2. **Synthesis of amide derivatives of piperinic acid**

2.1 **Preparation of piperinic acid (RV-A00)**

To piperine (1) (2g, 0.7mmol, 1eq), 20% of methanolic KOH (100ml) was added and refluxed for 2 days. After completion of the hydrolysis, methanol was removed under reduced pressure and a yellow coloured oily solid was obtained. This residue was dissolved in water (50ml) and acidified with 6N HCl to pH <1 yielding a yellowish precipitate of piperinic acid. Recrystallization from methanol gave yellow needles (0.9g, 60% yield). m.p. 206°-208°C (Lit m.p. 217°-218°C)\(^1\)

\[\text{O} \quad \text{O} \quad \text{N} \quad \text{20% KOH} \quad \text{O} \quad \text{O} \quad \text{H} \]

Piperine (1) \quad \rightarrow \quad \text{Piperinic acid}

2.2 **Synthesis of piperlongumine (RV-A06)**

A mixture of piperinic acid (350mg, 0.0016mole, 1eq) and triethylamine (0.4ml, 0.0032mole, 2eq) in dichloromethane (50ml) was stirred for 15min at 0°C. To this mixture methanesulfonyl chloride (0.18ml, 0.0024mole, 1.5eq) was added and stirred for further 30 min at 0°C. Isobutylamine (0.23ml, 0.0024mole, 1.5eq) was added to the mixture and stirred for 1h at 0°C and 2h at room temperature. Dichloromethane (50ml) was added to the mixture which was then washed with 5% HCl (3x100ml), saturated aqueous NaHCO\(_3\) (3x100ml) and water (3x100ml). The organic fraction was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield a yellowish solid residue. Recrystallisation from methanol yielded colourless needles of piperlongumine (120mg, 32% yield)\(^2\). The reaction is presumed to proceed through a mesylate ester intermediate.