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| --- | --- | --- | --- | --- | --- | --- |
| **TKI/drug properties** | **Imatinib** | **Nilotinib** | **Dazatinib** | **Bosutinib** | **Ponatinib** | **Asciminib** |
| Chemical structure |  |  |  |  |  |  |
| International Union of Pure and Applied Chemistry (IUAPC) name | 4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]phenyl]benzamide | 4-methyl-N-[3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]benzamide | N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl]amino]-1,3-thiazole-5-carboxamide | 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile | 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]benzamide | N-[4-[chloro(difluoro)methoxy]phenyl]-6-[(3R)-3-hydroxypyrrolidin-1-yl]-5-(1H-pyrazol-5-yl)pyridine-3-carboxamide |
| Molecular formula | C29H31N7O | C28H22F3N7O | C22H26ClN7O2S | C26H29Cl2N5O3 | C29H27F3N6O | C20H18ClF2N5O3 |
| Spectrum of inhibitory activity | ABL1ARGBCR-ABLKITPDGFRDDR1NQO2 | ABL1ARGBCR-ABLKITPDGFRDDR1NQO2 | ABL1, ARG, BCR-ABL, KIT, PDGFR, SRC,YES,FYN, LYN, HCK, LCK, FGR, BLK, FRK, CSK,BTK, TEC, BMX, TXK, DDR1, DDR2, ACK, ACTR2B, ACVR2, BRAF, EGFR/ERBB1-5, EPHA8,EPHB1-2, EPHB4, EPHB6, ERBB2, ERBB4,FAK, GAK, GCK, HH498/TNNI3K, ILK, LIMK1-2, MAP2K5, MAP3K1-4, MAP4K1, MAP4K5/KHS1, MAPK11/p38 beta, MAPK14/p38 alpha, MYT1,NLK, PTK6/Brk, QIK, QSK, RAF1, RET, RIPK2, SLK, STK36/ULK, SYK, TAO3, TESK2, TYK2, ZAK [6] | BCR-ABL1, ABL1, SRC, LYN, HCK | *ABL1*, *KIT, PDGFR, SRC* family, *VEGFR, EGFR, HER2, FLT3, FGFR*, and *JAK2* [7] | BCR-ABL1 [8] |
| BCR-ABL tyrosine kinase inhibitory mode of action | Works by binding close to the ATP binding site, locking it in a closed or self-inhibited conformation, therefore inhibiting the enzyme activity of the protein semicompetitively [9] [10] | Binds to and stabilizes inactive conformation of kinase domain of Abl protein [11] | Binds to ATP-binding site, but extends in opposite direction from imatinib. Binds inactive and active conformation of ABL kinase domain, requires fewer contact points with ABL, and has a greater affinity to ABL kinase domain compared to IM [12, 13] | ATP-competitive inhibitor of Src and Abl tyrosine kinases [14] | Acts as a multikinase inhibitor. Introduction of a triple bond ethynyl linker allowed spanning of bulky T315I isoleucine residue side chain in ATP-binding site, and overcame resistance to prior generation TKIs [15, 16] | Acts as an allosteric inhibitor and engages a vacant pocket at site of kinase domain normally occupied by myristoylated N-terminal of ABL1 — a motif that serves as an allosteric negative regulatory element lost on fusion of ABL1 to BCRBCR, myristoylated N-terminal is lost and ABL1 kinase is activated. By allosterically binding, to myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity [4] |
| BCR-ABL tyrosine kinase binding conformation | Inactive | Inactive | Active | Both | Inactive | Specifically targeting ABL myristoyl pocket  |
| Half life time (T1/2) | ~20 hours | ~17 hours | 3–5 hours | 32.4–41.2 hours enabling daily dose [17] | 24 hours | 5.5 hours (40 mg/d)9 hours (200 mg bid) |
| Resistant BCR-ABL KD mutants\*\*[8, 15, 18–23] | **Y253****E255****T315**M244L248G250 | Q252F317M351M355F359H396 | **T315**L248Y253E255F359 | **T315**V299F317 | **T315****V299**L248G250 E255F317 | E250\*Y253\*E255\*F311 | **A337****W464****P465****V468****I502** |
| Oral dose per day | CP 400 mg/dAP 600 mg/dBP 800 mg/d | CP 2 × 300 mg(2nd-line)2 × 400mg (1st-line) | CP 100 mg/dAP/BP 140 mg/d | CP 500 mg/d | CP 15–45 mg/d | CP 80 mg/dor 40 mg bid |
| Main off-target effect | **Hematologic:*** anemia
* neutropenia
* thrombocytopenia

**Non-hematologic:*** edema (periorbital and ● peripheral)
* muscle cramps
* musculoskeletal pain
* diarrhea [24]
 | **Hematologic:*** thrombocytopenia
* granulocytopenia
* anemia

**Non-hematologic:*** pruritus
* asthenia

**Cardiovascular:*** cardiovascular

ischemic adverse events [25, 26] | **Hematologic:*** thrombocytopenia
* anemia
* neutropenia

**Non-hematologic**: * endocrine disorders (gynecomastia, irregular menses, hypoglycemia, hyperglycemia, increased triglyceride and cholesterol levels)
* fluid retention
* nausea, vomiting, diarrhea

**Cardiovascular*** pericardial effusion
* pulmonary artery hypertension [27, 28]
 | **Hematologic:*** thrombocytopenia
* neutropenia

**Non-hematologic:*** rash
* nausea
* diarrhea
* vomiting
* elevated serum aminotransferases [29]
 | **Hematologic:*** anemia
* thrombocytopenia
* neutropenia

**Non-hematologic:*** rash
* elevated serum lipase
* pancreatitis

**Cardiovascular*** hypertension
* chest pain [30]
 | **Hematologic:*** thrombocytopenia and/or neutropenia

**Non-hematologic:*** hepatic impairment
* asymptomatic amylase and/or lipase elevations

**Cardiovascular:*** hypertension
* pericardial effusion

[4, 5, 31] |

\*Increase in IC50 for ponatinib as a sole anomaly typically not leading to clinical resistance, which is observed in cases of a compound mutation including T315I; \*\*strong resistance is indicated in bold; CP — chronic phase; AP — acceleration phase; BP — blastic phase; bid (bid in die) — twice daily