

Small Molecule Oral Kinase Inhibitors in Oncology

Richard D. Taylor and Stuart Bailey



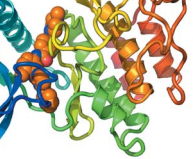
newmedicines
vital science, new ways

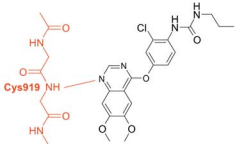
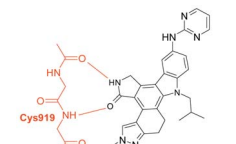
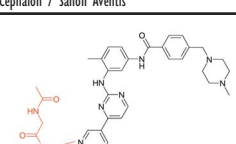
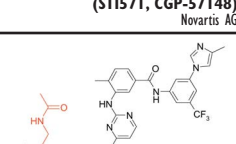
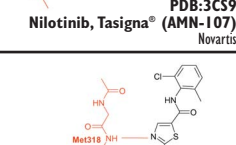
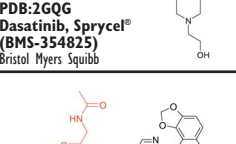
EGFr		Launched: NSCLC Phase III: (discontinued - head & neck) Phase II: Uterine, bladder, stomach, ovarian, prostate, solid, brain, esophageal, glioma, mesothelioma, RCC (discontinued - breast, liver, colorectal)
EGFr		Launched: NSCLC, pancreatic Phase II: Colorectal, glioma, RCC, breast, esophageal, ovarian, head & neck
EGFr HER-2		Launched: Breast Phase III: Head & neck, stomach (RCC - no recent development) Phase II: (colorectal NSCLC, uterine - no recent development)
EGFr		Phase II: (Programme assumed to be discontinued)
EGFr HER-2		Phase I: (No recent development)
EGFr HER-2		Phase II: Breast (NSCLC - no recent development)

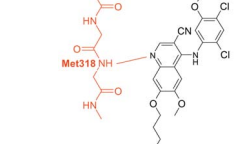
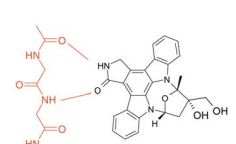
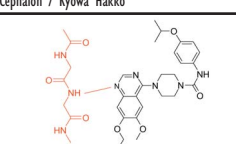
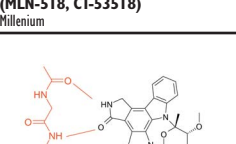
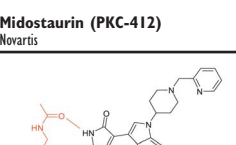
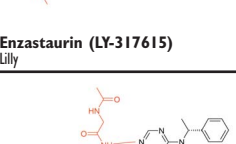
HER-2		Phase I: (Programme assumed to be discontinued)
HER-2		Phase I: (Programme assumed to be discontinued)
VEGFr		Launched: RCC, GIST Phase III: Breast, NSCLC colorectal, Phase II: Genitourinary, neuroendocrine, liver, stomach, thyroid
VEGFr		Phase III: (discontinued - colorectal) Phase II: myelodysplastic syndrome, meningioma (discontinued - glioma, solid tumours) Phase I: AML (discontinued - NSCLC, prostate, ovarian)
VEGFr		Phase II: (NSCLC, ovarian cancer, solid tumours - no recent development, assumed to be discontinued)
VEGFr EGFr RET-TKtr		Phase III: NSCLC, thyroid Phase II: Colorectal, breast, prostate, MM, brain, SCLC, head & neck

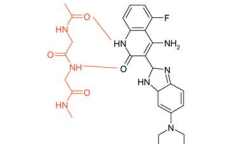
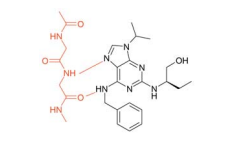
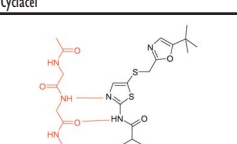
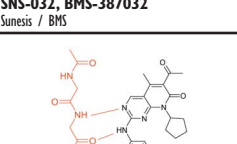
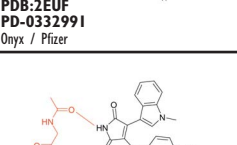
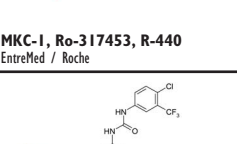
VEGFr PDGFr Kit		Phase III: RCC, breast Phase II: NSCLC, ovarian, glioma, fallopian, sarcoma, uterine, MM Phase I: Colorectal, liver, solid tumours
VEGFr PDGFr CSF-1		Phase III: Pancreatic, thyroid Phase II: Breast, colorectal, melanoma, NSCLC, RCC Phase I: Solid tumours
VEGFr PDGFr Kit		Phase III: NSCLC Phase II: GIST, breast, thyroid Phase I: Colorectal, solid tumours
VEGFr Kit KDR		Phase I: Cancer
VEGFr		Phase III: colorectal, glioblastoma, NSCLC Phase II: Liver, breast, leukemia, ovarian, solid, prostate, mesothelioma, melanoma, RCC, nerve Phase I: AML, colorectal, head, neck
VEGFr PDGFr FIt-3 Kit		Phase II: RCC Phase I: Solid tumours

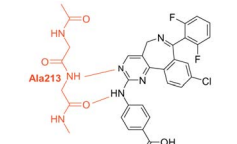
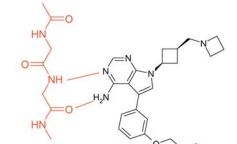
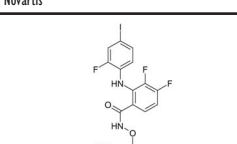
VEGFr PDGFr		Phase II: RCC, HCC, NSCLC Phase I: AML, myelodysplastic syndrome
VEGFr FGFr		Phase III: Colorectal Phase II: HCC Phase I: Cancer
VEGFr		Phase II: Metastatic breast
VEGFr PDGFr c-Kit		Phase II: Solid tumours
VEGFr PDGFr FGFr		Phase II: HCC, RCC, breast Phase I: Solid tumours
VEGFr		Phase I: (AML, solid tumours - no recent development)



VEGFR Pan Kinase	 KRN-633 Kinin	Phase I: Solid tumours
VEGFR Tie-2	 CEP-11981 Cephalon / Sanofi Aventis	Phase I: Solid tumours
Abl	 PDB:1IEP Gleevec[®], Imatinib (ST1571, CGP-57148) Novartis AG	Launched: CML, ALL, GIST Phase III: (discontinued - glioblastoma) Phase II: Prostate, sarcoma, solid tumours (discontinued - glioma, SCLC) Phase I: Leukemia
Abl PDGFR c-Kit	 PDB:3CS9 Nilotinib, Tasigna[®] (AMN-107) Novartis	Launched: CML Phase III: GIST Phase II: ALL, mastocytosis, hypereosinophilic syndrome
Src Abl Broad Spectrum	 PDB:2GQG Dasatinib, Sprycel[®] (BMS-354825) Bristol Myers Squibb	Launched: CML, ALL Phase II: Breast, prostate, mastocytosis Phase I: Solid tumours
Src Abl	 PDB:2H8H AZM-475271 AstraZeneca	Phase II: Colorectal, haematological Phase I: Solid tumours

Src Abl	 Bosutinib (SKI-606) Wyeth	Phase III: CML Phase II: Breast, lung, pancreatic, solid tumours Phase I: ALL
Flt-3 TrkA Jak-2	 Lestaurtinib (CEP-701) Cephalon / Kyowa Hakko	Phase III: AML Phase II: Myelofibrosis Phase I: Solid tumours (discontinued - pancreatic, prostate)
Flt-3 PDGFR c-Kit	 Tandutinib (MLN-518, CT-53518) Millenium	Phase II: AML, RCC, glioma, prostate Phase I: (No recent development)
PKC Flt-3	 Midostaurin (PKC-412) Novartis	Phase III: AML Phase I: (GIST, melanoma, colorectal, breast, CLL - no recent development)
PKCβ GSK-3 Akt	 Enzastaurin (LY-317615) Lilly	Phase III: Glioma, non-Hodgkin lymphoma Phase II: NSCLC, prostate, breast, ovarian, carcinoma Phase I: Solid tumours, CLL
Broad Spectrum	 PDB:2J6M AEE-788 Novartis	Phase II: Glioblastoma Phase I: Colorectal, solid tumours

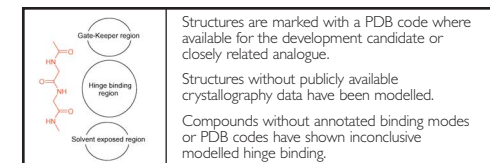
Broad Spectrum	 Dovitinib (TKI-258, CHIR-258) Novartis/Chiron	Phase I: AML, MM, solid tumours
CDKs	 PDB:2A4I Seliciclib, (R)-roscovitine (CYC-202, NSC-701554) Cyclacel	Phase II: NSCLC, lymphoid leukemia, mast cell leukemia, MM, nasopharyngeal Phase I: Glomerulonephritis
CDKs	 SNS-032, BMS-387032 Sunesis / BMS	Phase I: Solid and B-cell lymphomas
CDK4 CDK6	 PDB:2EUF PD-0332991 Onyx / Pfizer	Phase II: MM Phase I: Breast, colorectal, liposarcoma, melanoma, mantle cell lymphoma
CDKs	 MKC-1, Ro-317453, R-440 EntreMed / Roche	Phase II: NSCLC, breast, pancreatic, ovarian, endometrial Phase I: Various solid tumours, leukemia
RAF Pan Kinase	 PDB:1UWH Sorafenib, Nexavar[®] (BAY 43-9006) Bayer / Onyx	Launched: RCC, HCC Phase III: NSCLC, melanoma Phase II: Breast, colorectal, ovarian, AML, SCLC, pancreatic, head & neck, prostate, ovarian Phase I: Solid tumours

Aurora	 MLN-8054 Millennium	Phase I: Solid tumours, lymphoma, liver metastases
IGF-1r	 AEW-541, NVP-AEW-541 Novartis	Phase I: Various cancers, MM
MEK	 PDB:1S9J Allosteric Binder PD-0325901 Pfizer	Phase II: (discontinued - breast, colon, melanoma, NSCLC) Phase I: Solid tumours

CLL	Chronic Lymphocytic Leukemia	ALL	Acute Lymphoblastic Leukemia
GIST	Gastrointestinal Tumour	MM	Multiple Myeloma
AML	Acute Myelogenous Leukemia	HCC	Hepatocellular Carcinoma
NSCLC	Non Small Cell Lung Cancer	NHL	Non-Hodgkins Lymphoma
SCLC	Small Cell Lung Cancer	RCC	Renal Cell Carcinoma

Notes from the authors:

The primary hydrogen bond hinge interaction is shown using the alignment given below (other interactions eg CH...O interactions are not shown).



Major reference source:
Gill AL, Verdonk M, Boyle RG, Taylor R Curr Top Med Chem. 2007;7(14):1408-22

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