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Chemistry & Drug Discovery

Supporting Information

Targeting a Targeted Drug: An Approach Toward Hypoxia-Activatable Tyrosine Kinase Inhibitor Prodrugs

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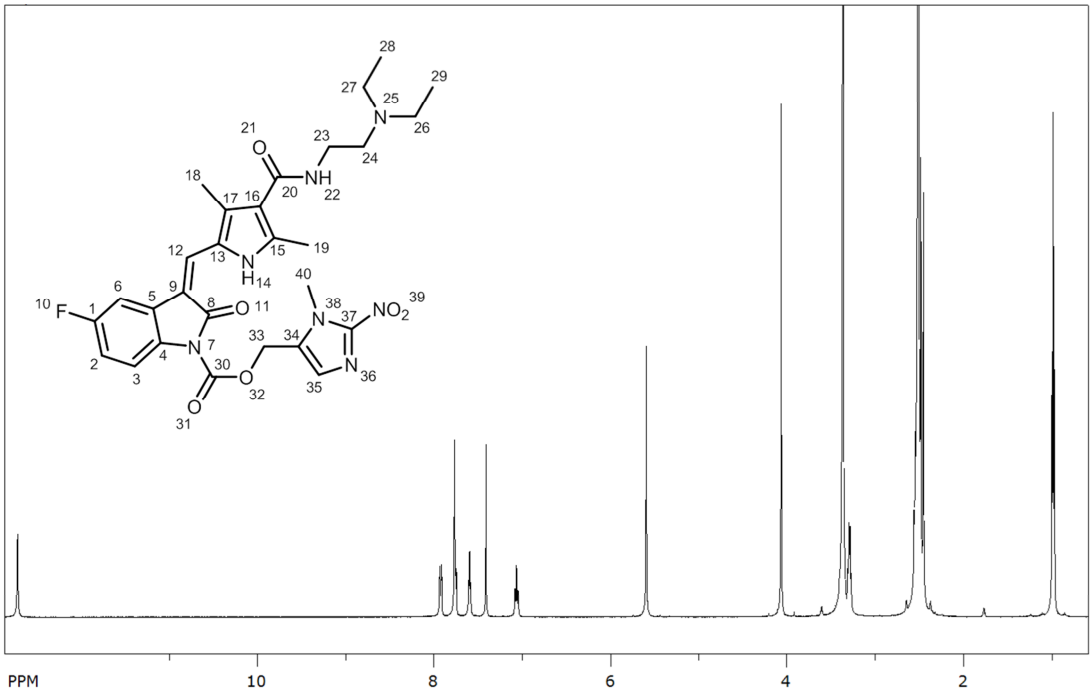

Figure S1. ^{1}H NMR spectrum of compound **1a**.

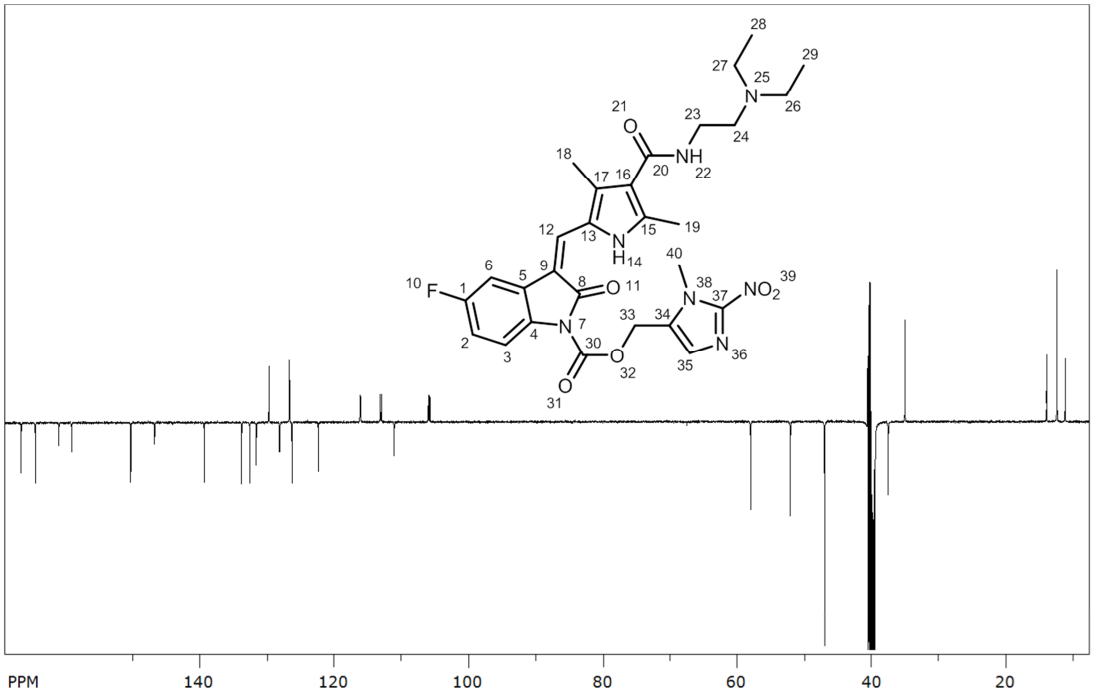

Figure S2. ^{13}C NMR spectrum (broadband proton decoupled, j-modulated) of compound **1a**.

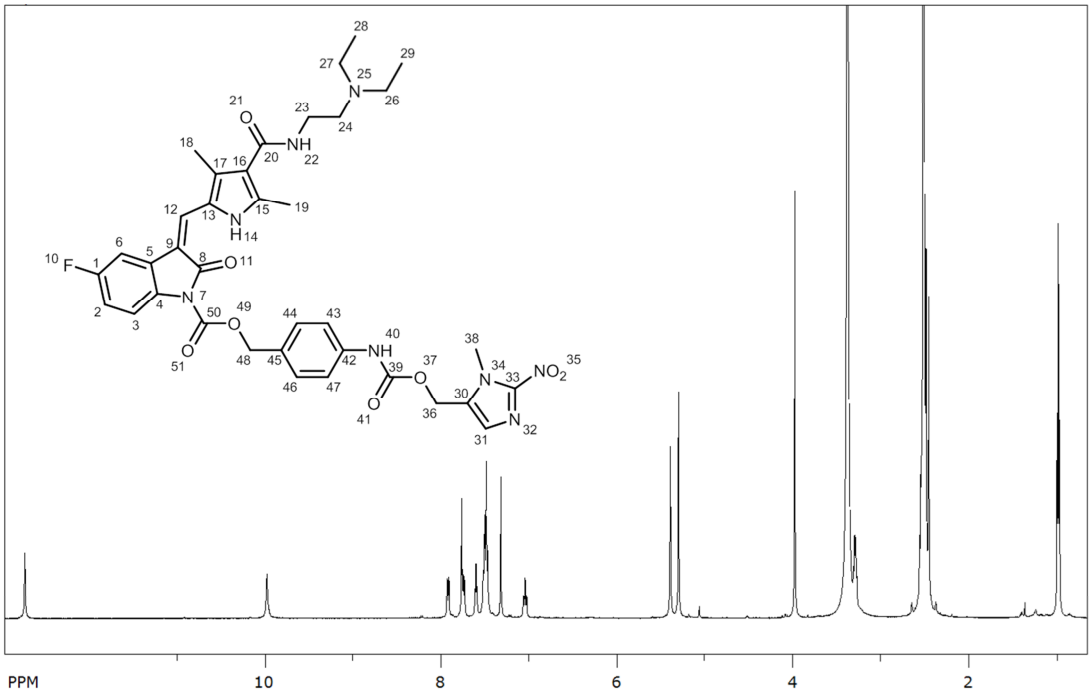

Figure S3. ^{1}H NMR spectrum of compound **1b**.

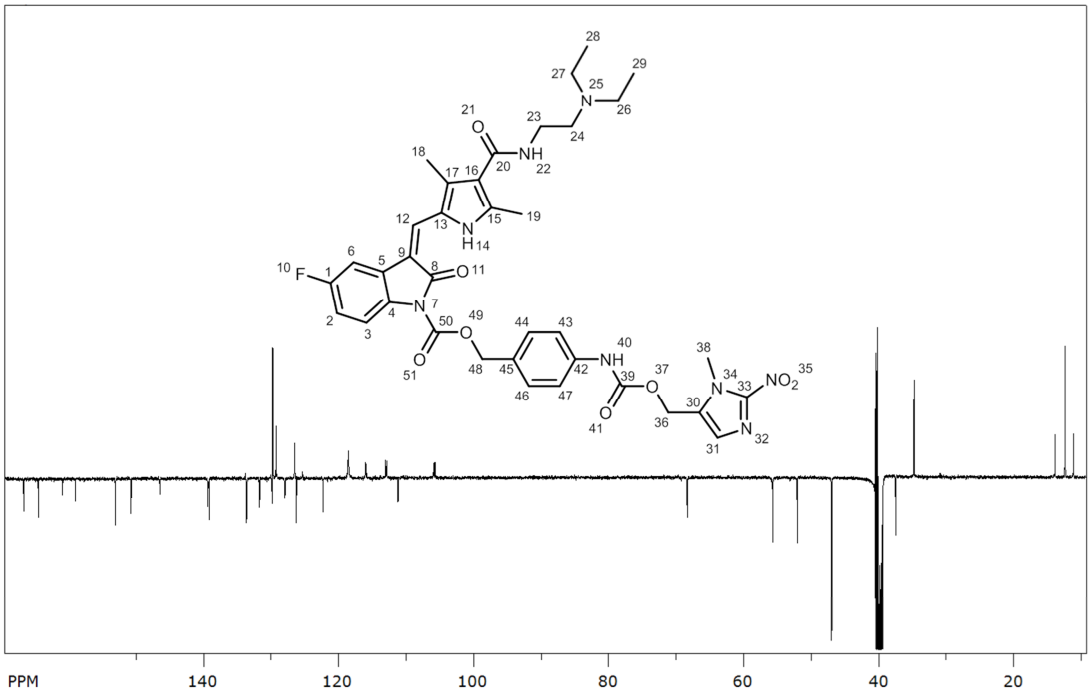

Figure S4. ^{13}C NMR spectrum (broadband proton decoupled, j-modulated) of compound **1b**.

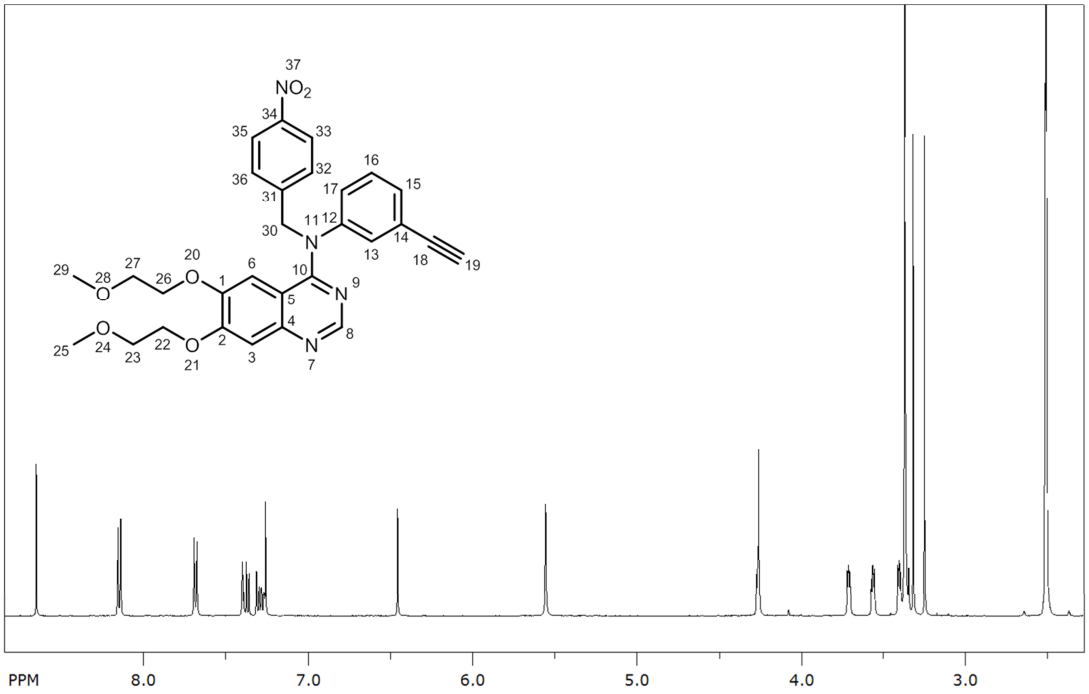

Figure S5. ^{1}H NMR spectrum of compound **2a**.

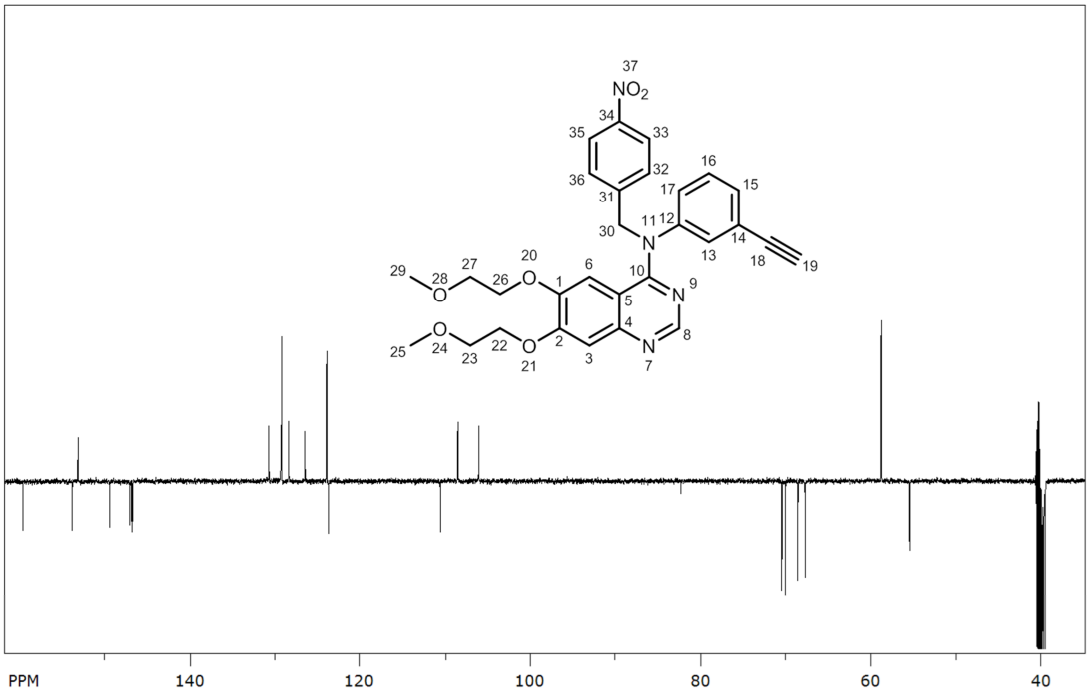

Figure S6. ^{13}C NMR spectrum (broadband proton decoupled, j-modulated) of compound **2a**.

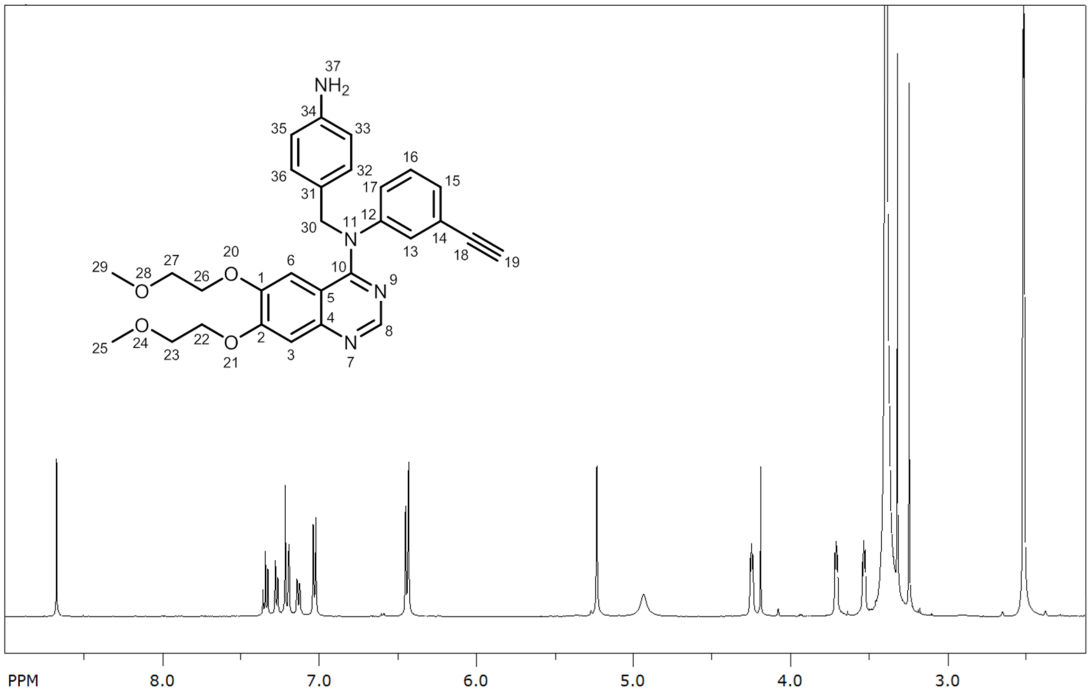

Figure S 7. ^{1}H NMR spectrum of compound **2b**.

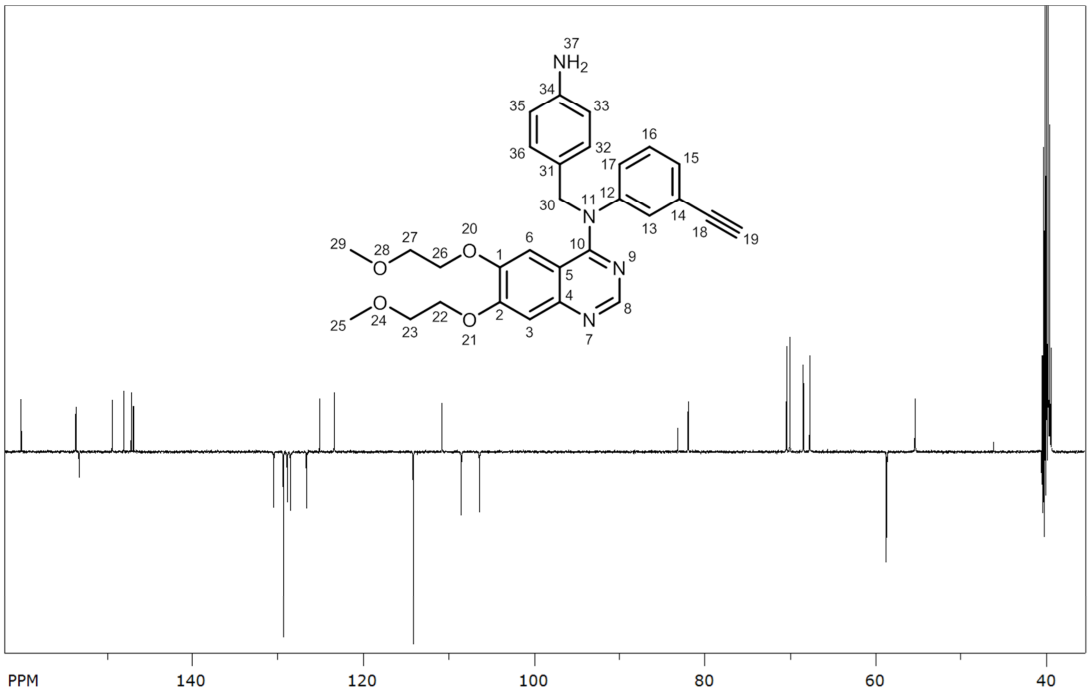

Figure S8. ^{13}C NMR spectrum (broadband proton decoupled, j-modulated) of compound **2b**.

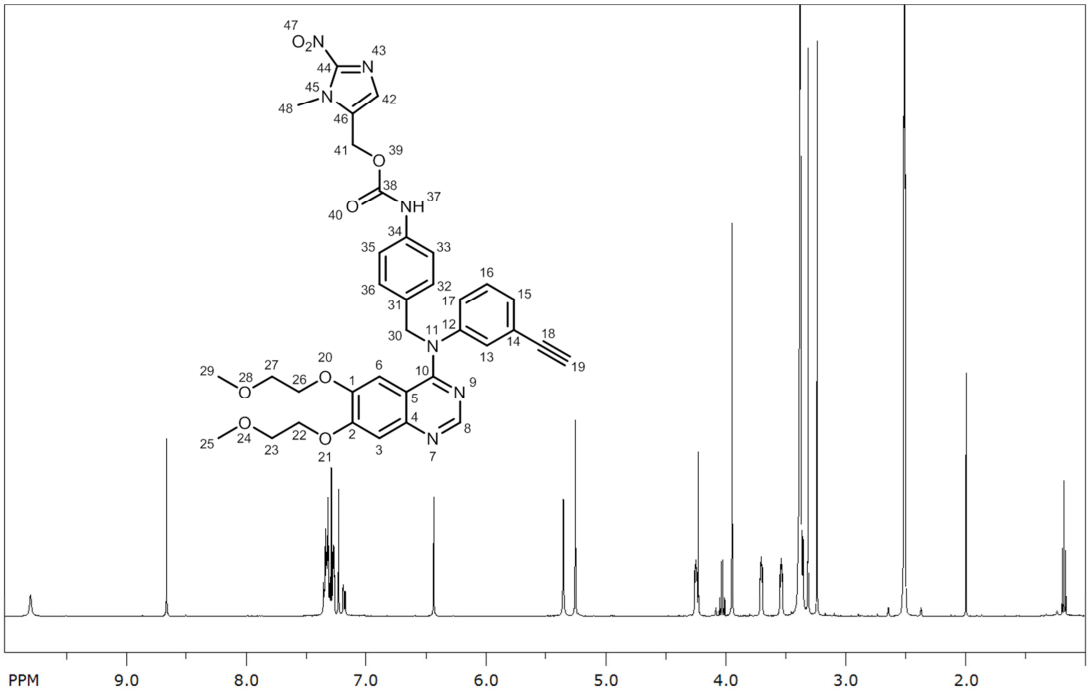

Figure S9. ^{1}H NMR spectrum of compound **2c**.

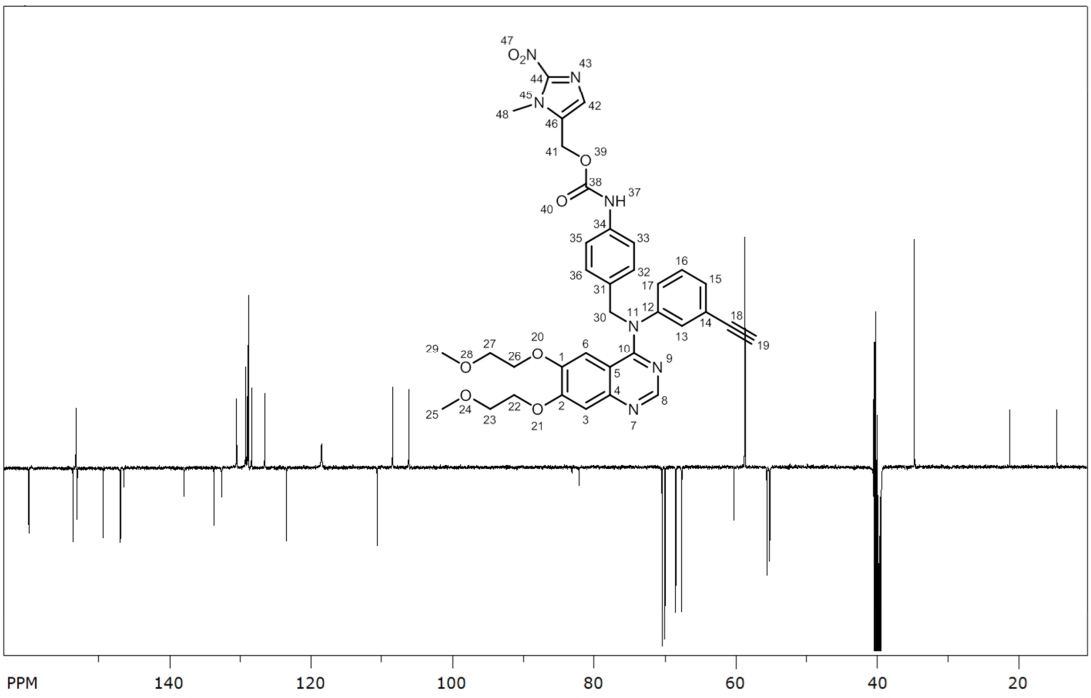

Figure S10. ^{13}C NMR spectrum (broadband proton decoupled, j-modulated) of compound **2c**.

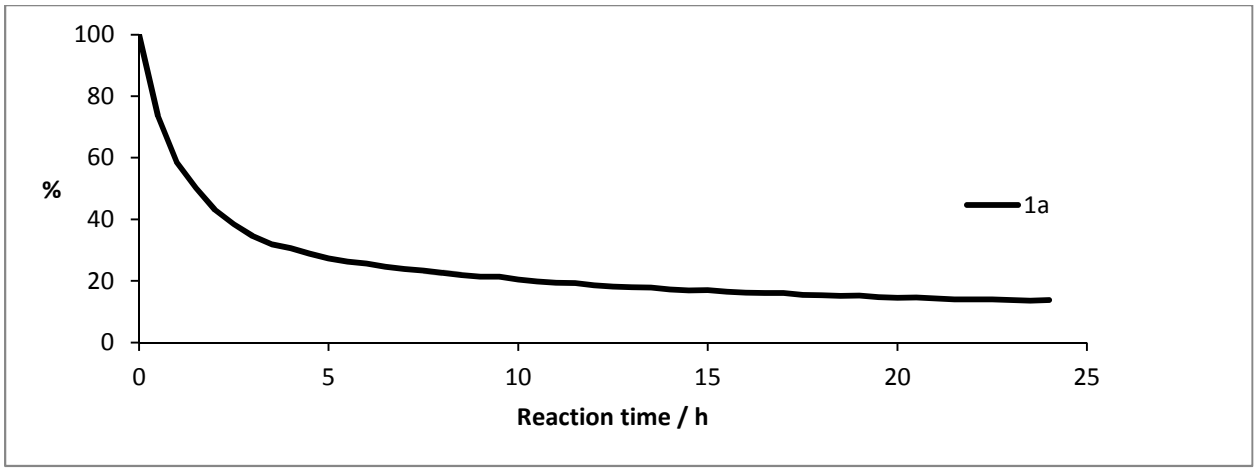

Figure S11. Time curve of compound **1a** in 10 mM phosphate buffer, 1% DMSO, pH 7.4, at 37°. Reactions were followed by HPLC.

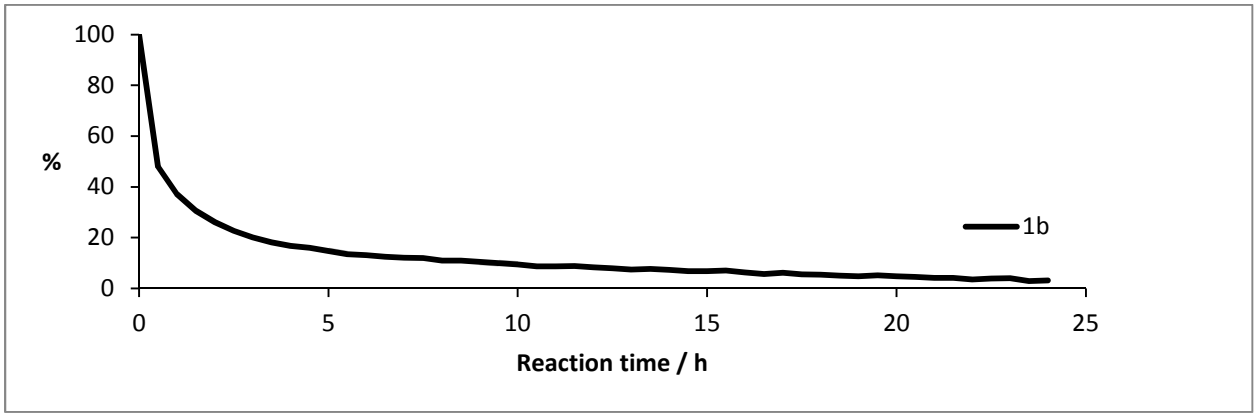

Figure S12. Time curve of compound **1b** in 10 mM phosphate buffer, 1% DMSO, pH 7.4, at 37°. Reactions were followed by HPLC.

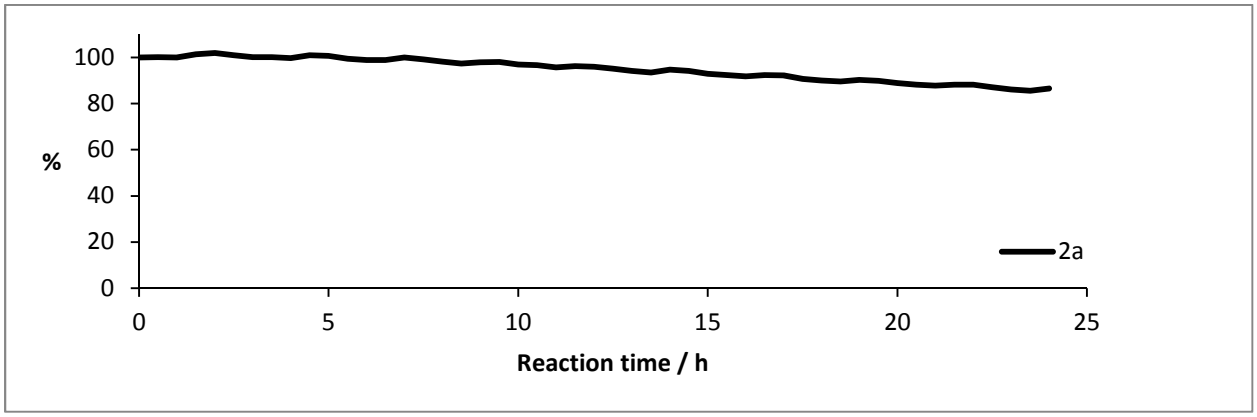

Figure S13. Time curve of compound **2a** in 10 mM phosphate buffer, 1% DMSO, pH 7.4, at 37°. Reactions were followed by HPLC.

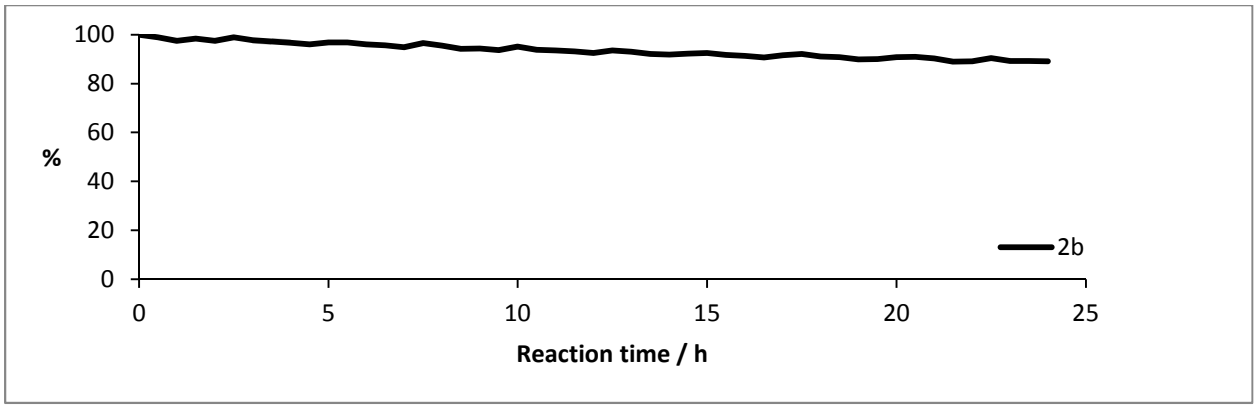

Figure S14. Time curve of compound **2b** in 10 mM phosphate buffer, 1% DMSO, pH 7.4, at 37°. Reactions were followed by HPLC.

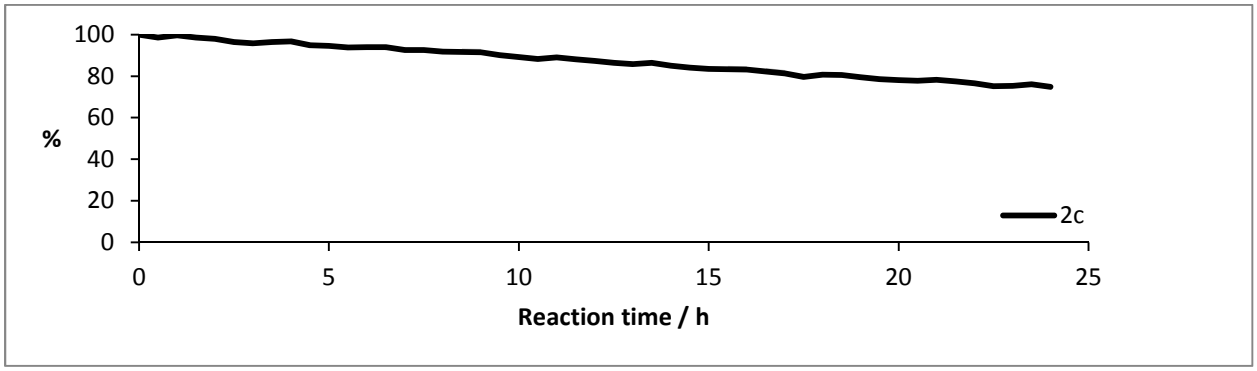

Figure S15. Time curve of compound **2c** in 10 mM phosphate buffer, 1% DMSO, pH 7.4, at 37°. Reactions were followed by HPLC.

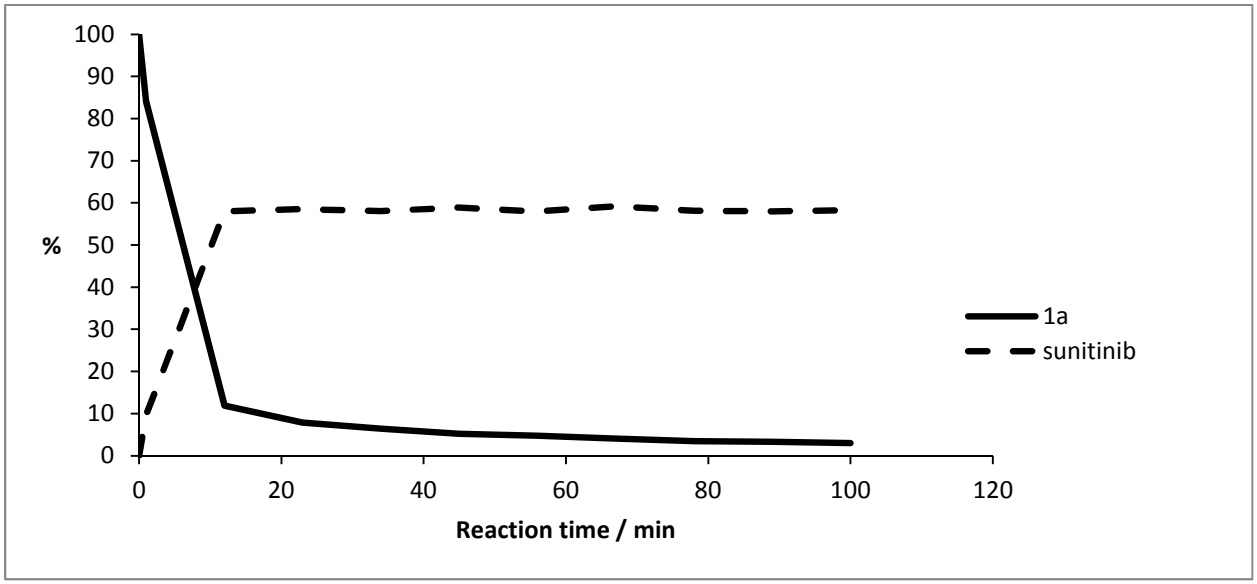

Figure S16. Release of sunitinib from prodrug **1b** (2.5 μM) upon incubation with NADH (50 μM) and NTR (1.33 μg/mL) at 37°C. Reactions were followed by HPLC.

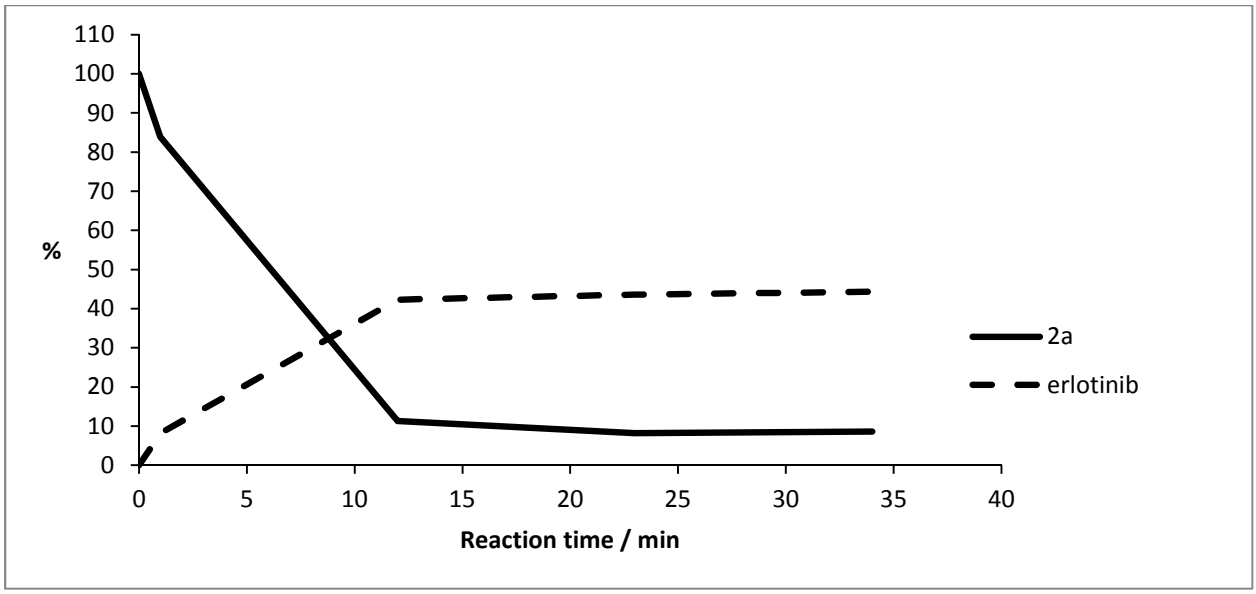

Figure S17. Release of erlotinib from prodrug **2a** (2.5 μM) upon incubation with NADH (50 μM) and NTR (1.33 μg/mL) at 37°C. Reactions were followed by HPLC.

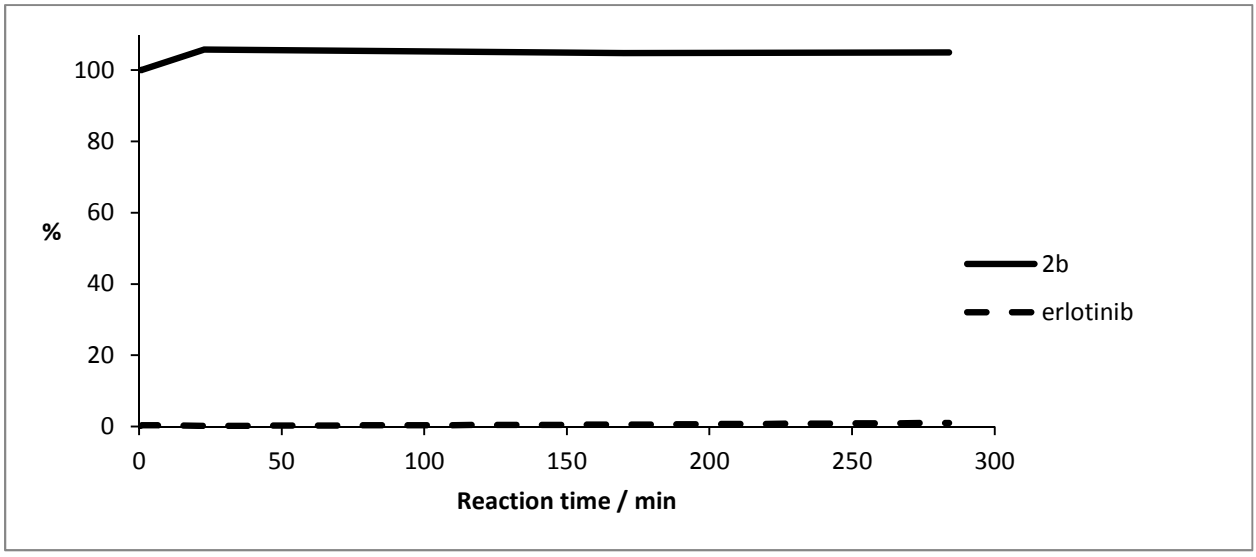

Figure S18. Release of erlotinib from prodrug **2b** (2.5 μM) upon incubation with NADH (50 μM) and NTR (1.33 μg/mL) at 37°C. Reactions were followed by HPLC.

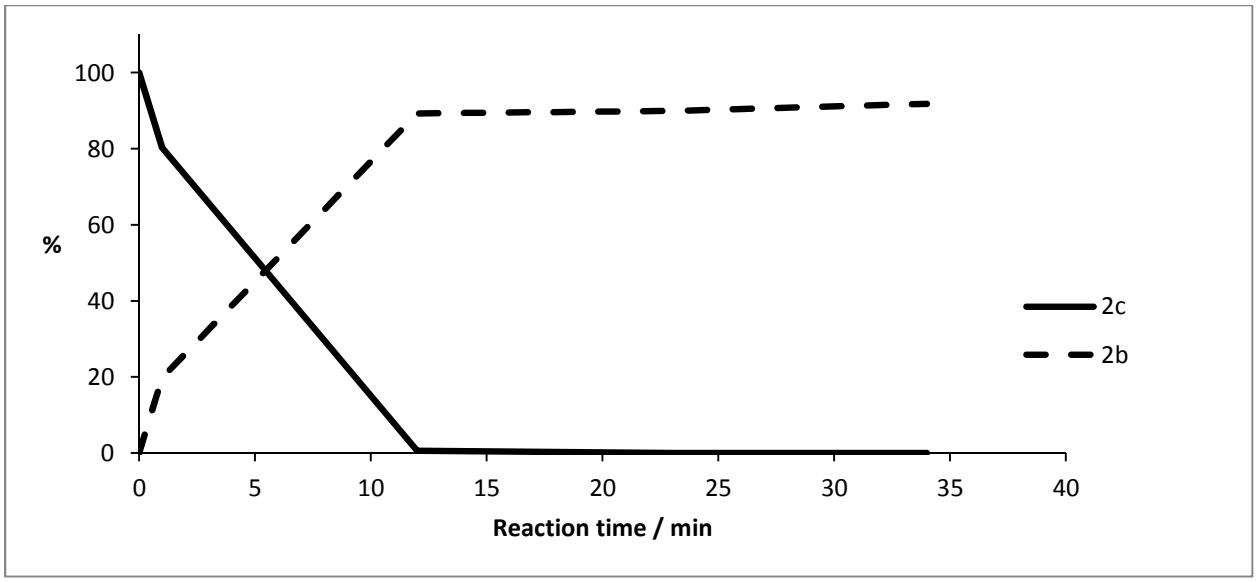

Figure S19. Release of **2b** from prodrug **2c** (2.5 μM) upon incubation with NADH (50 μM) and NTR (1.33 μg/mL) at 37°C. Reactions were followed by HPLC.

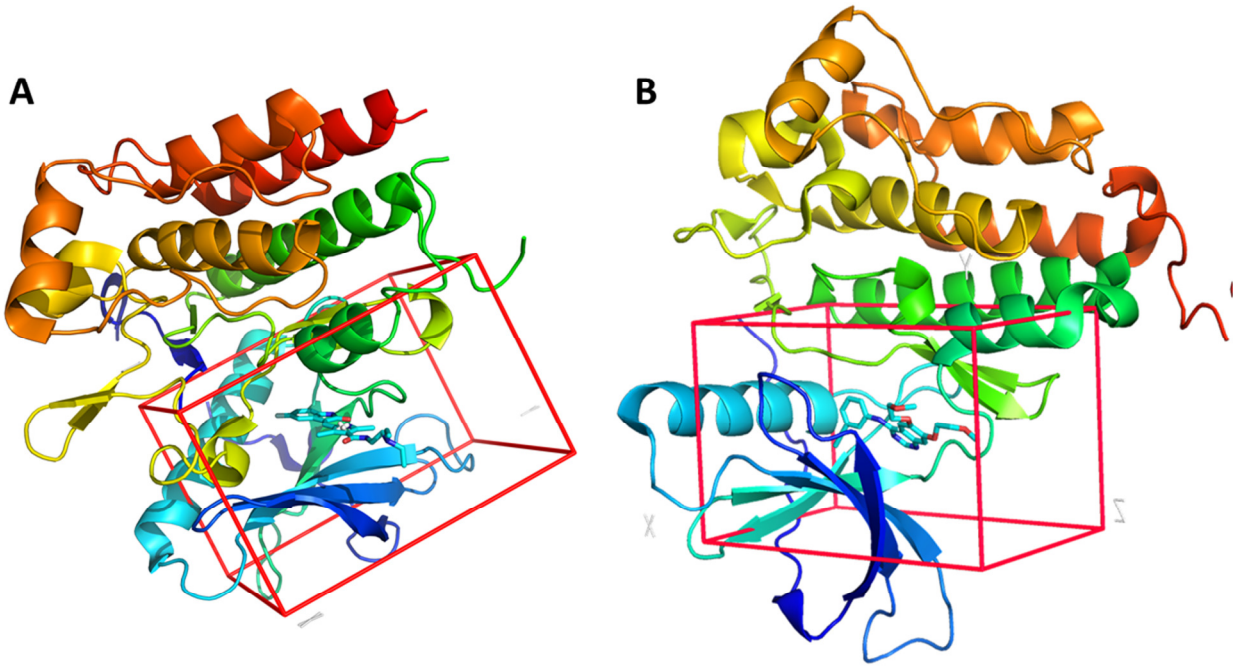

Figure S20. Grid sizes for (A) sunitinib in complex with VEGFR-2 (PDB ID: 4AGD), and (B) erlotinib in complex with EGFR (PDB ID: 1M17). Proteins are depicted in ribbon representation while compounds are shown in capped stick representation. Pictures were generated using Pymol.

Table S1. Docking scores of docked erlotinib, sunitinib, **1a**, **1b**, and **2a** – **c**.

VGFR2 (4AGD)	Score (kcal/mol)	EGFR (1M17)	Score (kcal/mol)
Sunitinib docked	– 9.1	Erlotinib docked	– 10.6
1a	– 7.3	**2a**	– 8.3
1b	– 7.7	**2c**	– 8.4
		2b	– 7.8

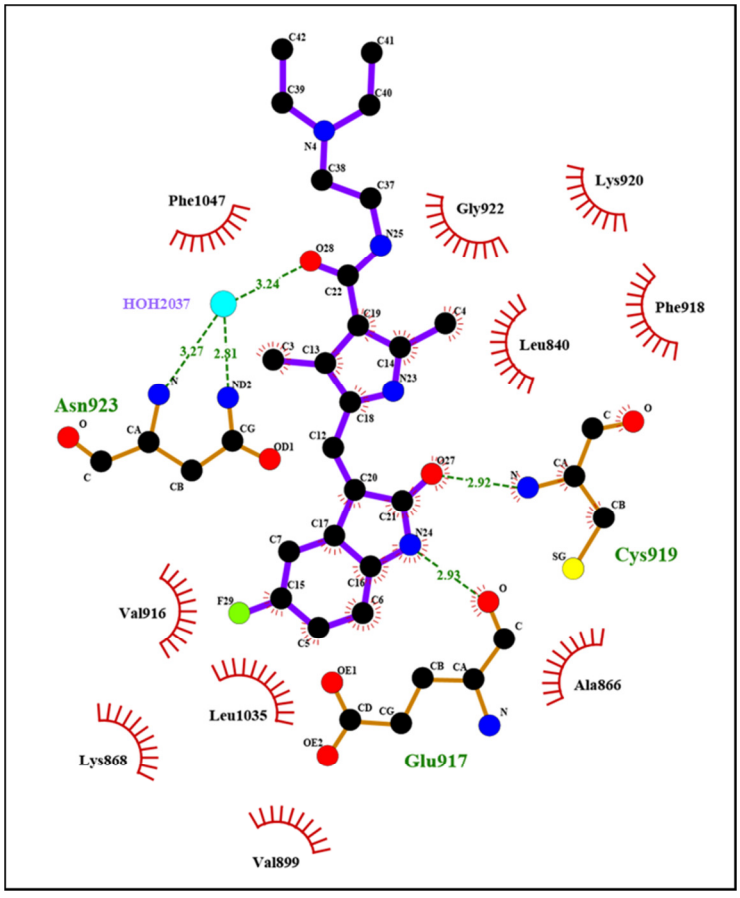

Figure S21. Schematic 2D diagram of protein-ligand interactions for VEGFR-2 in complex with sunitinib (PDB ID: 4AGD). Hydrogen bonds are indicated by dashed lines, while hydrophobic contacts are represented by an arc with spokes radiating towards the ligand atoms they contact. The contacted atoms are shown with spokes radiating back.

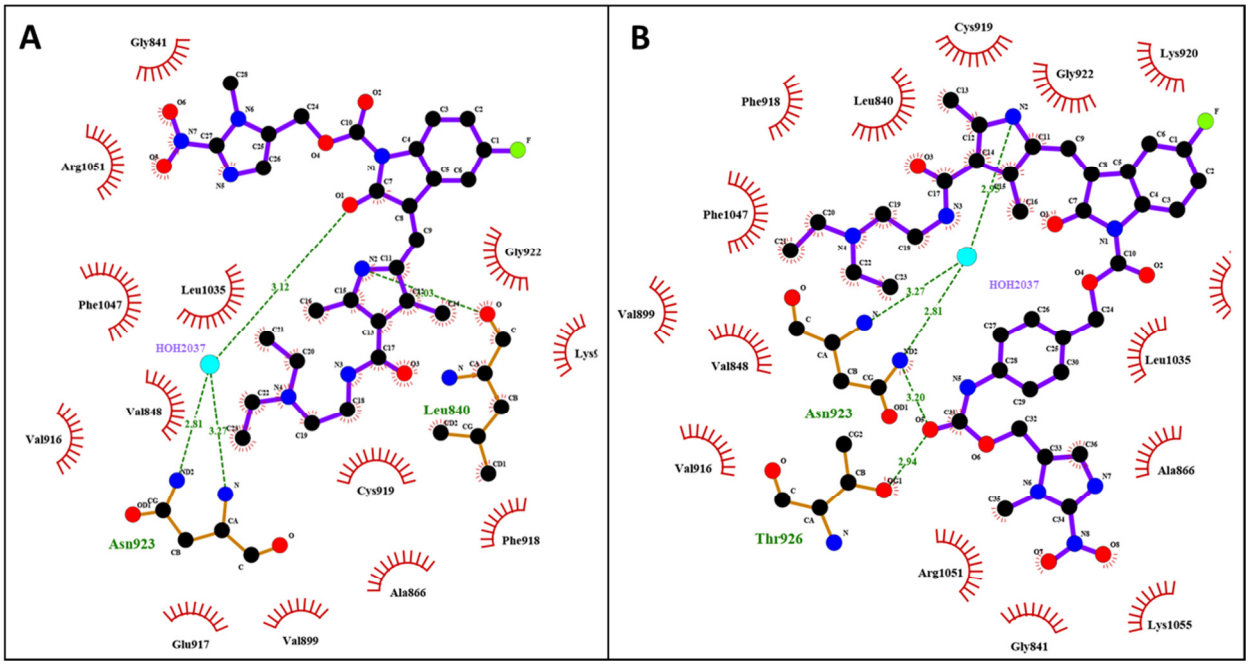

Figure S22. Schematic 2D diagram of protein-ligand interactions for VEGFR-2 in complex with (A) **1a**, and (B) **1b**. VEGFR-2 structure was obtained from PDB ID: 4AGD. Hydrogen bonds are indicated by dashed lines, while hydrophobic contacts are represented by an arc with spokes radiating towards the ligand atoms they contact. The contacted atoms are shown with spokes radiating back.