Simple Summary

Our work has led to the identification of three novel BH4 mimetics, SM216, SM396, and SM949, with nanomolar activities both *in vitro* and *in vivo* assays. SM396 binds covalently to the BH4 domain of BCL-2 while the compounds SM216 and SM949 are non-covalent BH4 binders. Our results illustrate that these compounds are highly specific to the triple-negative breast cancer cells with no effect on normal cells. Elevated levels of Cyt-c induced by these compounds suggest significant inhibition of BCL-2 leading to apoptosis. Further investigations of these potent lead compounds will lead to clinical translations in targeting challenging tumor types.