Bedaquiline derivatives

THERAPEUTIC: Infectious Disease

Product Type	Small molecule
Indication/ROA	Tuberculosis (TB *Mycobacterium tuberculosis*) - oral
Target/MoA	Our derivatives rely on the MoA of the original compound, bedaquiline (BDQ) that targets and inhibits the proton pump of mycobacterial ATP synthase. BDQ is effective against susceptible, dormant and resistant strains of TB.
Development Stage	Lead series, *in-vitro* efficacy demonstrated
Brief Description & Differentiation	BDQ has received an FDA black box safety warning due to its extreme lipophilicity, hERG-mediated cardiotoxicity, CYP3A4 mediated drug-drug interactions and high toxicity resulting from phospholipid accumulation within cells, and a very long half-life. We have developed new compounds with improved properties that address these liabilities and have shown: • Potent inhibitory activity • Reduced lipophilicity • Novel synthetic route with NCE distinct from competition • Predicted potency/efficacy, safety/toxicity and DMPK
Research Team	Prof Jonathan Baell, Ms Lisa Barbaro (MIPS)
Intellectual Property	Australian provisional patent application filed in 2018 on composition of matter and method of using the compounds to treat bacterial infections, especially tuberculosis infections. Medicinal Chemistry, TB microbiology, Murine TB models
Key Publications	Priebbenow DL, Barbaro L, Baell JB*. New synthetic approaches towards bedaquiline. *Org. Biomol. Chem. 14* (2016) 9622 – 9628.
Future	Lead optimisation, validation of efficacy, safety pharmacology and expansion of the structure-activity relationship (SAR) around the key regions of molecular difference.

➢ Key Data

- ✓ New analogues with validated core structure essential for retaining TB-activity
- ✓ Quantified MICs (µM) are comparable with BDQ MICs
- ✓ Compounds with superior lipophilicity to BDQ (lower cLogP)
- ✓ Completely novel synthetic route developed
- ✓ Chiral separation is currently underway

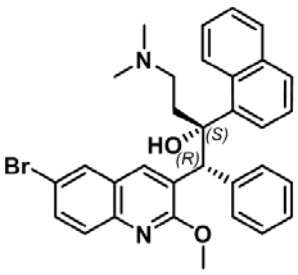

Figure 1. Bedaquiline Structure