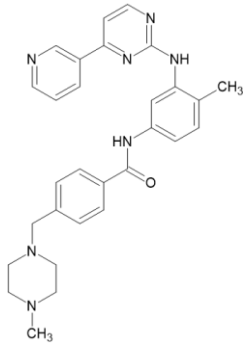
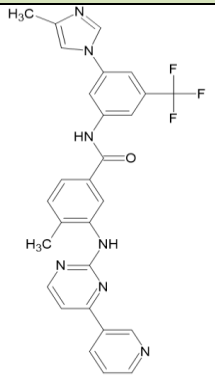
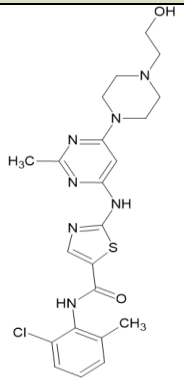
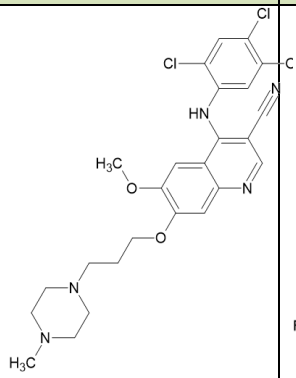
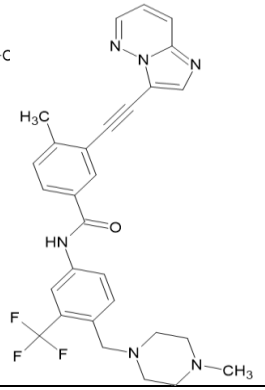
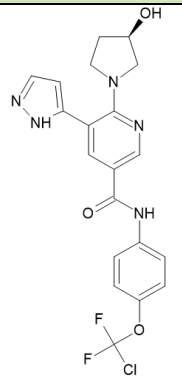
TKI/drug propertie	Imatinib	Nilotinib	Dazatinib	Bosutinib	Ponatinib	Asciminib
Chemical structure						
International Union of Pure and Applied Chemistry (IUAPC) nam	4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]phenyl]benzamide	4-methyl-N-[3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-ylpyrimidin-2-yl)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	ABL1 ARG BCR-ABL KIT PDGFR DDR1 NQO2	ABL1 ARG BCR-ABL KIT PDGFR DDR1 NQO2	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*, *HEF FLT3*, *FGFR*, and *JAK2* [7]	BCR-ABL1 [8]

BCR-ABL tyrosine kinas inhibitory mode of actior	Works by binding close to ATP binding site, locking i a closed or self-inhibited c inhibiting the enzyme activ 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 BCR BCR, 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 kinas binding conformation	Inactive	Inactive	Active	Both	Inactive	Specifically targeting ABL myristoyl pocket
Half life time ($T_{1/2}$)	~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** M244 L248 G250	Q252 F317 M351 M355 F359 H396 **T315** L248 Y253 E255 F359	**T315** V299 F317	**T315** **V299** L248 G250 E255 F317	E250* Y253* E255* F311	**A337** **W464** **P465** **V468** **I502**
Oral dose per day	CP 400 mg/d AP 600 mg/d BP 800 mg/d	CP 2 × 300 mg (2^{nd}-line) 2 × 400mg (1^{st}-line)	CP 100 mg/d AP/BP 140 mg/d	CP 500 mg/d	CP 15–45 mg/d	CP 80 mg/d or 40 mg bid

Main off-target effect	**Hematologic:** • anemia • neutropenia • thrombocytopenia **Non-hematologic:** • edema (periorbita and ● peripheral) • muscle cramps • musculoskeletal p • diarrhea [24]	**Hematologic:** • thrombocytopenia • granulocytopenia • anemia **Non-hematologic:** • pruritus • asthenia **Cardiovascular:** • cardiovascular ischemic adverse events [25,	**Hematologic:** • thrombocytopenia • anemia • neutropenia **Non-hematologic:** • endocrine disorde (gynecomastia, irregular menses, hypoglycemia, hyperglycemia, increased triglyce and cholesterol levels) • fluid retention • nausea, vomiting, diarrhea **Cardiovascular** • pericardial effusic • pulmonary artery hypertension [27,	**Hematologic:** • thrombocytopen • neutropenia **Non-hematologic:** • rash • nausea • diarrhea • vomiting • elevated serum aminotransferas [29]	**Hematologic:** • anemia • thrombocytopenia • neutropenia **Non-hematologic:** • rash • elevated serum lipa • pancreatitis **Cardiovascular** • hypertension • chest pain [30]	**Hematologic:** • thrombocytopenia and/or neutropenia **Non-hematologic:** • hepatic impairment • asymptomatic amyl and/or lipase elevat **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