Fig. S4.

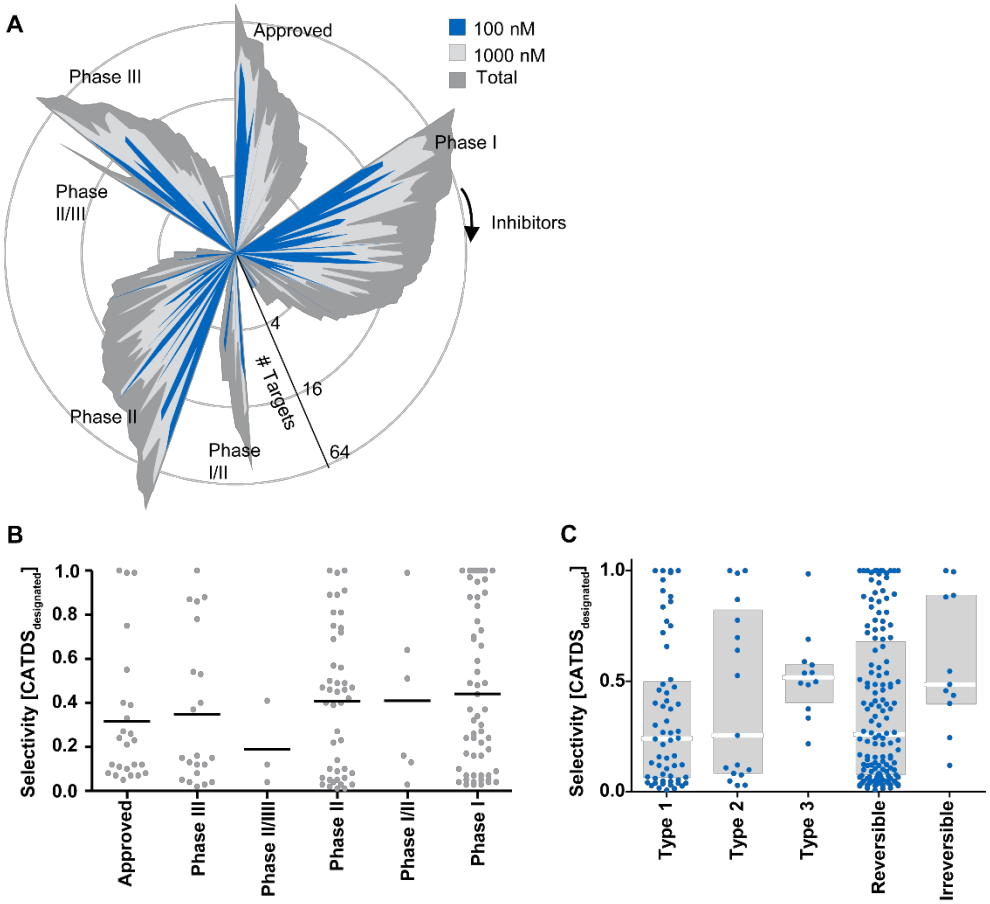

Fig. S4 | Evaluation of drug selectivity – global dataset. (A) Inhibitors grouped by status of clinical evaluation. Given is the number of targets with a potency of below 100 nM (blue), 1,000 nM (light grey) and any concentration (total; dark grey). **(B)** CATDS analysis of drug selectivity according to clinical status (determined from the CATDS for all designated targets at the concentration of the most potent designated target; $CATDS_{designated}$). There was no difference in selectivity between clinical phases confirming that selectivity is not a strict requirement for progressing a compound in the clinic. **(C)** Selectivity analysis of 137 kinase inhibitors with annotated binding type according to $CATDS_{designated}$ (the most potent designated target of a compound at its K_d^{app}). Type 1 and 2 inhibitors did not differ in median selectivity; while type 3 inhibitors were generally more selective. Irreversible and reversible inhibitors spanned a broad range of selectivity, albeit highly selective molecules were apparent in both.

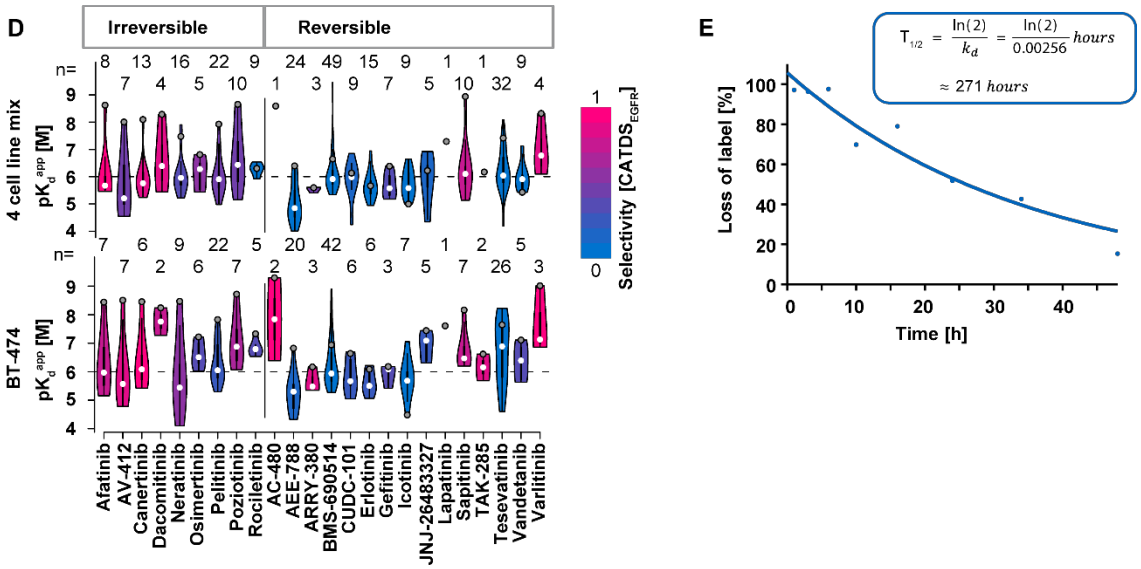

Fig. S4 continued | Evaluation of drug selectivity – irreversible and reversible EGFR inhibitors.

(D) Violin plots of EGFR inhibitors profiled in the lysate mixture of the four cell lines (top panel) as well as BT-474 cells (bottom panel). Given are pK_d^{app} values of all high-confidence, direct-binder targets (pK_d^{app} of EGFR highlighted as a grey circle). The shape of the violin indicates the number of targets at the respective pK_d^{app}. The total number of targets is printed at the top (e.g. n=8). Violins are colored according to selectivity for EGFR ($CATDS_{EGFR}$). **(E)** EGFR turnover measured by pulsed SILAC mass spectrometry and monitoring the loss of a heavy label over time. EGFR turnover was corrected for cell doubling to obtain protein half-lives.

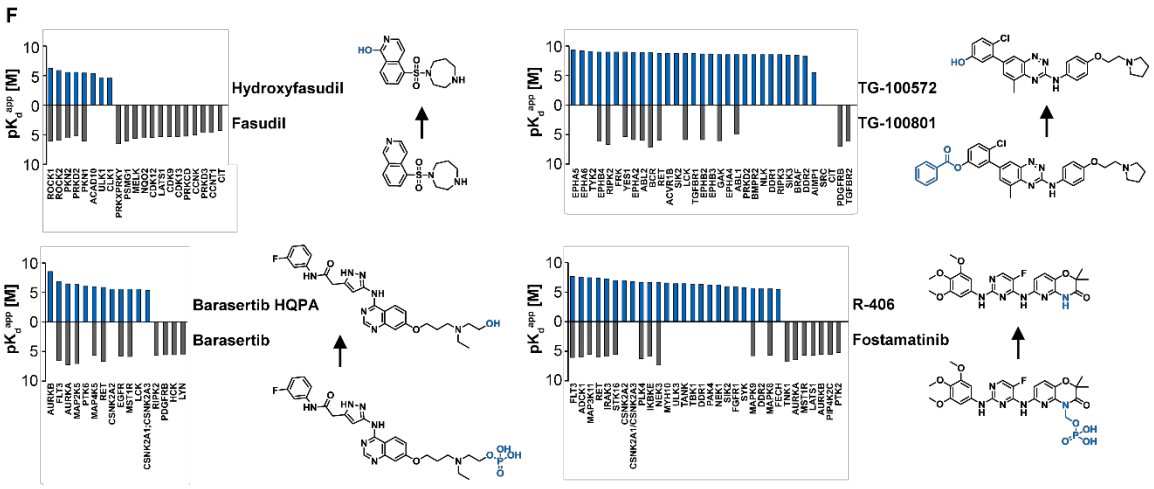

Fig. S4 continued| Evaluation of drug selectivity. (F) Kinobeads target profiling data of a prodrug (grey) compared to the active drug (blue) for different compounds that are formulated as prodrugs.