Salt Screen of Bedaquiline using a Combination of Techniques to Identify Promising New Salts for Development

Authors: M Okezue[a], D Smith[a], SJ Bogdanowich-Knipp[b], PA Smith[c], SR Byrn[a], and DK Purcell[d]

Affiliations: a) Purdue University, b) Ravine Pharmaceuticals LLC, c) Leading with Smart Science LC, d) Chemical Microscopy LLC

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is a currently marketed drug product approved
bination therapy for the treatment of multi-drug
s (MDR-TB) in adults and children twelve years
nd Melinda Gates Foundation is interested in
laquiline salts with acceptable development
as a treatment in developing countries where
nt threat[2]. This poster describes the results of
using powerful, orthogonal analytical techniques
ss, as well as a potential development path
s and/or cocrystals of Bedaquiline.

E(S)

or cocrystals of Bedaquiline (Figure 1) using
acceptable counterions.

alts and/or cocrystals using appropriate
o-chemical techniques.

s for further development based upon all results.

S)

armaceutically accepted counterions based upon
rties to form suitable salts with Bedaquiline API:
acid, benzenesulfonic acid, hydrobromic acid,
ctic acid, malic acid, maleic acid, methanesulfonic
cid (1:1 and 1:2, counterion:API).
low (SE), fast evaporation (FE), heating, and
addition; chose solvents based upon solubility of
counterions, polarity and dielectric constant;
nts in two separate laboratories to increase the
additional salts.
ained by polarized light microscopy (PLM) to
that were crystalline, Raman microscopy and/or
oscopy (R/A and/or ATR) and compared to a
iline (free form) to determine if a salt had been

Bedaquiline salts by proton nuclear magnetic
netry (^{1}H NMR) and laboratory single crystal X-ray
the counterion stoichiometry and possible solvent
tal lattice. Laboratory (Purdue) or synchrotron
abs) X-ray powder diffraction (XRPD) were used
ization and to identify possible polymorphs of

Bedaquiline salts by hot stage optical microscopy
int, differential scanning calorimetry (DSC),
G), weight gain to evaluate hygroscopicity, and
d gastric fluid (SGF) using HPLC with UV /VIS
appropriate salts for development.

RESULT(S)

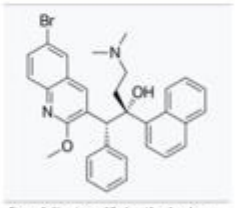

Figure 1. Structure of Bedaquiline free base

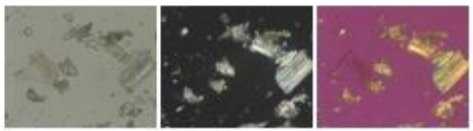

Figure 2. PLM images of Bedaquiline benzoate. Left to right plane polarized light, cross-polarized light, cross-polarized light with red compensator

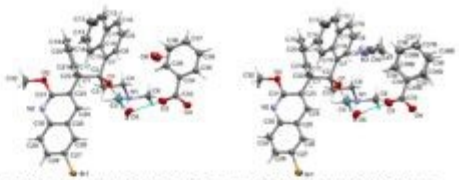

Figure 4. Single crystal structures for Bedaquiline benzoic acid salt: left) hydrate, right) ACN solvate

Five crystalline salt candidates of Bedaquiline were obtained (1:1): benzoic, maleic, besylate, mesylate and hydrochloric. The salts displayed low solubility in SGF (<15 μg/mL) which is not uncommon for Bedaquiline. All physicochemical characterization data is displayed in Table 1 for these salts. An example of one of the Bedaquiline salts (benzoate) is presented in this poster.

The crystalline benzoate salt has been confirmed by PLM (Figure 2), IR microspectroscopy using both R/A and ATR (Figure 3), XRPD, ^{1}H NMR and single crystal x-ray. The structure exists as a hydrate with 1.17 mols of water or an ACN solvate with 0.75 mols ACN occupancy and 1 mol water (Figure 4). High resolution synchrotron XRPD data revealed subtle differences between hydrate and solvated salts (Figure 5). The material is moderately hygroscopic (<5% weight gain) upon exposure to high relative humidity (75% RH). Thermal properties were evaluated further by TG (3.2% volatiles supporting single crystal data), DSC (desolvation/melting endotherms of 109.0/124.7 °C) and HSOM (supporting melt behavior) as shown in Figures 6 – 7. A small-scale polymorph screen revealed no change in crystalline structure.

For Bedaquiline, Raman microscopy could not be used as a pre-screening tool for determination of small scale crystallization experiments due to its lack of specificity as shown in Figure 8.

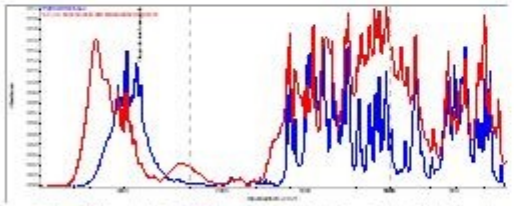

Figure 3. Infrared R/A spectra of Bedaquiline benzoate (red) and Bedaquiline free base (blue). Diagnostic peaks are labeled

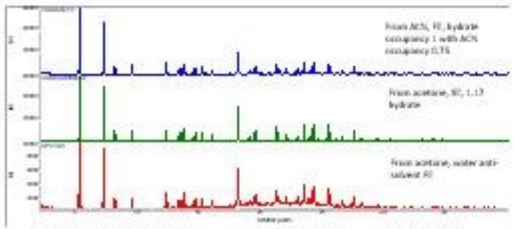

Figure 5. Synchrotron XRPD of Bedaquiline benzoic acid salts, top to bottom: crystallized from ACN, acetone, and acetone/water

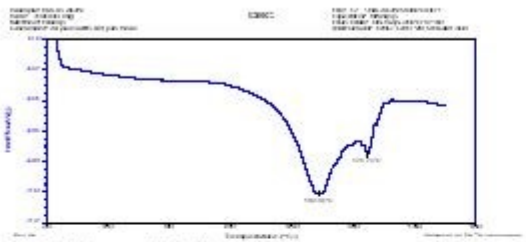

Figure 6. DSC thermogram of Bedaquiline benzoate (blue)

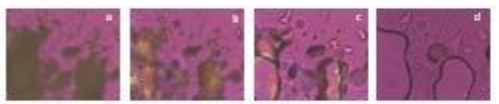

Figure 7. HSOM images of Bedaquiline benzoate using cross-polarized light with red compensator. Left to right: a) 92.2 °C, start of melt; b) 100.5 °C, melting; c) 105.0 °C, melting; d) 109.5 °C, melt nearly complete

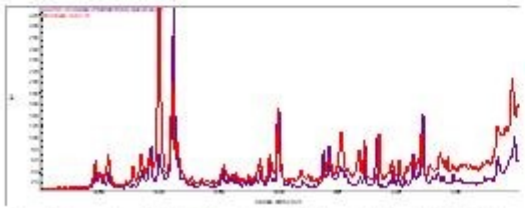

Figure 8. Raman spectra of Bedaquiline benzoate (purple) and Bedaquiline free base (red). Note lack of specificity between the spectra

Table 1. Physicochemical Characterization Data for Bedaqu

	Benzoate	Maleate	Besylate	
^{1}H NMR	(1:1) Salt confirmed	(1:1) Salt confirmed	(1:1) Salt confirmed	(1:1
Synchotron XRPD	Crystalline	Crystalline	Crystalline	Cry
Single Crystal	1.17 mols water or 0.75 mol ACN with 1 mol water	2 mols THF	1 mol THF and 1 mol water	
IR (R/A)	Salt confirmed	Salt confirmed	Salt confirmed	Salt
IR (ATR)	Salt confirmed	Salt confirmed	Salt confirmed	Salt
HSOM	Desolvation?/melt	Desolvation?/melt	Desolvation/melt/ recrystallization/melt	Des
DSC	Endos @ 109.0, 124.7 °C	Endos @ 143.0 °C	Endos @ 81.8, 106.7, 192.4°C; exo @ 198.8°C	End 186
TG	~3.2% volatiles	–	–	
PLM	Blades, Anhedral-platy	Anhedral-platy, polycrystalline, agglomerates	Anhedral-platy, polycrystalline, agglomerates	Anh poly agg
HPLC (solubility)	~12.7 μg/mL (SGF)	~2.9 μg/mL (SGF)	~7.6 μg/mL (SGF)	~2.1

CONCLUSION(S)

Five different Bedaquiline salts (1:1) were made and
up using various pharmaceutically acceptable counte
suitable for further development: benzoic acid, maleic
benzenesulfonic acid, methansulfonic acid and hydro
and IR micro-spectroscopy (R/A and/or ATR) were sh
pre-screening tools for determining salt formation; ho
microscopy, due to lack of specificity, was not a usefu
for Bedaquiline salt formation. These newly identified
characterized using physico-chemical techniques inc
XRPD, HSOM, DSC, and/or TG. The increased sensi
of Argonne National Labs synchrotron XRPD data all
possible polymorphs, and/or contaminants. Upon suc
single crystals from select salts, the single crystal x-r
used to confirm stoichiometry and solvent inclusion fo
maleic acid, benzenesulfonic acid, and hydrochloride
solubility of the five select salts was determined in sir
to be < 15 μg/mL.

FUNDING

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REFERENCES

1. Janssen Therapeutics. Sirturo™ website http://www.sirturo.com/.
2. World Health Organization. Global Tuberculosis Report 2019.

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