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Strategy for Salt Screening Using Crystallographic and Microscopic Methods

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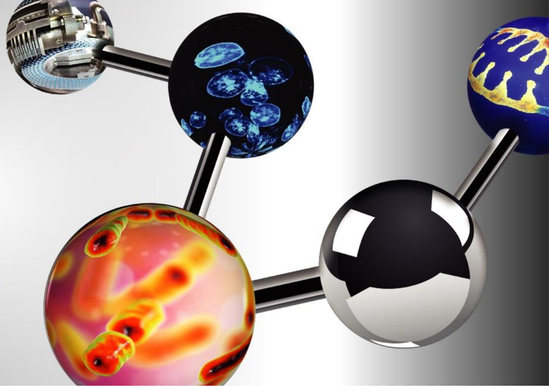


PURPOSE

- Bedaquiline fumarate is an exciting new drug discovered by Janssen to treat tuberculosis and multi-drug resistant TB (MDRTB)
- A recent clinical trial of this drug in MDRTB suggests this drug significantly improves the way MDRTB can be treated
- The Bill and Melinda Gates Foundation is interested in finding additional bedaquiline salts with acceptable development properties to be used as a treatment in developing countries where TB is a highly prevalent threat
- Our team employed the title methods to discover seven additional new salts

OBJECTIVE

- We report a new combination of method for finding salts that require small amounts of compounds, is highly efficient and can be incorporated into S-fIND, Improved Pharma's fast to IND development strategy.

METHODS

- Employed a combination of small-scale salt and polymorph crystallization experiments, single crystal and synchrotron XRD, and microscopical/ microspectroscopical analyses
- Conducted an initial salt screening using a small-scale crystallization study of bedaquiline free base with stoichiometric amounts of 10 salt formers
- Used microscopy and visual analyses to monitor formation of single crystals in some experiments
- Removed crystals from the vials using a probe or by filtration and analyzed by single-crystal X-ray diffraction within 24 hours
- Carried out a polymorph screen and additional salt crystallizations using well plates with microscopical analysis

RESULTS

Table. 1 *Acids (salt formers) and equivalent weights used in synthesis of the new bedaquiline salts*

Acid (salt former) used	Acid (weight, mg) equivalent to 30 mg bedaquiline base (0.054 mmoles)
Benzenesulfonic acid	8.54
Benzoic acid	6.60
Hydrochloric acid aq.	1.97
Maleic acid	6.27
Methanesulfonic acid (methylsulfonic acid)	5.19
Fumaric acid	6.27

Fig. 1 PXRD of benzoate salts formed from 1:1 stoichiometric reactions
a*: PXRD of Bedaquiline free base*
b*: PXRD of benzoic acid*
c*: PXRD of bedaquiline benzoate solvate from acetonitrile slow evaporation experiment*
d*: PXRD of bedaquiline benzoate hydrate from acetone slow evaporation experiment*

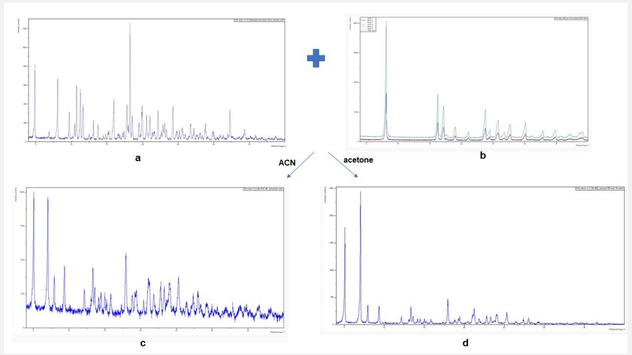


Fig. 2 X-ray single crystals for the new bedaquiline salts
a*: bedaquiline benzoate acetonitrile solvate single crystal.*
b*: bedaquiline benzoate single crystal from methanol.*
c: *bedaquiline maleate (1:1) single crystal as a THF solvate containing 2 molecules of THF*

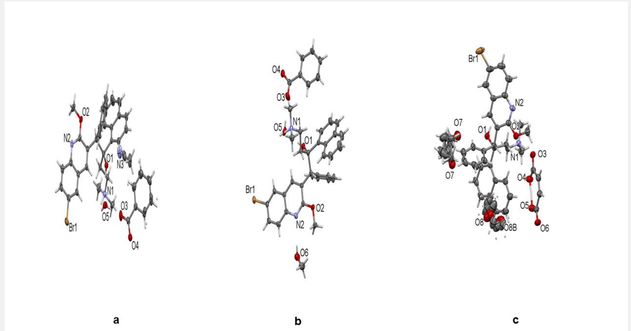


Fig. 3 Hot Stage Optical Microscopy melt of the new bedaquiline salts
a*: bedaquiline maleate (n-hexanes/acetone). Temperature: 33.3 ˚C, start of heating*
b*: bedaquiline maleate (n-hexanes/acetone). Temperature: 122.1 ˚C, exhibiting first sign of "wetting"*
c*: bedaquiline maleate (n-hexanes/acetone). Temperature: 124.7 ˚C, melting*
d*: bedaquiline maleate (n-hexanes/acetone). Temperature: 126.0 ˚C, melting*
e*: bedaquiline maleate (n-hexanes/acetone). Temperature: 130.3 ˚C, melting*
f: *bedaquiline maleate (n-hexanes/acetone). Temperature: 133.7 ˚C, melt complete*

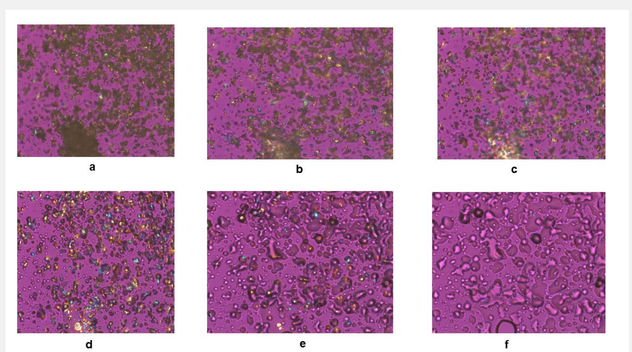
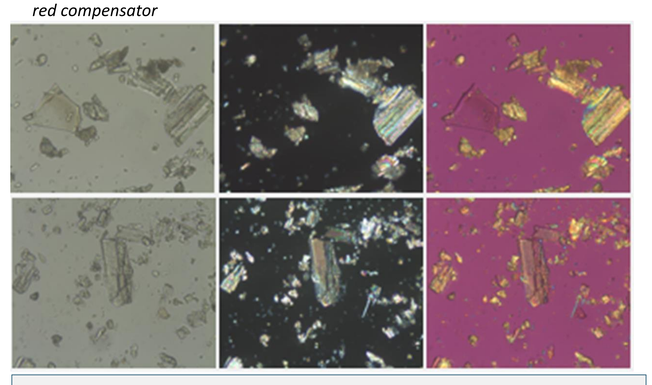


Fig. 4 Polarized Light Microscopy of a new bedaquiline salt
Polarized light microscopy of bedaquiline benzoate with (left to right) plane polarized light, crossed polarized light, and crossed polarized light with first-order red compensator



CONCLUSIONS

- Fast development to an IND utilizing small amounts of drug is critical as scientists move into the post-COVID era of drug development.
- Our study of Bedaquiline salts shows that accelerated development can be achieved using fast, small-scale development combined with several microtechniques, including single-crystal structure determination (which can be carried out in a matter of hours), microscopy, microspectroscopy, and Synchrotron-based X-ray diffraction combined with microscale stability studies.
- The increased sensitivity of these methods allows faster and more accurate analysis that can be easily incorporated into a fast to IND development approach like Improved Pharma's S-fIND (Synchrotron-based fast to IND).

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