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**Supporting information for article:**

**Exploring solid states of atovaquone: crystal or glass?**

**Xin-Yi Teoh, Chye-Teik Teh and Siok-Yee Chan**

Table S1: The compilation of ATQ polymorphs preparation methods.

| <b>Form/Polymorph</b> | <b>Preparation Method</b>                                    |   | <b>Reference</b>                            |
|-----------------------|--|---|---|
|                       | <b>Starting Material</b>                                     | <b>Procedures</b>   |   |
| <b>Crude/I</b>        | 2-[4-(4-chlorophenyl)cyclohexyl-3-chloro-1,4-naphthoquinone] | <ol style="list-style-type: none"> <li>1. Suspend in boiling methanol</li> <li>2. Add potassium hydroxide solution dropwise over 15 minutes</li> <li>3. Add concentrated hydrochloric acid dropwise and reflux to a dark red solution</li> <li>4. Cool the mixture</li> <li>5. Filter and wash solid residues with water</li> <li>6. Reacidify and filter the water washings</li> <li>7. Recrystallise combined solid residues from acetonitrile</li> </ol> | US 4981874<br>(Latter and Gutteridge, 1991) |
| Form I crude          |  | <ol style="list-style-type: none"> <li>1. Dissolve in methylene dichloride at room temperature</li> <li>2. Add methanol/n-heptane dropwise under stirring condition</li> <li>3. Stir for 4 hours</li> </ol>   | WO 2006/008752 A1<br>(Tarur et al., 2006)   |

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|--|--|--|
| 2-[4-(4-chlorophenyl)cyclohexyl]-3-chloro-1,4-naphthoquinone         | 1. Add to methanol at 25-30 °C and heat to reflux<br>2. Add potassium hydroxide solution slowly for 15-20 minutes<br>3. Cool to 25-30 °C<br>4. Cool to 0 °C and stir for 1 hour at 0-5 °C  | WO 2009/001367<br>(Reddy et al., 2008) |
| Crude  | 1. Dissolve in refluxing dichloromethane at 40 °C<br>2. Cool and add <i>n</i> -heptane dropwise<br>3. Reflux for 4 hours under stirring condition<br>4. Cool the mixture slowly  | (Malpezzi et al., 2010)                |
| trans-2-(4-(4-chlorophenyl)cyclohexyl)-3-chloronaphthalene-1,4-dione | 1. Dissolve in methanol<br>2. Add potassium hydroxide solution slowly and stir for 20 minutes<br>3. Reflux for 6 hours until dark red colour<br>4. Cool on ice bath<br>5. Add concentrated hydrochloric acid to obtain yellow solid<br>6. Filter and wash with water to obtain trans-atovaquone<br>7. Grow crystal by slow evaporation from the solvents methylene chloride: hexane (2:1, v/v) at room temperature | (Nayak et al., 2013)                   |

|            |  |   |   |
|------------|--|---|---|
| <b>II</b>  | Form I   | 1. Dissolve in 1,4-dioxane under reflux condition<br>2. Cool to room temperature for 30 minutes<br>3. Cool at 5 °C for 4 hours  | WO 2006/008752 A1<br>(Tarur et al., 2006) |
|            | trans-2-(4-(49-chlorophenyl)cyclohexyl)-3-chloronaphthalene-1,4-dione. | 1. Dissolve in methanol<br>2. Add potassium hydroxide solution slowly and stir for 20 minutes<br>3. Reflux for 6 hours until dark red colour<br>4. Cool on ice bath<br>5. Add concentrated hydrochloric acid to obtain yellow solid<br>6. Filter and wash with water to obtain trans-atovaquone<br>7. Grow crystal by slow evaporation from the solvents acetone:water (2:1, v/v) at room temperature | (Nayak et al., 2013)                      |
|            | Form I   | 1. Dissolve in acetone under reflux condition<br>2. Add hot solution dropwise with stirring into 0 °C water<br>3. Maintain temperature for 1 hour   | WO 2006/008752 A1<br>(Tarur et al., 2006) |
| <b>III</b> | Form I   | 1. Dissolve in chloroform at room temperature<br>2. Add methanol dropwise under stirring  |   |

|                 |        |   |   |
|-----------------|--------|---|---|
|                 |        | 3. Stir for 4 hours   |   |
|                 | Form I | 1. Dissolve in diisopropyl ether under reflux condition<br>2. Cool to room temperature and maintain for 4 hours   |   |
|                 | Crude  | 1. Dissolve in acetonitrile at 40 °C<br>2. Distil out acetonitrile to turbid solution<br>3. Add a few drops of acetonitrile to get a clear solution<br>4. Cool to room temperature<br>5. Slow solvent evaporation | (Malpezzi et al., 2010)                       |
|                 | Form I | 1. Heat to at least 140 °C or 160 °C<br>2. Cool   | US 2015/0307431 A1<br>(Baidossi et al., 2015) |
| <b>A</b>        | Form I | 1. Reflux in acetonitrile at least 70 mL/g to form a clear solution<br>2. Cool to 0-30 °C   | WO 2009/001367<br>(Reddy et al., 2008)        |
| <b>B</b>        | Form I | 1. Dissolve in tetrahydrofuran/chloroform at 25-30 °C<br>2. Stir for 5 minutes<br>3. Spray drying at about 50 °C for 5 hours  | WO 2009/001367<br>(Reddy et al., 2008)        |
| <b>IPCA-ATO</b> | Form I | 1. Dissolve in dichloromethane at room temperature  | US 2009/0221715 A1                            |

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4. Chill on a nitrogen bath until solidified

(Kumar et al., 2009)

5. Lyophilise to remove dichloromethane

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Form I

1. Dissolve in dichloromethane at room temperature

2. Pour solution on liquid nitrogen until solidified

3. Lyophilise to remove dichloromethane

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Form I

1. Dissolve in chloroform at room temperature

2. Cool to 0 °C

3. Add methanol dropwise at 0 °C

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Form I

1. Dissolve in dichloromethane at room temperature

2. Add dimethyl formamide

3. Filter and add the solution to a reaction flask

4. Maintain at -20 °C and stir for 1 hour

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Form I

1. Dissolve in dichloromethane at room temperature

2. Filter and add the solution to a reaction flask pre-chilled to -20 °C

3. Partly distilled the solvent under vacuum while maintaining at -20 °C

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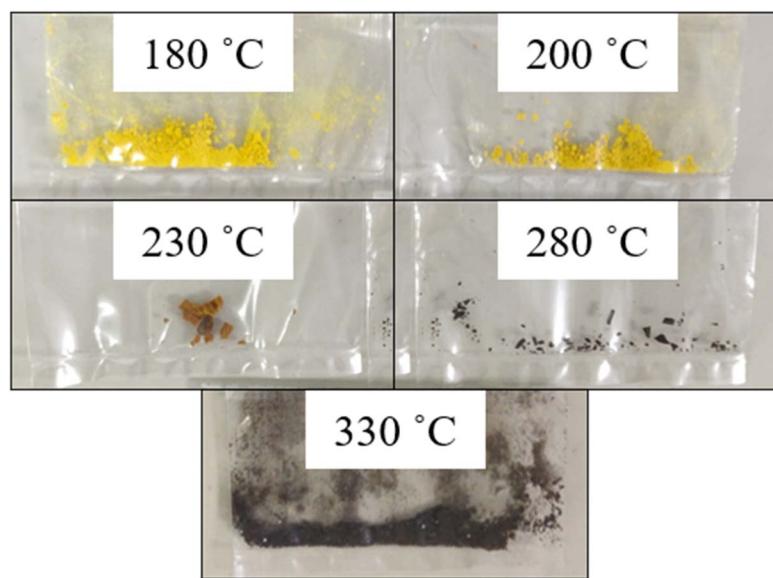


Fig. S1: Physical observation of ATQ after heating at specified temperatures.

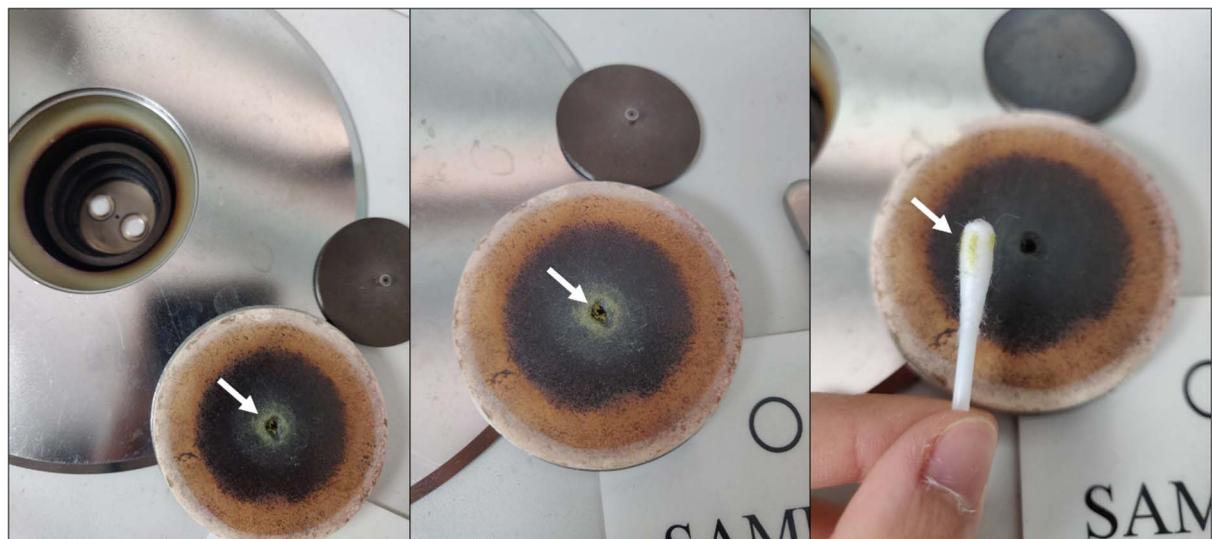


Fig. S2: Formation of sublimated ATQ traces on DSC furnace lid.

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