Development of covalent inhibitors that can overcome resistance to first generation FGFR kinase inhibitors

Supplemental Information

Li Tan[1,4,†], Jun Wang[5†], Junko Tanizaki[5,6†], Zhifeng Huang[11,12†], Amir R. Aref[2,5†], Maria Rusan[5,13], Su-Jie Zhu[14], Yiyun Zhang[3,10], Dalia Ercan[5,6], Rachel G. Liao[5,9], Marzia Capelletti[5,6], Wenjun Zhou[1,4], Wooyoung Hur[1,4,15], NamDoo Kim[17], Taebo Sim[15,16], Suzanne Gaudet[2,4,8], David A. Barbie[5], Jing-Ruey Joanna Yeh[3,10], Cai-Hong Yun[14], Peter S. Hammerman[5,9*], Moosa Mohammadi[11*], Pasi A. Jänne[5,6,7*], Nathanael S. Gray[1,4*]

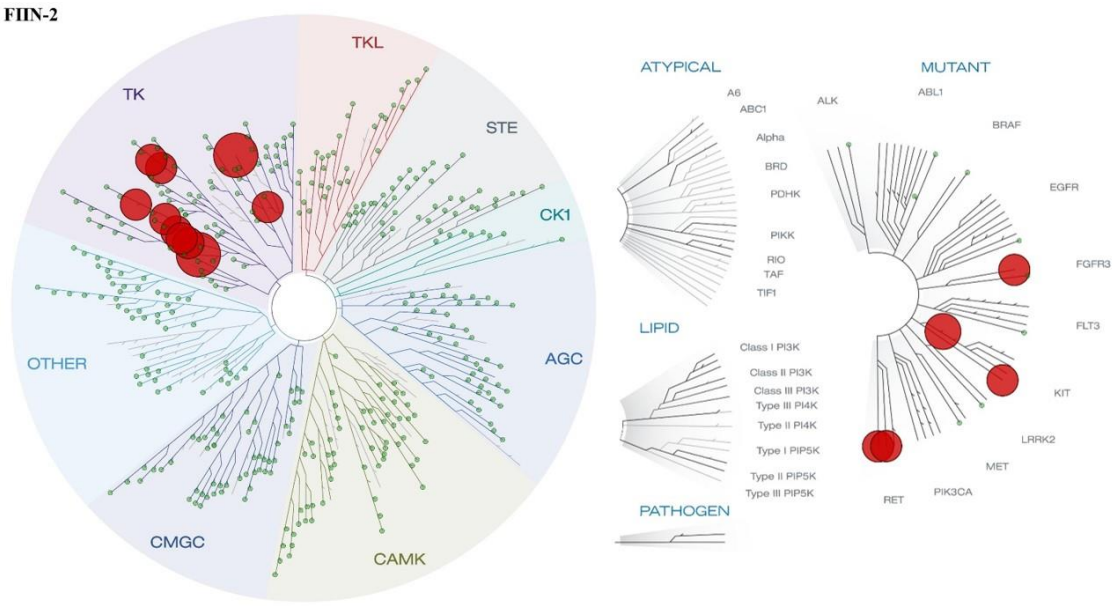
[1]Department of Biological Chemistry and Molecular Pharmacology, [2]Department of Genetics, [3]Department of Medicine, Harvard Medical School, Boston, MA 02115 (USA); [4]Department of Cancer Biology, [5]Department of Medical Oncology, [6]The Lowe Center for Thoracic Oncology, [7]Belfer Institute for Applied Cancer Science, [8]Center for Systems Cancer Biology, Dana Farber Cancer Institute, Boston, MA 02215 (USA); [9]Cancer program, Broad Institute of Harvard and MIT, Cambridge, MA 02141 (USA); [10]Cardiovascular Research Center, Massachusetts General Hospital, Charlestown, MA 02129 (USA); [11]Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, NY 10016 (USA); [12]School of Pharmacy, Wenzhou Medical University, Wenzhou, 325035 (CN); [13]Department of Clinical Medicine, Aarhus University, Aarhus, 8200 (DK); [14] Peking University Health Science Center, Beijing, 100191 (CN); [15]Chemical Kinomics Research Center, Korea Institute of Science and Technology, Seoul, 136-791 (KR); [16]KU-KIST Graduate School of Converging Science and Technology, Seoul, 136-713 (KR); [17]New Drug Development Center, Daegu-Gyeongbuk Medical Innovation Foundation, Daegu, 706-010 (KR). [†]These authors contributed equally.

*Correspondence: Peter_Hammerman@dfci.harvard.edu (PSH), Moosa.Mohammadi@nyumc.org (MM), Pasi_Janne@dfci.harvard.edu (PAJ), Nathanael_Gray@dfci.harvard.edu (NSG)

Contents:

Figure S1. KinomeScan™ kinase selectivity profiles for FIIN2 (A), FIIN3 (B), FRIN-2 (C) and FRIN-3 (D). All four inhibitors were profiled at a concentration of 1 μM against a diverse panel of more than 456 kinases (354 non-mutants kinases) by Ambit Biosciences. Scores for primary screen hits are reported as a percent of the DMSO control (% control). For kinases where no score is shown, no measurable binding was detected. The lower the score, the lower the Kd is likely to be, such that scores of zero represent strong hits. Scores are related to the probability of a hit but are not strictly an affinity measurement. At a screening concentration of 1.0 μM, a score of less than 10% implies that the false positive probability is less than 20% and the Kd is likely less than 100 nM. A score between 1% and 10% implies that the false positive probability is less than 10%, although it is difficult to assign a quantitative affinity from a single-point primary screen. A score of less than 1% implies that the false positive probability is less than 5% and the Kd is most likely less than 100 nM. (1, 2)

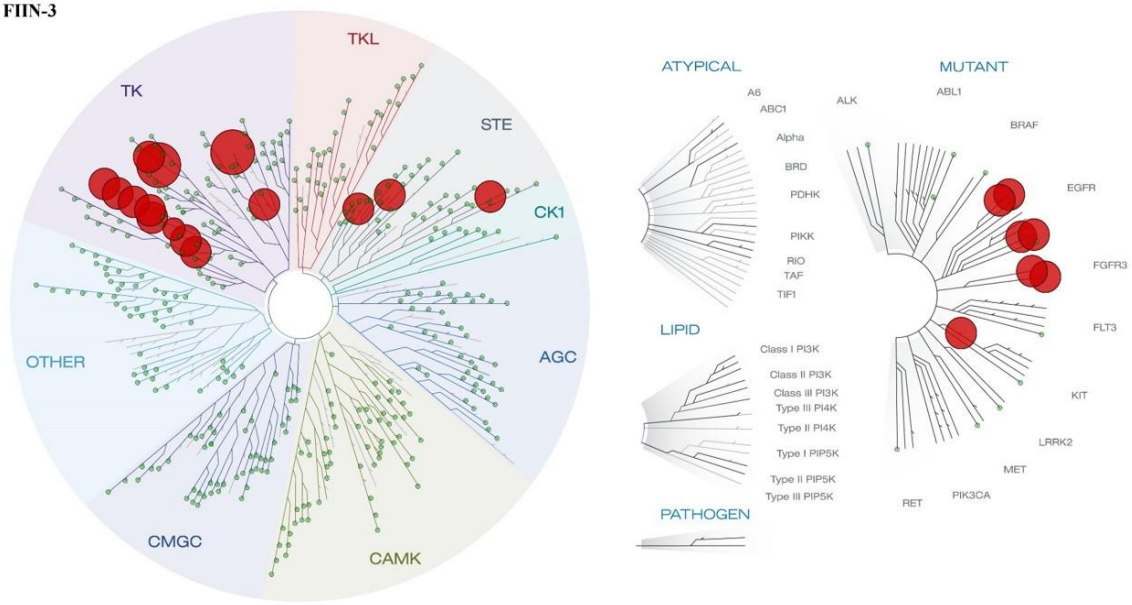
A



Compound Name	Selectivity Score Type	Non-Mutant Hits	Number of Assays	Screening Concentration (nM)	Selectivity Score
FIIN-2	S(10)	23	456	1000	0.06
FIIN-2	S(5)	17	456	1000	0.04
FIIN-2	S(1)	10	456	1000	0.03

B

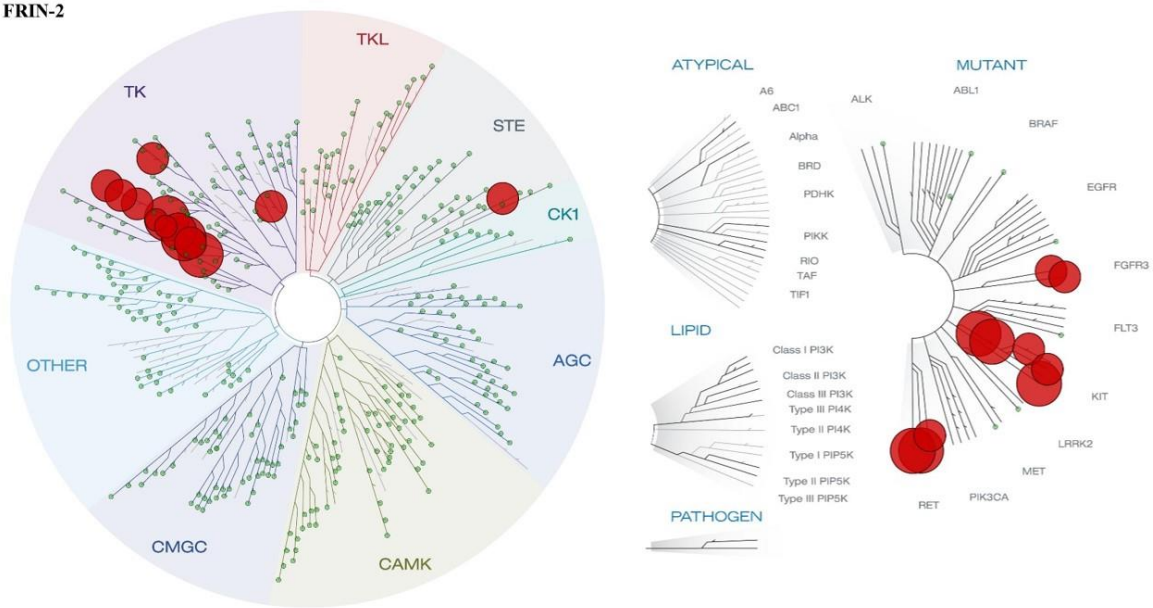
FIIN-3



Compound Name	Selectivity Score Type	Non-Mutant Hits	Number of Assays	Screening Concentration (nM)	Selectivity Score
FIIN-3	S(10)	31	456	1000	0.08
FIIN-3	S(5)	23	456	1000	0.06
FIIN-3	S(1)	15	456	1000	0.04

C

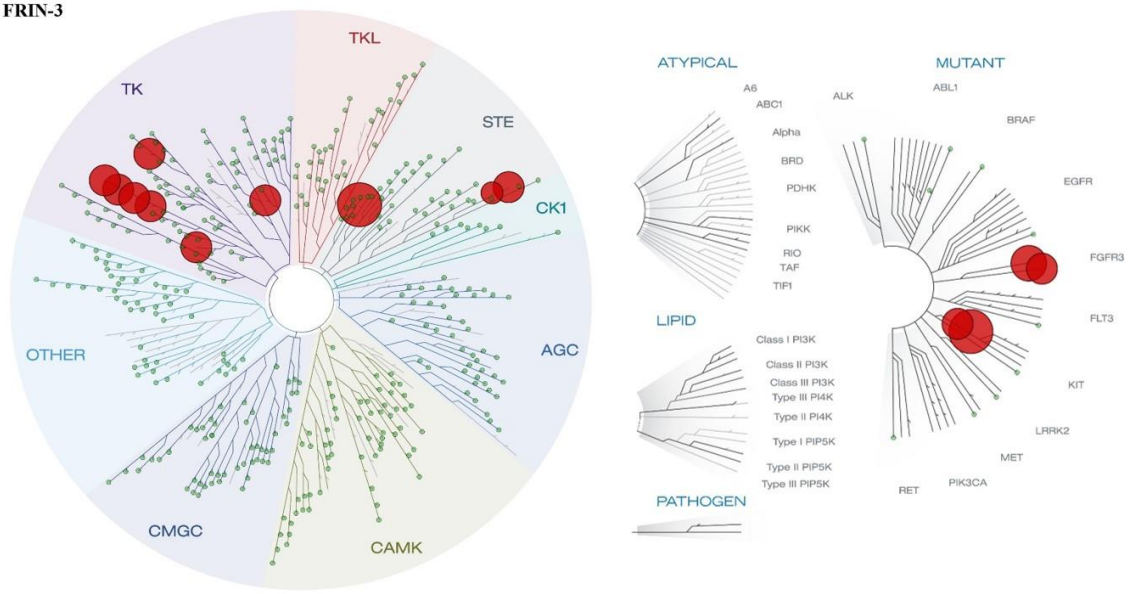
FRIN-2



Compound Name	Selectivity Score Type	Non-Mutant Hits	Number of Assays	Screening Concentration (nM)	Selectivity Score
FRIN-2	S(10)	19	456	1000	0.05
FRIN-2	S(5)	17	456	1000	0.04
FRIN-2	S(1)	13	456	1000	0.03

D

FRIN-3



Compound Name	Selectivity Score Type	Non-Mutant Hits	Number of Assays	Screening Concentration (nM)	Selectivity Score
FRIN-3	S(10)	24	456	1000	0.06
FRIN-3	S(5)	18	456	1000	0.05
FRIN-3	S(1)	10	456	1000	0.03

Figure S2. Inhibition of signaling by BGJ398, FIIN-3 and FIIN-2 in TEL/FGFR WT (**A**) or V564M (**B**) Ba/F3 cells. Cells were treated with indicated inhibitors and doses for 6 h then lysed and subjected to western blot for phospho-FGFR (Y653/Y654) or total FGFR2.

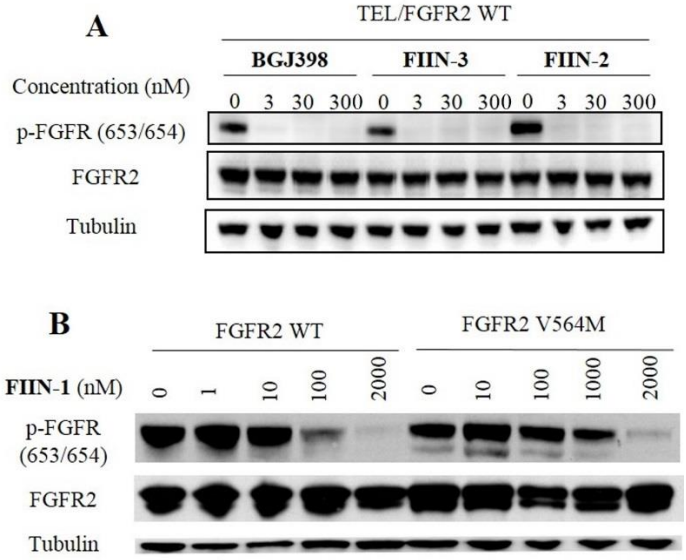


Figure S3. FIIN-2 and FIIN-3 are covalent, irreversible FGFR inhibitors. WT FGFR2 or C491A FGFR2 Ba/F3 cells were treated with BGJ398, FIIN-2 or FIIN-3 at 20 nM for 3 h, washed extensively with PBS, allowed to recover for 4 h, then lysed and subjected to western blot for phospho-FGFR and total FGFR2 (**A**). WT FGFR2 or Ba/F3 cells were treated BGJ398, FIIN-2 or FIIN-3 at 20 nM for 3 h, and the resulting cell lysates were treated with FIIN-1-biotin (5.0 μM, 1 h), followed by pull-down with anti-FGFR2 antibody beads and immunoblotting with streptavidin-HRP conjugate (**B**).

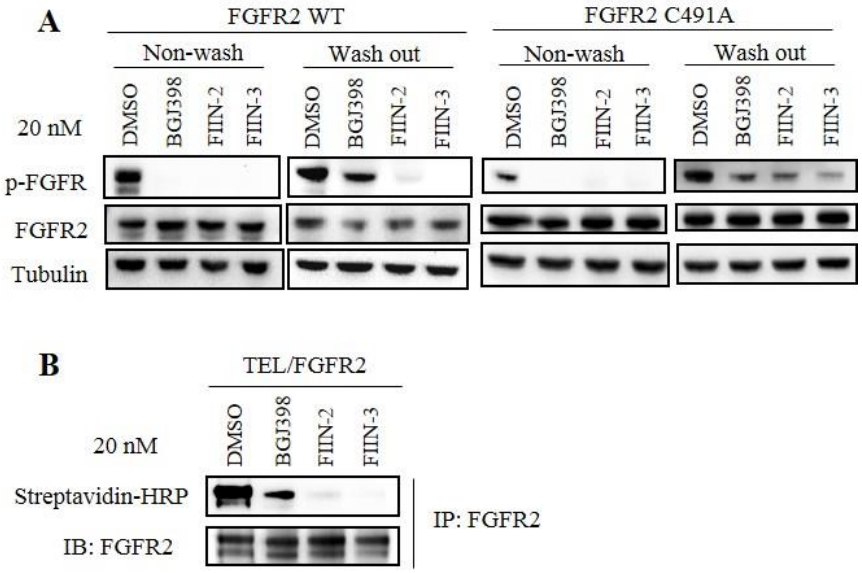


Figure S4. Inhibition of signaling by BGJ398, FIIN-3 and FIIN-2 in KATO III and RT112 cells after treatment at 1.0 μM (**A**), in H1581 (FGFR V561M) cells after treatment with indicated doses (**B**) for 12 h, then lysed and subjected to western-blotted for the indicated proteins or phosphoproteins.

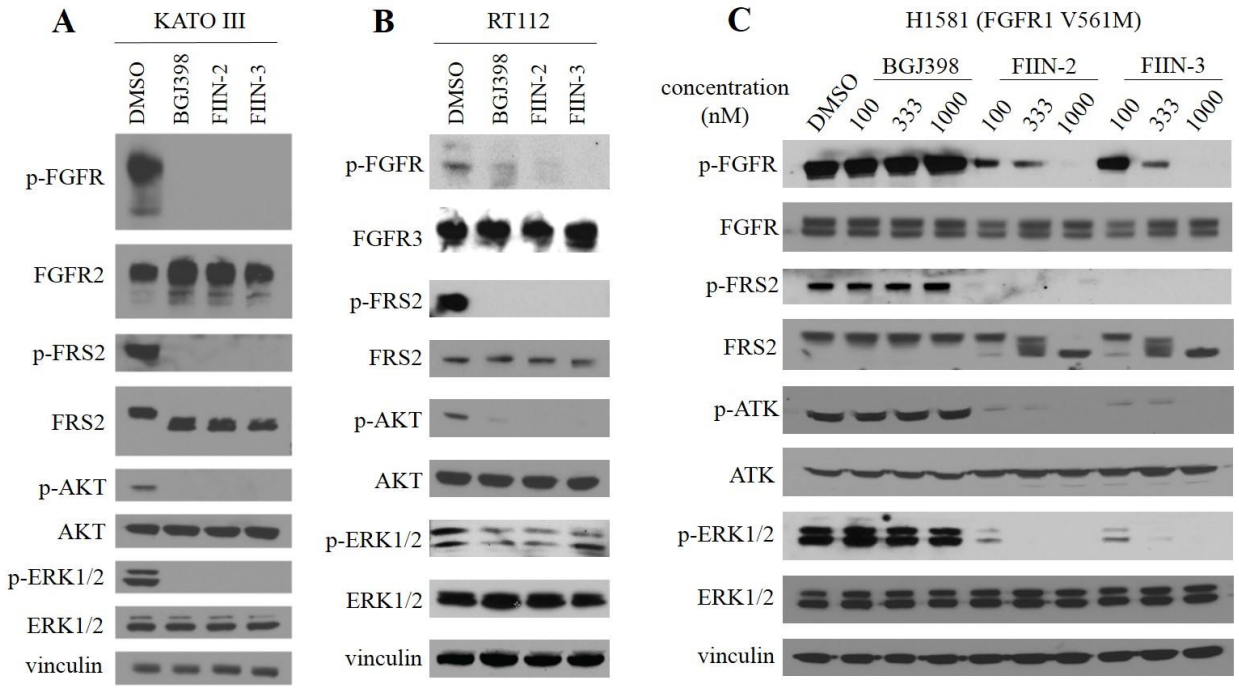


Figure S5. Percent proliferation of SK-OV3 cells in the absence (white bars) or presence (black bars) of FGF (10 ng/mL) (**A**) or EGF (10 ng/mL) (**B**) in the presence of a dose escalation of BGJ398, FIIN-2 and FIIN-3 (0.1, 0.3 1.0 and 3.0 μM) relative to the DMSO control in the absence of FGF/EGF (set to 100%).

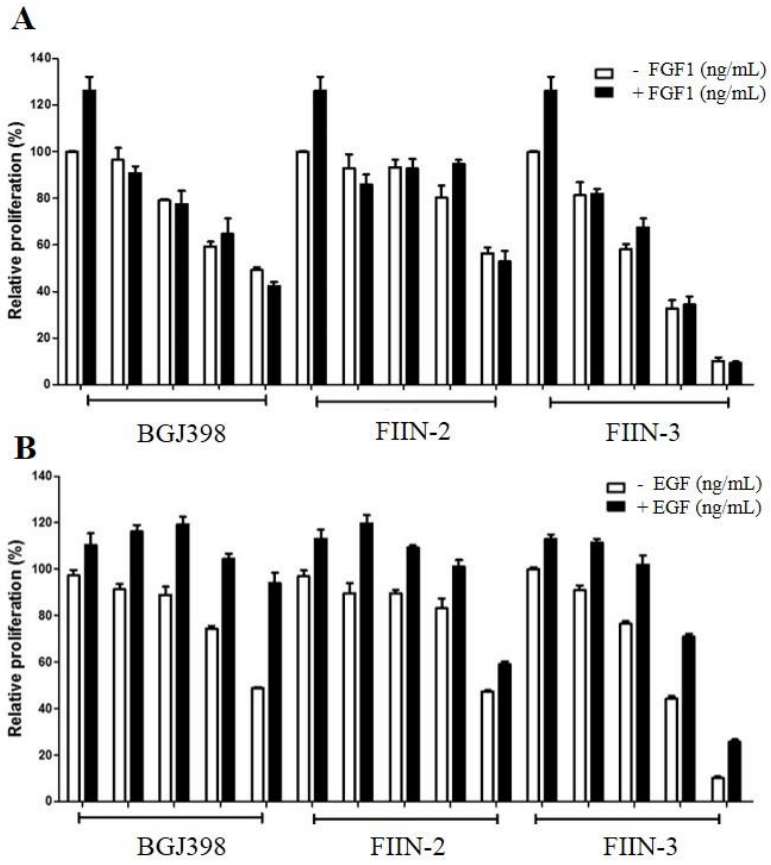


Figure S6. Inhibition of FGF1-induced signaling by BGJ398, FIIN-2 and FIIN-3 in SKOV-3 cells. Cells were treated with or without FGR1 (10 ng/mL) and with or without 1.0 μM inhibitor for 15 min then lysed and subjected to western blot for the indicated proteins or phosphoproteins.

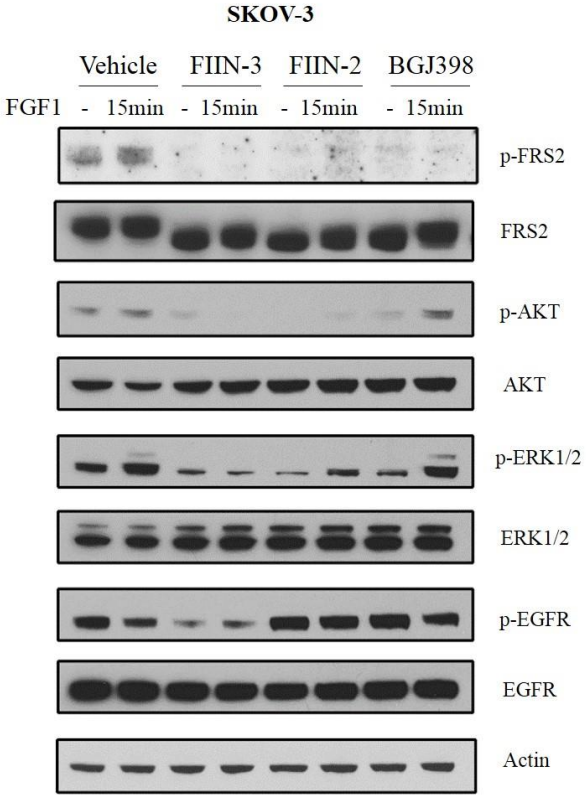


Figure S7. No dispersion of SKOV-3 spheroids was detected without growth factor stimulation (**A**). The SKOV-3 spheroids were treated with 20 ng/mL of FGF1 (**B**) or EGF (**C**) with or without 1.0 μM of FIIN-2, FIIN-3 or FRIN-3 for 48 h, bar-graphs score the percentage of cell dispersion (**B**, **C**). The cell number dispersion of each gel region was determined by drawing a line from the edge of the spheroids to the tip of the furthest grown sprout or cells are completely separated, using Image J software (http://rsbweb. nih.gov/ij/). The cell number is quantified by using the inbuilt Image J function; to measure the cells are separated from spheroids (3).

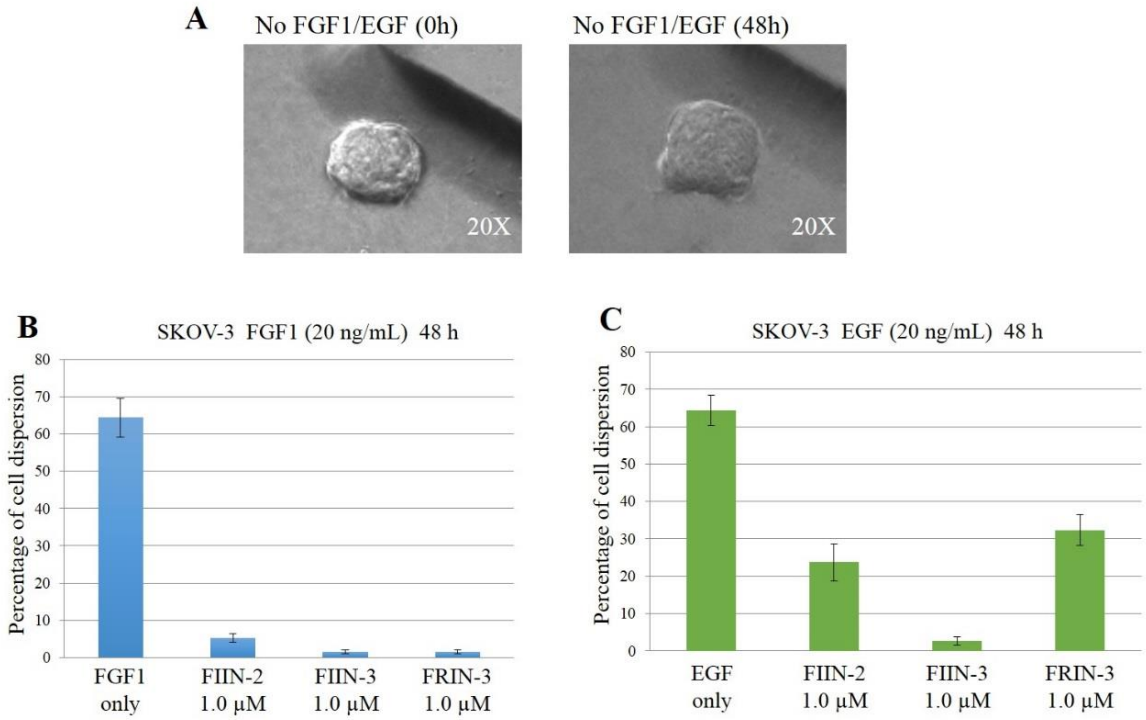
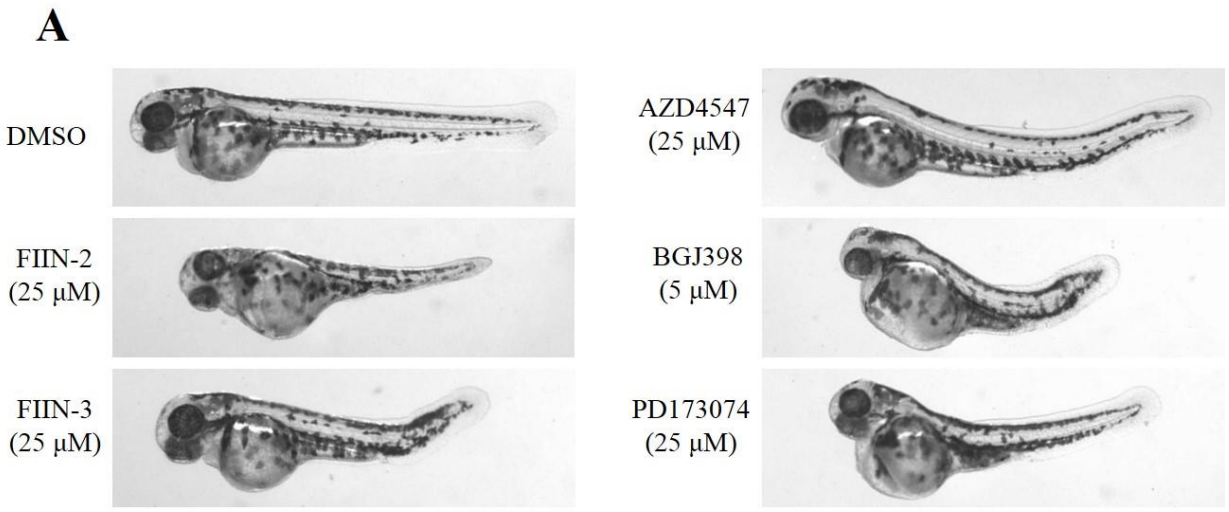


Figure S8. FIIN-2 and FIIN-3 induce zebrafish embryo developmental defects similar to AZD4547, BGJ398 and PD173074. Images of representative fish after treatment with inhibitor at indicated concentration for 48 h. FIIN-2 and FIIN-3 induce Zebrafish embryo developmental defects similar to other known FGFR inhibitors (**A**). The bar-graph indicates the scoring of the posterior phenotypes in 30 fish as normal, mild or severe for the drugs (**B**).



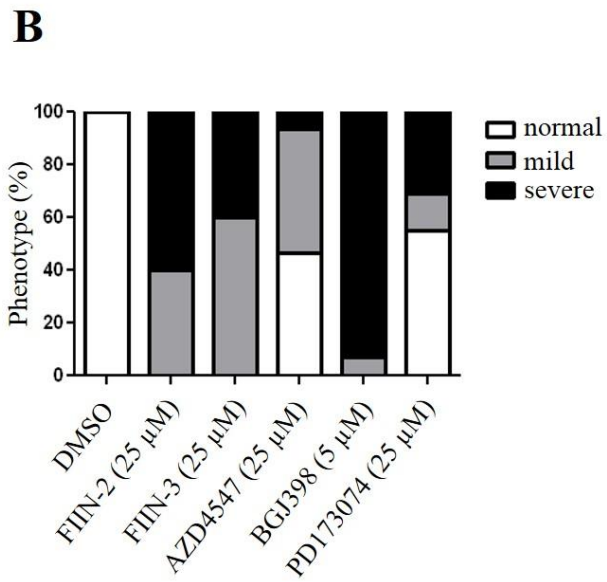


Table S1. Profiling of FGFR inhibitors for binding against a panel of 456 kinases.

Kinases	FIIN-1 (10 uM)		FIIN-2 (1 uM)		FIIN-3 (1 uM)		FRIN-2 (1 uM)	FRIN-3 (1 uM)
	Score (%)	IC50 (nM)	Score (%)	IC50 (nM)	Score	IC50 (nM)	Score (%)	Score (%)
BLK	0.5		0.45		0.1		1.8	2.6
BTK	100		3.4		1.2		99	94
CSF1R	0.2		0.15		0		0.9	1.6
CSF1R-autoinhibited			2.2				0.95	2.8
DDR1	0.1		0.7		0		0.35	0.45
EGFR	100		57	204	0.35	43.1	85	76
EGFR(E746-A750del)	100		48		0.6		74	84
EGFR(G719C)	100		6.5		0.1		95	87
EGFR(G719S)	100		24		0.15		92	90
EGFR(L747-E749del, A750P)	100		41		0.55		73	75
EGFR(L747-S752del, P753S)	100		37		0.45		90	97
EGFR(L747-T751del,Sins)	100		49		0.65		76	98
EGFR(L858R)	100		24		0.2		76	72
EGFR(L861Q)	100		6		0.1		100	100
EGFR(S752-I759del)	100		56		2.3		62	79
FGFR1	0	9.2	0.25	3.09	2.2	13.1	0.4	0.4
FGFR2	2.1	6.2	2.6	4.3	1.9	21	0.35	0.75
FGFR3	1.8	11.9	1.4	27	4.5	31.4	0.5	0.45
FGFR3(G697C)	0.35		0.7		1.4		0.4	0.1
FGFR4	0.1	189	1.4	45.3	0.1	35.3	1.6	0.3
FLT1	0.3		3.2		0.3		1	1.6
FLT4	0.2		0.3		0.1		0.1	2.2
JAK3(JH1domain-catalytic)	6.4		0		0.15		32	26
KIT	1.2		0.25		0.3		0.05	1.9
KIT(A829P)			1.2				5.4	22
KIT(D816V)	100		3.3		7.2		0.8	13
KIT(L576P)	2.7		1.2				0	0
KIT(V559D)	0.55		0.1		0.1		0	0.65
LCK	0.7		0.95		0.2		0.15	0.35
MAP3K3	0.5		3.8		5.8		2.9	0.85
PDGFRB	2.4		0.05		0		0	0.95
RET	25		0.15		0.6		0	11
RET(M918T)	100		0.2		0.4		0	9.6
RET(V804M)	100		3.6		100		0.35	84
YSK4	100		4.8				5.4	100

Table shows the subset of kinases that exhibited a score of 5 or below (score is percent relative to DMSO control, smaller numbers indicate stronger binding). Biochemical kinase IC50s (performed at ATP concentrations equal to the apparent Km) were determined for some kinase targets using enzymatic assays and are reported in nanomolar. Biochemical assays were performed by Life technology according to their published procedures. (4)

Table S2. Antiproliferative activity of FGFR and EGFR inhibitors on transformed Ba/F3 cells.

Ba/F3 cell lines	EC50 (nM)			
	FIIN-2	FIIN-3	BIBW2992	WZ4002
FGFR2	1	<1	>3300	1216
FGFR2 (V564M)	58	64	>3300	726
RET	196	211		
BTK	>1000	>1000		
FLT1	1000	700		
FLT4	240	700		
KIT	>1000	>1000		

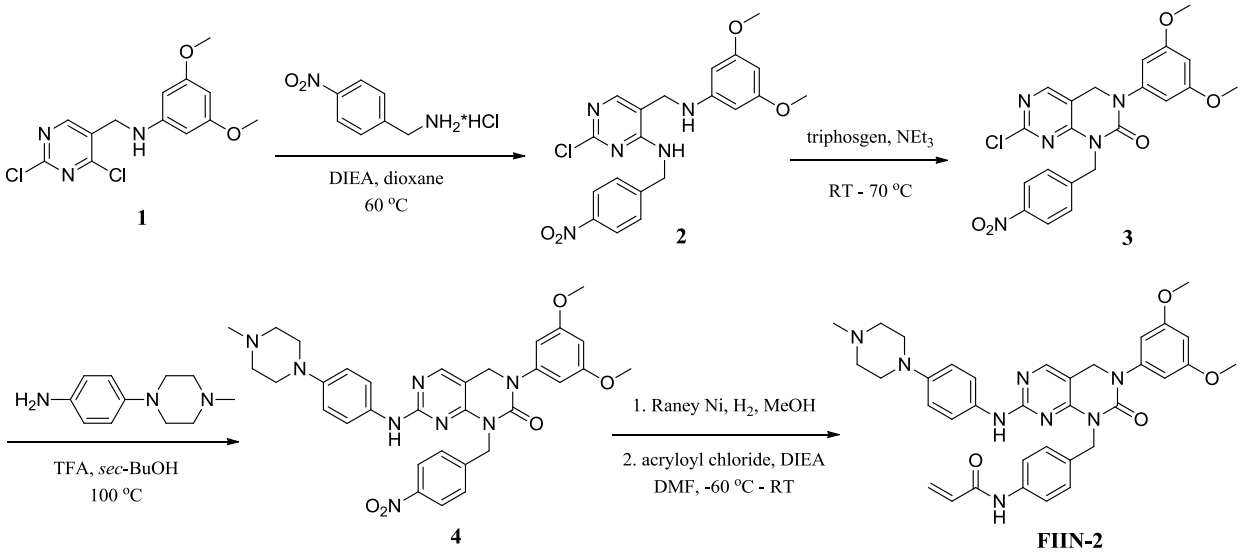
Table S3. Crystallographic Data and Refinement Statistics

Construct	**FGFR4K-FIIN-2**	**FGFR4K^{V550L}-FIIN-3**
Data Collection		
Resolution (Å)	50-2.35 (2.39-2.35)	50-2.35 (2.39-2.35)
Space group	R3	R3
Unit Cell Parameters (Å, °)	a = 139.83	a = 139.38
	b = 139.83	b = 139.38
	c = 49.486	c = 50.09
	α = 90.00	α = 90.00
	β = 90.00	β = 90.00
	γ = 120.00	γ = 120.00
Content of the asymmetric unit	1	1
Measured reflections (#)	172427	43068
Unique Reflections (#)	15298	14984
Data redundancy	11.3 (5.9)	2.9 (2.6)
Data completeness (%)	100 (99.6)	99.6 (98.2)
R_{sym} (%)	10.6 (40.9)	7.8 (34.5)
I/sig	29.7 (4.0)	12.2 (2.0)
Refinement		
R factor/R free	17.4/22.8	17.8/23.7
Number of protein atoms	2138	2110
Number of non-protein/solvent atoms	47	48
Number of solvent atoms	0	10
Rmsd bond length (Å)	0.009	0.008
Rmsd bond angle (°)	1.19	1.16
PDB ID	**4QQC**	**4R6V**

	EGFR^{L858R}/FIIN-3
Data collection	
Space group	I23
Cell dimensions	
a, *b*, *c* (Å)	147.9, 147.9, 147.9
α, β, γ (°)	90.0, 90.0, 90.0
Resolution (Å)	50.0-3.0 (3.23-3.0)
R_{pim}	0.033 (0.317)
I/σ	19.5 (2.4)
Completeness (%)	99.9 (99.7)
Redundancy	6.6 (6.0)
Refinement	
Resolution (Å)	46.8-3.0
No. reflections	10942
$R_{work/}$ R_{free}	0.202/0.239
No. atoms	
Protein	2367
Ligand/ion	48
Water	22
B-factors	
Protein	78.1
Ligand/ion	82.3
Water	78.1
R.m.s deviations	
Bond lengths (Å)	0.013
Bond angles ( )	1.425
Ramachandran Plot	
Favored region	94.54%
Allowed region	5.46%
Disallowed region	0%
PDB ID	**4R5S**

Chemistry. Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. 1H NMR spectra were recorded on 600 MHz (Varian AS600), and chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hz. Spin multiplicities are described as s (singlet), br (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on a Waters Micromass ZQ instrument. Preparative HPLC was performed on a Waters Sunfire C18 column (19 x 50 mm, 5μM) using a gradient of 15-95% methanol in water containing 0.05% trifluoacetic acid (TFA) over 22 min (28 min run time) at a flow rate of 20 mL/min. Purities of assayed compounds were in all cases greater than 95%, as determined by reverse-phase HPLC analysis.

Synthesis of FIIN-2



***N*-((2,4-dichloropyrimidin-5-yl)methyl)-3,5-dimethoxyaniline (1).** Prepared as reported in literature (5).

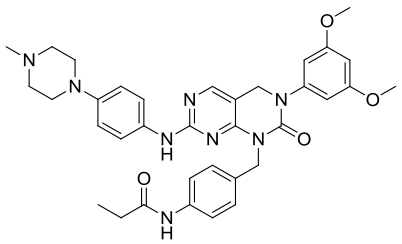
2-chloro-5-(((3,5-dimethoxyphenyl)amino)methyl)-*N*-(4-nitrobenzyl)pyrimidin-4-amine (2). The mixture of **1** (628 mg, 2.0 mmol), 4-nitrobenzylamine hydrochloride (500 mg, 2.6 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (1.05 mL, 6.0 mmol) in 5 mL of dioxane was heated to 60 °C overnight. After removal of solvent, the residue was purified by flash chromatography (hexane : ethyl acetate = 1:1) to afford 662 mg (77%) of title compound as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.0 Hz, 1H), 7.95 (s, 1H), 7.50 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.05 (s, 1H), 5.98 (s, 2H), 4.78 (d, *J* = 6.0Hz, 2H), 4.26 (s, 2H), 3.71 (s, 6H); MS m/z: 430 $(M+H)^+$.

7-chloro-3-(3,5-dimethoxyphenyl)-1-(4-nitrobenzyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (3). To **2** (430 mg, 1.0 mmol) in 5 ml of anhydrous THF was added triphosgene (119 mg, 0.4 mmol). Triethylamine (TEA) (0.42 mL, 3.0 mmol) was then added slowly. After completion of addition, the mixture was stirred for 1 h, and heated to 70 ^{o}C overnight. After the reaction was cooled down, it was diluted with ethyl acetate, washed with saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified through a short pipette column to afford 365 mg (80%) of the title compound as a pale yellow solid. ^{1}H NMR (600 MHz, MeOH) δ 8.11 (d, *J* = 9.0 Hz, 1H), 8.09 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 6.40 (s, 2H), 6.32 (m, 1H), 5.28 (s,2H), 4.74 (s, 2H), 3.72 (s, 6H); MS m/z: 456 $(M+H)^{+}$.

3-(3,5-dimethoxyphenyl)-7-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1-(4-nitrobenzyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (4). The mixture of **3** (223 mg, 0.5 mmol), 4-(4-methylpiperazin-1-yl)aniline (143 mg, 0.75 mmol) and trifluoroacetic acid (TFA) (58 μL, 0.75 mmol) in 5 mL of *sec*-butanol was heated to 100 ^{o}C overnight. After cooling and removal of solvent, the residue was purified by flash chromatography (dichloromethane : methanol = 15:1) to afford 428 mg (70%) of title compound as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.98 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.08 (br, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.47 (s, 2H), 6.39 (m, 1H), 5.30 (s, 2H), 4.68 (s, 2H), 3.78 (s, 6H), 3.30 (m, 4H), 2.83 (m, 4H), 2.52 (s, 3H); MS m/z: 611 $(M+H)^{+}$.

***N*-(4-((3-(3,5-dimethoxyphenyl)-7-((4-(4-methylpiperazin-1-yl)phenyl)amino)-2-oxo-3,4-dihydropyrimido[4,5-*d*]pyrimidin-1(2*H*)-yl)methyl)phenyl)acrylamide (FIIN-2**). To **4** (122 mg, 0.2 mmol) in MeOH (20 mL) was added 1 mL Raney nickel suspension in MeOH, then the reaction mixture was stirred for 3 h under 1 atm of hydrogen. The mixture was then filtered through Celite and the filtrate was concentrated and dried under vacuum to give crude product as a white solid. To the obtained white solid in DMF (2 mL) was added DIEA (53 μL, 0.3 mmol), the stirred mixture was then cooled to -60 ^{o}C and acryloyl chloride (17.8 μL, 0.22 mmol) was added dropwise. The reaction was stirred at -60 ^{o}C for 10 min and allowed to recover to RT gradually over 30 min, then purified by reverse phase HPLC to give 108 mg (TFA salt, 72% for 2 steps) of title compound as a white solid. ^{1}H NMR (600 MHz, DMSO) δ 10.04 (s, 1H), 9.18 (s, 1H), 8.05 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.32 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.37 (s, 1H), 6.41

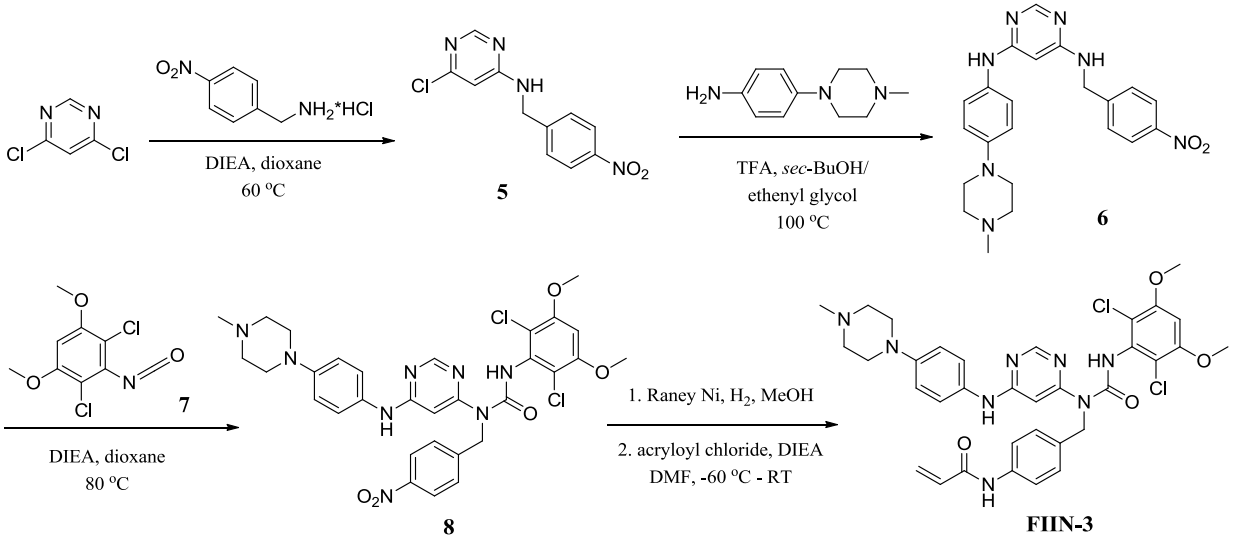
(dd, *J* = 16.8, 9.6 Hz, 1H), 6.23 (d, *J* = 16.8 Hz, 1H), 5.72 (*J* = 11.2 Hz, 1H), 5.15 (s, 2H), 4.74 (s, 1H), 3.75 (s, 6H), 3.09 (m, 4H), 2.61 (m, 4H), 2.34 (s, 3H); MS m/z: 635 $(M+H)^+$.



FRIN-2

***N*-(4-((3-(3,5-dimethoxyphenyl)-7-((4-(4-methylpiperazin-1-yl)phenyl)amino)-2-oxo-3,4-dihydropyrimido[4,5-*d*]pyrimidin-1(2*H*)-yl)methyl)phenyl)propionamide (FRIN-2).** Prepared with same method as **FIIN-2**. ^{1}H NMR (600 MHz, DMSO)) δ 9.73 (s, 1H), 9.16 (s, 1H), 8.04 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.31 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.52 (s, 2H), 6.37 (s, 1H), 5.07 (s, 2H), 4.66 (s, 2H), 3.68 (s, 6H), 2.97 (m, 4H), 2.38 (m, 4H), 2.28 (q, *J* = 7.2 Hz, 2H), 2.22 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 2H); MS m/z: 637 $(M+H)^+$.

Synthesis of FIIN-3



6-chloro-*N*-(4-nitrobenzyl)pyrimidin-4-amine (5). The mixture of 4,6-dichloropyrimidine (447 mg, 3.0 mmol), 4-nitrobenzylamine hydrochloride (755 mg, 4.0 mmol) and DIEA (1.57 mL, 9.0 mmol) in 20 mL of dioxane was heated to 60 °C overnight. After cooling and removal of solvent, the residue was purified by flash chromatography (hexane : ethyl acetate = 1:1) to afford 588 mg (74%) of title compound as a pale yellow solid. ^{1}H NMR (600 MHz, DMSO) δ 8.36 (br, 1H), 8.27

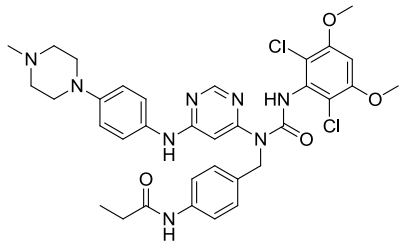
(s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 6.64(s, 1H), 4.69 (br, 2H); MS m/z: 265 $(M+H)^+$.

***N*^{4}-(4-(4-methylpiperazin-1-yl)phenyl)-*N*^{6}-(4-nitrobenzyl)pyrimidine-4,6-diamine (6).** The mixture of **5** (530 mg, 2.0 mmol), 4-(4-methylpiperazin-1-yl)aniline (460 mg, 2.4 mmol) and trifluoroacetic acid (TFA) (184 μL, 2.4 mmol) in 3 mL of *sec*-butanol and 1 mL of ethylene glycol was heated to 120 ^oC overnight. After cooling and removal of solvent, the residue was purified by flash chromatography (dichloromethane : methanol = 10:1) to afford 670 mg (80%) of title compound as a pale brown solid. ^1H NMR (600 MHz, MeOH) δ 8.21 (d, *J* = 9.0 Hz, 2H), 8.00 (s, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 1H), 5.58 (br, 1H), 4.57 (s, 2H), 3.20 (m, 4H), 2.67 (m, 4H), 2.40 (s, 3H); MS m/z: 420 $(M+H)^+$.

3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-(4-nitrobenzyl)urea (8). To 2,6-dichloro-3,5-dimethoxyaniline (330 mg, 1.5 mmol) in 6 ml of anhydrous THF was added triphosgene (178 mg, 0.6 mmol). Triethylamine (TEA) (0.42 mL, 3.0 mmol) was then added slowly. After completion of addition, the mixture was stirred overnight, then was concentrated. The crude product was purified through a very short pipette column to afford 186 mg (50%) of 2,4-dichloro-3-isocyanato-1,5-dimethoxybenzene (**7**) as a white solid.

To the mixture of **6** (420 mg, 1.0 mmol) and **7** (250 mg, 1.0 mmol) in 5 mL of dioxane was added DIEA (350 μL, 2.0 mmol), then the reaction mixture was heated to 80 ^oC for 2 h. After cooling and removal of solvent, the residue was purified by flash chromatography (dichloromethane : methanol = 15:1) to afford 454 mg (68%) of title compound as a pale yellow solid. ^1H NMR (600 MHz, TFA salt, MeOH) δ 8.41 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.20 (m, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.85 (s, 1H), 6.06 (s, 1H), 5.29 (s, 2H), 3.98 (s, 6H), 3.84 (m, 2H), 3.66 (m, 2H), 3.33 (m, 2H), 3.06 (m, 2H), 3.02 (s, 3H); MS m/z: 667 $(M+H)^+$.

***N*-(4-((3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ureido)methyl)phenyl)acrylamide (FIIN-3).** Prepared with same method as **FIIN-2**. ^1H NMR (400 MHz, DMSO)) δ 12.35 (s, 1H), 10.16 (s, 1H), 9.37 (s, 1H), 8.39 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.16 (m, 2H), 6.92 (s, 1H), 6.85 (d, *J* = 9.2 Hz, 2H), 6.44 (dd, *J* = 16.8, 10.0 Hz, 1H), 6.20 (s, 1H), 6.26 (d, *J* = 16.8 Hz, 1H), 5.75 (*J* = 10.0 Hz, 1H), 5.05 (s, 2H), 3.96 (s, 6H), 3.68 (s, 6H), 3.10 (m, 4H), 2.51 (m, 4H), 2.26 (s, 3H); MS m/z: 691 $(M+H)^+$.



FRIN-3

***N*-(4-((3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)ureido)methyl)phenyl)propionamide (FRIN-3).** Prepared with same method as **FIIN-2**. ^{1}H NMR (600 MHz, DMSO)) δ 12.36 (s, 1H), 9.86 (s, 1H), 9.35 (s, 1H), 8.38 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.14 (m, 2H), 6.92 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.19 (s, 1H), 5.03 (s, 2H), 3.95 (s, 6H), 3.09 (m, 4H), 2.47 (m, 4H), 2.31 (q, *J* = 7.8 Hz, 2H), 2.24 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 2H); MS m/z: 693 $(M+H)^{+}$.

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