

## Integrating Green Synthesis and Liquid-Liquid Extraction of Lidocaine in Deep Eutectic Solvents

Assunta Perri,<sup>#,a</sup> Leonardo C. Parrotta,<sup>#,a</sup> Stefania Gencarelli,<sup>a</sup> Roberta Sole,<sup>a</sup> Oana M. Dragostin,<sup>b</sup> Gabriela Guillena,<sup>c</sup> and Maria L. Di Gioia<sup>\*,a</sup>

<sup>a</sup> Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Arcavacata of Rende, Italy. E-mail: [ml.digioia@unical.it](mailto:ml.digioia@unical.it)

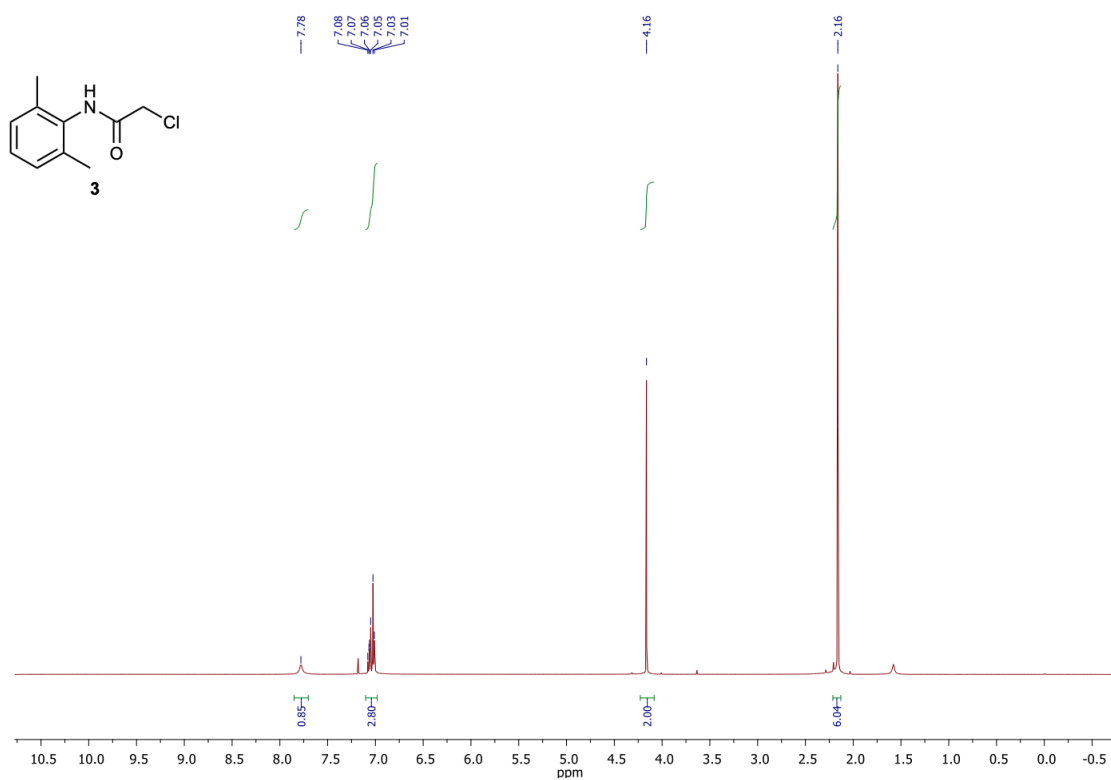
<sup>b</sup> Research Centre in the Medicinal-Pharmaceutical Field, Faculty of Medicine and Pharmacy, "Dunarea de Jos" University of Galati, 800010 Galati, Romania

<sup>c</sup> Department of Organic Chemistry, Institute of Organic Synthesis (ISO), University of Alicante, 03080 Alicante, Spain

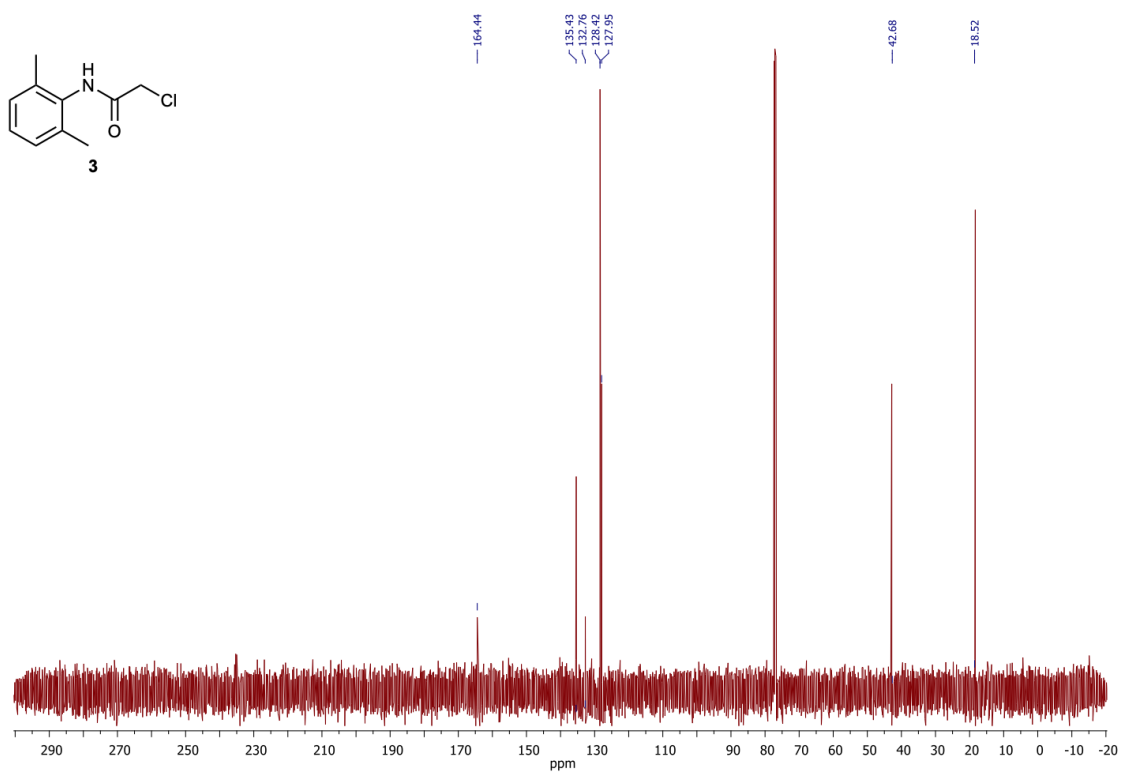
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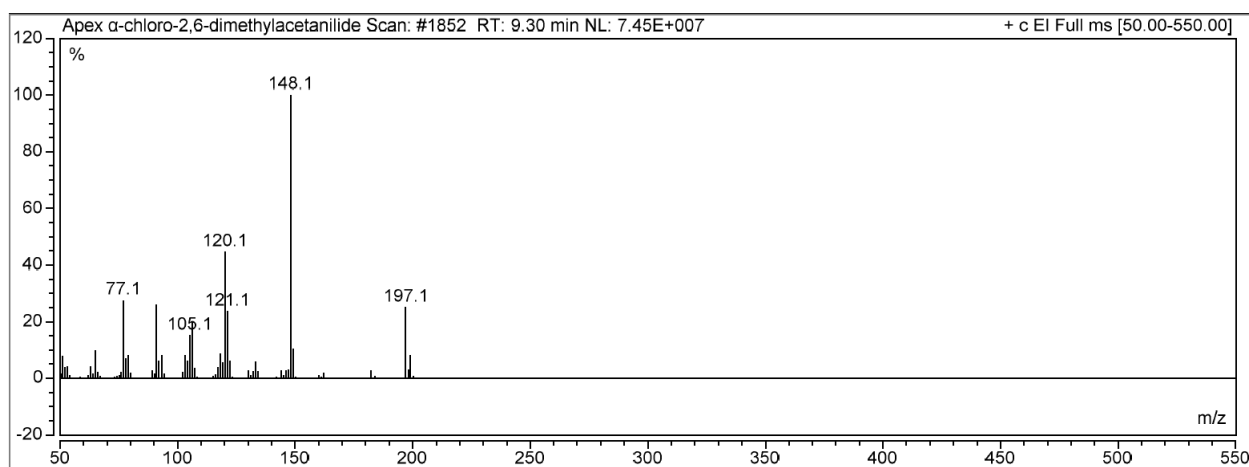
$^1\text{H}$  NMR spectrum of  $\alpha$ -chloro-2,6-dimethylacetanilide (**3**)



$^{13}\text{C}$  NMR spectrum of  $\alpha$ -chloro-2,6-dimethylacetanilide (**3**)

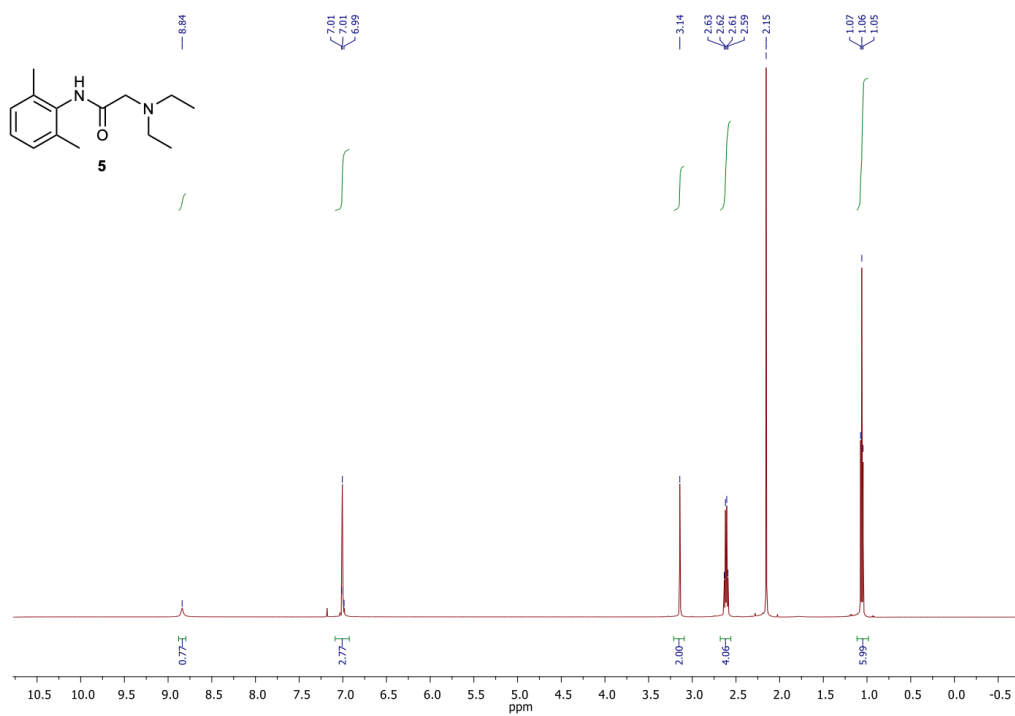


EL-Mass Spectrum of  $\alpha$ -chloro-2,6-dimethylacetanilide (**3**)

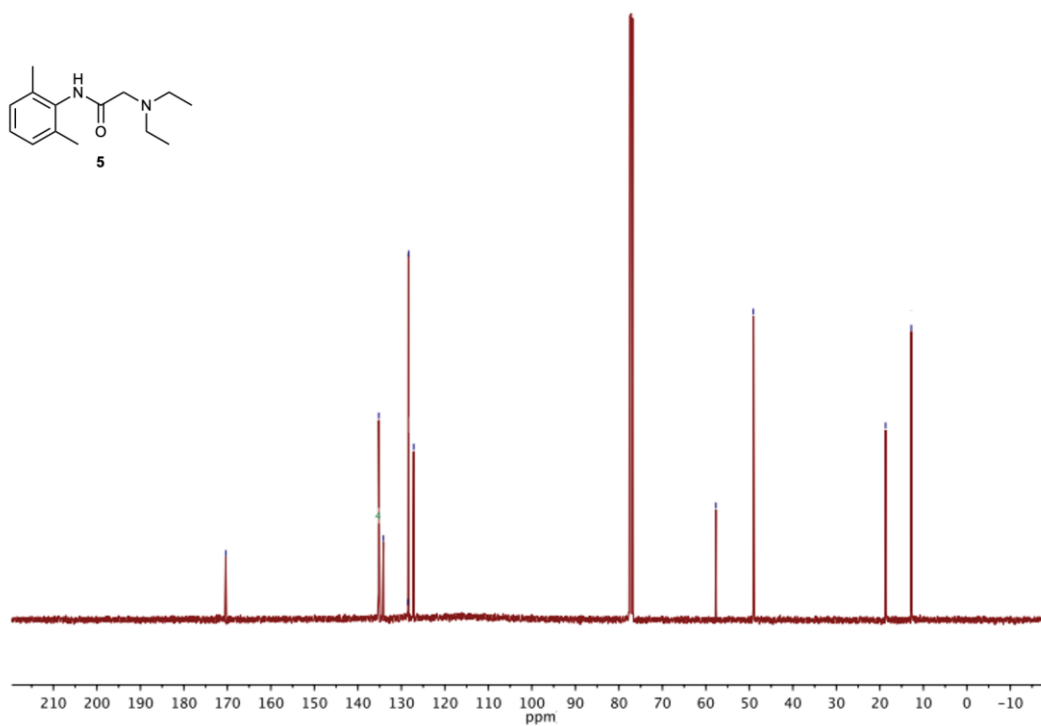




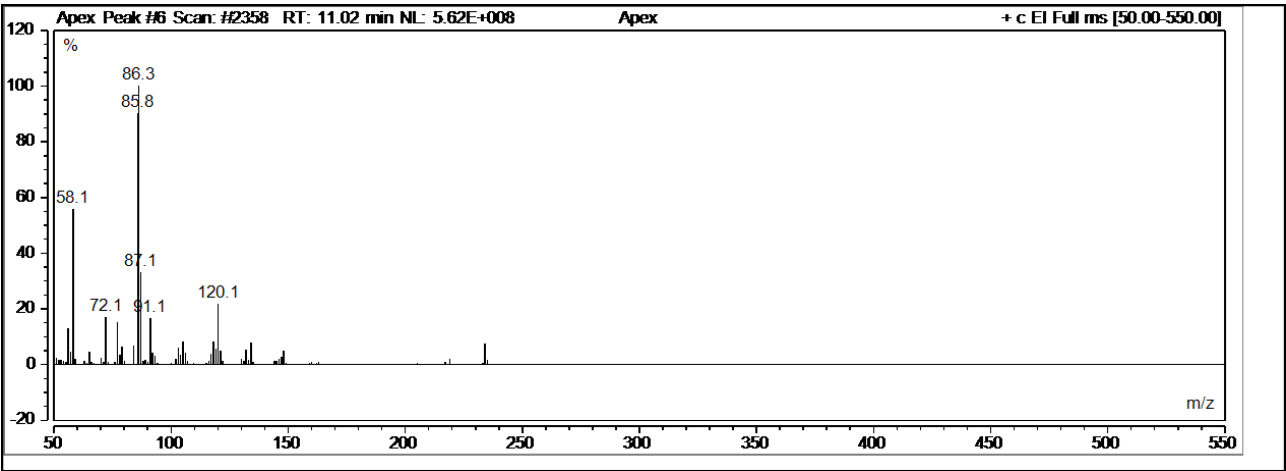
# <sup>1</sup>H NMR spectrum of Lidocaine (5)



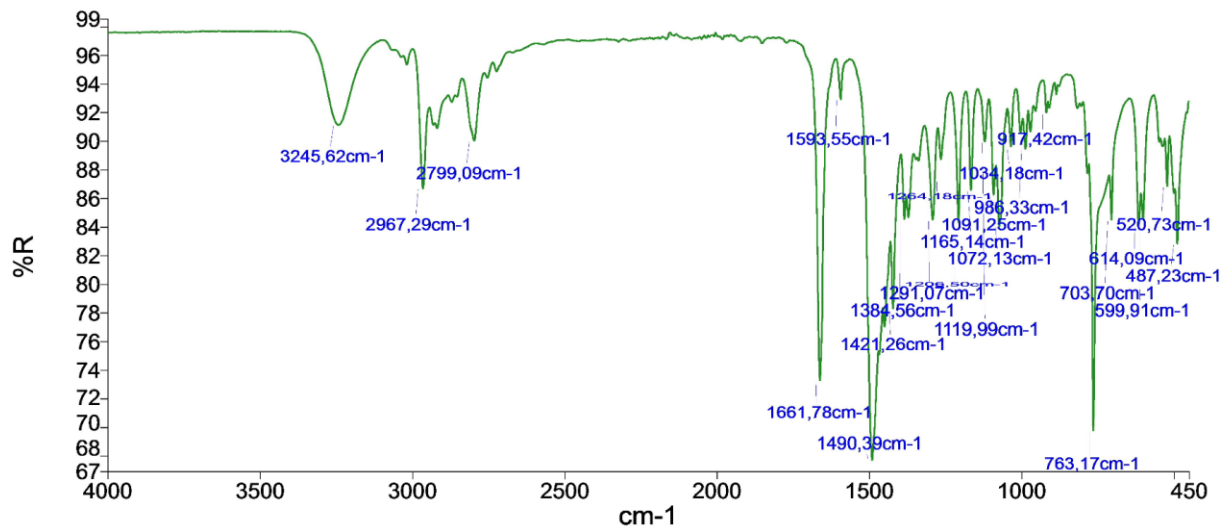
# <sup>13</sup>C NMR spectrum of Lidocaine (5)



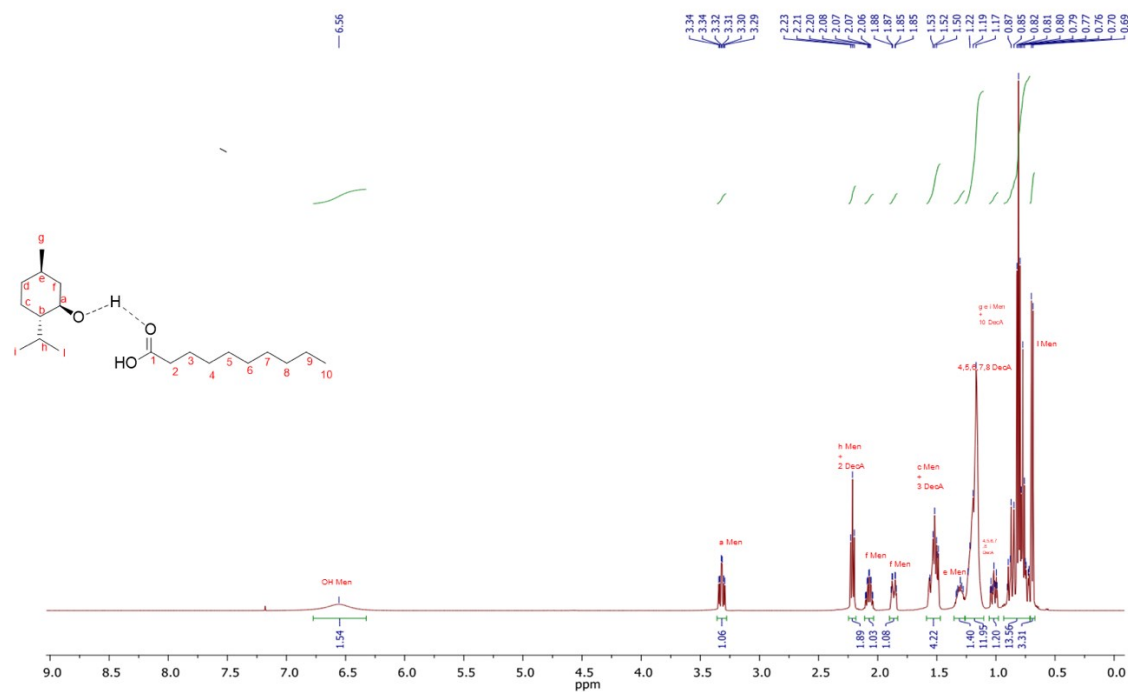
El-Mass spectrum of Lidocaine (5)



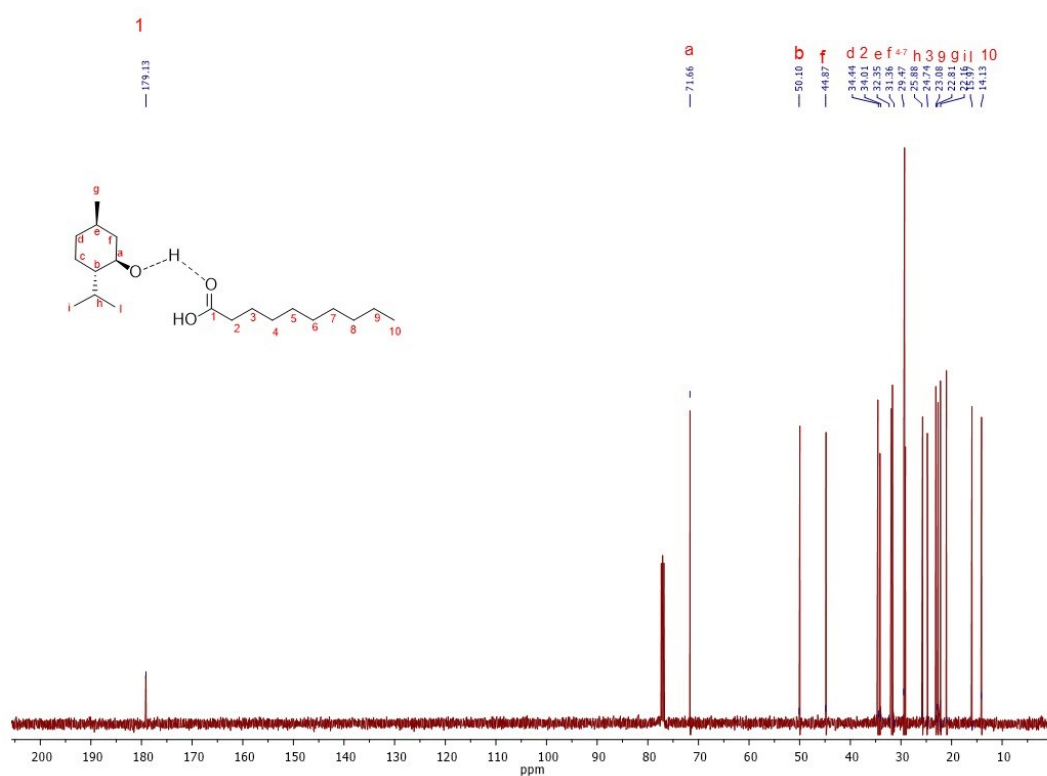
FT-IR spectrum of Lidocaine (5)



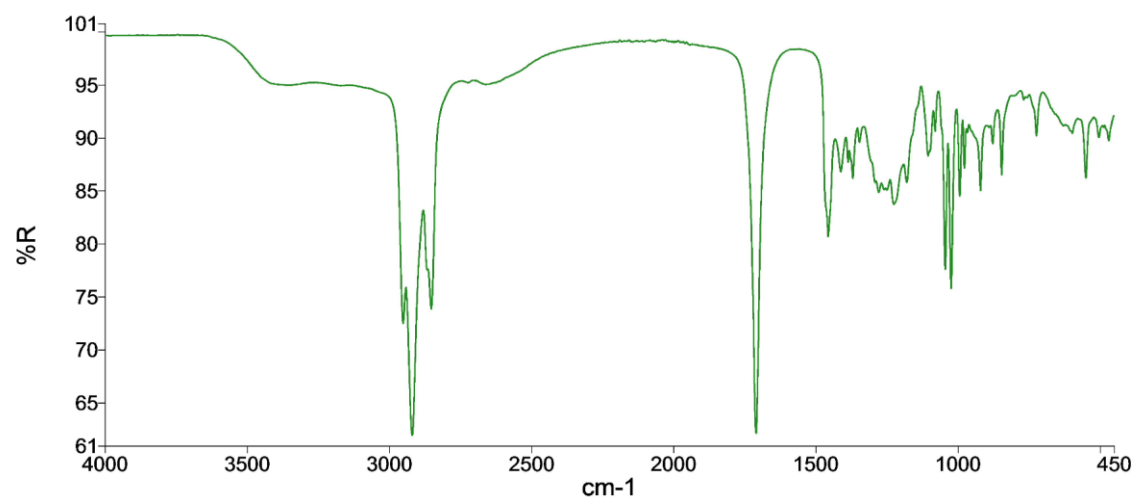
# <sup>1</sup>H NMR spectrum of L-Men:DecA (1:1) HDES



# <sup>13</sup>C NMR spectrum of L-Men:DecA HDES

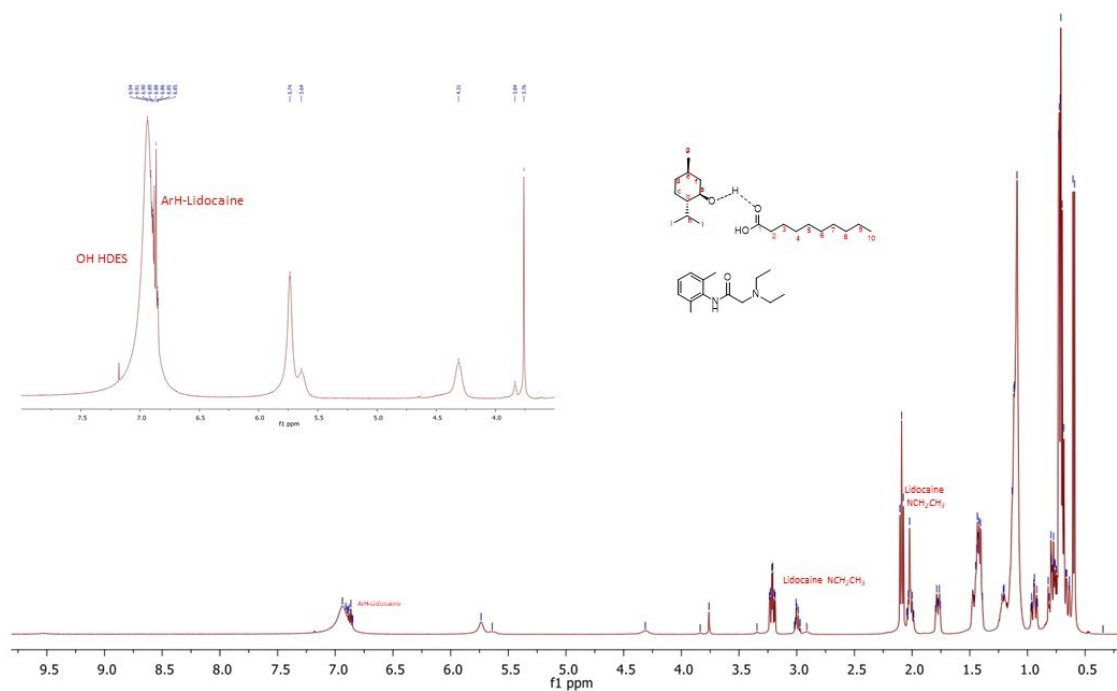


FT-IR spectrum of L-Men:DecA (1:1) HDES

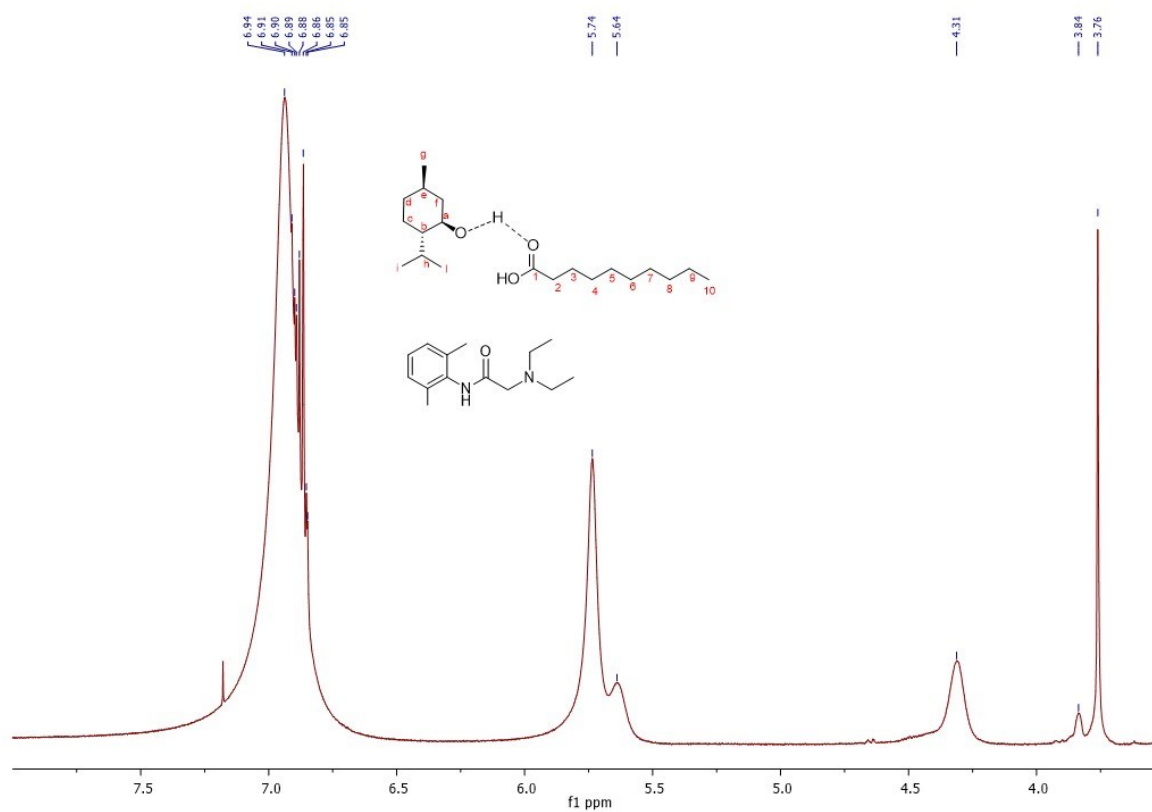




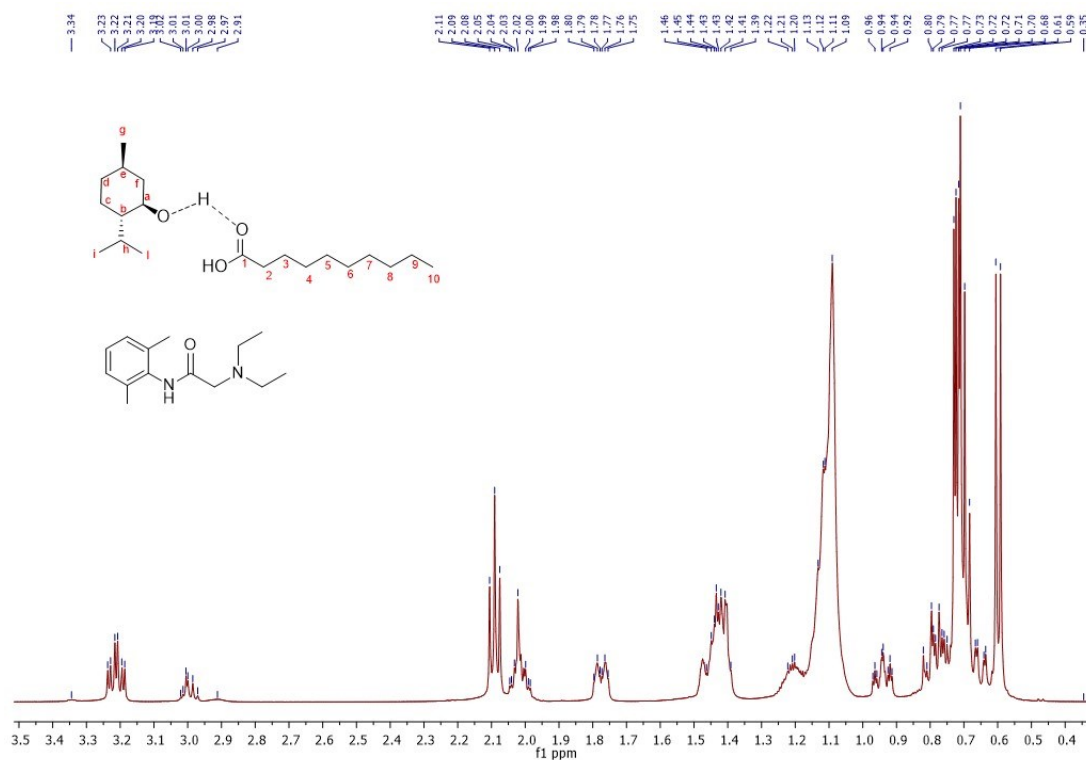
$^1\text{H}$  NMR spectrum of Lidocaine (5) extracted by L-Men:DecA (1:1) HDES



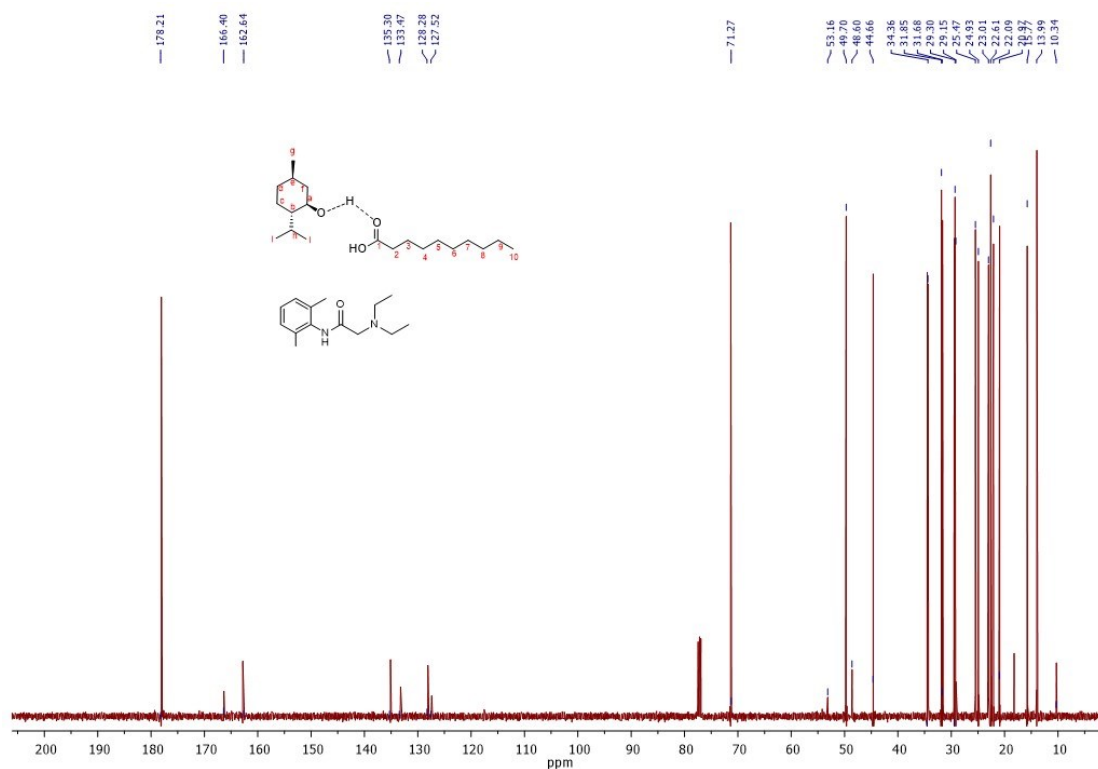
$^1\text{H}$  NMR spectrum of Lidocaine (5) extracted by L-Men:DecA (1:1) HDES :  
Expanded left region of the spectrum



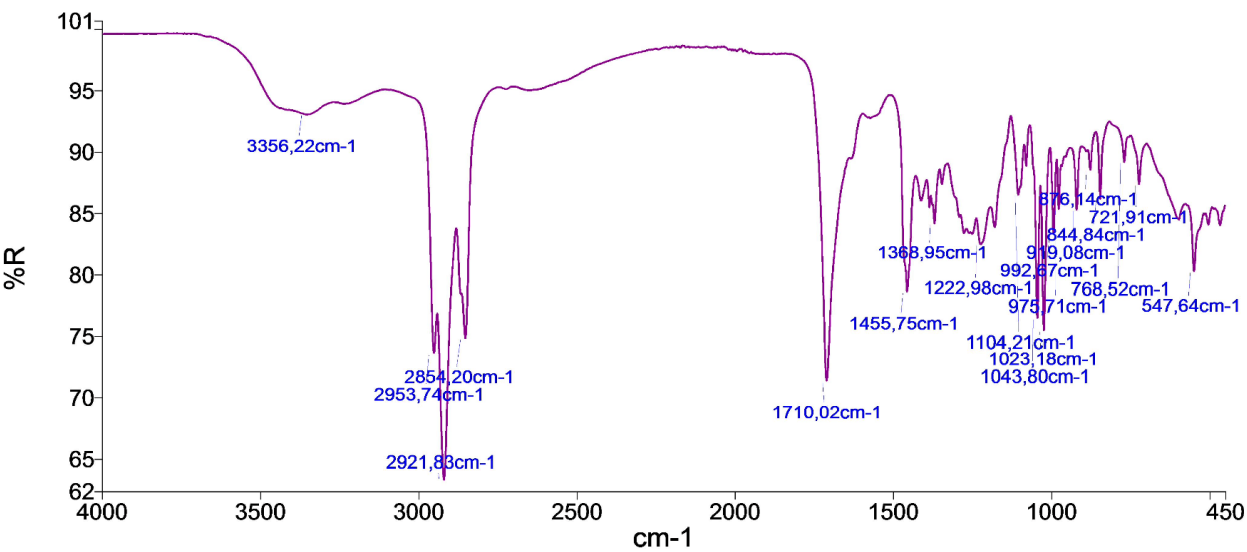
$^1\text{H}$  NMR spectrum of Lidocaine (5) extracted by L-Men:DecA (1:1) HDES :  
Expanded right region of the spectrum

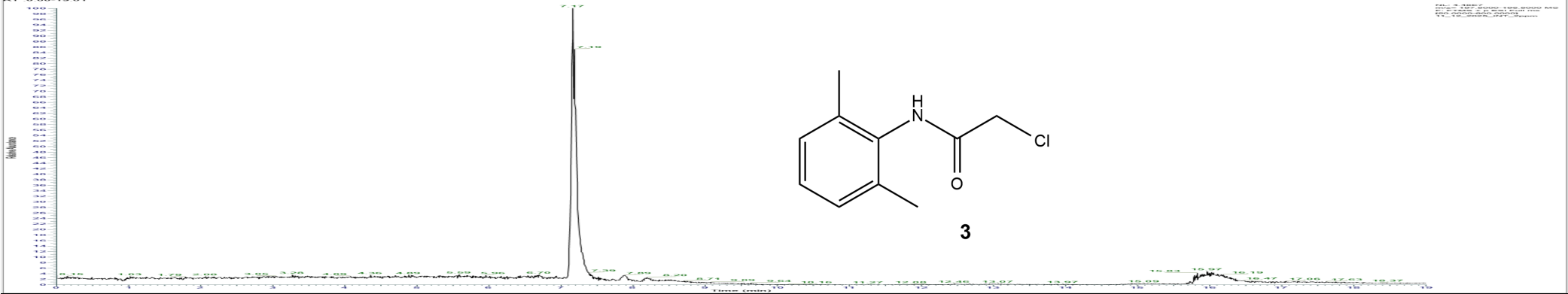


$^{13}\text{C}$  NMR spectrum of Lidocaine (5) extracted by L-Men:DecA (1:1) HDES

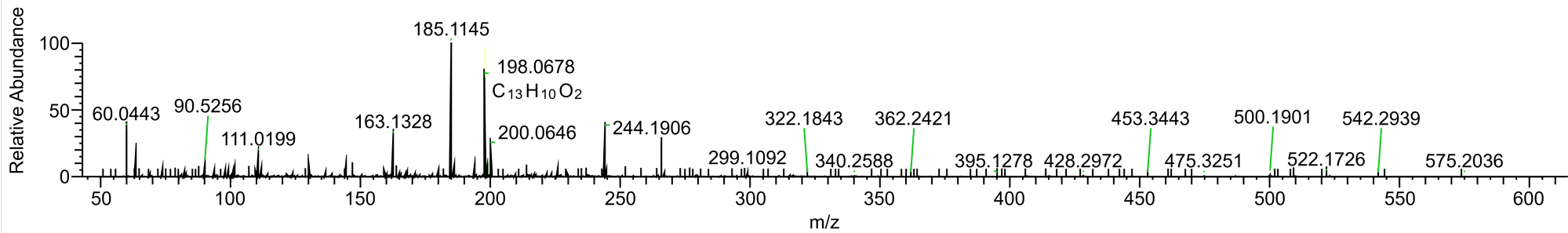


FT-IR spectrum of Lidocaine (5) extracted by L-Men:DecA HDES



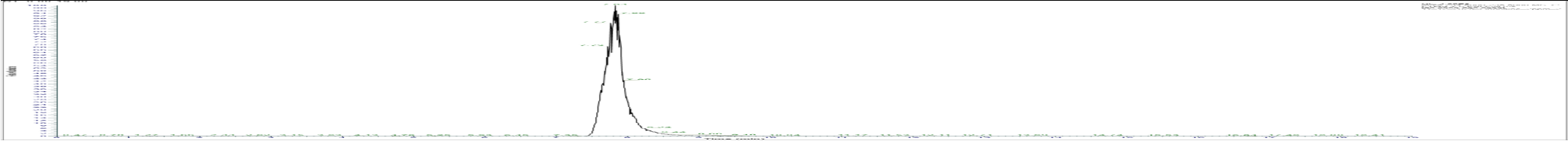


11\_12\_2025\_INT\_2ppm #1820-1879 RT: 7.11-7.35 AV: 30 NL: 1.90E7  
T: FTMS + p ESI Full ms [50.0000-600.0000]

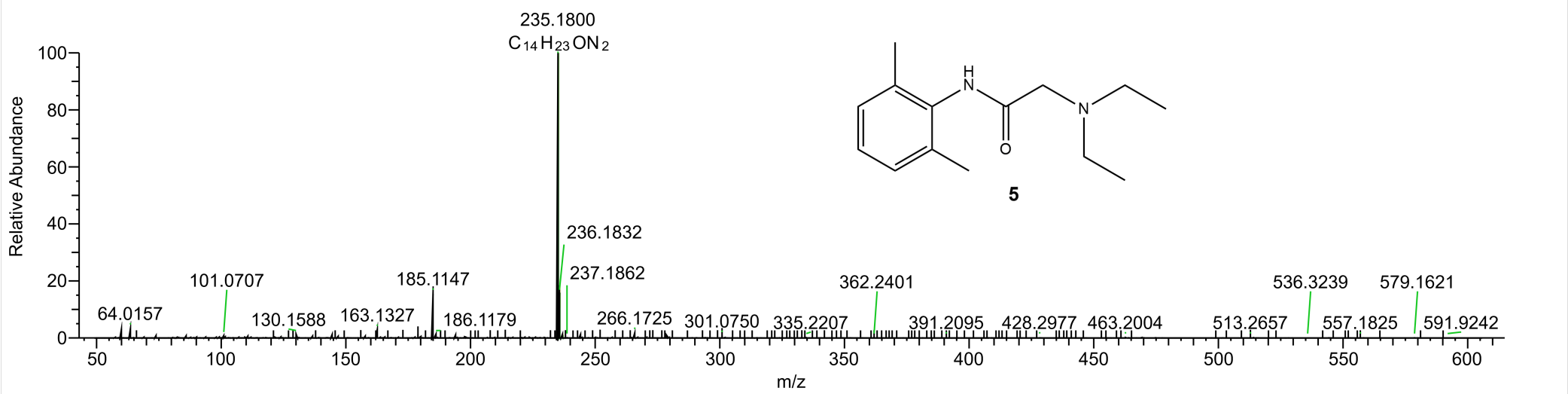


| Display | Detector... | File Name                                                  | Filter                                  | Trace Type | Mass Def... | Ranges   | Smoothing | Chemical... | Mass Tole... | Delay Time | Reference | Plot Oper... | Trace Typ... | Range2 | Comment |
|---------|-------------|------------------------------------------------------------|-----------------------------------------|------------|-------------|----------|-----------|-------------|--------------|------------|-----------|--------------|--------------|--------|---------|
| True    | MS          | D:\Xcalibur\Data\studenti\nov 2025\11_12_2025_INT_2ppm.raw | FTMS + p ESI Full ms [50.0000-600.0000] | Mass Range | MDF Ranges  | 198.0000 | None      |             | 0.5          | 0          | False     |              |              |        |         |
| False   |             |                                                            |                                         |            | MDF Ranges  |          |           |             | NaN          | 0          | False     |              |              |        |         |

| Peak Mass | Display Formula                                | S Fit            | RDB  | Delta [ppm] | Theo. mass | MSMS Matched Fragments |
|-----------|------------------------------------------------|------------------|------|-------------|------------|------------------------|
| 198.0678  | C <sub>13</sub> H <sub>10</sub> O <sub>2</sub> | 32.0577582461258 | 9.00 | 1.13        | 198.06753  | (Collection)           |



11\_12\_2025\_Linocaine\_2ppm\_2 #1926-2093 RT: 7.52-8.18 AV: 84 NL: 1.85E8  
T: FTMS + p ESI Full ms [50.0000-600.0000]

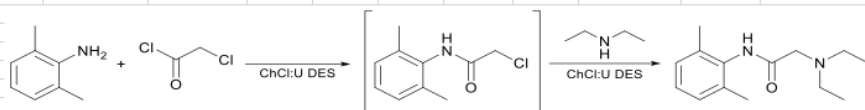


| Display | Detector... | File Name                                                          | Filter                                  | Trace Type | Mass Def... | Ranges   | Smoothing | Chemical... | Mass Tole... | Delay Time | Reference | Plot Oper... | Trace Typ... | Range2 | Comment |
|---------|-------------|--------------------------------------------------------------------|-----------------------------------------|------------|-------------|----------|-----------|-------------|--------------|------------|-----------|--------------|--------------|--------|---------|
| True    | MS          | D:\Xcalibur\Data\studenti\nov 2025\11_12_2025_Linocaine_2ppm_2.raw | FTMS + p ESI Full ms [50.0000-600.0000] | Mass Range | MDF Ranges  | 235.0000 | None      |             | 0.5          | 0          | False     |              |              |        |         |
| MDF     |             |                                                                    |                                         |            |             |          |           |             |              |            |           |              |              |        |         |

| Peak Mass | Display Formula                                 | S Fit            | RDB  | Delta [ppm] | Theo. mass | MSMS Matched Fragments |
|-----------|-------------------------------------------------|------------------|------|-------------|------------|------------------------|
| 235.1800  | C <sub>14</sub> H <sub>23</sub> ON <sub>2</sub> | 73.9792038989505 | 4.50 | -2.17       | 235.18049  | (Collection)           |
| 235.1800  | C <sub>12</sub> H <sub>21</sub> N <sub>5</sub>  | 13.382979834354  | 5.00 | 3.54        | 235.17915  | (Collection)           |

# Green Metrics Evaluation

## Our work

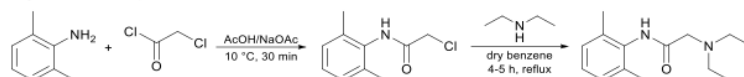


## METRICS

| Reactant (Limiting Reactant First) | Mass (g)     | MW (g mmol <sup>-1</sup> ) | equiv | Mol             | Catalyst | Mass (g)     | Reagent | MW (g mmol <sup>-1</sup> ) | Mass (g)     | Reaction Solvent | Volume (mL) | Density (g.mL <sup>-1</sup> ) | Mass (g)    |
|------------------------------------|--------------|----------------------------|-------|-----------------|----------|--------------|---------|----------------------------|--------------|------------------|-------------|-------------------------------|-------------|
| 2,6-dimethylaniline                | 0,246        | 121,18                     | 1,00  | 0,00203         |          |              |         |                            | 0,000        | DES              | 1,65        | 1,24                          | 2,05        |
| chloroacetyl chloride              | 0,229        | 112,94                     | 1,00  | 0,00203         |          |              |         |                            |              |                  |             |                               |             |
| diethylamine                       | 0,223        | 73,14                      | 1,50  | 0,00305         |          |              |         |                            |              |                  |             |                               |             |
| <b>Total</b>                       | <b>0,698</b> | <b>307,26</b>              |       | <b>0,007105</b> |          | <b>0,000</b> |         |                            | <b>0,000</b> |                  |             |                               | <b>2,05</b> |
| Yield (%)                          |              | 90                         |       |                 |          |              |         |                            | mass (g)     | MW               | mol         |                               |             |
| AE (%)                             |              | 76                         |       |                 |          |              |         |                            | Product      | 0,428            | 234,34      | 0,00183                       |             |
| RME (%)                            |              | 61                         |       |                 |          |              |         |                            |              |                  |             |                               |             |
| OE                                 |              | 80,4                       |       |                 |          |              |         |                            |              |                  |             |                               |             |
| MI total (g g <sup>-1</sup> )      |              | 6,4                        |       |                 |          |              |         |                            |              |                  |             |                               |             |
| MI RRC (g g <sup>-1</sup> )        |              | 1,6                        |       |                 |          |              |         |                            |              |                  |             |                               |             |
| MI Solvents (g g <sup>-1</sup> )   |              | 4,8                        |       |                 | Conc (M) | 1,23         |         |                            |              |                  |             |                               |             |

## N. Löfgren and B. Lundqvist, US Pat., 2441498A, 1948

N. Löfgren and B. Lundqvist, US Pat., 2441498A, 1948



## METRICS - First Step

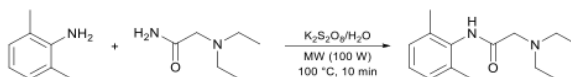
| Reactant (Limiting Reactant First) | Mass (g)       | MW (g mmol <sup>-1</sup> ) | equiv | Mol             | Catalyst | Mass (g)     | Reagent | MW (g mmol <sup>-1</sup> ) | Mass (g)     | Reaction Solvent | Volume (mL) | Density (g.mL <sup>-1</sup> ) | Mass (g)       |
|------------------------------------|----------------|----------------------------|-------|-----------------|----------|--------------|---------|----------------------------|--------------|------------------|-------------|-------------------------------|----------------|
| 2,6-dimethylaniline                | 121,18         | 121,18                     | 1,00  | 1,00000         |          |              |         |                            | 0,000        | glacial AcOH     | 800,00      | 1,05                          | 840,00         |
| chloroacetyl chloride              | 124,234        | 112,94                     | 1,10  | 1,10000         |          |              |         |                            |              | NaOAc            | 1000,00     | 1,2                           | 1200,00        |
| <b>Total</b>                       | <b>245,414</b> | <b>234,12</b>              |       | <b>2,100000</b> |          | <b>0,000</b> |         |                            | <b>0,000</b> |                  |             |                               | <b>2040,00</b> |
| Yield (%)                          |                | 75                         |       |                 |          |              |         |                            | mass (g)     | MW               | mol         |                               |                |
| AE (%)                             |                | 84                         |       |                 |          |              |         |                            | Product      | 148,25           | 197,66      | 0,75000                       |                |
| RME (%)                            |                | 60                         |       |                 |          |              |         |                            |              |                  |             |                               |                |
| OE                                 |                | 71,5                       |       |                 |          |              |         |                            |              |                  |             |                               |                |
| MI total (g g <sup>-1</sup> )      |                | 15,4                       |       |                 |          |              |         |                            |              |                  |             |                               |                |
| MI RRC (g g <sup>-1</sup> )        |                | 1,7                        |       |                 |          |              |         |                            |              |                  |             |                               |                |
| MI Solvents (g g <sup>-1</sup> )   |                | 13,8                       |       |                 | Conc (M) | 1,25         |         |                            |              |                  |             |                               |                |

## METRICS - Second Step

| Reactant (Limiting Reactant First)    | Mass (g)       | MW (g mmol <sup>-1</sup> ) | equiv | Mol             | Catalyst | Mass (g)     | Reagent | MW (g mmol <sup>-1</sup> ) | Mass (g)     | Reaction Solvent | Volume (mL) | Density (g.mL <sup>-1</sup> ) | Mass (g)      |
|---------------------------------------|----------------|----------------------------|-------|-----------------|----------|--------------|---------|----------------------------|--------------|------------------|-------------|-------------------------------|---------------|
| N-(2,6-Dimethylphenyl)chloroacetamide | 197,66         | 197,66                     | 1,00  | 1,00000         |          |              |         |                            | 0,000        | dry benzene      | 1000,00     | 0,87                          | 874,00        |
| diethylamine                          | 219,420        | 73,14                      | 3,00  | 3,00000         |          |              |         |                            |              |                  |             |                               |               |
| <b>Total</b>                          | <b>417,080</b> | <b>270,80</b>              |       | <b>4,000000</b> |          | <b>0,000</b> |         |                            | <b>0,000</b> |                  |             |                               | <b>874,00</b> |
| Yield (%)                             |                | 90                         |       |                 |          |              |         |                            | mass (g)     | MW               | mol         |                               |               |
| AE (%)                                |                | 87                         |       |                 |          |              |         |                            | Product      | 210,91           | 234,34      | 0,90000                       |               |
| RME (%)                               |                | 51                         |       |                 |          |              |         |                            |              |                  |             |                               |               |
| OE                                    |                | 58,4                       |       |                 |          |              |         |                            |              |                  |             |                               |               |
| MI total (g g <sup>-1</sup> )         |                | 6,1                        |       |                 |          |              |         |                            |              |                  |             |                               |               |
| MI RRC (g g <sup>-1</sup> )           |                | 2,0                        |       |                 |          |              |         |                            |              |                  |             |                               |               |
| MI Solvents (g g <sup>-1</sup> )      |                | 4,1                        |       |                 | Conc (M) | 1,00         |         |                            |              |                  |             |                               |               |

M. Srinivas, A. D. Hudwekar, V. Venkateswarlu, G. L. Reddy, K. A. A. Kumar, R. A. Vishwakarma and S. D. Sawant, *Tetrahedron Lett.*, 2015, 56, 4775-4779

M. Srinivas *et al.*, *Tetrahedron Lett.*, 2015, 56, 4775-4779



#### METRICS

| Reactant (Limiting Reactant First) | Mass (g)     | MW (g mmol <sup>-1</sup> ) | equiv | Mol             | Catalyst                                     | Mass (g)     | Reagent | MW (g mmol <sup>-1</sup> ) | Mass (g)     | Reaction Solvent | Volume (mL) | Density (g mL <sup>-1</sup> ) | Mass (g)    |
|------------------------------------|--------------|----------------------------|-------|-----------------|----------------------------------------------|--------------|---------|----------------------------|--------------|------------------|-------------|-------------------------------|-------------|
| 2,6-dimethylaniline                | 0,121        | 121,18                     | 1,00  | 0,00100         | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> | 0,4055       |         |                            | 0,000        | H <sub>2</sub> O | 2,00        | 1,00                          | 2,00        |
| 2-(diethylamino)acetamide          | 0,130        | 130,19                     | 1,00  | 0,00100         |                                              |              |         |                            |              |                  |             |                               | 0,00        |
|                                    |              |                            |       |                 |                                              |              |         |                            |              |                  |             |                               | 0,00        |
|                                    |              |                            |       |                 |                                              |              |         |                            |              |                  |             |                               | 0,00        |
| <b>Total</b>                       | <b>0,251</b> | <b>251,37</b>              |       | <b>0,002000</b> |                                              | <b>0,406</b> |         |                            | <b>0,000</b> |                  |             |                               | <b>2,00</b> |

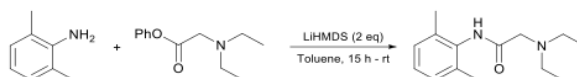
|                                  |      |
|----------------------------------|------|
| Yield (%)                        | 95   |
| AE (%)                           | 93   |
| RME (%)                          | 89   |
| OE                               | 95,0 |
| MI total (g g <sup>-1</sup> )    | 11,9 |
| MI RRC (g g <sup>-1</sup> )      | 3,0  |
| MI Solvents (g g <sup>-1</sup> ) | 9,0  |

Conc (M) 0,50

|              |        |         |
|--------------|--------|---------|
| mass (g)     | MW     | mol     |
| Product 0,22 | 234,34 | 0,00095 |

G. Li and M. Szostak, *Nat. Commun.*, 2018, 9, 1-8

G. Li and M. Szostak, *Nat. Commun.*, 2018, 9, 1-8



#### METRICS

| Reactant (Limiting Reactant First) | Mass (g)     | MW (g mmol <sup>-1</sup> ) | equiv | Mol             | Catalyst | Mass (g)     | Reagent | MW (g mmol <sup>-1</sup> ) | Mass (g)     | Reaction Solvent | Volume (mL) | Density (g mL <sup>-1</sup> ) | Mass (g)     |
|------------------------------------|--------------|----------------------------|-------|-----------------|----------|--------------|---------|----------------------------|--------------|------------------|-------------|-------------------------------|--------------|
| 2,6-dimethylaniline                | 0,012        | 121,18                     | 1,00  | 0,00010         | LiHMDS   | 0,0335       |         |                            | 0,000        | toluene          | 20,00       | 0,87                          | 17,34        |
| phenyl diethylglycinate            | 0,021        | 207,27                     | 1,00  | 0,00010         |          |              |         |                            |              |                  |             |                               | 0,00         |
|                                    |              |                            |       |                 |          |              |         |                            |              |                  |             |                               | 0,00         |
|                                    |              |                            |       |                 |          |              |         |                            |              |                  |             |                               | 0,00         |
| <b>Total</b>                       | <b>0,033</b> | <b>328,45</b>              |       | <b>0,000200</b> |          | <b>0,033</b> |         |                            | <b>0,000</b> |                  |             |                               | <b>17,34</b> |

|                                  |       |
|----------------------------------|-------|
| Yield (%)                        | 91    |
| AE (%)                           | 71    |
| RME (%)                          | 65    |
| OE                               | 91,0  |
| MI total (g g <sup>-1</sup> )    | 816,2 |
| MI RRC (g g <sup>-1</sup> )      | 3,1   |
| MI Solvents (g g <sup>-1</sup> ) | 813,1 |

Conc (M) 0,01

|                |        |         |
|----------------|--------|---------|
| mass (g)       | MW     | mol     |
| Product 0,0213 | 234,34 | 0,00009 |

## Reaction Steps

| Step 01                                |       | Step 02                                |       |
|----------------------------------------|-------|----------------------------------------|-------|
| <b>Substrate</b> g                     |       | <b>Substrate</b> g                     |       |
| 2,6-dimethylaniline                    | 0,246 | N-(2,6-Dimethylphenyl) chloroacetamide | 0,367 |
| <b>Reagents</b> g                      |       | <b>Reagents</b> g                      |       |
| chloroacetyl chloride                  | 0,229 | diethylamine                           | 0,223 |
| <b>Organic Solvents</b> g              |       | <b>Organic Solvents</b> g              |       |
| DES                                    | 2,000 | Ethyl acetate                          | 4,000 |
| <b>Water or Aqueous Solutions</b> g    |       | <b>Water or Aqueous Solutions</b> g    |       |
|                                        |       | Water                                  | 5,0   |
| <b>Desired Product</b> g               |       | <b>Desired Product</b> g               |       |
| N-(2,6-Dimethylphenyl) chloroacetamide | 0,367 | Lidocaine                              | 0,428 |
| <b>Material Inputs</b> 0               |       | <b>Material Inputs</b> 0               |       |
| Substrate                              | 0,2   | Substrate                              | 0,4   |
| Reagents                               | 0,2   | Reagents                               | 0,2   |
| Solvents                               | 2,0   | Solvents                               | 4,0   |
| Aqueous                                | 0,0   | Aqueous                                | 5,0   |
| Total                                  | 2,5   | Total                                  | 9,6   |
| <b>Material Outputs</b> 0              |       | <b>Material Outputs</b> 0              |       |
| Product                                | 0,4   | Product                                | 0,4   |
| Waste                                  | 2,1   | Waste                                  | 9,2   |
| <b>PMI</b> 7                           |       | <b>PMI</b> 22                          |       |
| <b>E-factor</b> 6                      |       | <b>PMI (cumulative)</b> 27             |       |
|                                        |       | <b>E-factor</b> 21                     |       |
|                                        |       | <b>E-factor (cumulative)</b> 26        |       |

**E-factor** = mass of waste / mass of product.

An ideal value is **close to 0** (i.e. no waste).

This calculation tool was brought to you by GreenChemWeb ([www.greenchem.org](http://www.greenchem.org))

We wish to acknowledge the ACS-GCI Pharmaceutical Roundtable for the concept of Process Mass Intensity and for producing the first calculation tool upon which this is based. Prof. Roger Sheldon of the Delft University of Technology is acknowledged for the concept of E-factor.