Supporting Materials

Table S1. Average and standard deviations (SD) of RMSF of the ATP binding sites

Complex	COM8/β	COM8/δ	IC87114/β	IC87114/δ	GDC-0941/β	GDC-0941/δ
average	1.34	1.66	1.84	1.06	1.82	1.51
SD	0.04	0.49	0.80	0.07	0.33	0.32

Table S2. The contributions of the important residues for the binding of COM8 with PI3Kβ and δ (kcal/mol).

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{SA}	ΔG_{GB}	$\Delta G_{non\text{-}polar}$	ΔG_{polar}	ΔG_{total}
				PI3K/β			
Lys771	-2.60±0.25	1.70±0.30	-0.24±0.03	-1.04	-2.84	0.66	-2.18±0.24
Tyr772	-1.46±0.17	-0.56±0.10	-0.08±0.02	0.44	-1.54	-0.12	-1.66±0.22
Met773	-5.00±0.48	0.18±0.12	-0.58±0.04	0.06	-5.58	0.24	-5.34±0.49
Pro779	-2.72±0.25	-0.28±0.09	-0.18±0.02	0.78	-2.90	0.50	-2.40±0.26
Leu780	-1.20±0.16	0.40±0.05	0.00±0.00	-0.30	-1.20	0.10	-1.08±0.13
Trp781	-5.82±0.36	-0.34±0.05	-0.44±0.03	1.14	-6.26	0.80	-5.48±0.37
Ile797	-4.52±0.38	-0.24±0.05	-0.38±0.02	0.18	-4.90	-0.06	-4.98±0.39
Lys799	-0.14±0.60	-9.86±1.19	-0.12±0.02	8.24	-0.26	-1.44	-1.70±0.37
Ile845	-2.16±0.23	0.04±0.09	-0.06±0.01	-0.12	-2.22	-0.08	-2.32±0.22
Val847	-3.00±0.22	-0.90±0.13	-0.08±0.01	0.16	-3.08	-0.74	-3.80±0.27
Val848	-1.66±0.52	-1.32±0.23	-0.12±0.02	0.82	-1.78	-0.50	-2.28±0.45
Thr853	-1.22±0.17	0.40±0.17	-0.18±0.04	-0.14	-1.40	0.26	-1.12±0.17
Met920	-3.30±0.23	0.38±0.12	-0.26±0.03	0.10	-3.56	0.48	-3.10±0.23
Phe928	-1.34±0.20	-0.10±0.03	-0.10±0.01	0.40	-1.44	0.30	-1.14±0.20
Ile930	-4.12±0.32	0.68±0.10	-0.38±0.03	-0.60	-4.50	0.08	-4.42±0.32
				PI3K/δ			
Phe751	-1.26±0.17	-0.32±0.07	-0.06±0.01	0.16±0.06	-1.32	-0.16	-1.46±0.20
Met752	-4.46±0.43	0.04±0.21	-0.80±0.05	0.28±0.14	-5.26	0.32	-4.94±0.43
Pro758	-1.68±0.26	-0.14±0.07	-0.10±0.02	0.50±0.07	-1.78	0.36	-1.42±0.28
Leu759	-1.26±0.12	0.34±0.05	-0.02±0.00	-0.16±0.05	-1.28	0.18	-1.10±0.16
Trp760	-4.76±0.42	-0.42±0.06	-0.66±0.04	1.36±0.11	-5.42	0.94	-4.48±0.40
Ile777	-5.10±0.34	-0.14±0.03	-0.52±0.03	0.06±0.03	-5.62	-0.08	-5.68±0.36
Tyr813	-2.78±0.22	-0.08±0.10	-0.08±0.02	0.56±0.10	-2.86	0.48	-2.38±0.22
Ile825	-2.68±0.24	0.10±0.03	-0.30±0.03	-0.20±0.04	-2.98	-0.10	-3.08±0.26
Val827	-2.64±0.24	-0.78±0.11	-0.06±0.02	-0.04±0.06	-2.70	-0.82	-3.52±0.33
Val828	-1.80±0.36	-1.14±0.19	-0.10±0.01	0.46±0.06	-1.90	-0.68	-2.56±0.29
Met900	-1.46±0.15	-0.12±0.08	-0.14±0.02	0.36±0.06	-1.60	0.24	-1.36±0.15
Phe908	-1.30±0.19	-0.08±0.05	-0.06±0.01	0.36±0.04	-1.36	0.28	-1.10±0.19
Ile910	-5.26±0.35	-0.66±0.15	-0.64±0.03	0.38±0.06	-5.90	-0.28	-6.18±0.36
Asp911	-2.04±0.32	-1.96±1.32	-0.30±0.04	2.00±1.27	-2.34	0.04	-2.30±0.33

Table S3. The contributions of the important residues for the binding of IC87114 with PI3Kβ and δ (kcal/mol).

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{SA}	ΔG_{GB}	$\Delta G_{non\text{-}polar}$	ΔG_{polar}	ΔG_{total}
				PI3K/β			
Lys771	-2.40±0.29	-1.18±0.25	-0.24±0.03	1.96±0.34	-2.64	0.78	-1.86±0.22
Tyr772	-1.84±0.18	-0.14±0.10	-0.10±0.02	0.32±0.09	-1.94	0.18	-1.72±0.23
Met773	-6.02±0.34	-0.66±0.12	-0.96±0.04	0.84±0.11	-6.98	0.18	-6.80±0.35
Pro779	-2.40±0.17	0.00±0.10	-0.14±0.02	0.40±0.07	-2.54	0.40	-2.14±0.18
Trp781	-5.38±0.42	-0.32±0.09	-0.66±0.05	0.76±0.10	-6.04	0.44	-5.58±0.42
Ile797	-4.62±0.42	-0.06±0.04	-0.46±0.03	0.08±0.04	-5.08	0.02	-5.06±0.42
Tyr833	-1.88±0.32	-0.32±0.26	-0.10±0.02	0.62±0.12	-1.98	0.30	-1.68±0.43
Ile845	-1.94±0.32	0.18±0.09	-0.18±0.02	-0.10±0.05	-2.12	0.08	-2.04±0.32
Val847	-1.46±0.32	-0.48±0.14	-0.10±0.02	0.42±0.07	-1.56	-0.06	-1.64±0.39
Thr853	-1.02±0.17	0.08±0.06	-0.20±0.05	0.06±0.10	-1.22	0.14	-1.06±0.18
Met920	-1.58±0.25	-0.06±0.10	-0.24±0.04	0.22±0.07	-1.82	0.16	-1.66±0.26
Ile930	-5.42±0.77	0.04±0.09	-0.84±0.07	0.18±0.08	-6.26	0.22	-6.02±0.83
				PI3K/δ			
Thr750	-1.10±0.83	-0.18±0.05	-0.20±0.02	0.36±0.07	-1.30	0.18	-1.10±0.21
Phe751	-1.46±0.16	0.30±0.07	-0.08±0.01	0.02±0.08	-1.54	0.32	-1.20±0.18
Met752	-4.58±0.52	-0.24±0.11	-0.80±0.09	0.50±0.09	-5.38	0.26	-5.12±0.57
Pro758	-1.64±0.19	-0.08±0.09	-0.10±0.02	0.36±0.09	-1.74	0.28	-1.46±0.17
Trp760	-6.86±0.42	-0.40±0.09	-0.90±0.04	1.14±0.08	-7.76	0.74	-7.02±0.42
Ile777	-4.14±0.35	0.08±0.03	-0.44±0.03	-0.10±0.02	-4.58	-0.02	-4.58±0.37
Tyr813	-2.18±0.22	-0.02±0.17	-0.08±0.01	0.22±0.08	-2.26	0.20	-2.04±0.29
Ile825	-1.32±0.19	0.18±0.03	-0.08±0..02	-0.16±0.03	-1.30	0.02	-1.28±0.20
Glu826	-0.24±0.41	-2.40±0.43	-0.04±0.01	1.30±0.16	-0.28	-1.10	-1.36±0.34
Val827	-2.48±0.17	-1.14±0.14	-0.06±0.02	0.56±0.06	-2.54	-0.58	-3.12±0.19
Val828	-1.94±0.26	-1.72±0.28	-0.14±0.02	0.88±0.99	-2.08	-0.84	-2.90±0.29
Thr833	-1.14±0.22	0.14±0.08	-0.28±0.03	0.10±0.10	-1.42	0.24	-1.16±0.20
Met900	-2.26±0.36	0.20±0.09	-0.34±0.05	-0.02±0.07	-2.60	0.18	-2.42±0.39
Ile910	-4.58±0.34	-0.36±0.09	-0.50±0.04	0.30±0.06	-5.08	-0.06	-5.14±0.35
Asp911	-1.78±0.33	-2.18±0.40	-0.28±0.04	2.74±0.03	-2.06	0.56	-1.50±0.30

Table S4. The contributions of the important residues for the binding of GDC-0941 with PI3Kβ and δ (kcal/mol).

Residue	ΔE_{vdw}	ΔE_{ele}	ΔG_{SA}	ΔG_{GB}	$\Delta G_{non\text{-}polar}$	ΔG_{polar}	ΔG_{total}
				PI3K/β			
Met773	-7.08±0.52	-1.78±0.40	-0.82±0.04	1.62±0.26	-7.90	-0.16	-8.04±0.62
Asp774	-0.96±0.41	0.00±0.52	-0.28±0.05	-0.42±0.57	-1.24	-0.42	-1.66±0.39
Trp781	-3.76±0.39	-0.28±0.13	-0.36±0.05	1.08±0.11	-4.12	0.80	-3.32±0.36
Ile797	-3.66±0.28	-0.10±0.03	-0.26±0.03	0.02±0.03	-3.92	-0.08	-4.00±0.30
Tyr833	-2.06±0.50	-2.64±0.33	-0.14±0.02	2.14±0.12	-3.20	-0.50	-3.70±0.41
Ile845	-4.26±0.37	-0.18±0.03	-0.38±0.03	-0.02±0.03	-4.64	-0.20	-4.84±0.39
Val847	-2.92±0.20	-0.94±0.09	-0.08±0.01	0.06±0.07	-3.00	-0.88	-3.88±0.21
Val848	-1.62±0.47	-1.30±0.19	-0.16±0.02	0.68±0.07	-1.78	-0.62	-2.40±0.41
Thr853	-2.20±0.38	0.34±0.11	-0.40±0.05	-0.22±0.10	-2.60	0.12	-2.48±0.40
Met920	-2.64±0.30	0.24±0.13	-0.26±0.04	0.22±0.08	-2.90	0.46	-2.46±0.28
Ile930	-6.72±0.48	0.50±0.18	-0.86±0.04	0.16±0.14	-7.58	0.66	-6.94±0.48
Asp931	-1.48±0.34	0.24±0.20	-0.06±0.02	0.28±0.22	-1.54	0.52	-1.04±0.33
Phe932	-1.20±0.25	-0.04±0.13	0.00±0.01	0.26±0.13	-1.20	0.22	-1.00±0.23
				PI3K/δ			
Thr750	-1.54±0.32	-0.48±0.51	-0.42±0.03	0.48	-1.96	0.00	-1.96±0.33
Met752	-4.50±0.35	-0.18±0.09	-0.74±0.03	0.56	-5.24	0.38	-4.86±0.36
Pro758	-1.36±0.16	-0.12±0.09	-0.16±0.02	0.22	-1.52	0.10	-1.42±0.17
Trp760	-4.36±0.50	-0.26±0.23	-0.60±0.06	1.26	-4.96	1.00	-3.96±0.51
Ile777	-5.00±0.50	-0.06±0.04	-0.52±0.03	0.02	-5.52	-0.04	-5.54±0.33
Leu784	-1.04±0.14	-0.04±0.03	-0.04±0.01	0.04	-1.08	0.00	-1.08±0.15
Asp787	-0.88±0.53	-5.78±0.75	-0.08±0.01	5.46	-0.96	-0.32	-1.28±0.42
Tyr813	-3.68±0.27	-0.04±0.09	-0.06±0.01	0.82	-3.74	0.78	-2.96±0.23
Ile825	-4.96±0.29	-0.22±0.09	-0.40±0.02	-0.04	-5.36	-0.26	-5.60±0.31
Val827	-2.72±0.17	-0.46±0.13	-0.06±0.01	-0.20	-2.78	-0.66	-3.44±0.27
Val828	-2.00±0.35	-1.52±0.21	-0.12±0.01	0.78	-2.12	-0.76	-2.88±0.32
Thr833	-2.10±0.23	0.04±0.22	-0.28±0.03	0.50	-2.38	0.54	-1.84±0.20
Asn836	-1.20±0.02	-0.42±0.79	-0.42±0.07	0.60	-1.62	0.18	-1.44±0.40
Met900	-2.64±0.24	0.18±0.08	-0.20±0.02	0.38	-2.84	0.56	-2.28±0.25
Ile910	-7.12±0.35	-0.88±0.08	-0.58±0.03	0.40	-7.70	-0.48	-8.20±0.35
Asp911	-4.24±0.40	-0.12±0.27	-0.36±0.02	0.86	-4.60	0.74	-3.86±0.30
Phe912	-1.58±0.15	0.32±0.10	0.00±0.00	0.06	-1.58	0.38	-1.22±0.12

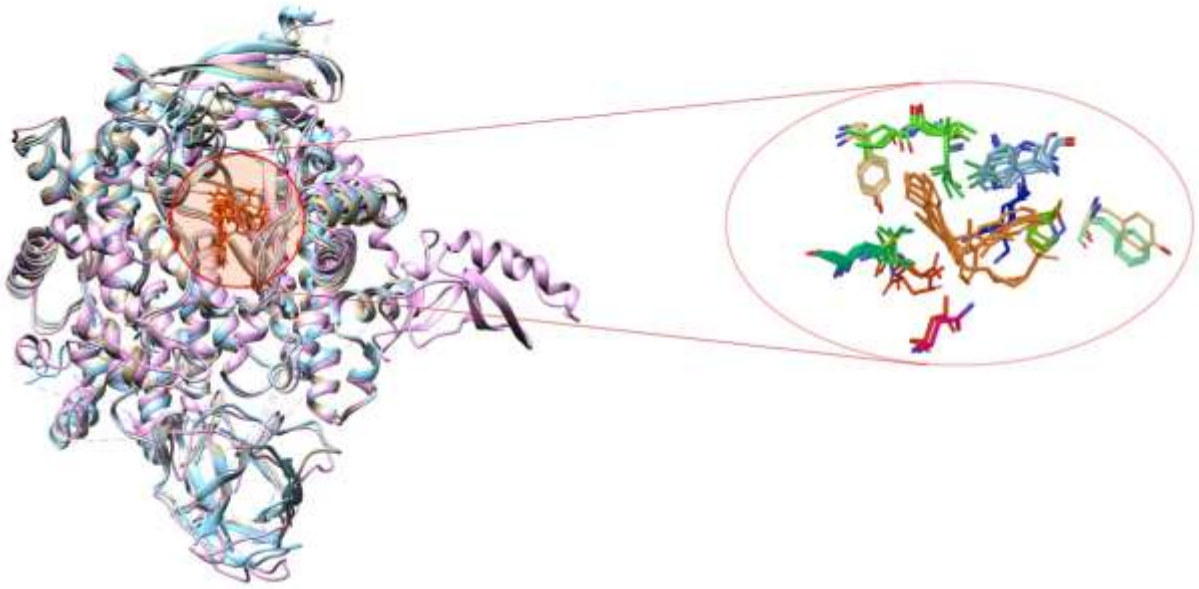

Figure S1. Structural alignment of binding sites between the three complexes and the residues within 5Å of the ligands. *purple*: GDC-0941/β complex, *Yellow*: COM8/δ complex, *cyan*: IC87114/δ. *orange*: ligands.

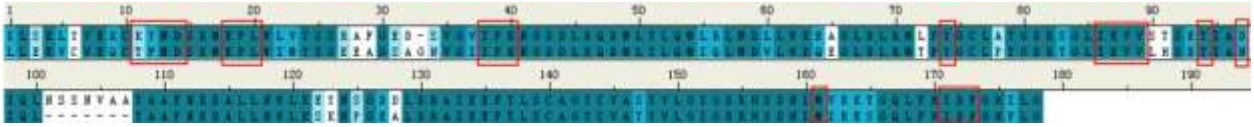

Figure S2. Sequences alignment of the residues of the ATP binding pockets (Ile761 to Gly937 for PI3Kβ and Leu740 to Gly917 for PI3Kδ). The residues within 5Å of the ligands colored in red frame.

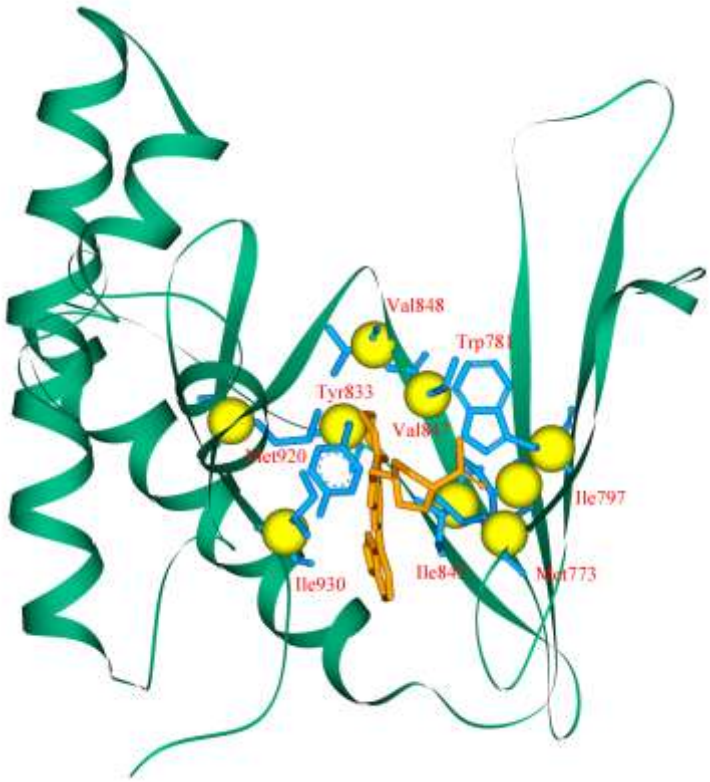

Figure S3. The GDC-0941 and β residues from Ile761 to Gly937 (the resides and Cα carbon atoms of the "hydrophobic pocket" colored in blue and yellow CPK model).

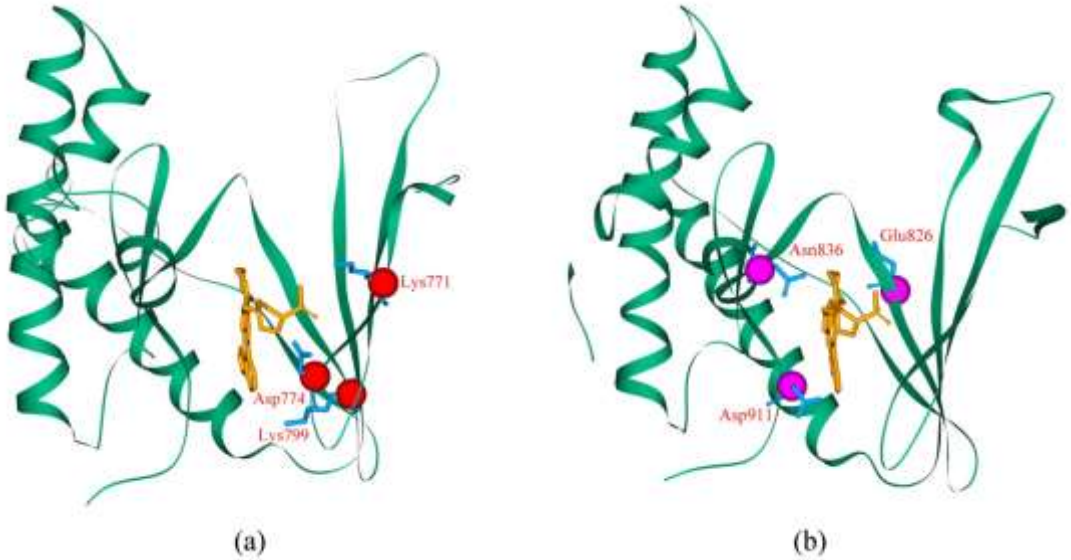

Figure S4. (a) The GDC-0941 and residues important for β selectivity (the residues colored in blue stick model and the C_α carbon in red CPK model) and (b) the GDC-0941 and residues important for δ selectivity (the residues colored in blue stick model and the C_α carbon in purple CPK model)