Nature of Invention: Chemical molecule and synthesis route

Applicant: Chimique Inc.

Inventors: Anisurya Jana

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Chemical Formula: $C_{29}H_{30}N_6O_6$

Chemical Name: Olmesartan medoxomil

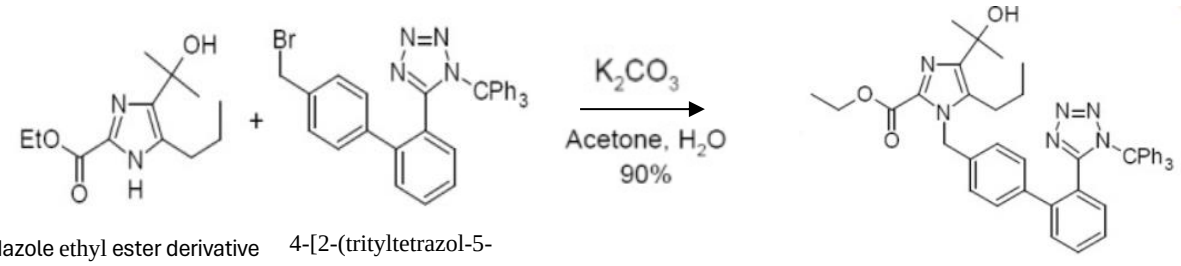
Chemical synthesis routes:

Raw Materials –

- Imidazole ethyl ester derivative
- 4-[2-(trityltetrazol-5-yl)phenyl]benzyl bromide
- *N,N*-Dimethylacetamide
- Acetone
- Tetrahydrofuran
- Ethanol
- Aqueous sodium hydroxide
- 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one
- Sodium iodide
- Ethyl acetate
- Sodium metabisulphite
- Diisopropyl ether
- Aqueous acetic acid
- Methylene chloride
- Sodium bicarbonate
- Demineralized water
- Sodium chloride solution

Reaction steps –

1. Preparation of Trityl Olmesartan Ethyl Ester –
   - Add powdered anhydrous potassium carbonate (72 g, 0.5217 mol) to a solution of **imidazole ethyl ester derivative** (100 g, 0.4166 mol) in *N,N*-Dimethylacetamide (300 mL) followed by 4-[2-(trityltetrazol-5-yl)phenyl]benzyl bromide (227.5 g, 0.4084 mol) at 25–30°C.
   - After completion of the reaction, add acetone (700 mL) to the reaction mass at 35-40°C, which resulted in a slurry mass.
   - To this slurry mass, add demineralized water (300 mL) at 20–25°C and cool to 0–5°C to produce **trityl olmesartan ethyl ester** (268 g, 90%) as a white crystalline solid with 98% purity by HPLC (high performance liquid chromatography).

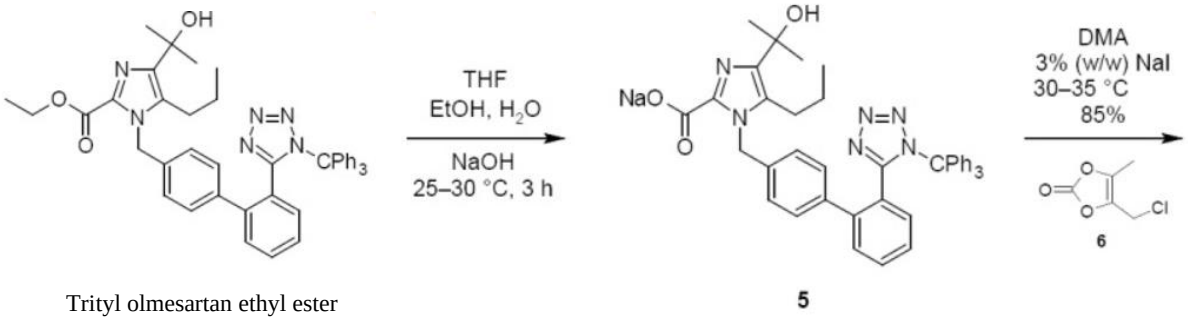


Imidazole ethyl ester derivative

4-[2-(trityltetrazol-5-yl)phenyl]benzyl bromide

Trityl olmesartan ethyl ester

2. Preparation of Trityl Olmesartan Medoxomil –
   - Add ethanol (200 ml) and pre-cooled aqueous sodium hydroxide (11.73 g, 0.2932 mol) solution in demineralized water (1200 mL) to a pre-cooled solution of **trityl olmesartan ethyl ester** in a mixture of tetrahydrofuran (1200 mL) at 10–15°C.
   - Concentrated the reaction mass to below 20°C under reduced pressure to afford **trityl olmesartan sodium salt** as a thick oily mass.
   - To the solution of trityl olmesartan sodium salt in DMA (dimethyl acetamide) (600 mL) add **4-(chloromethyl)-5-methyl-1,3-dioxol-2-one** (50.69 g, 0.3072 mol) and sodium iodide (6 g, 3% w/w) at 25-30°C. The contents were heated and stirred for 5 h at 30–35°C.
   - To the resulting clear solution add ethyl acetate (2000 mL), demineralized water (2000 mL), followed by sodium metabisulphite (2 g) at 30–35°C and stir for 15 min.
   - Separate the layers and wash the organic layer with 20% w/w aqueous sodium chloride solution at 30-35°C. Concentrate the organic layer at 30–40°C under reduced pressure till the distillate volume becomes 1150 mL, and then add diisopropyl ether (1000 mL).
   - Cool the slurry to 0–5°C and stir for 30 min. Filter the product to obtain **trityl olmesartan medoxomil** as a white powder (203 g, 90%) with 99.47% purity by HPLC.



Trityl olmesartan ethyl ester

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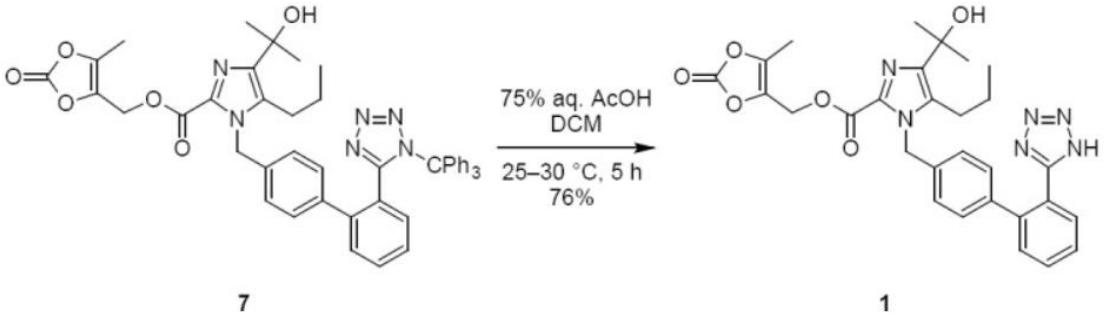

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5 – Trityl olmesartan sodium salt

6 – 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one

7 – Trityl olmesartan medoxomil

1 – Olmesartan medoxomil (final product)

3. Preparation of Olmesartan Medoxomil –
   - Stir the suspension of **trityl olmesartan medoxomil** (175 g) in 75% v/v aqueous acetic acid (875 mL) at 25–30°C for 10 h. Filter the byproduct, trityl alcohol, through hyflo (filtration agent) and wash with 75% v/v aqueous acetic acid (200 mL).
   - Add methylene chloride (1225 mL) to the filtrate followed by demineralized water (875 mL), at 20–30°C and stir for 15 min. The layers were separated and the aqueous layer was extracted with methylene chloride (525 mL) at 20–30°C.
   - Wash the combined organic extract with demineralized water at 20-30°C. Add water at 20–30°C to the organic layer and to adjust its pH to 7.30–7.50 add 5% w/w **aqueous sodium bicarbonate** (4.3 g in 81 mL of DM water) at 20–30°C.
   - The organic layer has to be separated and concentrated at 30-40 °C under reduced pressure. Add acetone (700 mL) to the concentrated mass and continue distillation at 50–55°C, at ambient pressure, till the distillate volume becomes 600 mL. Cool the resulting slurry to 0–5°C and continue stirring for 1 h.
   - **Fiter the product and dry it to afford olmesartan medoxomil (109 g, 89%) with 99.7% purity by HPLC.**

References: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727774/#ref6

List the contributions of each author:

- Author 3 , 4 and 5 carried out the literature search
- Authors 1,2 and 3 found the reaction steps, product yield, necessary separation steps to achieve desired product purity.

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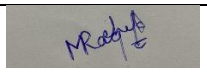
Mehek Agarwal	220646	
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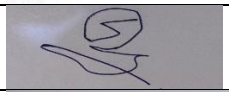
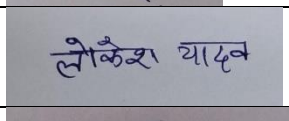
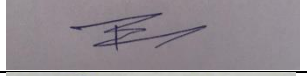
Sujal Jain	221100	
Lokesh Yadav	220594	
Ram Aggarwal	220864	
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