

OSI-930 analogues as novel reversal agents for ABCG2-mediated multidrug resistance.

Abstract

OSI-930, a dual c-Kit and KDR tyrosine kinase inhibitor, is reported to have undergone a Phase I dose escalation study in patients with advanced solid tumors. A series of fifteen pyridyl and phenyl analogues of OSI-930 were designed and synthesized. Extensive screening of these compounds led to the discovery that nitropyridyl and ortho-nitrophenyl analogues, VKJP1 and VKJP3, were effective in reversing ABC subfamily G member 2 (ABCG2) transporter-mediated multidrug resistance (MDR). VKJP1 and VKJP3 significantly sensitized ABCG2-expressing cells to established substrates of ABCG2 including mitoxantrone, SN-38, and doxorubicin in a concentration-dependent manner, but not to the non-ABCG2 substrate cisplatin. However, they were unable to reverse ABCB1- or ABCC1-mediated MDR indicating their selectivity for ABCG2. Western blotting analysis was performed to evaluate ABCG2 expression and it was found that neither VKJP1 nor VKJP3 significantly altered ABCG2 protein expression for up to 72 h. [(3)H]-mitoxantrone accumulation study demonstrated that VKJP1 and VKJP3 increased the intracellular accumulation of [(3)H]-mitoxantrone, a substrate of ABCG2. VKJP1 and VKJP3 also remarkably inhibited the transport of [(3)H]-methotrexate by ABCG2 membrane vesicles. Importantly, both VKJP1 and VKJP3 were efficacious in stimulating the activity of ATPase of ABCG2 and inhibited the photoaffinity labeling of this transporter by its substrate [(125)I]-iodoarylazidoprazosin. The results suggested that VKJP1 and VKJP3, specifically inhibit the function of ABCG2 through direct interaction with its substrate binding site(s). Thus VKJP1 and VKJP3 represent a new class of drugs for reducing MDR in ABCG2 over-expressing tumors