Synthesis of kinase inhibitors containing a pentafluorosulfanyl moiety.

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Figure S1. Structural studies comparing binding modes of methylidene indolinone-based kinase inhibitors 11 and 15 (A) with active and inactive kinase domains. Compound 15 (A) was co-crystallised with RET kinase domain (B, PDB: 2X2K) forcing a “DFG-in” kinase conformation. This 15-bound RET conformation was aligned with the PDGFRA crystal structure (B, PDB: 5K5X) revealing gross conformational shifts around the ATP-binding pocket, particularly between the RET and PDGFRA β-hairpin and Ca-helix (B), and compared to RET, the PDGFRA DFG catalytic-motif aspartic acid is pointing outside of the ATP-binding pocket; evidence for an inactive kinase conformation. Compound 11 displayed the greatest potency in the series against PDGFRA, a receptor tyrosine kinase containing a threonine gatekeeper. RET has a valine gatekeeper, and thus PTK6 (C, PDB: 5DA3), a non-receptor tyrosine kinase containing a threonine gatekeeper, was selected for docking studies with compound 10 - 11 (Fig. 5, main article) to ascertain the molecular determinants for the superior potency of 11 vs 10. The alignment between 15-bound RET and 11-docked PTK6 (C) reveals very similar binding modes between compounds 11 and 15 and an agreement in PTK6 and RET kinase conformation, both in the active state.

Figure S2. Proliferation assays. Dose-dependent inhibition of MCF7, T47D MDA-BM-231 and MCF10A cells by compounds 10 and 11.
Fig S3. NMRs

(Z)-3-((1H-Pyrrol-2-yl)methylene-5-pentafluorosulfanylidoline-2-one
(Z)-3-((1H-Pyrrol-2-yl)methylene-6-pentafluorosulfanylindoline-2-one
(E)-5-Pentafluorosulfanyl-3-ferrocenyldolin-2-one

(Z)-5-Pentafluorosulfanyl-3-ferrocenyldolin-2-one
(Z)-3-(2,4-dimethyl-5-((5-pentafluorosulfanyl-2-oxoindolin-3-ylidene)methyl)-1H-pyrrol-3-yl)propanoic acid
(Z)-3-(2,4-dimethyl-5-((6-pentafluorosulfanyl-2-oxoindolin-3-ylidene)methyl)-1H-pyrrol-3-yl)propanoic acid
^19F: (broad)