**Supplemental Table 1.** Biochemical and Cellular Potency and Selectivity of PF-02341066

| Assay | $IC_{50}$ nM | Selectivity Ratio[d] |
|---|---|---|
| **Biochemical Activity In Vitro** | | |
| c-Met/HGFR enzyme (Ki, nM)[a] | 4 | NA |
| **Cellular Activity In Vitro** | | |
| c-Met phosphorylation in human tumor cell lines (mean $IC_{50}$)[b,c] | 11 | NA |
| c-Met phosphorylation in mouse IMCD3 epithelial cells ($IC_{50}$)[b] | 5 | NA |
| Phosphorylation of c-Met WT in NIH3T3 cells ($IC_{50}$)[b] | 13 | NA |
| Phosphorylation of c-Met mutant V1092I in NIH3T3 cells ($IC_{50}$)[b] | 19 | NA |
| Phosphorylation of c-Met mutant H1094R in NIH3T3 cells ($IC_{50}$)[b] | 2 | 0.1X |
| Phosphorylation of c-Met mutant Y1230C in NIH3T3 cells ($IC_{50}$)[b] | 127 | 11X |
| Phosphorylation of c-Met mutant Y1235D in T47D cells ($IC_{50}$)[b] | 92 | 8X |
| Phosphorylation of c-Met mutant M1250T in NIH3T3 cells ($IC_{50}$)[b] | 15 | NA |
| Phosphorylation of c-Met in NCI-H69 cells expressing c-Met R988C variant ($IC_{50}$)[b] | 13 | NA |
| Phosphorylation of c-Met in HOP92 cells expressing c-Met T1010I variant ($IC_{50}$)[b] | 16 | NA |
| NPM-ALK phosphorylation in human Karpas299 lymphoma cells ($IC_{50}$)[b] | 24 | 2X |
| **Cellular Activity Against Non-Target Kinases In Vitro** | | |
| MSP-stimulated RON phosphorylation in NIH-3T3-RON cells (mean $IC_{50}$)[b] | 189 | 17X |
| RON phosphorylation in RON-GYRB cells (mean $IC_{50}$)[b] | 298 | 27X |
| Gas6-stimulated Axl phosphorylation in NIH-3T3-Axl cells (mean $IC_{50}$)[b] | 322 | 29X |
| Ligand-stimulated Tie-2 phosphorylation in NIH-3T3-Tie-2/EGFR cells (mean $IC_{50}$)[b] | 448 | 41X |
| NGF-stimulated TrkA phosphorylation in Trk A-PAE cells (mean $IC_{50}$)[b] | 580 | 53X |
| BDNF-stimulated TrkB phosphorylation in Trk B-PAE cells (mean $IC_{50}$)[b] | 399 | 36X |
| BCR-Abl phosphorylation in BCR-Abl-BaF3 cells (mean $IC_{50}$)[b,e] | 1159 | >100X |
| Insulin-stimulated insulin receptor phosphorylation in 293-IRK cells (mean $IC_{50}$)[b] | 2887 | >250X |
| CD3-stimulated Lck-dependent Zap70 phosphorylation in Jurkat cells (mean $IC_{50}$)[b] | 2741 | >250X |
| Gas6-stimulated Sky phosphorylation in NIH-3T3-Sky cells (mean $IC_{50}$)[b] | >10000 | ~1000X |

Definitions

[a] Ki for c-Met/HGFR enzyme inhibition determined by monitoring NADH oxidation coupled to ATP turnover.

[b] $IC_{50}$ values were determined after exposure of various cell lines to several concentrations of PF-02341066 for 1 hour and measuring phosphorylation in cellular protein lysates by ELISA as described in "Materials and Methods". $IC_{50}$ values were generated by curve fitting using a four-parameter analysis.

[c] Mean $IC_{50}$ value derived from mean $IC_{50}$ value for c-Met/HGFR phosphorylation across a panel of 7 human tumor cell lines (i.e., A549, MDA-MB-231, GTL-16, HT29, 786-O, Colo-205, A498).

[d] Mean [c] cell c-Met $IC_{50}$ was used to calculate the selectivity ratio for cell assays. Selectivity Index was calculated as $IC_{50}$, (c-Met)/$IC_{50}$, (target).

[e] BaF3 cells engineered to express human BCR-Abl were acquired from Dr. Brian Druker (Oregon Health and Science University, Portland).

WT = Wild Type

Antibody reagents and growth factors: Anti-phospho Zap70 was acquired from Zymed/Invitrogen (Carlsbad, CA). Anti-RON, FGFR1, PDGFRβ, Trk, Tie-2, and anti-phospho tyrosine (PY-20) were acquired from Santa Cruz Biotechnology (Santa Cruz, CA). Anti-Axl and Sky antibodies and MSP, Gas6, NGF, EGF, and Insulin were acquired from R&D Systems (Minneapolis, MN). Anti-IRK was acquired from BD Pharmingen (San Diego, CA). Anti-VEGFR2 was acquired from Novus Biologicals (Littleton, CO). Anti-total and –phospho ALK and anti-c-ABL were acquired from Cell Signaling Technologies (Boston, MA). BDGF was acquired from GibcoBRL/Invitrogen (Carlsbad, CA).

**Supplemental Table 2. Effect of PF-02341066 on c-Met -Dependent Phenotypes in Cancer Cells**

| Assay | PF-02314066 Concentration $IC_{50}$ (nM) [a] |
|---|---|
| **Tumor Cell Phenotypes** | |
| Proliferation (MTT assay) of GTL-16 gastric carcinoma cells (mean $IC_{50}$) | 9.7 |
| Apoptosis (ccDNA assay) of GTL-16 gastric carcinoma cells (mean $IC_{50}$) | 8.4 |
| HGF-stimulated NCI-H441 NSCLC cell Boyden Chamber migration ($IC_{50}$) | 11 |
| HGF-stimulated NCI-H441 NSCLC cell Boyden Chamber Matrigel invasion ($IC_{50}$) | 6.1 |
| HGF-stimulated MDCK cell colony scattering (mean $IC_{50}$) | 16 |
| **Endothelial Cell Phenotypes** | |
| HGF-stimulated HUVEC endothelial cell survival (MTT assay) (mean $IC_{50}$) | 11 |
| HGF-stimulated HUVEC cell Matrigel invasion (mean $IC_{50}$) | 35 |
| HMVEC endothelial cell tubulogenesis in fibrin gels (estimated $IC_{50}$) | 80 |

[a] $IC_{50}$ values were generated by curve fitting using a four-parameter analysis.

Definitions: NSCLC=non-small cell lung cancer; MDCK=Madin-Darby Canine Kidney; HUVEC=human umbilical vein endothelial cells; HMVEC=human microvascular endothelial cells

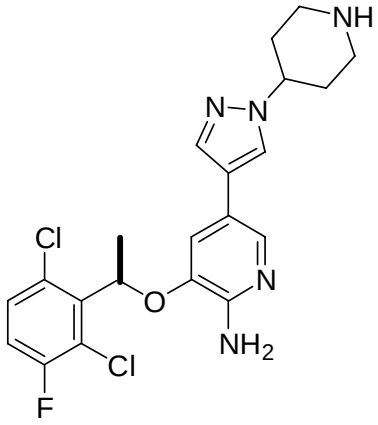
**Supplemental Figure Legends**

**Supplemental Figure 1.** PF-02341066 (R)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-pyridin-2-ylamine

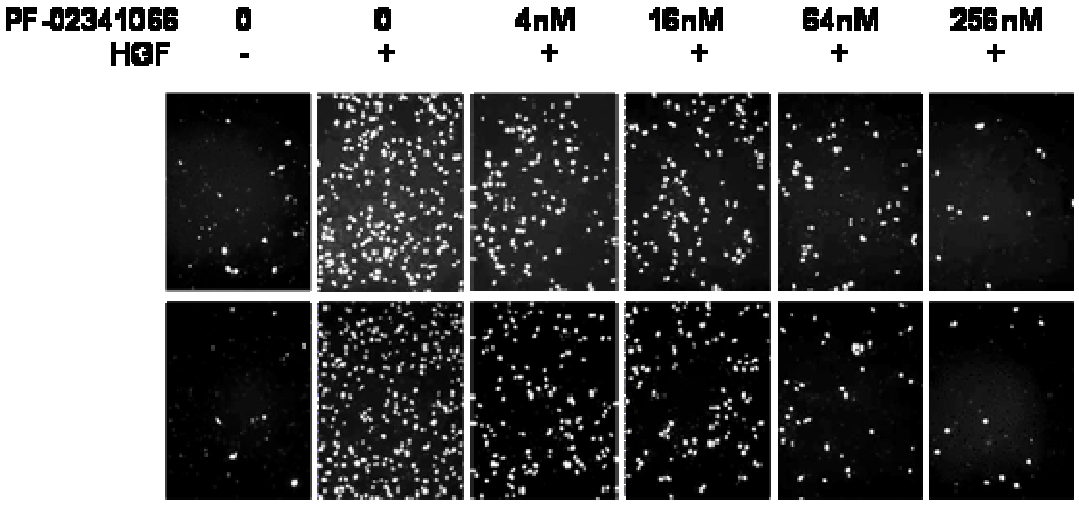
**Supplemental Figure 2. PF-02341066 Inhibited HGF-stimulated NCI-H441Cell Migration and Invasion in vitro-** NCI-H441 cells were treated with HGF (25 ng/mL) or designated concentrations of PF-02341066 and migration of cells across a membrane (Top Panel) and/or a layer of matrigel (Invasion--Lower Panel) to the lower well of a 2-chamber plate was assessed after 22 hours. Cells that invaded or migrated to the lower well of the plate were then fixed, nuclei were stained with DAPI, and the number of migrating or invading cells was determined utilzing ImagePro Plus software.

**Supplemental Figure 3. Dose-Dependent Induction of Apoptosis by PF-2341066 in Tumor Xenografts In Vivo.** Immunohistochemical evaluation of activated caspase-3 expression was determined in GTL-16 (**A**) or U87MG (**B**) tumors at 50 mg/kg/day qd on study day 4. For each study, athymic mice bearing established GTL-16 or U87MG xenografts were orally administered vehicle or PF-2341066 at the indicated dose levels qd. At designated study days at 4 hours post-administration of PF-2341066, mice were humanely euthanized, tumors were resected and fixed in 10% neutral buffered formalin for 24 hours, and then placed in 70% ethanol. Fixed tumors were embedded in paraffin, cut into 4 mm sections, and immunostained for activated caspase-3 as described in "Materials and Methods." Slides were visually assessed for expression and distribution of activated caspase-3 by light microscopy.

**Supplemental Figure 1**




**Supplemental Figure 2**




**Supplemental Figure 3**