**Supplemental Table A**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Inhibitor | PDB | ⍺C;DFG | BPs | BP H-bonds | ⍺C position | K-E |
| **Monomer selective** | | | | | | |
| Vemurafenib | 5JRQ | CODI | I,II | D594, G596 | 21.5/21.5 | 11.5/11.8 |
| Dabrafenib | 5CSW | CODI | I,II | K483, D594, G596 | 21.4/21.8 | 7.4/8.7 |
| PLX7904 | 4XV2 | CODI | I,II | D594, F595, G596 | 20.9/20.4 | 7.5/8.7 |
| **Equipotent** | | | | | | |
| AZ628 | 4G9R | CIDO | I,II,III | E501, D594 | 19.5/19.5 | 3.0/2.6 |
| TAK632 | 4KSP\* | CIDO | I,II,III | E501, D594 | 18.8/19.0 | 3.0/3.9 |
| LY3009120 | 5C9C | CIDO | I,II,III | E501, D594 | 19.2/19.2 | 2.7/2.7 |
| Ponatinib | 6P3D | CIDO | I,II,III | E501, D594, I573, H574 | 19.2/19.2 | 3.0/3.0 |
| Lifirafenib  (BGB2893) | 4R5Y | CIDO | I,II,III | E501 | 19.0/18.7 | 5.5/5.1 |
| Tovorafenib (TAK580) | 6V34 | CIDO | I,II,III | E501, D594 | 18.6/18.8 | 2.5/2.9 |
| SB5909885 | 2FB8\* | CIDI | I | E501 | 18.6/18.3 | 2.9/3.2 |
| GDC0879 | 4MNF | CIDI | I | E501 | 18.4/18.7 | 2.8/2.9 |
| **Dimer selective** | | | | | | |
| Naporafenib (LXH254) | 8F7P\* | CIDO | I,II,III | E501, D594 | 19.3/19.3 | 3.0/3.0 |
| RAF709 | 5VAM\* | CIDO | I,II,III | E501, D594 | 19.2/19.1 | 2.8/2.8 |
| Sorafenib | 1UWJ | CIDO | I,II,III | E501, D594 | 18.8/18.8 | 2.6/2.6 |
| Belvarafenib | 6XFP\* | CIDO | I,II,III | E501, D594 | 19.3/19.3 | 2.7/2.7 |
| PHI1 | 6P7G | CIDO | I,II,III | E501, D594, H574 | 19.1/19.0 | 2.5/2.5 |

**Supplemental Table B**

|  |  |  |  |
| --- | --- | --- | --- |
| System, protomer | ⍺C position (Å) | K-E distance (Å) | DFG dihedral (°) |
| Apo monomer, A | 23.3 ± 1.7 | 8.1 ± 3.1 | 214 ± 19 |
| Apo dimer, A | 22.2 ± 1.0 | 6.5 ± 2.9 | 250 ± 39 |
| Apo dimer, B | 22.0 ± 1.7 | 5.5 ± 2.2 | 201 ± 24 |
| PHI1 (mixed), apo | 21.3 ± 1.0 | 5.5 ± 3.1 | 239 ± 41 |
| PHI1 (mixed), holo | 18.9 ± 0.7 | 2.8 ± 0.3 | 283 ± 24 |
| LY (mixed), apo | 22.8 ± 1.7 | 5.3 ± 2.4 | 204 ± 35 |
| LY (mixed), holo | 19.0 ± 0.5 | 4.9 ± 1.2 | 295 ± 13 |
| PHI1 (holo), A | 18.3 ± 0.6 | 2.8 ± 0.1 | 285 ± 17 |
| PHI1 (holo), B | 18.7 ± 0.7 | 2.8 ± 0.1 | 303 ± 12 |
| LY (holo), A | 19.4 ± 0.6 | 3.4 ± 0.1 | 301 ± 18 |
| LY (holo), B | 19.3 ± 0.5 | 4.3 ± 1.4 | 295 ± 13 |