Inhibition of c-Kit, VEGFR-2 (KDR), and ABCG2 by analogues of OSI-930.

Abstract

The quinoline domain of OSI-930, a dual inhibitor of receptor tyrosine kinases (RTKs) c-Kit and KDR, was modified in an effort to further understand the SAR of OSI-930, and the binding site characteristics of c-Kit and KDR. A series of 16 compounds with heteroatom substituted pyridyl and phenyl ring systems was synthesized and evaluated against a panel of kinases including c-Kit and KDR. Aminopyridyl derivative 6 was found to be the most active member of the series with 91% and 57% inhibition of c-Kit at 10μM and 1μM, respectively and 88% and 50% inhibition of KDR at 10μM and 1μM, respectively. The target compounds were also tested for their ability to inhibit efflux of mitoxantrone through inhibition of ATP dependent ABCG2 pump. Nitropyridyl derivative 5 and o-nitrophenyl derivative 7 exhibited complete inhibition of the ABCG2 pump with IC(50) values of 13.67μM and 16.67μM, respectively.