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## **Appendix.**

### **Signaling pathway and small-molecule drug discovery of FGFR: A comprehensive review**

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**Appendix A. Summary of FGFR inhibitors**

<b>Name</b>	<b>Target</b>	<b>Indication</b>	<b>Clinical stage</b>	<b>Company or Sponsor</b>	<b>IC<sub>50</sub> *</b>	<b>References</b>
Ponatinib (AP24534)	Abl, PDGFR $\alpha$ , VEGFR, FGFR1	Lung cancer Acute and chronic leukemia	Phase 2 (NCT01935336) Phase 1/2 (NCT02398825; NCT02428543)	Ariad Pharmaceuticals	FGFR1, IC <sub>50</sub> =2.2 nM	(O'Hare et al., 2009)
Nintedanib (BIBF1120)	VEGFR, FGFR, PDGFR	Advanced pancreatic cancer	Phase 1/2 (NCT02902484)	Boehringer Ingelheim	FGFR1/2/3, IC <sub>50</sub> =69/37/108 nM	(Hilberg et al., 2008)
Dovitinib (TKI25)	c-Kit, VEGFR, PGFR, FLT, FGFR1/2/3	Hormone refractory prostate cancer	Phase 2 (NCT01741116)	Novartis Pharmaceuticals	FGFR1/3, IC <sub>50</sub> =8/9 nM	(Trudel et al., 2005)
S49076	MET, AXL, FGFR1/2/3	Advanced solid tumors	NA *	Oncology Research and Development Unit, Institut de Recherches Servier	FGFR1/2/3, IC <sub>50</sub> =18 nM	(Burbridge et al., 2013)
Orantinib (TSU-68, SU6668)	VEGFR-2, FGFR, PGFR	Hepatocellular carcinoma	Phase 3 (NCT01465464)	Taiho Pharmaceutical Co., Ltd.	FGFR1, K <sub>i</sub> =1.2 $\mu$ M	(Laird et al., 2000)
Lenvatinib (E7080)	RET, VEGFR, KDR, FLT, FGFR	Relapsed or refractory solid tumors	Phase 2 (NCT04447755)	Eisai Inc. Merck Sharp & Dohme Corp.	FGFR1, IC <sub>50</sub> =46 nM	(Matsui et al., 2008)
Brivanib Alaninate (BMS-582664)	VEGFR, Flk1, VEGFR, FGFR	Cervical cancer	Phase 2 NCT04395612	Bristol-Myers Squibb	FGFR1, IC <sub>50</sub> =148 nM	(Bhide et al., 2006)
Brivanib (BMS-540215)	VEGFR, FGFR 1	Cervical cancer	Phase 3 (NCT04395612)	Bristol-Myers Squibb	FGFR1, IC <sub>50</sub> =148 nM	(Bhide et al., 2006)

Lucitanib (E3810)	VEGFR, FGFR2, PDGFR	Solid tumors	Phase 1/2 (NCT01283945)	Eisai Inc.	FGFR1/2, IC <sub>50</sub> =17.5/ 82.5 nM	(Bello et al., 2011)
SKLB 610	VEGFR2, FGFR2, PDGFR	Non-small cell lung cancer	Preclinical study	State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University	Inhibition rate (10 μM) = 65%	(Cao et al., 2011)
SSR128129E	FGFR	Behcet's disease	Phase 3 (NCT04528082)	Amgen	FGFR, IC <sub>50</sub> =1.9 μM	(Bono et al., 2013)
Sulfatinib (HMPL-012)	VEGFR1, VEGFR2, VEGFR3, FGFR1, FMS	Tumor	Early Phase1 (NCT03627520)	Hutchison Medipharma Limited	FGFR1, IC <sub>50</sub> =15 nM	(J. M. Xu et al., 2017)
Pazopanib (GW786034)	VEGFR1, VEGFR2/3, PDGFR, FGFR, c-Kit, c-fms	Medical treatment for metastatic renal cell carcinoma	NCT04659343	Frede Donskov Odense University Hospital Herlev Hospital Rigshospitalet Denmark University of Aarhus	FGFR, IC <sub>50</sub> =74 nM	(Harris et al., 2008)
Danuseritib (PHA-739358)	AuroraA/B/C, Abl, TrkA, c-RET, FGFR1	Multiple myeloma	Phase 2 (NCT00872300)	Nerviano Medical Sciences	FGFR1, IC <sub>50</sub> =47 nM	(Carpinelli et al., 2007)
ENMD-2076	AuroraA, FLT3, RET, SRC, NTRK1, FMS, VEGFR2, FGFR, PDGFR $\alpha$	Ovarian clear cell carcinoma	Phase 2 (NCT01914510)	University Health Network, Toronto	FGFR1, IC <sub>50</sub> =92.7 nM	(Fletcher et al., 2011)
MK-2461	c-Met, Ron, FLT1/3/4, FGFR1/2/3, PDGFR $\beta$ , KDR	c-Met and FGFR2-driven tumors	Phase 1 (NCT00518739)	Merck Sharp & Dohme Corp.	FGFR1/2/3, IC <sub>50</sub> =65/39/50 nM	(Pan et al., 2010)

Tyrphostin AG 1296	PDGFR, FGFR, c-Kit	Cancers	Preclinical study	NA	FGFR (Swiss 3T3), IC <sub>50</sub> = 12.3 μM	(Kovalenko et al., 1994)
ON123300	PDGFRβ, FGFR, RET, Fyn	Solid tumors, adult (Carpinelli et al., 2007)	Phase 1 (NCT04739293)	Onconova Therapeutics, Inc.	FGFR1, IC <sub>50</sub> =26 nM	(X. Zhang et al., 2014)
SU 5402	VEGFR2, FGFR1, PDGFRβ	Cancers	Preclinical study	Department of Pharmacology, New York University Medical Center	FGFR1, IC <sub>50</sub> =30 nM	(Sun et al., 1999)
Erdafitinib (JNJ42756493)	FGFR1-4	Locally advanced or metastatic bladder cancer, etc.	Approved in 2019	Janssen Research & Development, LLC	FGFR1/2/3/4, IC <sub>50</sub> =1.2/2.5/3.0/5.7 nM	(Perera et al., 2017)
ASP-5878	FGFR1-4	Solid tumors	Phase 1 (NCT02038673)	Astellas Pharma Inc	FGFR1/2/3/4, IC <sub>50</sub> = 0.47/0.6/0.74/0.74 nM	(Futami et al., 2017)
Derazantinib (ARQ-087)	FGFR1-4	Advanced intrahepatic cholangiocarcinoma with FGFR2 Gene amplifications/ mutations/ fusions	Phase 2 (NCT03230318)	Basilea Pharmaceutica	FGFR1/2/3/4, IC <sub>50</sub> =4.5/1.8/4.5/34 nM	(Hall et al., 2016)
Rogaratinib (BAY1163877)	FGFR1-4	Neoplasms	Phase 1 (NCT03788603)	Bayer	FGFR1/2/3/4, IC <sub>50</sub> =1.8/<1/9.2/1.2 nM	(Grunewald et al., 2019)
FIIN-1	FGFR1-4	Drug-resistant tumors	Preclinical study	Harvard Medical School	FGFR1/2/3/4, IC <sub>50</sub> = 9.2/6.2/11.9/182 nM	(Zhou et al., 2010)
FIIN-2	FGFR1-4	Drug-resistant tumors	Preclinical study	Harvard Medical School	FGFR1/2/3/4, IC <sub>50</sub> = 3.09/4.3/27/45.3 nM	(Tan et al., 2014)
FIIN-3	FGFR1-4	Drug-resistant tumors	Preclinical study	Harvard Medical School	FGFR1/2/3/4, IC <sub>50</sub> = 13.1/21/31.4/35.3 nM	(Tan et al., 2014)
LY2874455	FGFR1-4	Advanced cancer	Phase 1 (NCT01212107)	Eli Lilly	FGFR1/2/3/4, IC <sub>50</sub> =2.8/2.6/6.4/6 nM	(G. Zhao et al., 2011)

PRN-1371	FGFR1-4	Metastatic urothelial carcinoma & renal pelvis & ureter	Phase 1 (NCT02608125)	Principia Biopharma, a Sanofi Company	FGFR1/2/3/4, IC <sub>50</sub> =0.6/1.3/4.1/19.3 nM	(Brameld et al., 2017)
Futibatinib (TAS-120)	FGFR1-4	Metastatic breast cancer with FGFR2 amplification	Phase 2 (NCT04024436)	Taiho Oncology, Inc.	FGFR1/2/3/4, IC <sub>50</sub> =1.8/1.4/1.6/3.7 nM	(Sootome et al., 2020)
ICP-192	FGFR1-4	Urothelial carcinoma, cholangiocarcinoma	Phase 1/2 (NCT04565275)	Beijing InnoCare Pharma Tech Co., Ltd.	NA	<a href="https://clinicaltrials.gov/ct2/show/NCT04565275">https://clinicaltrials.gov/ct2/show/NCT04565275</a>
Pemigatinib (INCB054828)	FGFR1/2/3	Unresectable or metastatic cholangiocarcinoma	Approved in 2020	Incyte Corporation	FGFR1/2/3/4, IC <sub>50</sub> =0.4/0.5/1.2/30 nM	(Roskoski, 2020)
Infigratinib (BGJ398)	FGFR1/2/3	Advanced or metastatic cholangiocarcinoma	Approved in 2021	BridgeBio Pharma	FGFR1/2/3/4, IC <sub>50</sub> =0.9/1.4/1.0/60 nM FGFR3 (K650E), IC <sub>50</sub> =4.9 nM	(Guagnano et al., 2011)
AZD4547	FGFR1/2/3	ER+ breast cancer	Phase 2/3 (NCT01202591)	AstraZeneca	FGFR1/2/3, IC <sub>50</sub> =0.2/2.5/8 nM	(Gavine et al., 2012)
CPL304110	FGFR1/2/3	Advanced solid malignancies	Phase 1 (NCT04149691)	Celon Pharma S.A.	FGFR1/2/3/4, IC <sub>50</sub> =0.75/0.50/3.05/87.9 nM	(Yamani et al., 2021)
Zoligratinib (Debio1347)	FGFR1/2/3	Solid malignancies	Phase 1 (NCT01948297)	Debiopharm International SA	FGFR1/2/3/4, IC <sub>50</sub> =9.3/7.622/290 nM	(Nakanishi et al., 2014)

E7090	FGFR1/2/3	Cholangiocarcinoma	Phase 1 (NCT04565574) Phase 2 (NCT04238715)	Eisai Co., Ltd.	FGFR1/2/3/4, IC <sub>50</sub> = 0.71/0.50/1.2/120 nM FGFR3 (K650E), IC <sub>50</sub> =3.1 nM FGFR3 (K650M), IC <sub>50</sub> =16 nM	(Watanabe Miyano et al., 2016)
3D185	FGFR1/2/3	Advanced solid tumors, Cholangiocarcinoma	Phase 1 (NCT04221204) Phase 2 (NCT05039892)	3D Medicines Co., Ltd.	FGFR1/2/3, IC <sub>50</sub> = 0.5/1.3/3.6 nM	(Peng et al., 2019)
BLU9931	FGFR 4	Hepatocellular carcinoma	Preclinical study	Blueprint Medicines Corporation	FGFR4, IC <sub>50</sub> =3 nM	(Hagel et al., 2015)
Fisogatinib (BLU554)	FGFR 4	Advanced solid tumors, Hepatocellular carcinoma (HCC)	Phase 1b/2 (NCT04194801)	Blueprint Medicines Corporation	FGFR4, IC <sub>50</sub> =5 nM (FGFR1-3, IC <sub>50</sub> =624- 2203 nM)	Blueprint Medicines. 50th th international liver congress. 2015
FGF401	FGFR 4	Solid malignancies, Hepatocellular carcinoma (HCC)	Phase 1/2 (NCT02325739)	Novartis Pharmaceuticals	FGFR4, IC <sub>50</sub> =1.1 nM	(Fairhurst et al., 2020)
H3B-6527	FGFR 4	Advanced hepatocellular carcinoma	Phase 1 (NCT02834780)	H3 Biomedicine, Cambridge, Massachusetts	FGFR4, IC <sub>50</sub> < 1.2 nM	(Joshi et al., 2017)
ICP-105	FGFR 4	Advanced Solid Malignancies	Phase 1 (NCT03642834)	Beijing InnoCare Pharma Tech Co., Ltd.	NA	<a href="https://www.clinicaltrials.gov/ct2/show/NCT0364283">https://www.clinicaltrials.gov/ct2/show/NCT0364283</a>
EVER4010001	FGFR 4	Advanced Solid Tumors	Phase 1/2 (NCT04699643)	Chinese PLA General Hospital	Combination With PD-1 Inhibitor Pembrolizumab	<a href="https://www.clinicaltrials.gov/ct2/show/NCT04699643">https://www.clinicaltrials.gov/ct2/show/NCT04699643</a>

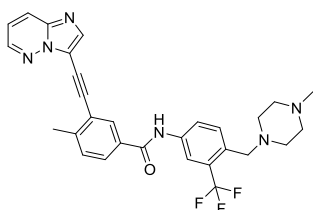
Vofatamab (B-701)	FGFR 3 (Anti-FGFR3 monoclonal antibody)	Locally advanced or metastatic urothelial cell Carcinoma	Phase 1/2 (NCT02401542)	Rainier Therapeutics	Combination With Pembrolizumab	<a href="https://www.clinicaltrials.gov/ct2/show/NCT03123055">https://www.clinicaltrials.gov/ct2/show/NCT03123055</a>
BO-264	FGFR3-TACC3	Specifically blocking the function of FGFR3-TACC3 fusion protein	Preclinical study	Department of Molecular Biology and Genetics, Faculty of Science, Bilkent University, Ankara, Turkey.	NA	(Akbulut et al., 2020)
Masitinib (AB1010)	FGFR 3	Multiple myeloma	Preclinical study	AB Science	NA	(Dubreuil et al., 2009)
RLY4008	FGFR 2	Solid tumor	Phase 1 (NCT04526106)	Relay Therapeutics, Inc.	NA	<a href="https://clinicaltrials.gov/ct2/show/NCT04526106">https://clinicaltrials.gov/ct2/show/NCT04526106</a>
Alofanib (RPT385)	FGFR 2	Ovarian cancer	Preclinical study	Ruspharmtech LLC	allosteric FGFR2 inhibitor, IC <sub>50</sub> < 10 nM	(Tyulyandina et al., 2017)
NSC12	FGFs (Small-Molecule extracellular FGF Trap)	Cancer	Preclinical study	Department of Molecular and Translational Medicine, University of Brescia	FGF2, IC <sub>50</sub> =30 nM	(Ronca et al., 2015)
Rosmarinic acid	FGF2/FGFR-D2 complex	FGF2-mediated drug resistance	Preclinical study	RagonaIstituto di Scienze e Tecnologie Chimiche (SCITEC), CNR Institution	IC <sub>50</sub> =17.7 ±2.1 μM	(Pagano et al., 2021)
PD-166866	FGFR1	Small cell lung cancer cell	Preclinical study	Warner-Lambert Company, Ann Arbor, Michigan, USA.	FGFR1, IC <sub>50</sub> = 52.4 nM	(Risuleo et al., 2009)

SU-4984	FGFR1	Malignant glioma and cancers	Preclinical study	State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University	FGFR1, IC <sub>50</sub> =20-40 μM	(Mohammadi et al., 1997)
Gambogenic acid	FGFR	Erlotinib-resistant non-small-cell lung cancer	Preclinical study	Shanghai University of Traditional Chinese Medicine	IC <sub>50</sub> of H1650 cells/HCC827 cells/HCC827ER cells = 0.909/1.328/1.51 μM	(L. Xu et al., 2018)
Ferulic Acid	FGFR1/2	Melanoma	Preclinical study	Zhejiang Provincial People's Hospital	FGFR1/2, IC <sub>50</sub> =3.78/12.5 μM	(G. W. Yang et al., 2015)
Cediranib (AZD2171)	VEGFR, FGFR	Advanced solid tumor, FGFR positive lung cancer	Phase 1 (NCT00979134) Phase 2/3 (NCT02965378)	AstraZeneca	FGFR1, IC <sub>50</sub> = 26 nM	(Wedge et al., 2005)
AT9283	FGFR1/2/3	Non-Hodgkins lymphoma Unspecified adult solid tumor	Phase 1 (NCT00443976)	Astex Pharmaceuticals, Inc.	FGFR1/2/3, IC <sub>50</sub> = 10-30/1-10/1-30nM FGFR1 (V561M), IC <sub>50</sub> =10-30 nM FGFR2 (N549H), IC <sub>50</sub> =10-30 nM	(Howard et al., 2009)
BZF-2	EGFR, FGFR	EGFR/FGFR1-positive NSCLC	Preclinical study	School of Pharmaceutical Science, Wenzhou Medical University,	NCI-H226, IC <sub>50</sub> = 2.11 μM HCC827GR, IC <sub>50</sub> = 0.93 μM	(Xie et al., 2020)

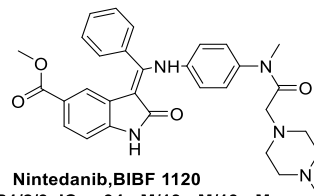


Ki23057	VEGFR, FGFR	Drug-resistant gastric cancer	Preclinical study	Kirin Brewery Co.,Ltd. (Gunma, Japan)	FGFR1/2, IC <sub>50</sub> = 89/91 nM VEGFR2, IC <sub>50</sub> = 38 nM	(Qiu et al., 2011)
MPT0L145	PI3K, FGFR	Bladder cancer	Preclinical study	Department of Pharmacology, School of Medicine, College of Medicine, Taipei Medical University	FGFR- dependent/independent, IC <sub>50</sub> = 1.83/6.74 μM	(C. H. Chen et al., 2016)
ODM-203	VEGFR, FGFR	Solid tumors	Phase 1 (NCT02264418)	Orion Corporation Orion Pharma, Finland	FGFR1/2/3/4, IC <sub>50</sub> = 11/16/6/35 nM VEGFR1/2/3, IC <sub>50</sub> = 26 /9/5 nM	(Holmström et al., 2019)
SOMCL-085	VEGFR, FGFR	FGFR-driven cancers	Preclinical study	Shanghai Institute of Materia Medica	FGFR1/2/3, IC <sub>50</sub> = 1.8/1.9 /6.9 nM	(Jiang et al., 2018)
SOMCL-286	VEGFR, FGFR	FGFR1/2 and VEGFR2 addictive cancer	Preclinical study	Shanghai Institute of Materia Medica	FGFR1/2/3, IC <sub>50</sub> = 1.0/4.5/2.9 nM,	(M. Wei et al., 2018)
PD173074	VEGFR, FGFR	Non-small cell lung cancer cell	Preclinical study	Department of Pharmacology, New York University Medical Center	FGFR1, IC <sub>50</sub> = 1-5 nM VEGFR2, IC <sub>50</sub> = 100-200 nM	(Mohammadi et al., 1998)

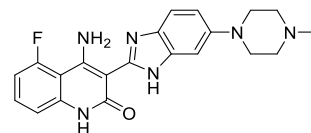
FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PI3K, phosphoinositide 3-kinase; EGFR, epidermal growth factor receptor; TACC, transforming acidic coiled-coil containing protein; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; Fyn, fyn proto-oncogene, src family tyrosine kinase; AXL, axl receptor tyrosine kinase; Flk, fetal liver kinase; FMS, colony-stimulating factor 1 receptor; Abl, Abl tyrosine kinase; AuroraA, aurora kinase A; SRC, src proto-oncogene, non-receptor tyrosine kinase; NTRK1, neurotrophic receptor tyrosine kinase; Ron, macrophage stimulating 1 receptor; KDR, kinase insert domain receptor; Flt, fms related receptor tyrosine kinase; Trk neurotrophic receptor tyrosine kinase; Kit, kit proto-oncogene receptor tyrosine kinase. \*IC<sub>50</sub>: The reference of IC<sub>50</sub> have been cited in the table. \*NA: Not available.



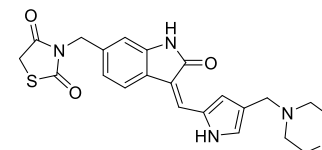
**Ponatinib, AP24534**  
 Abl, IC<sub>50</sub>=0.37 nM  
 PDGFR, IC<sub>50</sub>=1.1 nM  
 VEGFR2, IC<sub>50</sub>=1.5 nM  
 FGFR1, IC<sub>50</sub>=2.2 nM  
 Src, IC<sub>50</sub>=5.4 nM



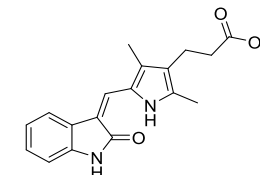
**Nintedanib, BIBF 1120**  
 VEGFR1/2/3, IC<sub>50</sub>=34 nM/13 nM/13 nM  
 FGFR1/2/3, IC<sub>50</sub>= 69 nM/37 nM/108 nM  
 PDGFR $\alpha/\beta$ , IC<sub>50</sub>=59 nM/65 nM



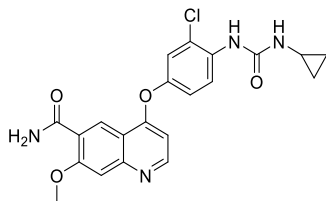
**Dovitinib, TKI258**  
 FLT3/c-Kit, IC<sub>50</sub>=1 nM/2 nM  
 FGFR1/3 and VEGFR1-4, IC<sub>50</sub>= 8-13 nM



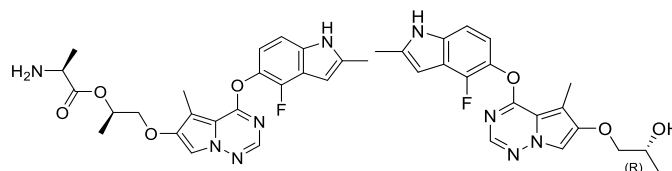
**S49076**  
 FGFR1/2/3, IC<sub>50</sub><20 nM



**Orantinib (TSU-68, SU6668)**  
 FGFR1, K<sub>i</sub> = 1.2  $\mu$ M

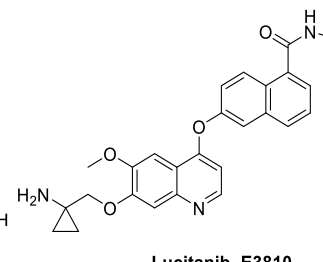


**Lenvatinib, E7080**  
 VEGFR2(KDR)/VEGFR3(Fit-4)  
 IC<sub>50</sub>=4 nM/5.2 nM  
 FGFR1-4, PDGFR, Kit (c-Kit), RET (c-RET)

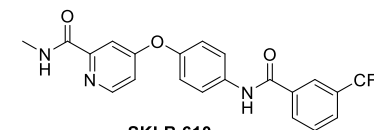


**BMS-582664**  
 FGFR1, IC<sub>50</sub>= 148 nM

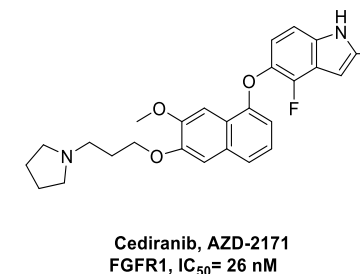
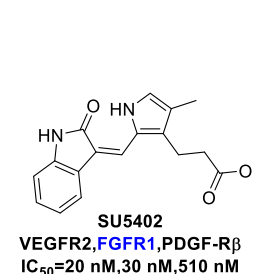
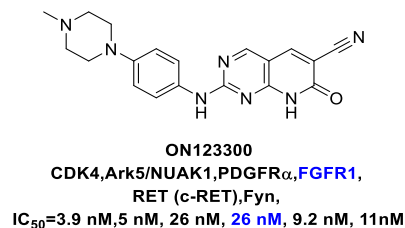
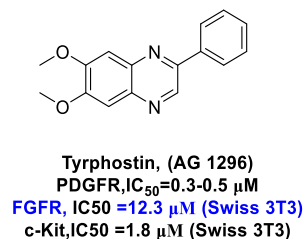
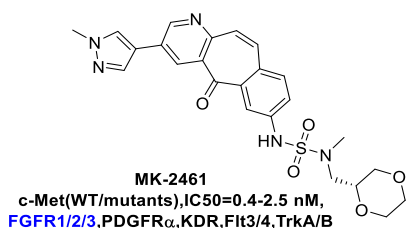
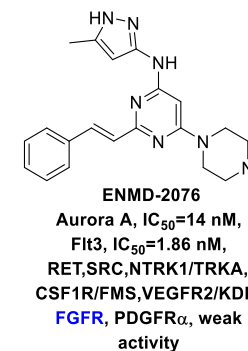
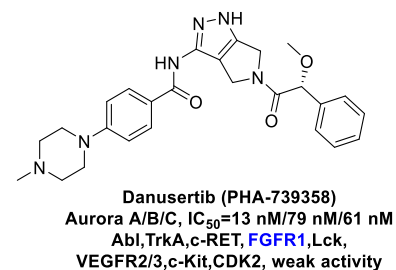
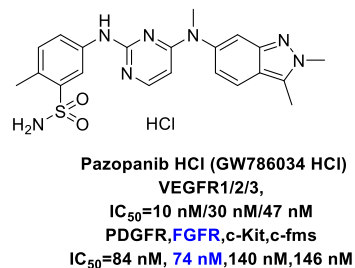
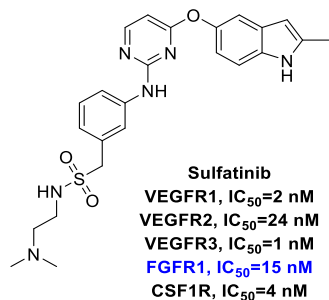
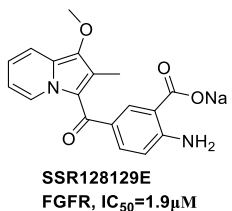
**BMS-540215**  
 FGFR1, IC<sub>50</sub>= 148 nM

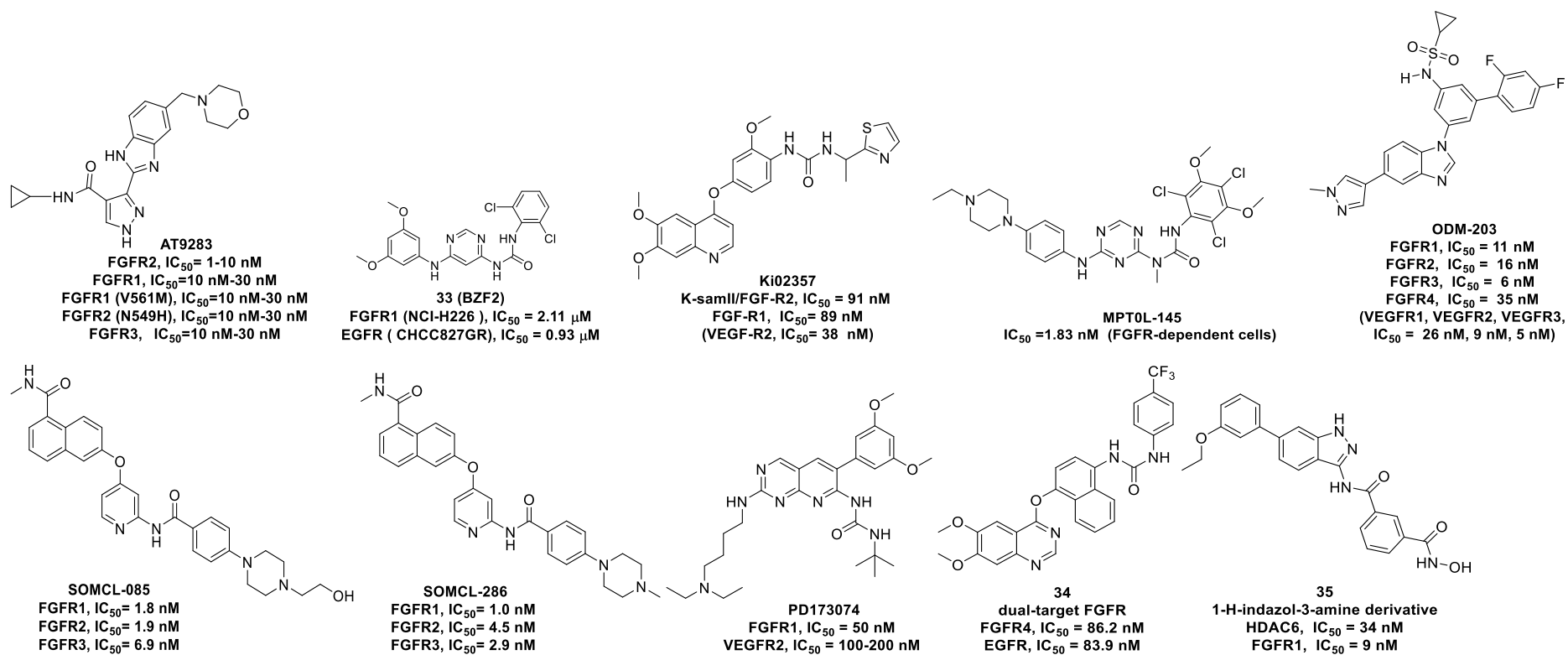


**Lucitanib, E3810**  
 FGFR1, IC<sub>50</sub>= 17.5 nM  
 FGFR2, IC<sub>50</sub>= 82.5 nM

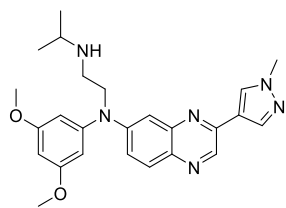


**SKLB 610**  
 Inhibiting FGFR2 at a rate of 65%, at the concentration of 10  $\mu$ M





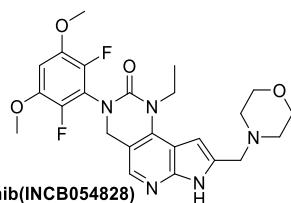
**Figure S1.** Reported multi-target or dual target FGFR inhibitors with targets and IC<sub>50</sub> values



**Balversa(Erdafitinib,JNJ42756493)**

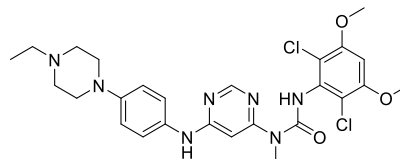
2019

FGFR1, IC<sub>50</sub>=1.2 nM  
 FGFR2, IC<sub>50</sub>=2.5 nM  
 FGFR3, IC<sub>50</sub>=3.0 nM  
 FGFR 4, IC<sub>50</sub>= 5.7 nM



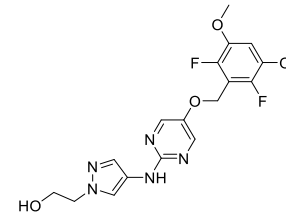
**Pemigatinib(incb054828)**

FGFR 1, IC<sub>50</sub>=0.4 nM  
 FGFR 2, IC<sub>50</sub>=0.5 nM  
 FGFR 3, IC<sub>50</sub>=1.2 nM  
 (FGFR 4, IC<sub>50</sub>=30 nM)



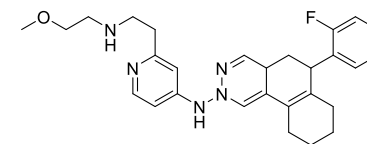
**Infigratinib(BGJ398)**

FGFR1, IC<sub>50</sub> =0.9 nM  
 FGFR2, IC<sub>50</sub> =1.4 nM  
 FGFR3, IC<sub>50</sub> =1.0 nM  
 (FGFR4, IC<sub>50</sub> = 60 nM)  
 FGFR3 (K650E), IC<sub>50</sub> =4.9 nM



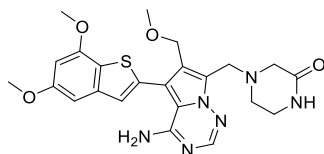
**ASP5878**

FGFR1, IC<sub>50</sub>=0.47nM  
 FGFR2, IC<sub>50</sub>=0.60nM  
 FGFR3, IC<sub>50</sub>=0.74nM  
 FGFR4, IC<sub>50</sub>= 0.74nM



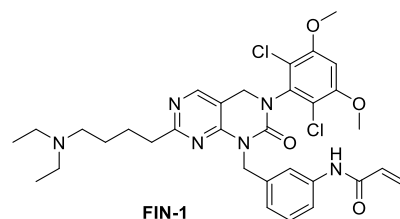
**ARQ-087**

FGFR1, IC<sub>50</sub>=4.5 nM  
 FGFR2, IC<sub>50</sub>=1.8 nM  
 FGFR3, IC<sub>50</sub>=4.5 nM  
 FGFR4, IC<sub>50</sub>= 34 nM



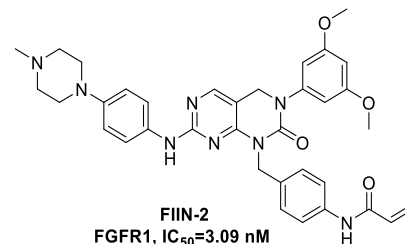
**Rogaratinib  
(BAY1163877)**

FGFR1, IC<sub>50</sub>=15 nM  
 FGFR2, IC<sub>50</sub>=1 nM  
 FGFR3, IC<sub>50</sub>=19 nM  
 FGFR4, IC<sub>50</sub>= 33 nM



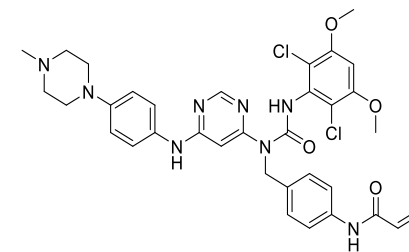
**FIN-1**

FGFR1, IC<sub>50</sub>=9.2 nM  
 FGFR2, IC<sub>50</sub>=6.2 nM  
 FGFR3, IC<sub>50</sub>=11.9 nM  
 FGFR4, IC<sub>50</sub>= 182 nM



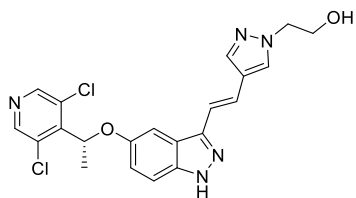
**FIIN-2**

FGFR1, IC<sub>50</sub>=3.09 nM  
 FGFR2, IC<sub>50</sub>=4.3 nM  
 FGFR3, IC<sub>50</sub>=27 nM  
 FGFR4, IC<sub>50</sub>=45.3 nM

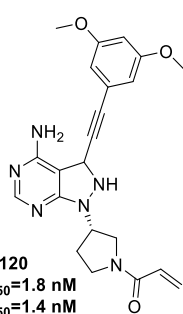


**FIIN-3**

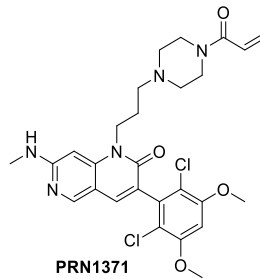
FGFR1, IC<sub>50</sub>=13.1 nM  
 FGFR2, IC<sub>50</sub>=21 nM  
 FGFR3, IC<sub>50</sub>=31.4 nM  
 FGFR4, IC<sub>50</sub>= 35.3 nM



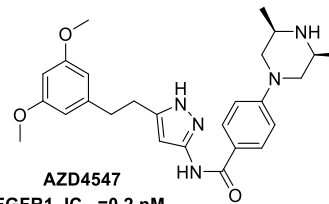
**LY287445**  
 FGFR1, IC<sub>50</sub>=2.8 nM  
 FGFR2, IC<sub>50</sub>=2.6 nM  
 FGFR3, IC<sub>50</sub>=6.4 nM  
 FGFR4, IC<sub>50</sub>=6 nM  
 VEGFR2, IC<sub>50</sub>=7 nM



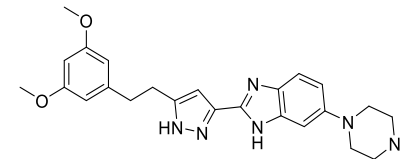
**TAS 120**  
 FGFR 1, IC<sub>50</sub>=1.8 nM  
 FGFR 2, IC<sub>50</sub>=1.4 nM  
 FGFR 3, IC<sub>50</sub>= 1.6 nM  
 FGFR 4, IC<sub>50</sub>=3.7 nM



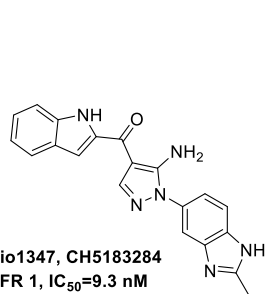
**PRN1371**  
 FGFR1, IC<sub>50</sub>=0.6 nM  
 FGFR2, IC<sub>50</sub>=1.3 nM  
 FGFR3, IC<sub>50</sub>=4.1nM  
 FGFR4, IC<sub>50</sub>=19.3 nM



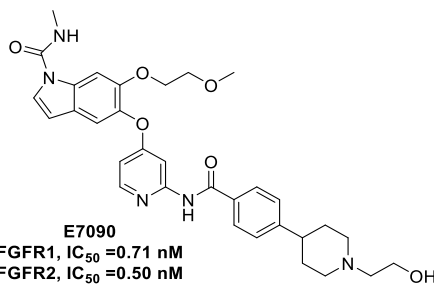
**AZD4547**  
 FGFR1, IC<sub>50</sub>=0.2 nM  
 FGFR2, IC<sub>50</sub>=2.5 nM  
 FGFR3, IC<sub>50</sub>=8 nM



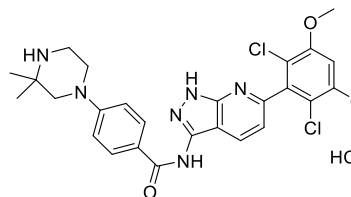
**CPL304110**  
 FGFR1, IC<sub>50</sub> = 0.75 nM  
 FGFR2, IC<sub>50</sub> = 0.50 nM  
 FGFR3, IC<sub>50</sub> = 3.05 nM  
 (FGFR4, IC<sub>50</sub> = 87.9 nM)



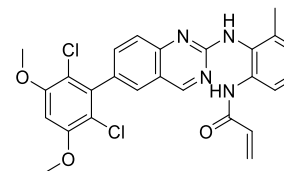
**Debio1347, CH5183284**  
 FGFR 1, IC<sub>50</sub>=9.3 nM  
 FGFR 2, IC<sub>50</sub>=7.6 nM  
 FGFR 3, IC<sub>50</sub>=22 nM  
 (FGFR 4, IC<sub>50</sub>=290 nM)



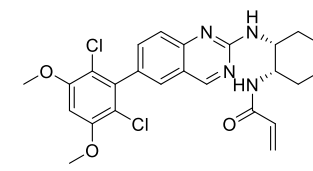
**E7090**  
 FGFR1, IC<sub>50</sub> =0.71 nM  
 FGFR2, IC<sub>50</sub> =0.50 nM  
 FGFR3, IC<sub>50</sub> =1.2 nM  
 (FGFR4, IC<sub>50</sub> = 120 nM)  
 FGFR3 (K650E), IC<sub>50</sub> =3.1 nM  
 FGFR3 (K650M) IC<sub>50</sub> =16 nM



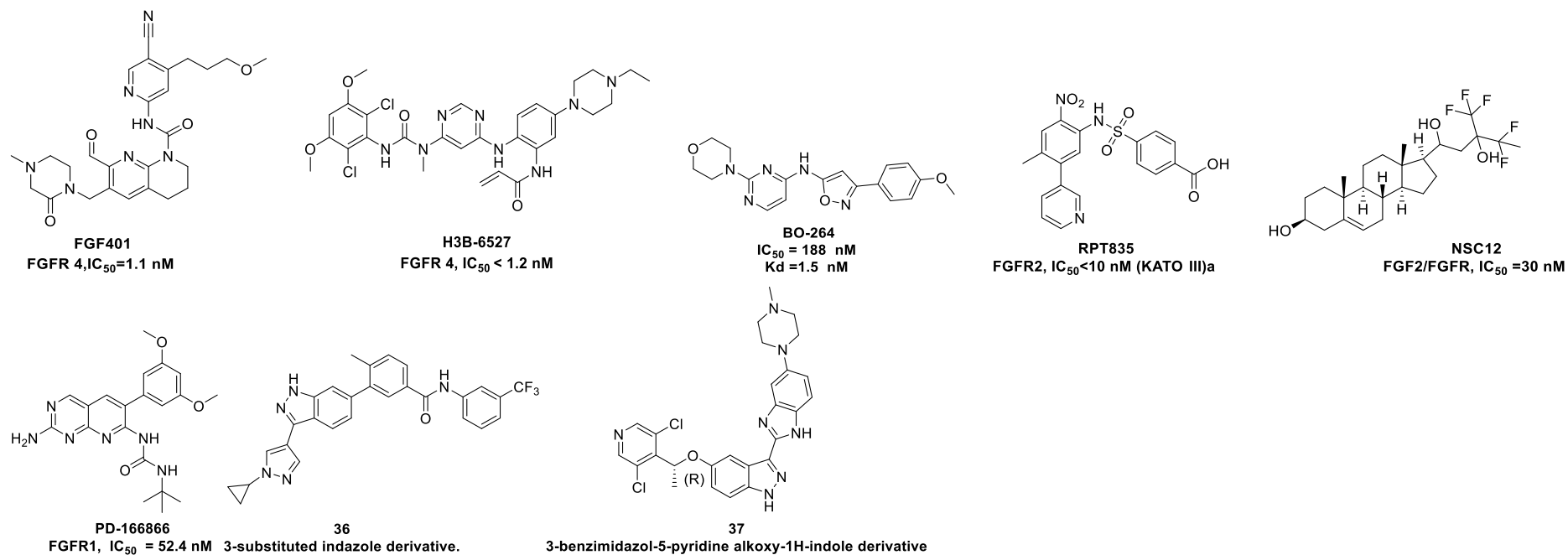
**3D185**  
 FGFR1, IC<sub>50</sub> = 0.5 nM  
 FGFR2, IC<sub>50</sub> = 1.3 nM  
 FGFR3, IC<sub>50</sub> = 13.6 nM



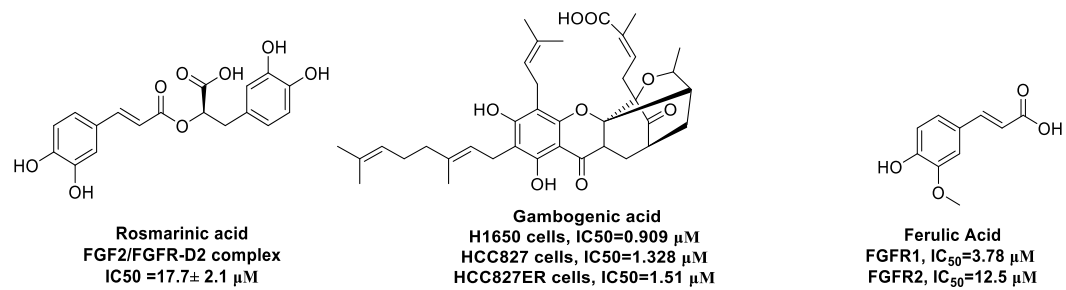
**BLU9931**  
 FGFR 4, IC<sub>50</sub>=3 nM



**BLU554**  
 FGFR4, IC<sub>50</sub>=5 nM  
 (FGFR1-3, IC<sub>50</sub>: 624-2203 nM)



**Figure S2.** Reported Selective FGFR inhibitors and FGFR Traps



**Figure S3.** Represent extracellular FGFR inhibitor and selective FGFR inhibitors originated from natural products