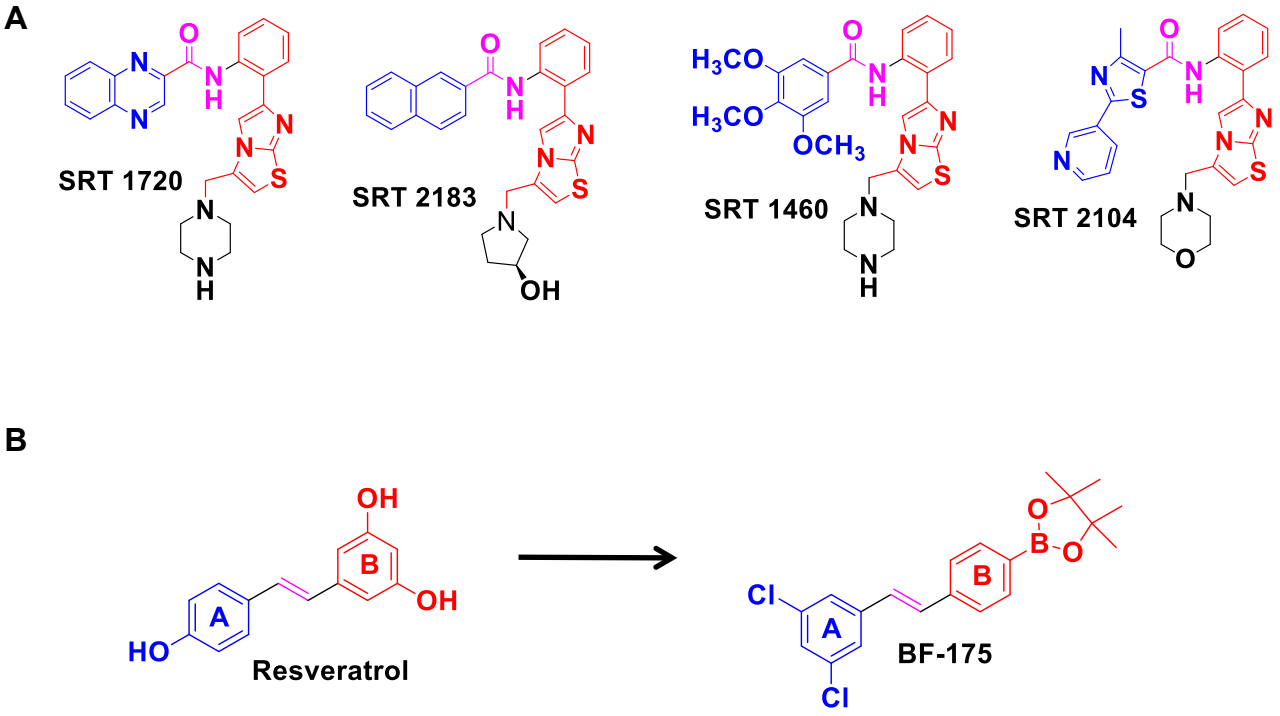
Supplementary Figure 2



Supp. Fig. 2: Development of novel SIRT1 agonist, BF175. (A) Chemical structures of other exisitng SIRT1 agonists, SRT1720, SRT2183, SRT1460 and SRT2104, which are high molecular weight amides containing imidazothiazole based pharmacophore groups that are prone to proteolytic cleavage. (B) Chemical structures of reveratrol and BF175. Since reseveratrol is toxic due to off-target binding and prone to metabolic oxidation of hydroxyl groups of the ring A and B by oxidizing enzymes (Cytochrome P450 class) to quinones, to improve efficacy and reduce toxicity, we synthesized a small library compounds and identified BF175 is a potent SIRT1 activator. In place of the hydroxyl group in ring A, chlorine group was introduced to increase hydrophobic character of the compound to facilitate the crossing of cell membranes, and pinacolato boronic ester was introduced in ring B in place of two meta hydroxyl groups to protect from Cytochrome P450 oxidation.