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Process for the preparation of Perampanel

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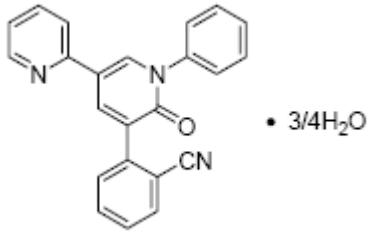
Perampanel hydrate (4:3) is chemically known as 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile hydrate (4:3) and it is a non-competitive AMPA glutamate receptor antagonist, is indicated as adjunctive therapy for the treatment of: Partial-Onset Seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older (1.1) and Primary Generalized Tonic-Clonic Seizures in patients with epilepsy 12 years of age and older (1.2) and which is approved the under the brand name of Fycompa®. The chemical structure Perampanel hydrate (4:3) is as follows:



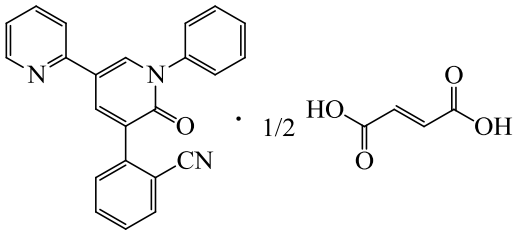
Perampanel hydrate (4:3) preparation was described in US8304548 in example-5 using acetone, water and small amount of seed crystals of Perampanel hydrate (4:3).

Perampanel hemi fumarate salt is used in the preparation of Perampanel hydrate (4:3) and Crystalline form-M of Peramapnel. Preparation of 3-bromo-1-phenyl-5-(pyridin-2yl)pyridin-2(1H)-one intermediate described in in US7939549 or any other literature.

Example-1: Preparation of Perampanel hemi fumarate:

Potassium carbonate (316.8 gms) was added to the mixture of 3-bromo-1-phenyl-5-(pyridin-2yl)pyridin-2(1H)-one (250 gms), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (178.6 gms) and 1,2-dimethyoxy ethane (3000 ml) at 25-30°C under nitrogen atmosphere. Palladium acetate (3.43 gms), triphenyl phosphine (16 gms) were added to the reaction mixture at 25-30°C and stirred the reaction mixture for 15 minutes under nitrogen atmosphere. Heated the reaction mixture to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and dichloromethane was added to the reaction mixture. Filtered the reaction mixture and washed with dichloromethane. Carbon treatment was given to the filtrate. Fumaric acid (97.55 gms) was added to the obtained filtrate at 25-30°C. Cooled the reaction mixture to 0-5°C and stirred at the same temperature. Filtered the precipitated solid and washed with dichloromethane. Methanol (2500 ml) was added to the obtained wet compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred. Cooled the reaction mixture to 25-30°C and stirred. Filtered the solid and washed with methanol. Water followed by dichloromethane were added to the obtained compound at 25-30°C and basified the reaction mixture using

ammonia. Separated both the aqueous and organic layers and the aqueous layer was extracted with dichloromethane. Distilled off the solvent completely from the organic layer under reduced pressure. Methanol (11250 ml) and thiourea resin (25 gms) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 60-65°C and stirred the reaction mixture at the same temperature. Filtered the reaction mixture and washed with methanol. Thiourea resin (12.5 gms) was added to the filtrate at 25-30°C. Heated the reaction mixture to 60-65°C and stirred it. Filtered the reaction mixture and washed with methanol. Fumaric acid (79.82 gms) was added to the filtrate at 25-30°C. Heated the reaction mixture to 60-65°C and stirred it for 15 minutes. Cooled the reaction mixture to 0-5°C and stirred at the same temperature. Filtered the precipitated solid, washed with methanol and dried. The obtained product has been now identified as Perampanel hemifumarate which is having the following chemical structure.



Yield: 205 gm. M.R.: 223.5-224.1°C. The PXRD pattern of the obtained compound was matching with the PXRD pattern of figure-8 of US7718807 B2.

Example-2: Preparation of Perampanel hydrate (4:3)

Basified the reaction mixture of water (500 ml), dichloromethane (500 ml) and Peramapanel hemifumarate (100 g) using aqueous ammonia solution at 25-30°C and stirred at the same temperature. Separated both the organic and aqueous layers and the aqueous layer was extracted with dichloromethane. Combined the organic layers and distilled off the solvent completely form the organic layer under reduced pressure. Dimethylformamide (750 ml) was added to the obtained compound at 25-30°C and stirred at the same temperature. Filtered the reaction mixture through hyflow bed and washed with Dimethylformamide. Water (3000 ml) was slowly added to the above obtained filtrate at 25-30°C and stirred at the same temperature. Filter the solid and washed with water. Slurried the obtained compound in Water (1125 ml) at 25-30°C and stirred at the same temperature. Filter the solid, washed with water and dried to get the title compound.

Yield: 72 g.

Example-3: Preparation of Crystalline form-M of Perampanel:

Dissolved Perampanel hemifumarate (100 gms) in the mixture of water (500 ml) and dichloromethane (500 ml) at 25-30°C. Basified the mixture using aqueous ammonia solution at 25-30°C. Separated both the organic and aqueous layers and the aqueous layer was extracted with dichloromethane. Combined the organic layers and washed with water. Distilled off the solvent completely form the organic layer. Ethyl acetate (180 ml) and dichloromethane (720 ml) were added to the obtained compound at 25-30°C and filtered the reaction mixture. Distilled off the solvent from the filtrate under reduced pressure and dried to get the title compound.

Yield: 56 gms. PXRD of the obtained compound is similar to the figure-1.

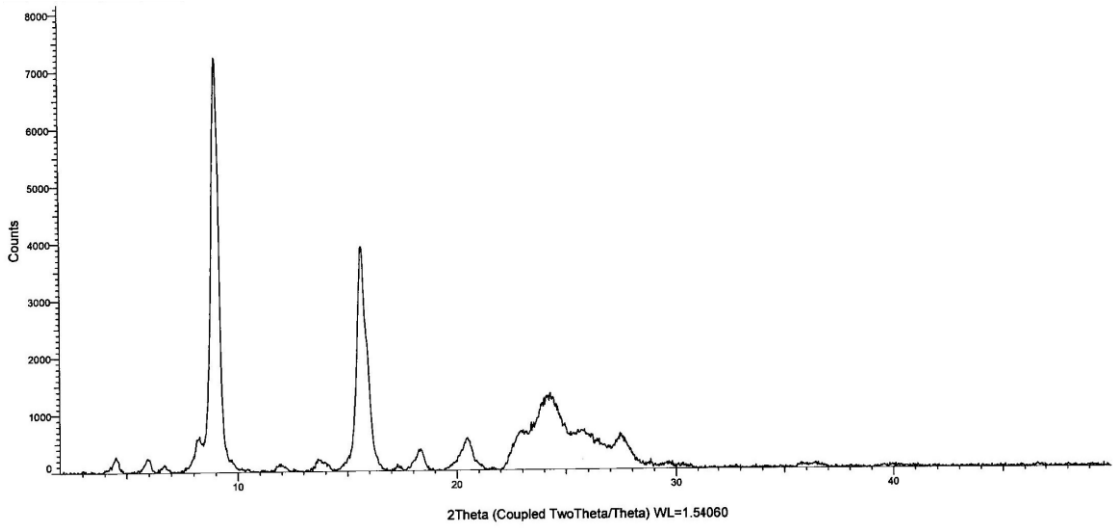


Figure-1

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