M2142

Polymorph Screen of Newly Discovered Salts of Bedaquiline

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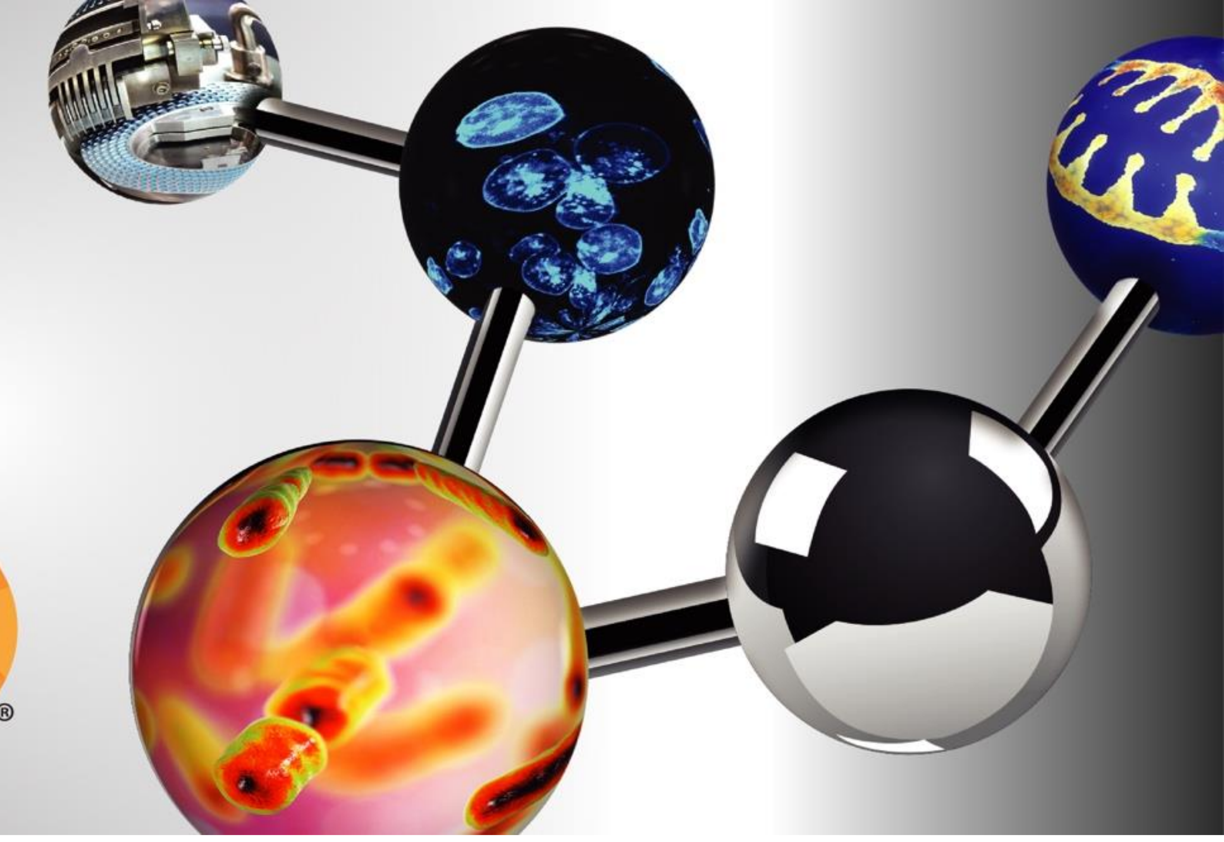

PURPOSE

Bedaquiline is used in the treatment of multidrug resistant tuberculosis (MDR TB), a disease commonly found in developing countries (1). Previously, a salt screen of Bedaquiline Fumarate, SIRTURO™, a first-in-class oral medication for the treatment of MDR TB had been completed in our laboratories (2, 3). The two most promising salt candidates, benzoate and maleate, (Figure 1) were selected for polymorph evaluation based upon ease of formation, scalability, hygroscopicity, and suitable solid-state properties. The current research focuses on screening the newly discovered salts for potential polymorphs to support further development of these salts into commercially available, life-saving products.

OBJECTIVE(S)

1. Prepare new polymorphs of Bedaquiline benzoate and maleate salts using pharmaceutically relevant solvents.
2. Characterize the new forms using appropriate physico-chemical techniques.
3. Identify new polymorphs, if any, for further development based upon all results.

METHOD(S)

- Carried out polymorph screen of both benzoate and maleate salts in two separate laboratories. Used various solvent systems that would likely encourage polymorphs or might be encountered during production by the following techniques:
  - slow (SE) and fast evaporation (FE)
  - Heating/cooling and thermal cycling
  - slurrying
  - solvent/anti-solvent precipitation
  - vapor diffusion
  - liquid/liquid diffusion
- Analyzed solids obtained by powder X-ray diffraction (XRPD) to determine the possible existence of new crystal structures.
- Confirmed the chemical structure of potential Bedaquiline polymorphs by proton nuclear magnetic resonance spectrometry (^{1}H NMR).
- Solved the single crystal structure when suitable single crystals resulted and analyzed by hot stage optical microscopy (HSOM); results reported in accompanying poster entitled, "Crystal Structures of Bedaquiline Salts", poster# M2143.

RESULT(S)

Subjecting Bedaquiline (Figure 1) maleate and benzoate salts to various polymorph screening techniques revealed previously-observed crystalline forms or amorphous material (Table 1). For the maleate salt, attempts using acetone, acetonitrile or ethyl acetate resulted in the hydrated material (Figure 2) while an attempt from n-propyl alcohol resulted in material with a structure comparable to the THF solvated material (Figure 3). In addition, disproportionation to the free base resulted from solvent/anti-solvent systems in which water was used as the anti-solvent (Figure 4). In all cases, Rietveld refinements against previously-acquired single crystal data set models showed agreement with allowed peak positions for the screening attempts. All thermal experiments yielded amorphous material without recrystallization.

The benzoate salt screening experiments yielded parent salt (Figure 5), the free base, or a mixture of both. As with the maleate salt solvent/anti-solvent experiments, disproportionation to the free base resulted from ethanol with water as the anti-solvent as well as from slurrying in isopropyl alcohol or methanol (Figure 6). In all cases, Rietveld refinements against previously-acquired single crystal data set models showed agreement with allowed peak positions for the screening attempts. Unlike the maleate salt, all thermal experiments yielded crystalline material (Figure 7).

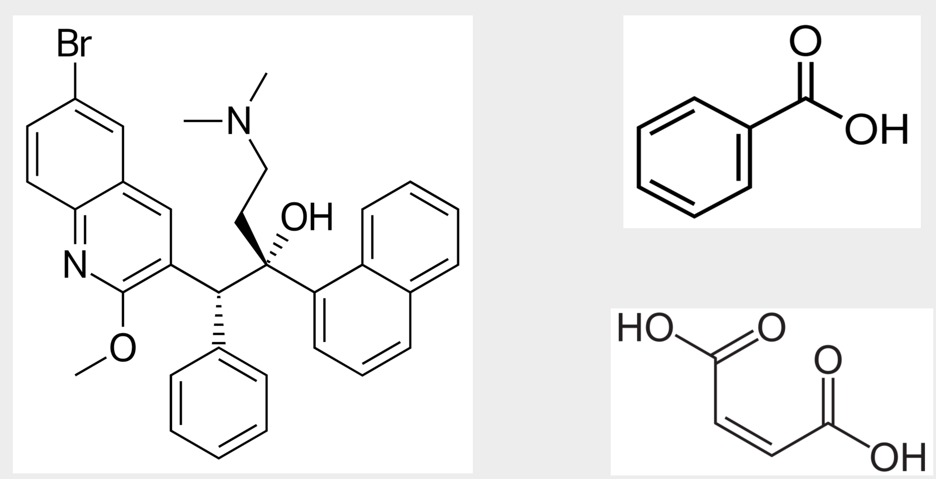

Figure 1. Structure of Bedaquiline free base along with benzoic acid (top) and maleic acid (bottom)

Table 1. Polymorph Screen Results for Bedaquiline Salts

Technique	Benzoate	Maleate
Slow Evaporation	Hydrate Hydrate + free base	Amorphous Hydrate + pk
Fast Evaporation	Hydrate Hydrate + free base	Amorphous Hydrate
Slow Evaporation from Saturated Solutions	–	Amorphous Hydrate + pks THF solvate
Slurrying	Free base Hydrate + Free base	–
Heating/Thermal Cycling	–	Amorphous
Heating/Cooling	Hydrate + Free base Amorphous	–
Amorphous Heating	Hydrate	–
Solvent/ Anti-Solvent	Hydrate Hydrate + free base	Amorphous Free base (>87%) + Hydrate
Vapor Diffusion	–	THF solvate
Liquid/liquid Diffusion	–	Single crystals made
Amorphous Solid Vapor Diffusion	–	Amorphous Hydrate + pk Hydrate (>98%) + Free base

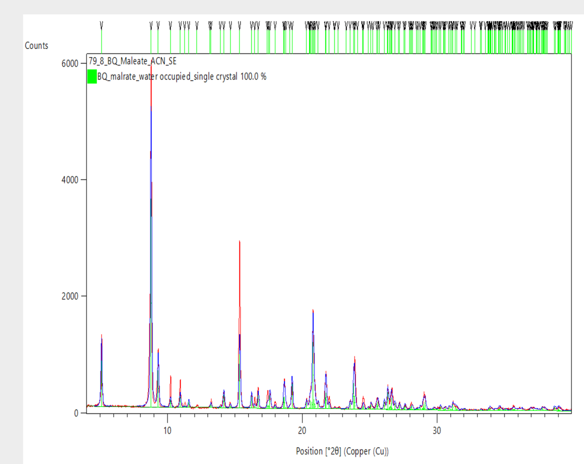

Figure 2. XRPD of Bedaquiline maleate from slow evaporation out of ACN, refined against the hydrate single crystal structure

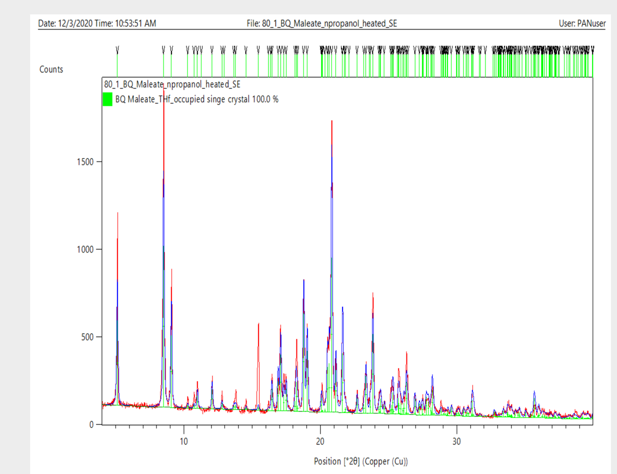

Figure 3. XRPD of Bedaquiline maleate from saturated solution/slow evaporation out of n-propanol, refined against the THF solvate single crystal structure

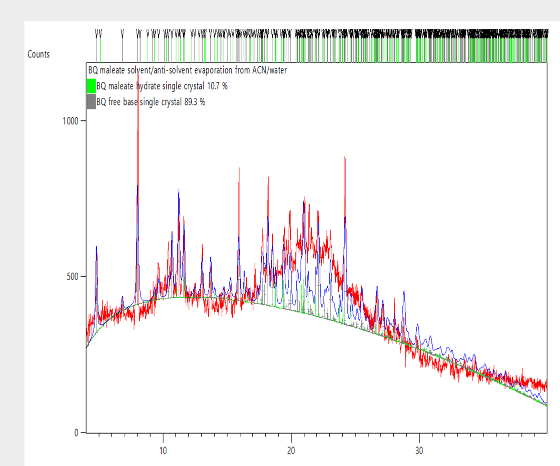

Figure 4. XRPD of Bedaquiline maleate from solvent/anti-solvent experiment out of ACN/water, and Rietveld refinement against the free base and hydrate single crystal structures

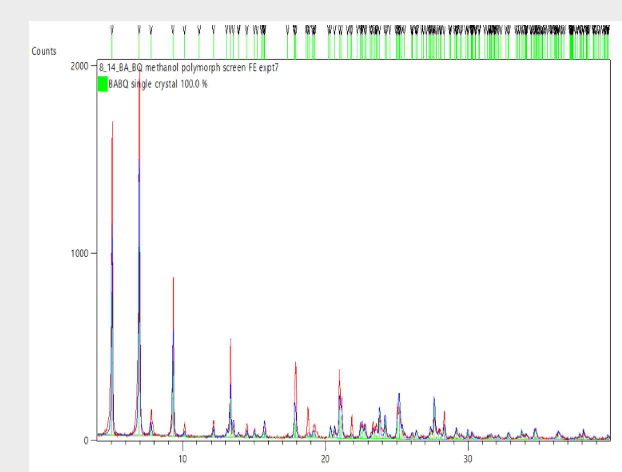

Figure 5. XRPD of Bedaquiline benzoate from fast evaporation out of methanol, and Rietveld refinement against the benzoate single crystal structure

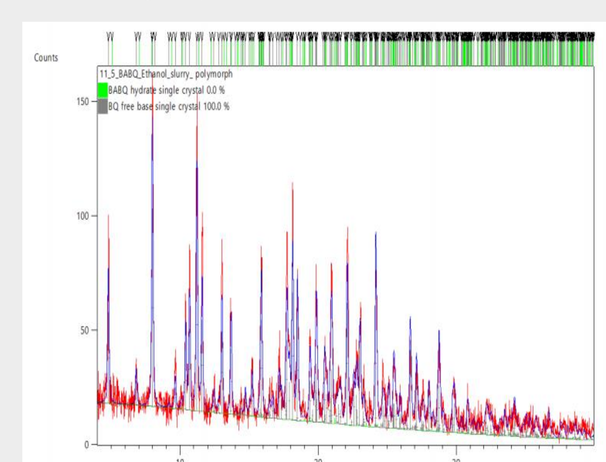

Figure 6. XRPD of Bedaquiline benzoate from slurrying for one week in ethanol, and Rietveld refinement against the hydrate and free base single crystal structures

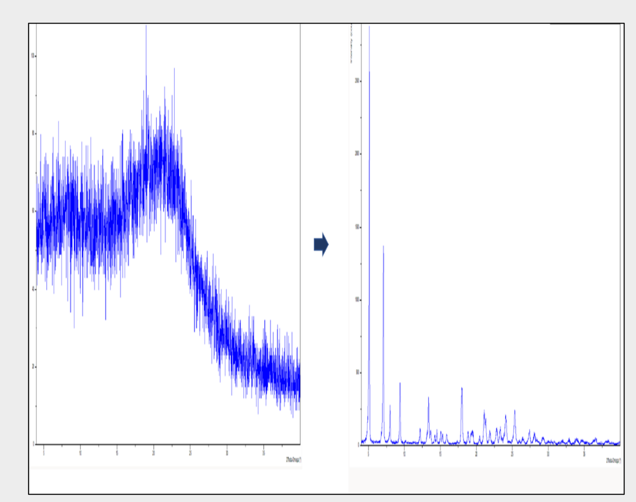

Figure 7. XRPD of amorphous Bedaquiline benzoate before and after heating at 60 °C for 24 hours

CONCLUSION(S)

A polymorph screen of previously discovered Bedaquiline salts, benzoate and maleate, was conducted in two separate laboratories via a variety of techniques. These included fast and slow evaporations, heating and thermal cycling, slurrying, vapor diffusion, liquid/liquid diffusion, and solvent/anti-solvent experiments from various solvent systems that might encourage new forms or be used in the production process. In general, no new polymorphs were discovered from either the maleate nor the benzoate salts. All attempts to generate new polymorphs resulted in either 1) the previously-solved structures obtained from a salt screen study or 2) amorphous materials. In addition, single crystals of Bedaquiline maleate solvates were inadvertently grown during the polymorph screen attempts and the structures successfully solved; they were similar in structure to the previously identified solvates, being isomorphous, with infinite solvent channels and a high degree of solvent disorder.

FUNDING

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REFERENCES

1. World Health Organization. Global Tuberculosis Report 2019.
2. Janssen Therapeutics. Sirturo ™ website http://www.sirturo.com/.
3. Scientific report to BMGF, "Salt Screen of Bedaquiline Fumarate," issued February 2021.

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