KCN1

While progress has been made in treating cancer, cytotoxic chemotherapeutic agents are still the most widely used drugs and are associated with severe side-effects. Drugs that target unique molecular signalling pathways are needed for treating cancer with low or no intrinsic toxicity to normal cells. Our goal is to target hypoxic tumours and specifically the hypoxia inducible factor (HIF) pathway for the development of new cancer therapies. To this end, we have previously developed benzopyran-based HIF-1 inhibitors such as arylsulfonamide KCN1. However, KCN1 and its earlier analogs have poor water solubility, which hamper their applications. Herein, we describe a series of KCN1 analogs that incorporate a morpholine moiety at various positions. We found that replacing the benzopyran group of KCN1 with a phenyl group with a morpholinomethyl moiety at the para positions had minimal effect on potency and improved the water solubility of two new compounds by more than 10-fold compared to KCN1, the lead compound [1)].

1)
Ferguson JH, De Los Santos Z, Devi SN, Kaluz S, Van Meir EG, Zingales SK, Wang B. Design and synthesis of benzopyran-based inhibitors of the hypoxia-inducible factor-1 pathway with improved water solubility. J Enzyme Inhib Med Chem. 2017 Dec;32(1):992-1001. doi: 10.1080/14756366.2017.1347784. PubMed PMID: 28766956.