

Mercy Okezue<sup>a</sup>, Susan Bogdanowich-Knipp<sup>b</sup>, Daniel Smith<sup>c</sup>, Matthias Zeller<sup>d</sup>,  
Stephen Byrn<sup>c,e</sup>, Pamela Smith<sup>e,f</sup>, Dale K. Purcell<sup>g</sup>, Kari Clase<sup>a,c</sup>

<sup>a</sup>Biotechnology Innovation and Regulatory Science Center, ABE, 225 S. University Str., Purdue University, West Lafayette (WL), IN 47906,

<sup>b</sup>Ravine Pharmaceuticals, LLC, 3425 DuBois St., WL, IN 47906, <sup>c</sup>Purdue University, IPPH, 575 Stadium Mall, WL, IN 47907, USA,

<sup>d</sup>Purdue University, Chemistry, 560 Oval Dr., WL, IN 47907-2084, USA, <sup>e</sup>Improved Pharma LLC, 1281 Win Hentschel Blvd., WL, IN 47906,

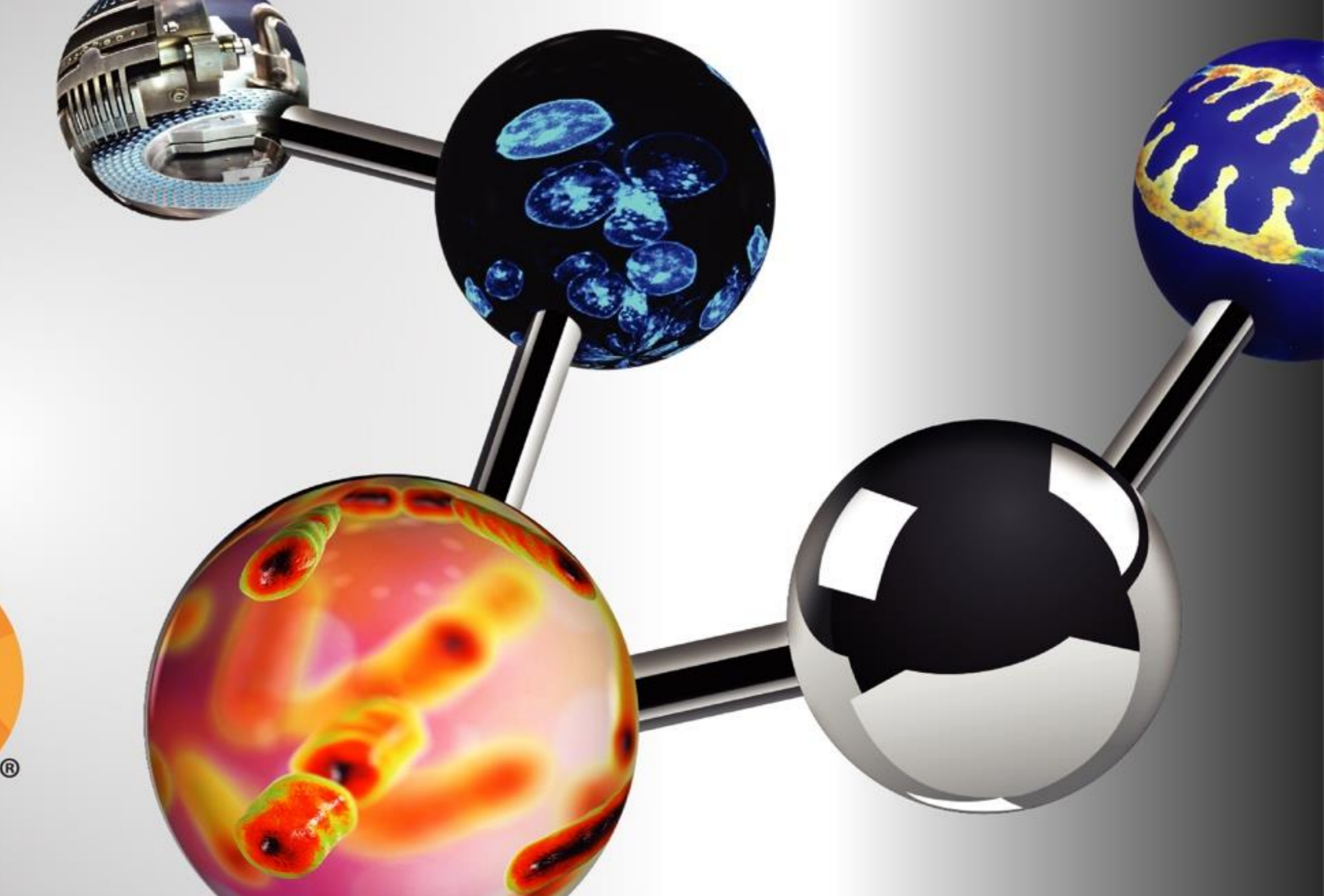
<sup>f</sup>Leading with Smart Science, LLC, 5315 Shootingstar Ln, WL, IN 47906, <sup>g</sup>Chemical Microscopy LLC, 1281 Win Hentschel Blvd., WL, IN 47906.

**CONTACT INFORMATION:** Mercy Okezue

mokezue@purdue.edu

+17654185733

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## PURPOSE

- Bedaquiline is one of two important new drugs for the treatment of drug-resistant tuberculosis (TB).
- It is marketed in the US as its fumarate salt, and several other salts of bedaquiline have been described in patent literature, but none have so far been structurally described.
- The lack of structural knowledge and even of basic chemical composition frustrates the understanding of the chemical, physical, and physiological properties of bedaquiline and its derivatives.

## OBJECTIVE

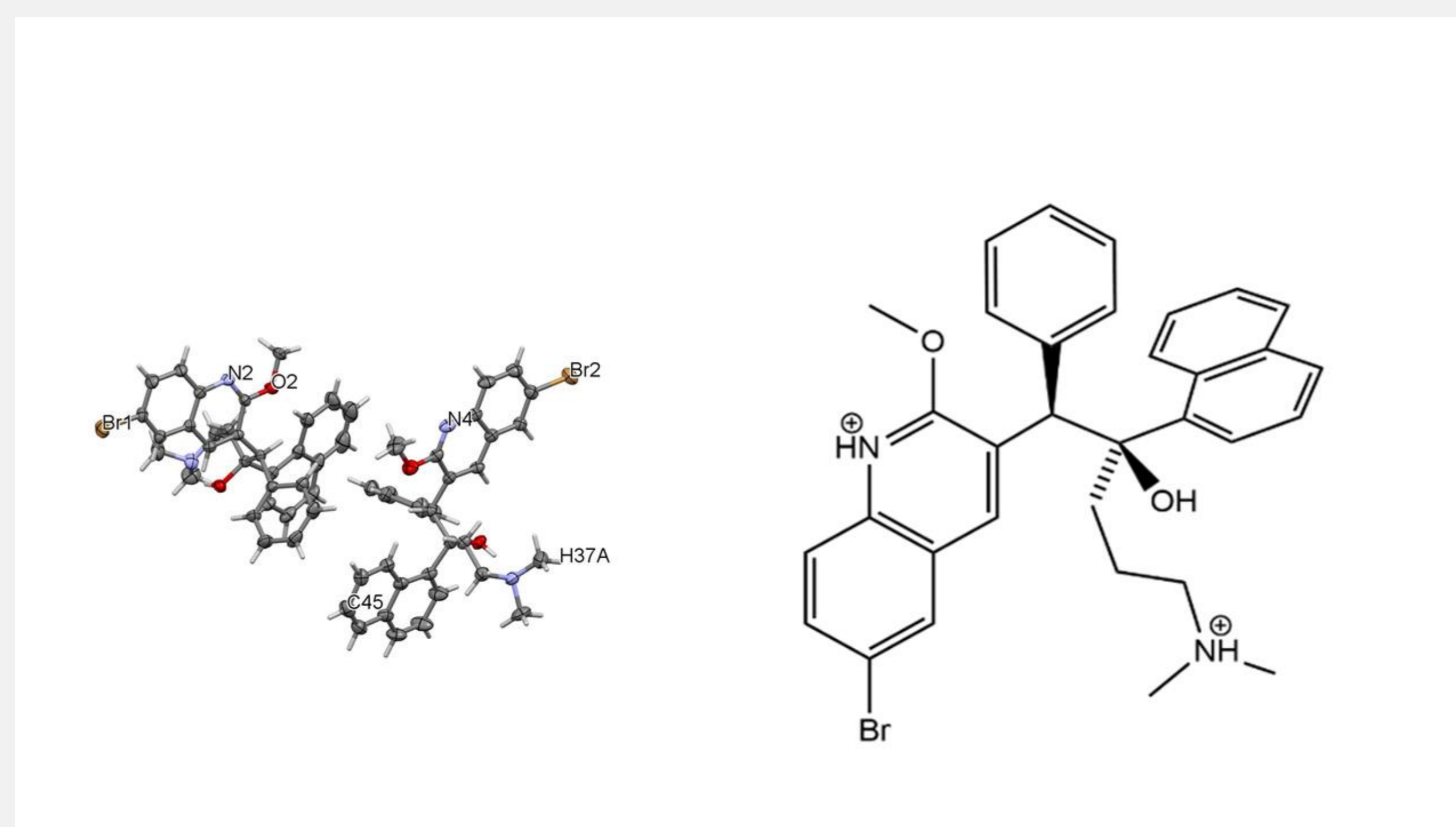
- To fill this gap, we have determined the single-crystal structures of salts of bedaquiline with fumaric, benzoic, maleic, malonic, nicotinic, benzenesulfonic as well as hydrochloric acid.

## METHODS

- Mixed stoichiometric amounts of bedaquiline with the acids at either 1:1 or 1:2 molar ratios in the respective solvents with or without the antisolvents water and hexane
- Evaporated either slowly or rapidly, and materials were screened using polarized light microscopy (PLM) to ensure that a crystalline material had formed, and that the sample was uniform
- Analyzed screened samples by NMR and infrared microspectroscopy.
- Analyzed materials by powder X-ray diffraction
- Identified known crystal phases using Rietveld refinement
- Set up single crystal growth experiments and analyzed crystals by X-ray diffraction

## RESULTS

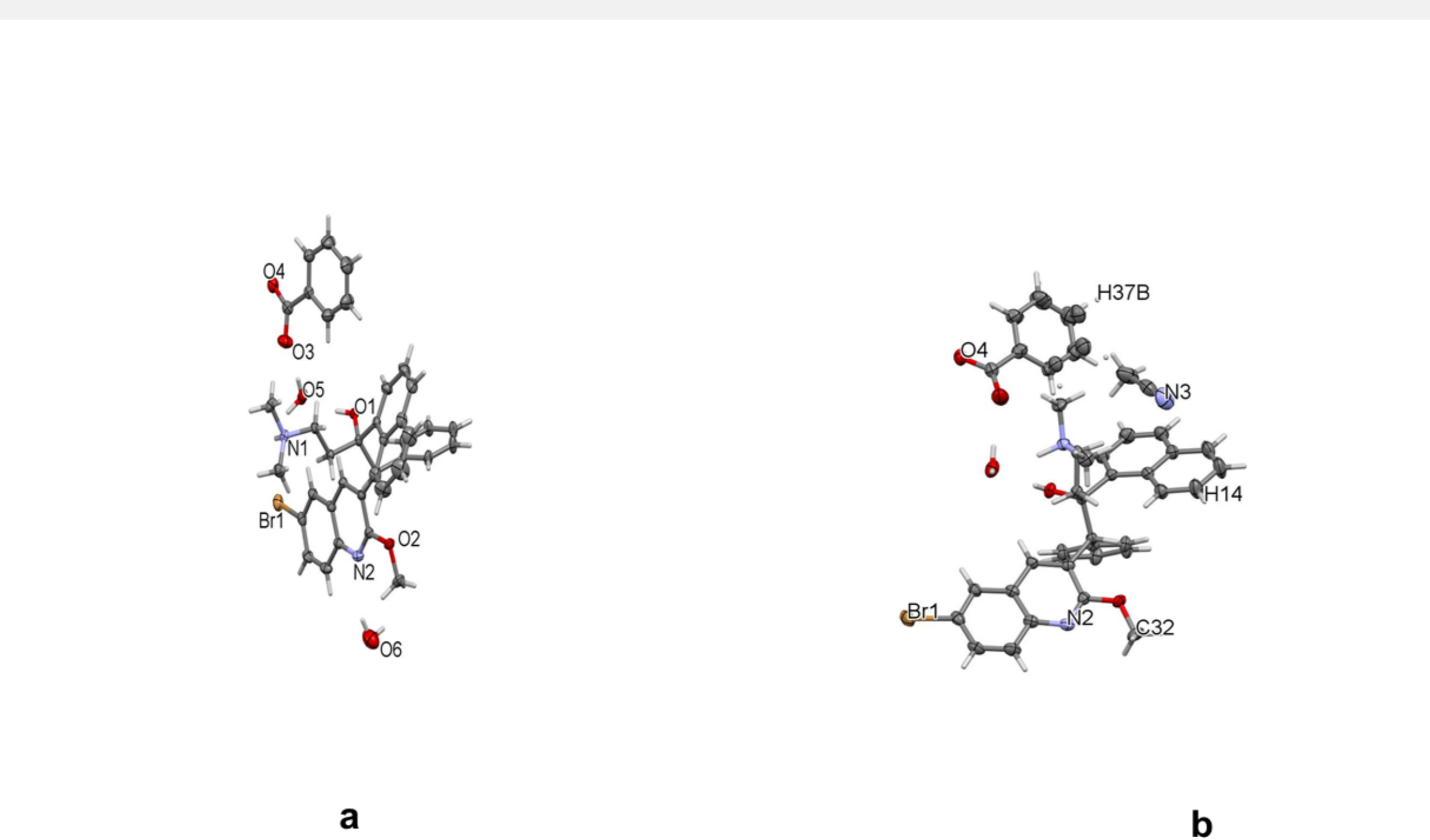
**Fig. 1 Single crystal structure of bedaquiline free base**



**Fig. 2 Single crystal structures of benzoate salts**

**a:** bedaquiline benzoate 1.17 hydrate

**b:** bedaquiline benzoate acetonitrile solvate

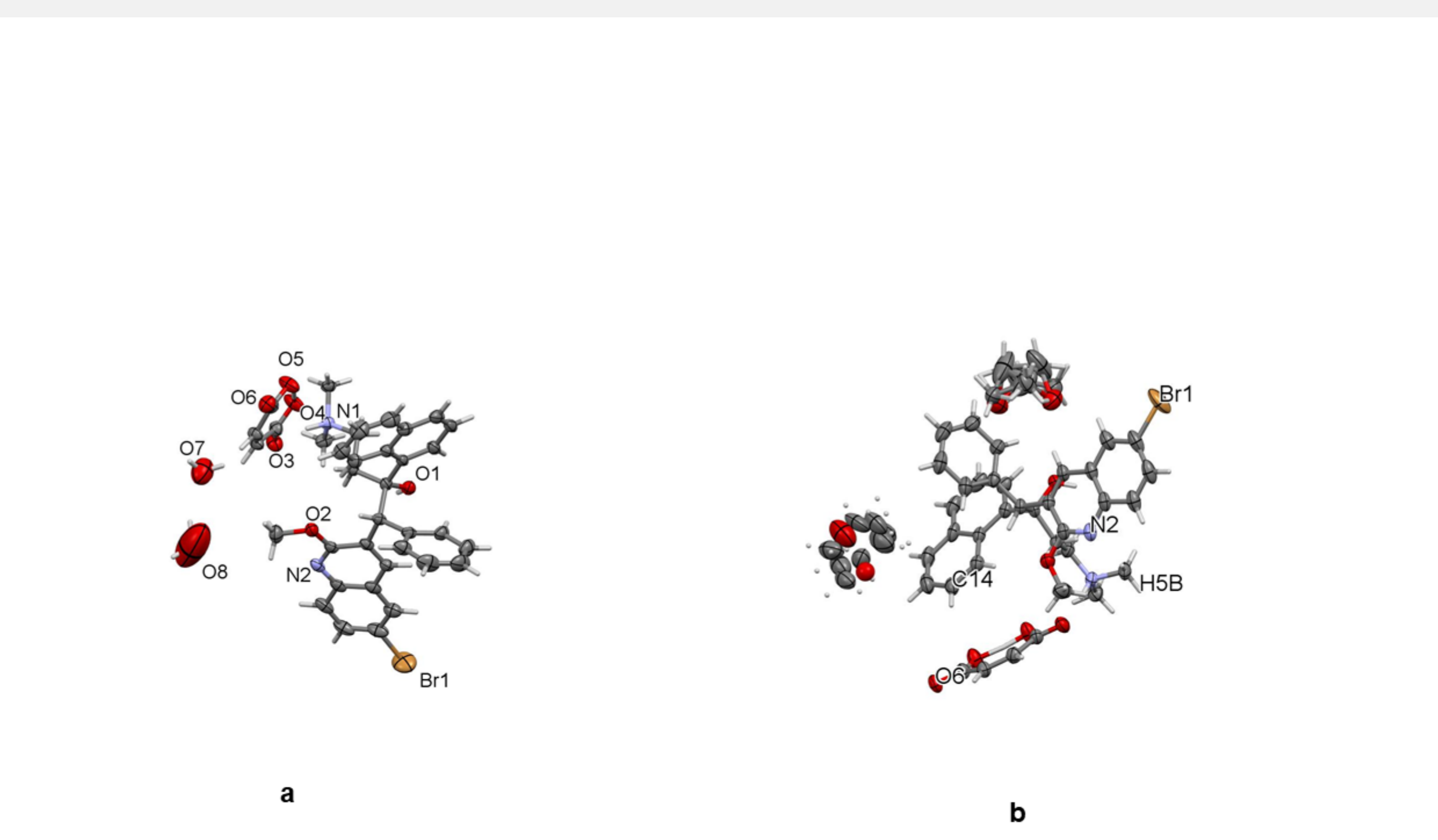


**Fig. 3 Single crystals of maleate salts**

**a:** bedaquiline maleate hydrate single crystal structure

**b:** bedaquiline maleate THF solvate Two THF molecules were refined as disordered.

One in a 1:1 ratio around a two-fold axis, the other in a general position

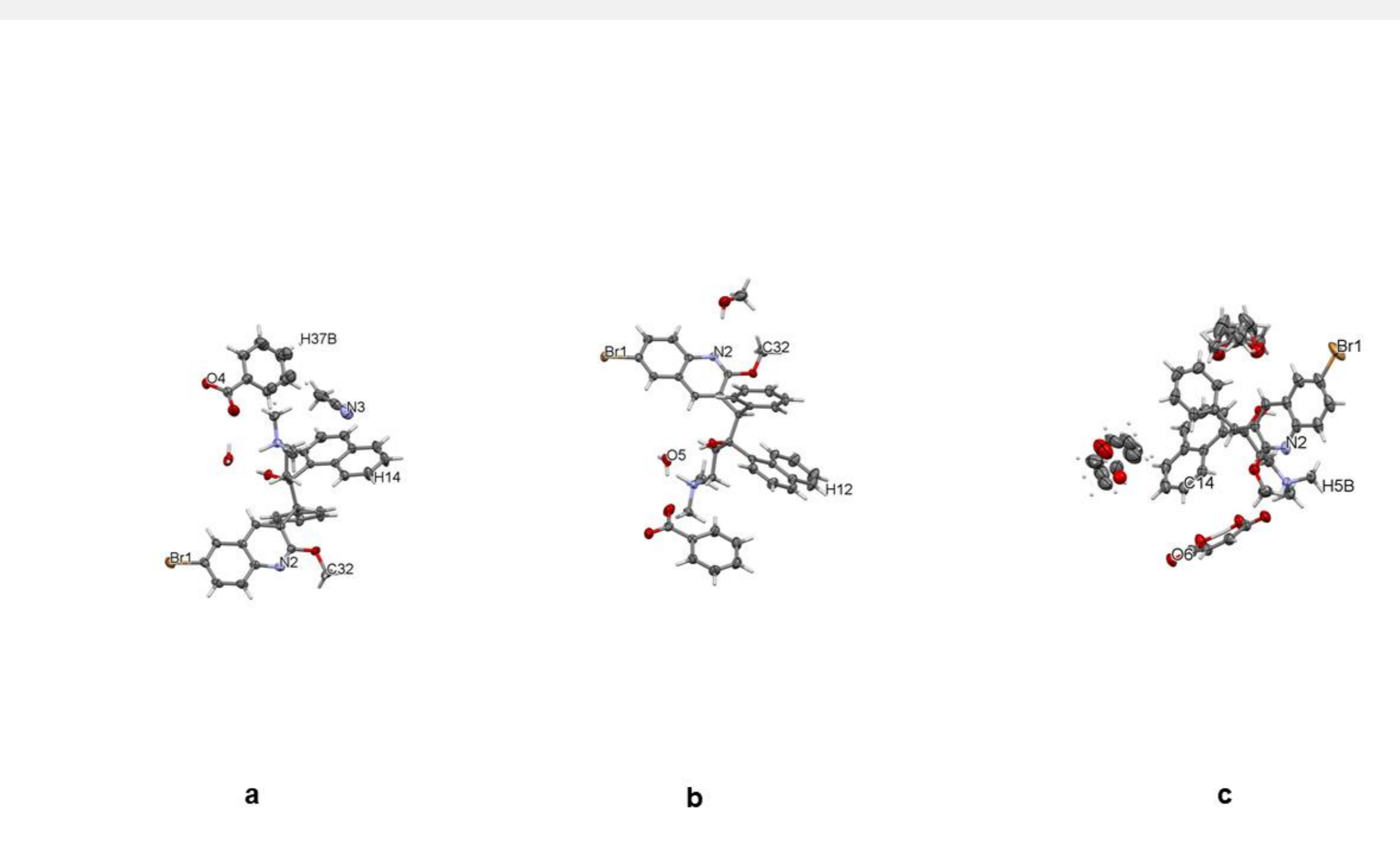


**Fig. 4 X-ray single crystals for the new bedaquiline salts**

**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. 5 X-ray more single crystals for the new bedaquiline salts**

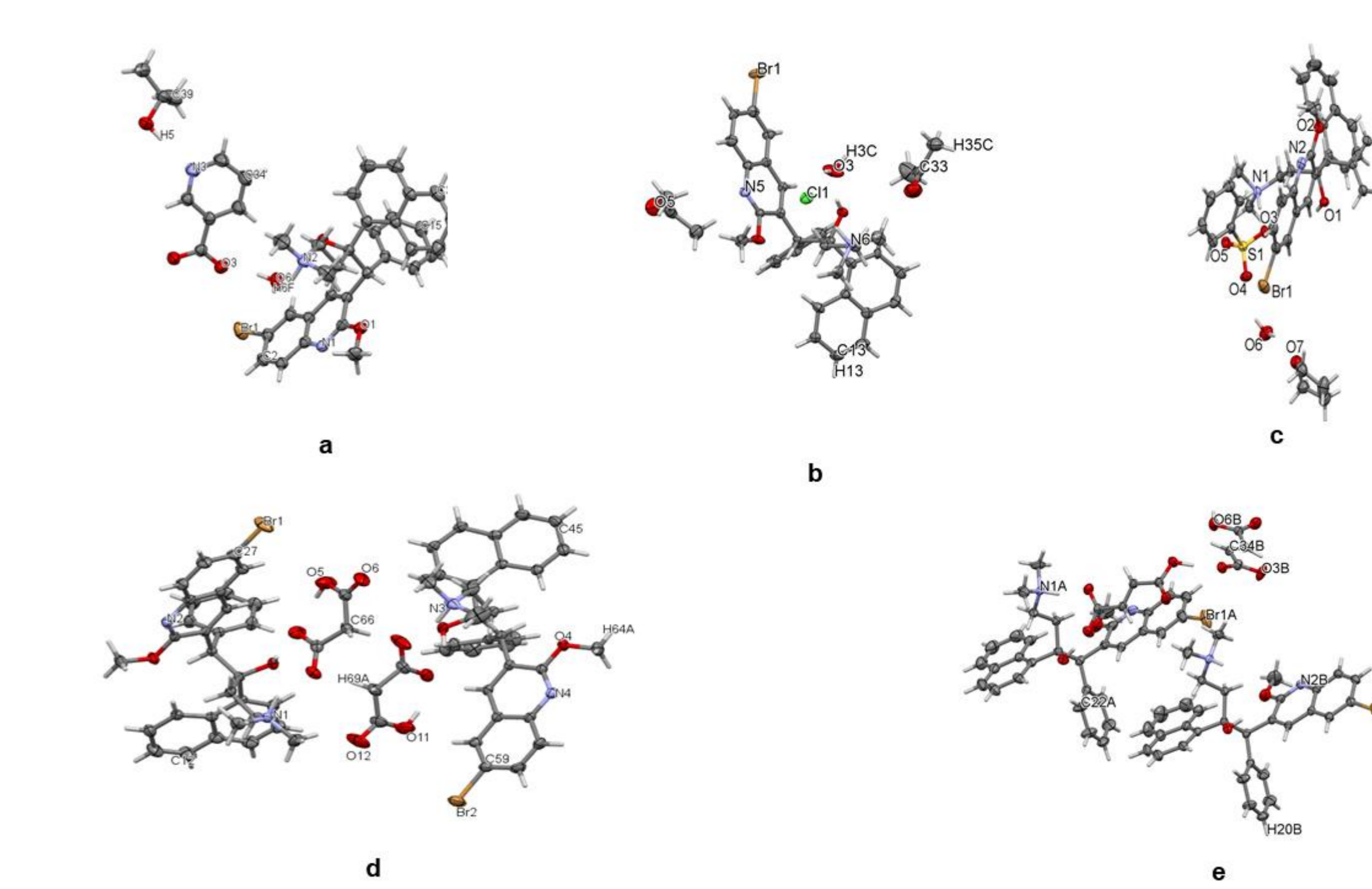
**a:** bedaquiline nicotinate single crystal

**b:** bedaquiline hydrochloride single crystal

**c:** bedaquiline benzene sulfonate single crystal

**d:** bedaquiline malonate single crystal

**e:** bedaquiline fumarate single crystal



## CONCLUSIONS

- Bedaquiline readily forms salts of its mono-cations with a range of organic and inorganic acids.
- Solvate and water free crystals were observed only for the fumarate and malonate salts.
- Crystalline solvate materials were obtained for the benzoate, benzenesulfonate, hydrochloride, maleate, and nicotinate salts
- Crystalline solvate free material were also obtained for the benzoate and maleate salts
- The crystal packing of the salts is dominated by strong hydrogen bonds and the bedaquilinium cation is characterized by a high degree of structural flexibility with a variety of conformations, leading to a multitude of unique structural arrangements.

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