Supplementary Figure Legends and Methods

Figure S1. Potency against FGFR family and kinome selectivity. Top panel: IC_{50}s for BLU9931, BGJ398 and LY2874455 against FGFR1-4. The overall kinome selectivity is depicted by the selectivity score S(10) (see text for description of selectivity score). Bottom panel: KINOME*scan* selectivity profile for LY2874455 (screened at 1 mM), BGJ398 and BLU9931 (both screened at 3 mM) against a panel of 456 wild-type and mutant kinases.

Figure S2. Kinases with a cysteine at the equivalent position to Cys552 in FGFR4. Top panel, shows kinases that possess a cysteine (Hinge-1 residue) at the equivalent position to Cys552 in FGFR4 (GK is the gatekeeper residue). Bottom panel, shows sequence homology among the kinases that possess a cysteine at the equivalent position to Cys552.

Figure S3. MALDI Mass Spectrometry of FGFR4. Top panel, shows FGFR4 recombinant protein only, middle panel BLU9931 with reduced warhead shows no mass shift of recombinant FGFR4. Bottom panel shows mass shift of FGFR4 in the presence of BLU9931. Shift is equivalent to the molecular weight of BLU9931.

Figure S4. Induction of Caspase 3/7 activity in Hep 3B cells. BLU9931 induces apoptosis in Hep 3B cells as evidenced by induction of Caspase 3/7 activity at concentrations similar to those that result in inhibition of proliferation. BGJ398 also induces Caspase 3/7 activity, but is less potent than BLU9931.

Figure S5. FGFR4 turnover rates in Hep 3B cells.

Treatment with 10ug/ml cycloheximide in Hep 3B cells leads to detectable loss of FGFR4 expression ≥8h post cycloheximide treatment. In contrast, cMyc expression is lost at the first time point tested. Actin expression levels are unchanged throughout the course of treatment.

Figure S6. Analysis of TCGA HCC samples. Comparison of *FGF19* mRNA expression levels with copy number data across 187 HCC samples from The Cancer Genome Atlas (TCGA) shows that *FGF19* can be overexpressed not only due to focal amplification of the chromosomal region 11q13.3, but also due to reasons unrelated to DNA copy number gains. Eleven of the 187 HCC samples analyzed (6%) exhibited focal *FGF19* amplification with copy number ≥ 3 and varying degrees of *FGF19* overexpression. Interestingly, 34% (63/187) of tumors with no evidence of *FGF19* copy number gain expressed *FGF19* at levels greater than or equal to the median level observed in *FGF19* focally amplified tumors, reflecting an additional patient population that might benefit from FGFR4 inhibition.

Supplementary Methods

The following reagents were used in the qRT-PCR assays

qRT-PCR reagents	**Vendor**
Probe - beta-actin, VIC, human	Life Technologies
Probe - FGFR4, FAM, human	Life Technologies
Probe - KLB, FAM, human	Life Technologies
Probe - FGF19, FAM, human	Life Technologies
Probe - CYP7A1, FAM, human	Life Technologies
Probe - EGR1, FAM, human	Life Technologies