (C-6), 166.76 (CON), 170.56 (COO).

MASS (m/z) : 216, 171 (100%), 128.

PREPARATION OF ALKYL ESTER PRODRUGS OF 6-METHOXY-2-NAPHTHYL-ACETIC ACID

Methyl 6-methoxy-2-naphthylacetate (154)

6-MNA (1.62 g, 0.0075 mol) was dissolved in dried methanol (50 ml). Sulphuric acid (0.5 ml) was added and the
reaction mixture was refluxed for 8 h. The solvent was removed under reduced pressure, the residue was taken in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined organic extract was washed successively with aqueous sodium bicarbonate (1%, 2 X 50 ml), water (3 X 50 ml) and dried over anhydrous magnesium sulphate. The solvent was removed under vacuum and residue on recrystallisation from ethyl acetate-hexane mixture afforded methyl 6-methoxy-2-naphthylacetate as white crystals (1.5 g, 87%), mp 74-75 °C (lit 73-74 °C)\(^{107}\).

**Anal:** Found C, 72.73; H, 6.16. \(C_{14}H_{14}O_3\) requires C, 73.02; H, 6.13.

**UV (CH\(_3\)CN):** \(\lambda_{\text{max}} 230.4 \text{ nm} \quad \log \varepsilon 5.0\)

**IR (KBr):** 1733 (C=O), 1264 (C-O-C), 1202, 1158, 1130, 1027 (C-O-C), 850, 815 cm\(^{-1}\).

**\(^1\text{H-NMR}\) (CDCl\(_3\)):** \(\delta 3.64 (3H, s, \text{COOCH}_3), 3.69 (2H, s, \text{ArCH}_2), 3.81 (3H, s, \text{OCH}_3), 7.04-7.13 (2H, m, \text{ArH}), 7.31-7.34 (1H, m, \text{ArH}), 7.58-7.66 (3H, m, \text{ArH}).\)

**\(^13\text{C-NMR}\) (CDCl\(_3\)):** \(\delta 41.03 (\text{ArCH}_2), 51.78 (\text{COOCH}_3), 55.01 (\text{OCH}_3), 105.47 (\text{C-5}), 118.80 (\text{C-7}), 126.90, 127.59, 127.66 and 128.96 (\text{C-1, C-3, C-4 and C-8}), 128.84, 128.96 and 133.45 (\text{C-2, C-9 and C-10}), 157.48 (\text{C-6}), 171.96 (\text{COO}).\)

**MASS (m/z):** 230 (M\(^+\)), 215, 171(100%), 156, 128.

**Ethyl 6-methoxy-2-naphthylacetate (155)**

A mixture of 6-MNA (1.62 g, 0.0075 mol), absolute ethanol (50 ml) and sulphuric acid (0.5 ml) was refluxed on
a water bath for 8 h. The solvent was removed under reduced pressure, the residue was diluted with water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined ethyl acetate extract was washed successively with aqueous sodium bicarbonate (1%, 2 X 50 ml), water (3 X 50 ml) and dried over anhydrous magnesium sulphate. After removing the solvent under reduced pressure, the residue was recrystallised from ethyl acetate-hexane mixture to yield white crystals of ethyl 6-methoxy-2-naphthylacetate (1.7 g, 92.9%), mp 55-56 °C.

**Anal**: Found C, 73.28; H, 6.20. C_{15}H_{16}O_{3} requires C, 73.75; H, 6.60.

**UV** (CH$_3$CN) : $\lambda$ max 230.4 nm  log $\varepsilon$ 5.0

**IR** (KBr) : 2840, 1736 (C=O), 1267 (C-O-C), 1202, 1150, 1029 (C-O-C), 852, 815 cm$^{-1}$.

$^1$H-NMR (CDCl$_3$) : $\delta$ 1.18-1.24 (3H, t, $J = 7.2$ Hz, COOCH$_2$CH$_3$), 3.69 (2H, s, ArCH$_2$), 3.82 (3H, s, OCH$_3$), 4.09-4.17 (2H, q, $J = 7.2$ Hz, COOCH$_2$CH$_3$), 7.05-7.13 (2H, m, ArH), 7.33-7.37 (1H, m, ArH), 7.60-7.67 (3H, m, ArH).

$^{13}$C-NMR (CDCl$_3$) : $\delta$ 14.02 (COOCH$_2$CH$_3$), 41.21 (ArCH$_2$), 55.03 (OCH$_3$), 60.66 (COOCH$_2$CH$_3$), 105.48 (C-5), 118.77 (C-7), 126.87, 127.58, 127.70 and 129.00 (C-1, C-3, C-4 and C-8), 128.79, 129.17 and 133.44 (C-2, C-9 and C-10), 157.46 (C-6) 171.55 (COO).

**MASS** (m/z) : 244 (M$^+$), 171(100%), 156, 128.
Propyl 6-methoxy-2-naphthylacetate (156)

6-MNA (1.62 g, 0.0075 mol) was taken in dried propanol (50 ml), sulphuric acid (0.5 ml) was added and reaction mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure, the residue was taken in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The ethyl acetate layer was successively washed with aqueous sodium bicarbonate (1%, 2 X 50 ml), water (3 X 50 ml) and dried over anhydrous magnesium sulphate. The residue thus obtained was recrystallised from ethyl acetate-hexane mixture to afford propyl 6-methoxy-2-naphthylacetate as white crystals (1.8 g, 93.0%), mp 51-52 °C.

Anal: Found C, 73.90; H, 7.23. C_{16}H_{18}O_{3} requires C, 74.39; H, 7.02.

UV (CH_{3}CN) : λ max 230.4 nm log ε 4.98

IR (KBr) : 2840, 1735 (C=O), 1267 (C-O-C), 1206, 1151, 1029 (C-O-C), 850, 814 cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\)) : δ 0.85-0.91 (3H, t, J = 7.0 Hz, COOCH\(_2\)CH\(_2\)CH\(_3\)), 1.55-1.67 (2H, sex, J = 7.0 Hz, COOCH\(_2\)CH\(_2\)CH\(_3\)), 3.72 (2H, s, ArCH\(_2\)), 3.85 (3H, s, OCH\(_3\)), 4.02-4.07 (2H, t, J = 7.0 Hz, COOCH\(_2\)CH\(_2\)CH\(_3\)), 7.07-7.14 (2H, m, ArH), 7.35-7.38 (1H, m, ArH), 7.62-7.69 (3H, m, ArH).

\(^13\)C-NMR (CDCl\(_3\)) : δ 10.33 (COOCH\(_2\)CH\(_2\)CH\(_3\)), 21.96 (COOCH\(_2\)CH\(_2\)CH\(_3\)), 41.41 (ArCH\(_2\)), 55.21 (OCH\(_3\)), 66.44 (COOCH\(_2\)CH\(_2\)CH\(_3\)), 105.63 (C-5), 118.97 (C-7), 127.01, 127.73, 127.87 and 129.13 (C-1, C-3, C-4 and C-8), 128.95, 129.36
and 133.59 (C-2, C-9 and C-10), 157.61 (C-6) 171.82 (COO).

**MASS** (m/z) : 258 (M⁺), 171(100%), 156, 128.

**Isopropyl 6-methoxy-2-naphthylacetate (157)**

6-MNA (1.62 g, 0.0075 mol) and sulphuric acid (0.5 ml) were added to dried isopropyl alcohol (50 ml) and the reaction mixture was refluxed for 12 h. The solvent was removed under reduced pressure, the residue was taken in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined organic extract was washed successively with aqueous sodium bicarbonate (1%, 2 X 50 ml) and water (3 X 50 ml). After drying over anhydrous magnesium sulphate, the ethyl acetate was distilled off and residue was recrystallised from ethyl acetate-hexane mixture to get white crystals of **isopropyl 6-methoxy-2-naphthylacetate** (1.6 g, 82.7 %), mp 71 °C.


**UV** (CH₃CN) : λ max 230.4 nm \( \log \epsilon \) 4.86

**IR** (KBr) : 2840, 1729 (C=O), 1264 (C-O-C), 1191, 1157, 1026 (C-O-C), 853, 812 cm⁻¹.

**¹H-NMR** (CDCl₃) : δ 1.19-1.23 (6H, d, \( J = 6.3 \) Hz, COOCH(CH₃)₂), 3.67 (2H, s, ArCH₂), 3.86 (3H, s, OCH₃), 4.95-5.07 (1H, sept, \( J = 6.3 \) Hz, COOCH(CH₃)₂), 7.07-7.13 (2H, m, ArH), 7.34-7.38 (1H, m, ArH), 7.62-7.68 (3H, m, ArH).
13C-NMR (CDCl3) : δ 21.76 (COOCH(CH3)2), 41.41 (ArCH2), 55.21 (COCH3), 68.18 (COOCH(CH3)2), 105.63 (C-5), 118.89 (C-7), 126.97, 127.68, 127.85 and 128.95 (C-1, C-3, C-4 and C-8), 129.16, 129.49 and 133.56 (C-2, C-9 and C-10), 157.58 (C-6), 171.29 (COO).

MASS (m/z) : 258 (M+), 171(100%), 156, 128.

Butyl 6-methoxy-2-naphthylacetate (158)

A mixture of 6-MNA (1.62 g, 0.0075 mol), dried butanol (50 ml) and sulphuric acid (0.5 ml) was refluxed for 8 h. The butanol was removed under reduced pressure, the residue obtained was taken in water (50 ml) and extracted with ethyl acetate (3 X 50 ml). The combined organic extract was washed successively with aqueous sodium bicarbonate (1%, 2 X 50 ml), water (3 X 50 ml) and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate-hexane mixture to yield butyl 6-methoxy-2-naphthylacetate as white crystals (1.7 g, 83.3%), mp 40-41 °C.

Anal : Found C, 74.78; H, 7.44. C17H20O3 requires C, 74.97; H, 7.40.

UV (CH3CN) : λ max 230.4 nm log ε 290.1

IR (KBr) : 2840, 1734 (C=O), 1267 (C-O-C), 1225, 1155, 1031 (C-O-C), 849, 811 cm⁻¹.

1H-NMR (CDCl3) : δ 0.83-0.89 (3H, t, J = 7.3 Hz, COOCH2CH2CH2CH3), 1.24-1.37 (2H, m, COOCH2CH2CH2CH3),
1.50-1.61 (2H, m, COOCH₂CH₂CH₂CH₃), 3.69 (2H, s, ArCH₂),
3.81 (3H, s, OCH₃), 4.04-4.10 (2H, t, J = 6.7 Hz,
COOCH₂CH₂CH₂CH₃), 7.04-7.17 (2H, m, ArH), 7.32-7.36 (1H, m,
ArH), 7.59-7.66 (3H, m, ArH).

¹³C-NMR (CDCl₃) : δ 13.65 (COOCH₂CH₂CH₂CH₃), 19.89
(COOCH₂CH₂CH₂CH₃), 30.62 (COOCH₂CH₂CH₂CH₃), 41.37 (ArCH₂),
55.14 (OCH₃), 66.70 (COOCH₂CH₂CH₂CH₃), 105.61 (C-5), 118.92
(C-7), 127.00, 127.73, 127.86 and 129.12 (C-1, C-3, C-4 and
C-8), 128.95, 129.35 and 133.60 (C-2, C-9 and C-10), 157.61
(C-6), 171.78 (COO).

**MASS (m/z) : 272 (M⁺), 171(100%), 156, 128.**

**Isobutyl 6-methoxy-2-naphthylacetate (159)**

6-MNA (1.62 g, 0.0075 mol) was dissolved in dried
isobutyl alcohol (50 ml) and after the addition of sulphuric
acid (0.5 ml), the reaction mixture was refluxed for 12 h.
The solvent was evaporated under reduced pressure and the
residue was taken in water (50 ml). The mixture was
extracted with ethyl acetate (3 X 50 ml). The combined
ethyl acetate extract was successively washed with aqueous
sodium bicarbonate (1%, 2 X 50 ml) and water (3 X 50 ml),
dried over anhydrous magnesium sulphate and recrystallised
from ethyl acetate-hexane mixture to afford **isobutyl
6-methoxy-2-naphthylacetate** (1.6 g, 78.4%), mp 45-46 °C as
white crystals.
Anal : Found C, 74.40; H, 7.17. C_{17}H_{20}O_3 requires C, 74.97; H, 7.40.

UV (CH_3CN) : \lambda_{\text{max}} 230.5 nm \log \varepsilon 4.90

IR (KBr) : 2840, 1729 (C=O), 1267 (C-O-C), 1209, 1142, 1028 (C-O-C), 852, 813 cm^{-1}.

^1H-NMR (CDCl_3) : \delta 0.85-0.88 (6H, d, J = 6.7 Hz, COOCH_2CH(CH_3)_2), 1.83-1.97 (1H, m, COOCH_2CH(CH_3)_2), 3.71 (2H, s, ArCH_2), 3.82 (3H, s, OCH_3), 3.85-3.89 (2H, d, J = 6.7 Hz, COOCH_2CH(CH_3)_2), 7.06-7.13 (2H, m, ArH), 7.34-7.38 (1H, m, ArH), 7.62-7.67 (3H, m, ArH).

^13C-NMR (CDCl_3) : \delta 19.01 (COOCH_2CH(CH_3)_2), 27.71 (COOCH_2CH(CH_3)_2), 41.42 (ArCH_2), 55.17 (COCH_3), 70.90 (COOCH_2CH(CH_3)_2), 105.63 (C-5), 118.92 (C-7), 126.99, 127.74, 127.89 and 129.12 (C-1, C-3, C-4 and C-8), 128.94, 129.36 and 133.58 (C-2, C-9 and C-10), 157.60 (C-6), 171.74 (COO).

MASS (m/z) : 272 (M^+), 171(100%), 156, 128.

HPLC METHOD FOR THE ANALYSIS OF ESTER PRODRUGS OF 6-MNA

In the HPLC method, a reversed-phase C-18 column was eluted with mixtures of methanol or acetonitrile and 0.02 M phosphate buffer (pH 3.5-4.5). The composition of the eluant and pH of the buffer were adjusted for each compound in order to provide an appropriate retention time and
separation of ester prodrugs and 6-MNA. The flow rate of 1 ml/min was used and column effluent was monitored at 230 nm. Quantification of the compounds was done by measurement of peak areas or peak heights in relation to those of standards chromatographed under the same conditions.

DETERMINATION OF SOLUBILITY OF ESTER PRODRUGS OF 6-MNA

The solubility of the ester prodrugs of 6-MNA was determined in 0.05 M phosphate buffer of pH 7.4 at 25 °C. Excess amount of the powdered prodrug was added to 2-5 ml of the buffer in screw-capped test tubes. The suspension was vortexed for 10 min and kept in a shaking incubator maintained at 25 °C for 24 h. The suspension was transferred to a 10 ml-glass syringe maintained at 25 °C and filtered through a 0.45 μ membrane filter in a warm test tube. After making appropriate dilutions in the same buffer, 20 μl of the solution was injected for HPLC analysis and the area under the curve was measured. The concentration of the compound was calculated from the standard plots obtained on the same day under similar conditions. Determinations were performed in triplicate for each compound. The results are listed in Table 26.
Table 26: Aqueous solubilities of various prodrugs of 6-MNA at 25 °C in 0.05 M phosphate buffer of pH 7.4.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solubility ± SEM µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 6-MNA</td>
<td>20.14 ± 0.56</td>
</tr>
<tr>
<td>133 H H</td>
<td>15.58 ± 0.18</td>
</tr>
<tr>
<td>134 H CH₃</td>
<td>46.77 ± 0.68</td>
</tr>
<tr>
<td>135 H CH₂CH₃</td>
<td>37.98 ± 0.05</td>
</tr>
<tr>
<td>136 H CH₂CH₂CH₃</td>
<td>7.95 ± 0.08</td>
</tr>
<tr>
<td>137 H CH(CH₃)₂</td>
<td>15.43 ± 0.23</td>
</tr>
<tr>
<td>138 H CH₂CH₂CH₂CH₃</td>
<td>3.54 ± 0.07</td>
</tr>
<tr>
<td>139 H CH(CH₃)CH₂CH₃</td>
<td>18.63 ± 0.21</td>
</tr>
<tr>
<td>140 H C(CH₃)₃</td>
<td>15.97 ± 0.12</td>
</tr>
<tr>
<td>141 H CH₃</td>
<td>1.55 ± 0.05</td>
</tr>
<tr>
<td>142 CH₃</td>
<td>45.44 ± 0.28</td>
</tr>
<tr>
<td>143 CH₂CH₃</td>
<td>CH₂CH₃</td>
</tr>
<tr>
<td>144 CH₂CH₂CH₃</td>
<td>CH₂CH₂CH₃</td>
</tr>
<tr>
<td>145 CH(CH₃)₂</td>
<td>CH(CH₃)₂</td>
</tr>
<tr>
<td>146 CH₂CH=CH₂</td>
<td>CH₂CH=CH₂</td>
</tr>
</tbody>
</table>
### DETERMINATION OF LIPOPHILICITY PARAMETERS OF ESTER PRODRUGS OF 6-MNA

The partition coefficient of ester derivatives of 6-MNA was determined in octanol-buffer system. The aqueous phase was 0.05 M phosphate buffer of pH 7.4. The buffer solution and octanol were mutually saturated at 25 °C before use. The traditional shake flask method was used, and concentrations were determined by HPLC to afford rapid evaluation and better reliability. The ester derivatives were dissolved in octanol (2 ml) in 10 ml-screw-capped tubes. After addition of the buffer.
(5 ml), the two phases were mixed on a cyclo-mixer for 15 min and kept in a shaking water bath maintained at 25 °C for 8 h. The tubes were centrifuged at 3000 rpm for half an hour. Octanol layer (1 ml) was removed, diluted, 20 μl of the resulting solution was injected into HPLC column and peak area \((AUC_{\text{oct}})\) was measured. The buffer layer was also removed, 20 μl of this solution was injected and the corresponding peak area was obtained \((AUC_{\text{buffer}})\). The partition coefficient \((P)\) was determined from the following expression:

\[
P = \frac{AUC_{\text{oct}}}{AUC_{\text{buffer}}} \times \text{dilution factor} \quad \text{(19)}
\]

For each compound, determinations were carried out in triplicate and the log \(P\) values are listed in Table 27.

The lipophilicity of these prodrug derivatives was also evaluated by means of reversed-phase chromatography\textsuperscript{153}. In this method, the capacity factor \((k')\) of a solute was taken as a measure of the relative lipophilicity and was calculated as:

\[
k' = \frac{(t_R - t_0)}{t_0} \quad \text{(20)}
\]

where \(t_R\) is the retention time of the solute and \(t_0\) is the elution time of the solvent. The \(k'\) values were determined using acetonitrile/phosphate buffer (0.02 M, 4.0 pH) in 70:30 ratio and methanol/phosphate buffer (0.02 M, 4.0 pH) in 80:20 ratio. The flow rate was maintained at 1 ml/min and column effluent was monitored at 230 nm. The values are listed in Table 27.
Table 27: Lipophilicity parameters of various prodrugs of 6-MNA.

<table>
<thead>
<tr>
<th>Compound</th>
<th>log $k'_a$</th>
<th>log $k'_b$</th>
<th>log $P$ (obs)</th>
<th>log $P$ (cal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MNA</td>
<td>-</td>
<td>-</td>
<td>2.811</td>
<td>2.87</td>
</tr>
<tr>
<td>R1</td>
<td>R2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>H</td>
<td>H</td>
<td>-0.253</td>
<td>-0.4102</td>
</tr>
<tr>
<td>134</td>
<td>H</td>
<td>CH$_3$</td>
<td>-0.1599</td>
<td>-0.3276</td>
</tr>
<tr>
<td>135</td>
<td>H</td>
<td>CH$_2$CH$_3$</td>
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<td>-0.2581</td>
</tr>
<tr>
<td>136</td>
<td>H</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>0.0058</td>
<td>-0.1713</td>
</tr>
<tr>
<td>137</td>
<td>H</td>
<td>CH(CH$_3$)$_2$</td>
<td>0.0019</td>
<td>-0.1883</td>
</tr>
<tr>
<td>138</td>
<td>H</td>
<td>CH$_2$CH$_2$CH$_2$CH$_3$</td>
<td>0.0985</td>
<td>-0.0659</td>
</tr>
<tr>
<td>139</td>
<td>H</td>
<td>CH(CH$_3$)$_2$CH$_2$CH$_3$</td>
<td>0.0799</td>
<td>-0.1009</td>
</tr>
<tr>
<td>140</td>
<td>H</td>
<td>C(CH$_3$)$_3$</td>
<td>0.1341</td>
<td>-0.0621</td>
</tr>
<tr>
<td>141</td>
<td>H</td>
<td></td>
<td>0.1999</td>
<td>0.0443</td>
</tr>
<tr>
<td>142</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>-0.0878</td>
<td>-0.2640</td>
</tr>
<tr>
<td>143</td>
<td>CH$_2$CH$_3$</td>
<td>CH$_2$CH$_3$</td>
<td>0.0680</td>
<td>-0.1260</td>
</tr>
<tr>
<td>144</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>0.2615</td>
<td>0.0751</td>
</tr>
<tr>
<td>145</td>
<td>CH(CH$_3$)$_2$</td>
<td>CH(CH$_3$)$_2$</td>
<td>0.2604</td>
<td>0.0572</td>
</tr>
<tr>
<td>146</td>
<td>CH$_2$CH=CH$_2$</td>
<td>CH$_2$CH=CH$_2$</td>
<td>0.1888</td>
<td>-0.0369</td>
</tr>
<tr>
<td>147</td>
<td></td>
<td></td>
<td>0.7680</td>
<td>0.6568</td>
</tr>
</tbody>
</table>

180
<table>
<thead>
<tr>
<th>148</th>
<th>(NR&lt;sub&gt;1&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;)</th>
<th></th>
<th>-0.0178</th>
<th>-0.1665</th>
<th>2.71</th>
<th>3.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>(NR&lt;sub&gt;1&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;)</td>
<td></td>
<td>-0.1047</td>
<td>-0.2978</td>
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<td>1.99</td>
</tr>
<tr>
<td>150</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>-0.2784</td>
<td>-0.3900</td>
<td>1.58</td>
<td>1.78</td>
</tr>
<tr>
<td>151</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>-0.2072</td>
<td>-0.3276</td>
<td>1.98</td>
<td>2.30</td>
</tr>
<tr>
<td>152</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>-0.4364</td>
<td>-0.4676</td>
<td>1.41</td>
<td>1.12</td>
</tr>
<tr>
<td>153</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>154</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>0.1630</td>
<td>-0.0548</td>
<td>3.04</td>
<td>3.16</td>
</tr>
<tr>
<td>155</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>0.2678</td>
<td>0.0600</td>
<td>3.60</td>
<td>3.68</td>
</tr>
<tr>
<td>156</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>0.3797</td>
<td>0.1888</td>
<td>4.14</td>
<td>4.20</td>
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<td>157</td>
<td>CH(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td>0.3674</td>
<td>0.1663</td>
<td>4.00</td>
<td>4.20</td>
</tr>
<tr>
<td>158</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>0.4961</td>
<td>0.3245</td>
<td>4.75</td>
<td>4.72</td>
</tr>
<tr>
<td>159</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td>0.4861</td>
<td>0.3066</td>
<td>4.71</td>
<td>4.72</td>
</tr>
</tbody>
</table>

**k'_a** : Capacity factor in mobile phase acetonitrile/phosphate buffer (0.02 M, 4.0 pH) in 70:30 ratio

**k'_b** : Capacity factor in mobile phase methanol/phosphate buffer (0.02 M, 4.0 pH) in 80:20 ratio

**P<sub>obs</sub>** : Observed partition coefficient in octanol/phosphate buffer of pH 7.4

**P<sub>cal</sub>** : Calculated partition coefficient from Rekker fragmentation constants

**P<sub>i</sub>** : Partition coefficient in octanol/0.1 M HCl system.

The log partition coefficient (log P) of the ester prodrugs was also calculated using Rekker fragmentation constants<sup>130,131</sup>. Examples of the calculation for compounds 135 and 155 are given below and the calculated log P values for various esters are listed in Table 27.
\[
\begin{align*}
\text{Fragment} & \quad \text{Contribution} \\
 f (\text{C}_{10}\text{H}_7) & \quad 3.113 \\
 - f (\text{H}) & \quad -0.182 \\
 f_{\text{ar}} (\text{H}) & \quad -0.439 \\
 2f (\text{CH}_3) & = 2 (0.701) \quad 1.402 \\
 3f (\text{CH}_2) & = 3 (0.519) \quad 1.038 \\
 f (\text{COO}) & \quad -1.251 \\
 \text{Log } P_{\text{obs}} & = 3.60 \quad \text{Log } P_{\text{cal}} = 3.681 \\
\end{align*}
\]

\[
\begin{align*}
\text{Fragment} & \quad \text{Contribution} \\
 f (\text{C}_{10}\text{H}_7) & \quad 3.113 \\
 - f (\text{H}) & \quad -0.182 \\
 f_{\text{ar}} (\text{H}) & \quad -0.439 \\
 2f (\text{CH}_3) & = 2 (0.701) \quad 1.402 \\
 3f (\text{CH}_2) & = 3 (0.519) \quad 1.557 \\
 f (\text{COO}) & \quad -1.251 \\
 f (\text{CONH}) & \quad -2.446 \\
 \text{p.e.}(1) & \quad 0.867 \\
 \text{Log } P_{\text{obs}} & = 2.65 \quad \text{Log } P_{\text{cal}} = 2.621 \\
\end{align*}
\]
HYDROLYSIS AND STABILITY STUDIES ON ESTER PRODRUGS OF 6-MNA

Hydrolysis of ester prodrugs of 6-MNA was studied at near physiological conditions at pH 7.4 in 0.05 M phosphate buffer at a constant temperature of 37 °C. The reaction was initiated by adding 50-100 µl of the stock solution (in CH$_3$CN) of the ester to 20 ml of preheated buffer solution in screw-capped test tubes. The final concentration of the compounds was in the range of 1.8 x 10$^{-6}$M to 2.0 x 10$^{-5}$M. The solution was kept in water bath at a constant temperature and at appropriate intervals, samples were withdrawn and chromatographed.

In case of esters, where rate of hydrolysis was found to be very slow in preliminary studies, 2 ml-aliquots of the ester solution were transferred to glass ampoules, flame sealed and kept immersed in water bath maintained at 37 °C for the entire study. Several of these ampoules were also refrigerated immediately after flame sealing and were later used as controls for the initial time points. At known appropriate time intervals ampoules were removed from the water bath and refrigerated. All the ampoules were removed from the refrigerator at the end of the study, allowed to attain room temperature and analysed on the same day by HPLC. Pseudo-first-order rate constants ($k_{obs}$) and half-lives ($t_{1/2}$) of overall degradations were determined from the slopes of linear plots obtained by plotting log (% of prodrug remaining) versus time, as per the expressions 21.
and 22. The values of rate constants and half-lives obtained are listed in Table 28 along with the correlation coefficients showing the linearity of pseudo-first-order plots.

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

Table 28: Rate data for the hydrolysis of various ester prodrugs of 6-MNA in phosphate buffer of pH 7.4 at 37 °C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( k(h^{-1}) )</th>
<th>( t_{1/2}(h) )</th>
<th>Statistical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>H</td>
<td>0.016399</td>
<td>42.26</td>
</tr>
<tr>
<td>134</td>
<td>H</td>
<td>0.021048</td>
<td>32.92</td>
</tr>
<tr>
<td>135</td>
<td>H</td>
<td>0.021861</td>
<td>31.70</td>
</tr>
<tr>
<td>136</td>
<td>H</td>
<td>0.026600</td>
<td>26.05</td>
</tr>
<tr>
<td>137</td>
<td>H</td>
<td>0.024048</td>
<td>28.82</td>
</tr>
<tr>
<td>138</td>
<td>H</td>
<td>0.029591</td>
<td>23.42</td>
</tr>
<tr>
<td>139</td>
<td>H</td>
<td>0.028129</td>
<td>24.64</td>
</tr>
<tr>
<td>140</td>
<td>H</td>
<td>0.017704</td>
<td>39.14</td>
</tr>
<tr>
<td>141</td>
<td>H</td>
<td>0.041838</td>
<td>16.56</td>
</tr>
<tr>
<td>142</td>
<td>CH₃</td>
<td>0.003324</td>
<td>208.48</td>
</tr>
</tbody>
</table>
Ester prodrugs 154 to 159, having large half-lives, were subjected to hydrolysis at pH 7.4 at elevated temperatures. The pseudo-first-order rate constants and half-lives are listed in Table 29. The activation energy of the reactions was calculated from the rate constants at elevated temperatures using Arrhenius equation:

\[ k = A \cdot e^{-\frac{E_a}{RT}} \] (23)

where \( E_a \) is the activation energy, \( R \) is the gas constant, \( A \) is the frequency factor, and \( T \) is the temperature in absolute. From the activation energies thus obtained, rate constants at 37 °C and corresponding half-lives were calculated.
Table 29: Rate constants ($k$) and half-lives ($t_{1/2}$) for the hydrolysis of various alkyl esters of 6-MNA in 0.05M phosphate buffer of pH 7.4 at elevated temperatures

![Chemical structure of 6-MNA](image)

(154-159)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Temp. (°C)</th>
<th>$k$ (h$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
<th>n</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>154</td>
<td>CH$_3$</td>
<td>60</td>
<td>2.127x10$^{-2}$</td>
<td>32.58</td>
<td>11</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td>6.257x10$^{-2}$</td>
<td>11.05</td>
<td>10</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>1.627x10$^{-1}$</td>
<td>4.26</td>
<td>10</td>
<td>1.000</td>
</tr>
<tr>
<td>155</td>
<td>CH$_2$CH$_3$</td>
<td>59</td>
<td>9.061x10$^{-3}$</td>
<td>76.48</td>
<td>10</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69</td>
<td>2.558x10$^{-2}$</td>
<td>27.10</td>
<td>11</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79</td>
<td>6.740x10$^{-2}$</td>
<td>10.28</td>
<td>11</td>
<td>0.999</td>
</tr>
<tr>
<td>156</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>80</td>
<td>6.821x10$^{-2}$</td>
<td>10.16</td>
<td>9</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84</td>
<td>1.007x10$^{-1}$</td>
<td>6.88</td>
<td>6</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>1.667x10$^{-1}$</td>
<td>4.16</td>
<td>7</td>
<td>0.999</td>
</tr>
<tr>
<td>157</td>
<td>CH(CH$_3$)$_2$</td>
<td>80</td>
<td>1.875x10$^{-2}$</td>
<td>36.96</td>
<td>10</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84</td>
<td>2.611x10$^{-2}$</td>
<td>26.54</td>
<td>5</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>4.481x10$^{-2}$</td>
<td>15.46</td>
<td>5</td>
<td>1.000</td>
</tr>
<tr>
<td>158</td>
<td>CH$_2$CH$_2$CH$_2$CH$_3$</td>
<td>70</td>
<td>2.169x10$^{-2}$</td>
<td>31.95</td>
<td>6</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>5.455x10$^{-2}$</td>
<td>12.70</td>
<td>7</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>1.244x10$^{-1}$</td>
<td>5.57</td>
<td>7</td>
<td>0.999</td>
</tr>
<tr>
<td>159</td>
<td>CH$_2$CH(CH$_3$)$_2$</td>
<td>70</td>
<td>1.675x10$^{-2}$</td>
<td>41.37</td>
<td>7</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>3.866x10$^{-2}$</td>
<td>17.92</td>
<td>7</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90</td>
<td>9.789x10$^{-2}$</td>
<td>7.08</td>
<td>7</td>
<td>1.000</td>
</tr>
</tbody>
</table>

$k$ : Pseudo-first-order rate constant  
$t_{1/2}$ : Half-life  
n : Number of observations  
r : Correlation coefficient.

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pH-hydrolysis profiles of $N,N$-dimethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (142) and methyl 6-methoxy-2-naphthylacetate (154), were determined over a pH range of 1.2 to 9.0 to find the pH of maximum stability (Table 30 and 31). The buffers used were hydrochloric acid, acetate, phosphate and carbonate buffers$^{154,155}$. A constant ionic strength of 0.5 was maintained by adding calculated amounts of potassium chloride.

Table 30: Rate data for the hydrolysis of $N,N$-dimethylcarbamoylmethyl 6-methoxy-2-naphthylacetate (142) in aqueous buffers (pH 1.2-9) at 70 °C.

<table>
<thead>
<tr>
<th>pH</th>
<th>$k$ (h$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
<th>n</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.20</td>
<td>0.17242</td>
<td>4.02</td>
<td>8</td>
<td>0.999</td>
</tr>
<tr>
<td>1.78</td>
<td>0.04203</td>
<td>16.49</td>
<td>5</td>
<td>0.999</td>
</tr>
<tr>
<td>2.80</td>
<td>0.00357</td>
<td>193.91</td>
<td>6</td>
<td>0.999</td>
</tr>
<tr>
<td>4.28</td>
<td>0.00222</td>
<td>312.25</td>
<td>7</td>
<td>0.999</td>
</tr>
<tr>
<td>4.86</td>
<td>0.00283</td>
<td>244.78</td>
<td>7</td>
<td>0.999</td>
</tr>
<tr>
<td>5.85</td>
<td>0.00910</td>
<td>76.14</td>
<td>6</td>
<td>1.000</td>
</tr>
<tr>
<td>6.89</td>
<td>0.04623</td>
<td>14.98</td>
<td>7</td>
<td>1.000</td>
</tr>
<tr>
<td>7.88</td>
<td>0.35300</td>
<td>1.96</td>
<td>7</td>
<td>0.997</td>
</tr>
<tr>
<td>8.95</td>
<td>4.28166</td>
<td>0.16</td>
<td>6</td>
<td>0.999</td>
</tr>
</tbody>
</table>

$k$ : Pseudo-first-order rate constant
$t_{1/2}$ : Half-life
n : Number of observations
r : Correlation coefficient.

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Table 31: Rate data for the hydrolysis of methyl 6-methoxy-2-naphthylacetate (154) in aqueous buffers (pH 1.2-9) at 70 °C.

![Chemical Structure](#)

<table>
<thead>
<tr>
<th>pH</th>
<th>$k$ (h$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
<th>n</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.20</td>
<td>0.83823</td>
<td>0.83</td>
<td>7</td>
<td>0.999</td>
</tr>
<tr>
<td>2.10</td>
<td>0.12480</td>
<td>5.55</td>
<td>6</td>
<td>1.000</td>
</tr>
<tr>
<td>3.10</td>
<td>0.01232</td>
<td>56.26</td>
<td>7</td>
<td>1.000</td>
</tr>
<tr>
<td>4.29</td>
<td>0.001685</td>
<td>411.25</td>
<td>5</td>
<td>0.999</td>
</tr>
<tr>
<td>4.87</td>
<td>0.000970</td>
<td>714.08</td>
<td>5</td>
<td>0.999</td>
</tr>
<tr>
<td>5.95</td>
<td>0.00361</td>
<td>191.99</td>
<td>6</td>
<td>1.000</td>
</tr>
<tr>
<td>6.90</td>
<td>0.02514</td>
<td>27.57</td>
<td>7</td>
<td>1.000</td>
</tr>
<tr>
<td>7.88</td>
<td>0.20386</td>
<td>3.40</td>
<td>5</td>
<td>0.999</td>
</tr>
<tr>
<td>8.92</td>
<td>3.09276</td>
<td>0.22</td>
<td>5</td>
<td>1.000</td>
</tr>
</tbody>
</table>

$k$ : Pseudo-first-order rate constant  
$t_{1/2}$ : Half-life  
n : Number of observations  
r : Correlation coefficient.

Pseudo-first-order rate constants for these esters 142 and 154 were determined at various temperatures at pH 4.5, range of maximum stability being pH 4 to 5 (Table 32).
The rate constants and shelf-lives \( t_{10} \) were predicted at room temperature \((20 \, ^\circ C)\) on the basis of linear relationship between \( \log k \) and \( 1/T \) (Arrhenius equation) and equation 24,

\[
t_{10} = 0.104 / k_{20}
\]  

where \( k_{20} \) is the first-order rate constant at \( 20 \, ^\circ C \).

**Table 32: Rate data for the hydrolysis of \( N,N \)-dimethyl-carbamoylmethyl 6-methoxy-2-naphthylacetate (142) and methyl 6-methoxy-2-naphthylacetate (154) in buffer solution of pH 4.5 at different temperatures.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Temp (°C)</th>
<th>( 10^{-3} x k ) (h(^{-1}))</th>
<th>( t_{1/2} ) (h)</th>
<th>Statistical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>142</td>
<td>80</td>
<td>5.162</td>
<td>134.3</td>
<td>7 0.995</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>8.776</td>
<td>79.0</td>
<td>7 1.000</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>11.792</td>
<td>58.8</td>
<td>7 0.998</td>
</tr>
<tr>
<td>154</td>
<td>80</td>
<td>2.028</td>
<td>341.6</td>
<td>7 0.997</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>3.779</td>
<td>183.4</td>
<td>6 0.999</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>4.831</td>
<td>143.3</td>
<td>7 0.998</td>
</tr>
</tbody>
</table>

\( k \) : Pseudo-first-order rate constant  
\( t_{1/2} \) : Half-life  
\( n \) : Number of observations  
\( r \) : Correlation coefficient.
ENZYMATIC HYDROLYSIS OF ESTER PRODRUGS OF 6-MNA

The hydrolysis of the ester prodrugs of 6-MNA, having solubility of more than 5 μg/ml, was studied in 80% human plasma at pH 7.4. The reaction was initiated by adding 20-50 μl of a stock solution of the ester in acetonitrile to 2-5 ml of preheated plasma solution, the final concentration of the compounds being 4.24 x 10^-5 to 1 x 10^-4 M. The solution was kept in water bath at 37 °C, at appropriate time intervals samples of 100 to 250 μl were withdrawn 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 analysed by HPLC for the remaining ester prodrug. The values of rate constants (k) and half-lives (t_{1/2}) were calculated from the slopes of linear plots of logarithms of remaining prodrug versus time using linear regression (Table 33).

The hydrolysis of simple alkyl esters 154 to 159 was also studied in 0.2% liver homogenate at 37 °C. Liver homogenate was prepared by homogenising the sections of rat livers in tissue homogeniser containing a glass body and a teflon pestle at 0-5 °C. The homogenate was diluted with 0.05 M phosphate buffer (pH 7.4) to make a 10% w/v liver homogenate, and centrifuged at 10,000 rpm at 4 °C. The
supernatant was diluted and used for the experiments. The reactions were studied in a way similar to that described under plasma hydrolysis (Table 34).

**Table 33: Rate data for the hydrolysis of various ester prodrugs of 6-MNA in 80% human plasma (pH 7.4) at 37 °C.**

![Chemical structures](Image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>k&lt;sub&gt;obs&lt;/sub&gt; (s&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (s)</th>
<th>Statistical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80% human plasma</td>
<td>80% human plasma</td>
<td>n</td>
</tr>
<tr>
<td>133</td>
<td>H</td>
<td>H</td>
<td>8.043 x 10&lt;sup&gt;-4&lt;/sup&gt;</td>
</tr>
<tr>
<td>134</td>
<td>H</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4.126 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>135</td>
<td>H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.493 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>136</td>
<td>H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>8.569 x 10&lt;sup&gt;-4&lt;/sup&gt;</td>
</tr>
<tr>
<td>137</td>
<td>H</td>
<td>CH(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.770 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>139</td>
<td>H</td>
<td>CH(CH&lt;sub&gt;3&lt;/sub&gt;)CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.067 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>140</td>
<td>H</td>
<td>C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.606 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>142</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>9.930 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
<tr>
<td>143</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>8.266 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
<tr>
<td>144</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.587 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
<tr>
<td>146</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2.586 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
<tr>
<td>148</td>
<td>(NR&lt;sub&gt;1&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>N</td>
<td>1.184 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 34: Rate data for the hydrolysis of various alkyl ester prodrugs of 6-MNA in 0.2% w/v liver homogenate (pH 7.4) at 37 °C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$k_{\text{obs}}$ (s$^{-1}$)</th>
<th>$t_{1/2}$ (s)</th>
<th>Statistical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2% w/v liver homogenate</td>
<td>0.2% w/v liver homogenate</td>
<td>( n )</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>154 CH$_3$</td>
<td>7.992 x 10$^{-3}$</td>
<td>87</td>
<td>6</td>
</tr>
<tr>
<td>155 CH$_2$CH$_3$</td>
<td>2.546 x 10$^{-2}$</td>
<td>27</td>
<td>6</td>
</tr>
</tbody>
</table>

$k_{\text{obs}}$: Pseudo-first-order rate constant
$t_{1/2}$: Half-life
\( n \): Number of observations
\( r \): Correlation coefficient.
<table>
<thead>
<tr>
<th></th>
<th>Compound</th>
<th>$k_{obs}$ ($10^{-2}$)</th>
<th>$t_{1/2}$</th>
<th>$n$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>156</td>
<td>$\text{CH}_2\text{CH}_2\text{CH}_3$</td>
<td>$5.808 \times 10^{-2}$</td>
<td>12</td>
<td>5</td>
<td>0.999</td>
</tr>
<tr>
<td>157</td>
<td>$\text{CH} (\text{CH}_3)_2$</td>
<td>$5.340 \times 10^{-3}$</td>
<td>130</td>
<td>6</td>
<td>0.998</td>
</tr>
<tr>
<td>158</td>
<td>$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$</td>
<td>$5.093 \times 10^{-3}$</td>
<td>14</td>
<td>5</td>
<td>0.989</td>
</tr>
<tr>
<td>159</td>
<td>$\text{CH}_2\text{CH} (\text{CH}_3)_2$</td>
<td>$3.273 \times 10^{-2}$</td>
<td>21</td>
<td>6</td>
<td>0.994</td>
</tr>
</tbody>
</table>

$k_{obs}$ : Pseudo-first-order rate constant  
$t_{1/2}$ : Half-life  
n : Number of observations  
r : Correlation coefficient.