Supplemental Materials

Novel hybrid molecule overcomes the limited response of solid tumours to HDAC inhibitors via suppressing JAK1-STAT3-BCL2 signalling

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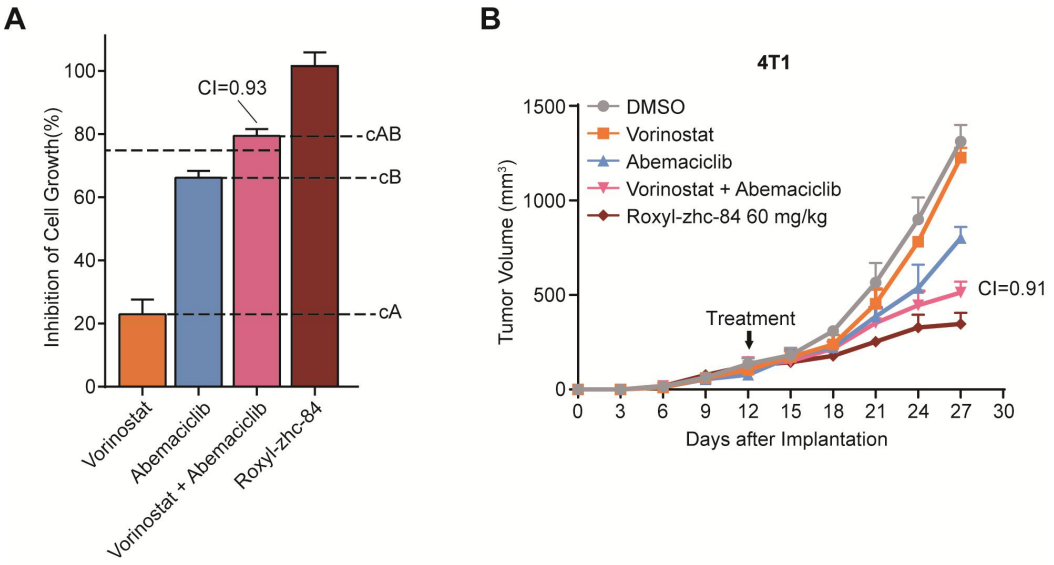
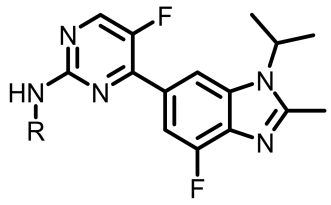
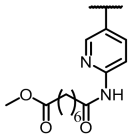
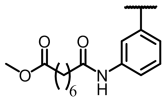
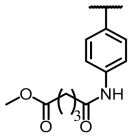
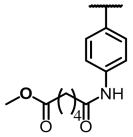
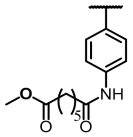
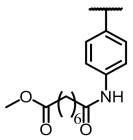
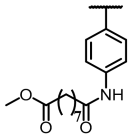
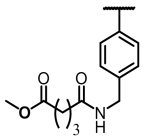
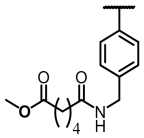
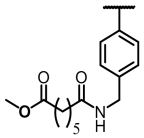
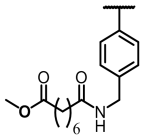
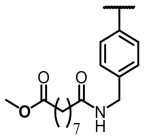
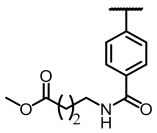
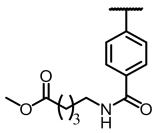
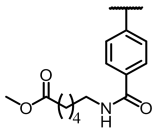
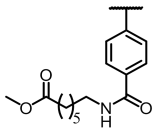
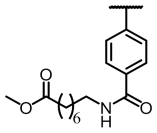


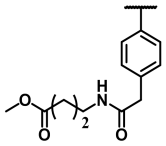
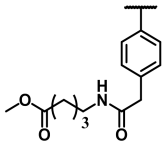
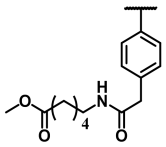
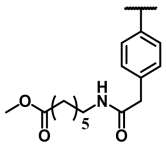
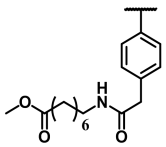
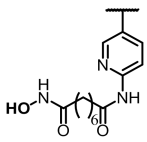
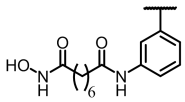
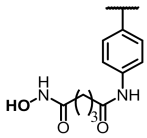
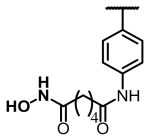
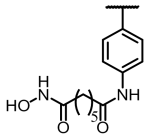
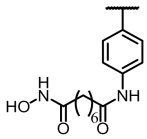
Figure S1. Synergic effect between Vorinostat and Abemaciclib. A. Synergic effects of HDAC inhibitor (Vorinostat, 1 μM) and CDK4/6 inhibitor (Abemaciclib, 2 μM) on growth of MDA-MB-231 breast cancer cell line. The combination index between Vorinostat and Abemaciclib is 0.93, which indicated an ideal synergy. Roxyl-zhc-84 (1μM) was used as a positive control. **B.** Tumor growth curve of model 4T1. Mice were treated with Vorinostat (60 mg/kg) and Abemaciclib (60 mg/kg) alone or in indicated combinations daily for 15 days. Growth curve was plotted by measuring the relative tumor volume every 3 days. Combination index (CI=0.91) was labeled to show the synergistic effect *in vivo*.

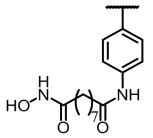
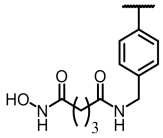
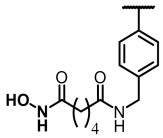
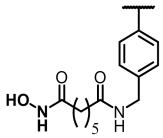
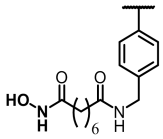
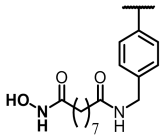
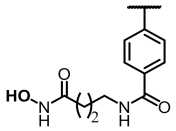
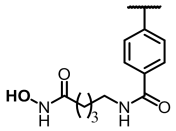
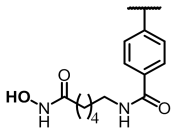
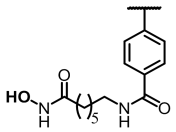
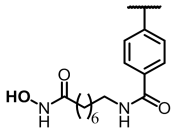
Table S1. IC_{50} values for enzymatic inhibition of HDAC1 and CDK4.

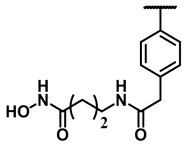
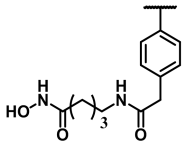
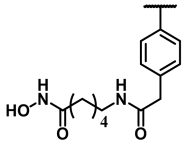
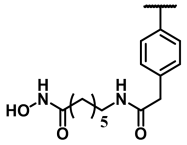
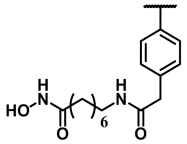
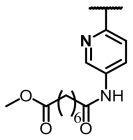
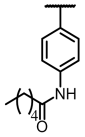
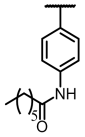
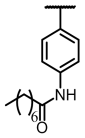
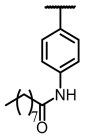
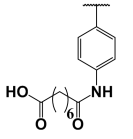


Compound	R	IC_{50} (nM) [a]	
		CDK4	HDAC1
CDK Inhibitor (Abemaciclib)	--	2	--
HDAC Inhibitor (Vorinostat)	--	--	27
Roxyl-zhc-52		2.8	>1000
Roxyl-zhc-53		4.9	>1000
Roxyl-zhc-54		2.1	>1000
Roxyl-zhc-55		1.5	>1000
Roxyl-zhc-56		2.1	>1000
Roxyl-zhc-57		2.2	>1000

Roxyl-zhc-58		4.3	>1000
Roxyl-zhc-59		1.2	>1000
Roxyl-zhc-60		1.0	>1000
Roxyl-zhc-61		1.1	>1000
Roxyl-zhc-62		2.1	>1000
Roxyl-zhc-63		1.1	>1000
Roxyl-zhc-64		12	>1000
Roxyl-zhc-65		9	>1000
Roxyl-zhc-66		1.9	>1000
Roxyl-zhc-67		2.8	>1000
Roxyl-zhc-68		6.2	>1000

Roxyl-zhc-69		1.6	>1000
Roxyl-zhc-70		1.6	>1000
Roxyl-zhc-71		2	>1000
Roxyl-zhc-72		2	>1000
Roxyl-zhc-73		3	>1000
Roxyl-zhc-74		2.1	6.9
Roxyl-zhc-75		2.3	4.5
Roxyl-zhc-76		1.6	91
Roxyl-zhc-77		1.2	228
Roxyl-zhc-78		1.2	17
Roxyl-zhc-79		<1.2	7.4

Roxyl-zhc-80		1.2	30
Roxyl-zhc-81		0.41	6.8
Roxyl-zhc-82		0.87	45
Roxyl-zhc-83		1.1	9.1
Roxyl-zhc-84		1.2	26
Roxyl-zhc-85		1.1	11
Roxyl-zhc-86		11	100
Roxyl-zhc-87		9	79
Roxyl-zhc-88		1.9	2.6
Roxyl-zhc-89		1.6	11
Roxyl-zhc-90		1.6	11

Roxyl-zhc-91		1.2	5.2
Roxyl-zhc-92		2	44
Roxyl-zhc-93		1.1	8.4
Roxyl-zhc-94		1.3	12
Roxyl-zhc-95		1.7	75
Roxyl-zhc-96		2.9	>1000
Roxyl-zhc-97		2.5	>1000
Roxyl-zhc-98		5.9	>1000
Roxyl-zhc-99		14	>1000
Roxyl-zhc-100		22	>1000
Roxyl-zhc-101		2.2	15

[a] IC_{50} values were determined by Shanghai ChemPartner CO., LTD. The data represent the mean values of two independent experiments. For detailed protocols, see http://www.chempartner.com.

Table S2. Inhibitory rate of candidate compounds against six cancer cell lines[a]

	Inhibitory Rate (300 nM)				
	Roxyl-zhc-81	Roxyl-zhc-83	Roxyl-zhc-84	Roxyl-zhc-85	Roxyl-zhc-88
4T1	58.4±5.7%	57.2±10.4%	101.3±3.2%	90.1±1.5%	48.6±1.4%
MDA-MB-468	82.9±10.3%	99.6±0.6%	100.4±1.2%	90.5±1.8%	42.0±5.3%
MDA-MB-231	77.8±4.3%	96.2±1.0%	98.7±1.3%	88.6±1.3%	96.0±1.2%
SK-OV-3	76.5±8.4%	97.3±1.3%	99.2±2.3%	92.3±0.2%	56.5±5.5%
OVCAR-5	87.5±4.4%	93.2±1.2%	98.9±1.8%	85.9±1.7%	104.1±0.5%
H460	98.8±0.2%	89.5±2.9%	99.6±0.8%	78.2±3.7%	99.1±0.5%

[a]The cytotoxic effect of compounds were assayed using CCK-8 assay with 48 hours incubation. Data are mean ± s.d. values from three independent experiments.

Table S3. Inhibitory effects of the compounds on HDAC activities (IC_{50}).

HDACs	IC_{50} (μM)		
	Roxyl-zhc-84	Vorinostat(SAHA)	TrichostatinA(TSA)
HDAC1	0.026	0.027	0.002
HDAC2	0.52	0.072	0.003
HDAC3	0.056	0.039	0.004
HDAC4	>10	1.6	4.2
HDAC5	>10	1.1	4.1
HDAC6	0.0059	0.0082	0.003
HDAC7	>10	0.8	2.2
HDAC8	>10	0.78	0.98
HDAC9	>10	3.1	3.3
HDAC10	0.073	0.029	-
HDAC11	6.8	8.7	9.9

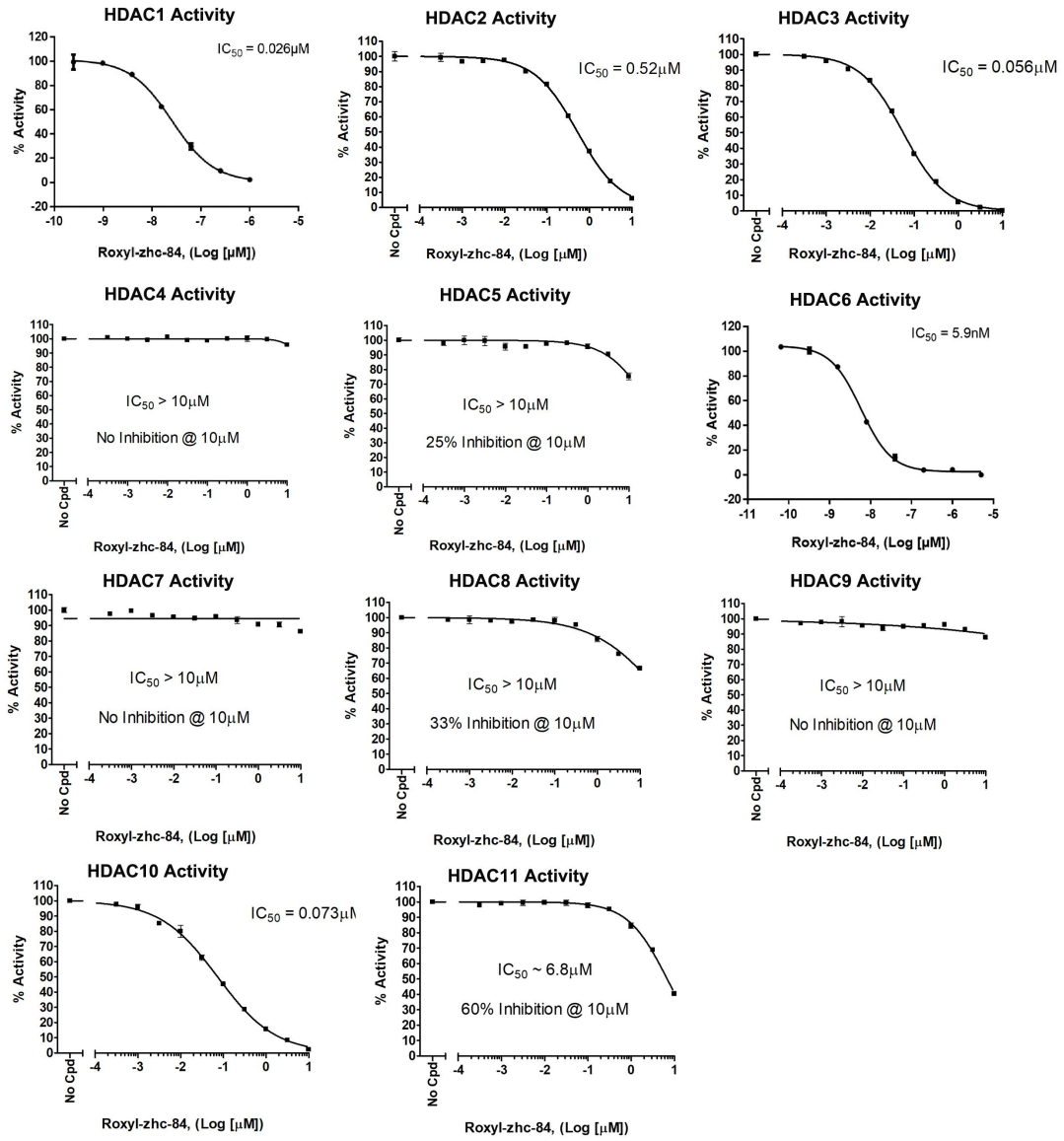


Figure S2. HDAC profiling of compound Roxyl-zhc-84.

Table S4. Kinase inhibition profile of Roxyl-zhc-84 [a]

Kinase	Roxyl-zhc-84 at 1 μM	Kinase	Roxyl-zhc-84 at 1 μM
ALK1(h)	61	IGF-1R(h), activated	74
ALK4(h)	49	IKKα(h)	80
ALK6(h)	21	IKKβ(h)	64
A-Raf(h)	66	PEK(h)	14
ASK1(h)	9	PDGFRα(h)	12
ATR/ATRIP(h)	0	PDGFRβ(h)	54
BRK(h)	49	PKCι(h)	28
BrSK1(h)	77	eEF-2K(h)	4
BrSK2(h)	80	EGFR(h)	21
BTK(h)	75	EphA3(h)	60
BTK(R28H)(h)	14	EphA4(h)	39
CaMKI(h)	43	EphA5(h)	55
CaMKIß(h)	42	EphA8(h)	52
CaMKIγ(h)	72	EphB3(h)	27
ATM(h)	4	EphB4(h)	61
DNA-PK(h)	6	ErbB2(h)	38
CaMKIV(h)	65	ErbB4(h)	36
ChaK1(h)	11	FGFR1(h)	66
CHK1(h)	76	FGFR2(h)	53
CHK2(h)	73	FGFR2(N549H)(h)	73
CHK2(I157T)(h)	60	FGFR3(h)	30
CHK2(R145W)(h)	64	FGFR4(h)	2
CK1γ1(h)	27	Fms(h)	73
CK1γ2(h)	55	GCN2(h)	72
CK1γ3(h)	33	GRK1(h)	0
cKit(D816V)(h)	27	GRK2(h)	0
CSK(h)	33	GRK3(h)	4
DAPK1(h)	50	GRK5(h)	3
DAPK2(h)	46	GRK6(h)	11
DCAMKL2(h)	41	GRK7(h)	19
DMPK(h)	23	cKit(h)	72
Hck(h)	78	IR(h)	67
Hck(h) activated	69	IRE1(h)	57
IGF-1R(h)	85	PKBγ(h)	56
IRAK4(h)	78	PDHK4(h)	0
JAK1(h)	97	PDK1(h)	68
JAK2(h)	100	CDK6/cyclinD3(h)	97
JAK3(h)	97	PKA(h)	13
LKB1(h)	34	PKBα(h)	30

MAPK1(h)	35	PKBβ(h)	31
MAPK2(h)	37	PKCζ(h)	13
MAPK2(m)	40	PKD2(h)	87
MAPKAP-K2(h)	13	PKG1α(h)	81
MAPKAP-K3(h)	14	PKG1β(h)	77
MEK1(h)	54	ZIPK(h)	69
MEK2(h)	57	Plk1(h)	70
MARK1(h)	22	Plk3(h)	56
MKK7β(h)	62	PRAK(h)	17
MLCK(h)	64	TTBK1(h)	8
MOK(h)	57	RIPK2(h)	77
MRCKα(h)	72	ROCK-I(h)	73
MRCKβ(h)	66	ZAK(h)	50
MSK1(h)	84	Rsk1(h)	66
MSK2(h)	82	Rsk1(r)	64
MSSK1(h)	80	Rsk2(h)	58
mTOR(h)	59	Rsk3(h)	78
mTOR/FKBP12(h)	55	Rsk4(h)	68
WNK2(h)	76	SAPK2a(h)	24
MYO3B(h)	82	ZAP-70(h)	52
VRK2(h)	8	SAPK2b(h)	26
NEK2(h)	76	SGK3(h)	26
NEK3(h)	88	SNRK(h)	0
NEK6(h)	30	SRPK1(h)	45
NEK7(h)	24	SRPK2(h)	48
NEK11(h)	72	PI3KC2α(h)	3
NLK(h)	68	PI3KC2γ(h)	61
p70S6K(h)	78	PIP4K2α(h)	0
PAK1(h)	77	PIP5Kα(h)	0
PAK2(h)	68	PIP5K1γ(h)	16
PAK4(h)	75	PI3 Kinase (p120γ)(h)	38
PAK3(h)	47	PI3 Kinase (p110α/p85α)(m)	18
ULK1(h)	34	PI3 Kinase (p110α(E545K)/p85α)(m)	26
ULK2(h)	20	PI3 Kinase (p110β/p85β)(m)	1
Wee1(h)	28	PI3 Kinase (p110δ/p85α)(m)	45
PAK5(h)	14	PI3 Kinase (p110α/p85α)(h)	30
PAK6(h)	41	PI3 Kinase (p110α(E542K)/p85α)(h)	14
PASK(h)	70	PI3 Kinase (p110α(E542K)/p85α)(m)	32
WNK3(h)	48	PI3 Kinase (p110α(H1047R)/p85α)(h)	53
TSSK1(h)	77	PI3 Kinase (p110α(E545K)/p85α)(h)	25
TSSK2(h)	24	PI3 Kinase (p110α/p65α)(h)	37
Snk(h)	51	PI3 Kinase (p110β/p85α)(h)	5
TSSK3(h)	13	PI3 Kinase (p110δ/p85α)(h)	47
TSSK4(h)	30	PI3 Kinase (p110α/p65α)(m)	27

TTBK2(h)	12	PI3 Kinase (p110α(H1047R)/p85α)(m)	21
TGFBR1(h)	44	PI3 Kinase (p110β/p85α)(m)	1

[a] The data represent the results were determined using the KinaseProfiler of Eurofins. For detailed protocols, see http://www.eurofins.com/pharmadiscovery.

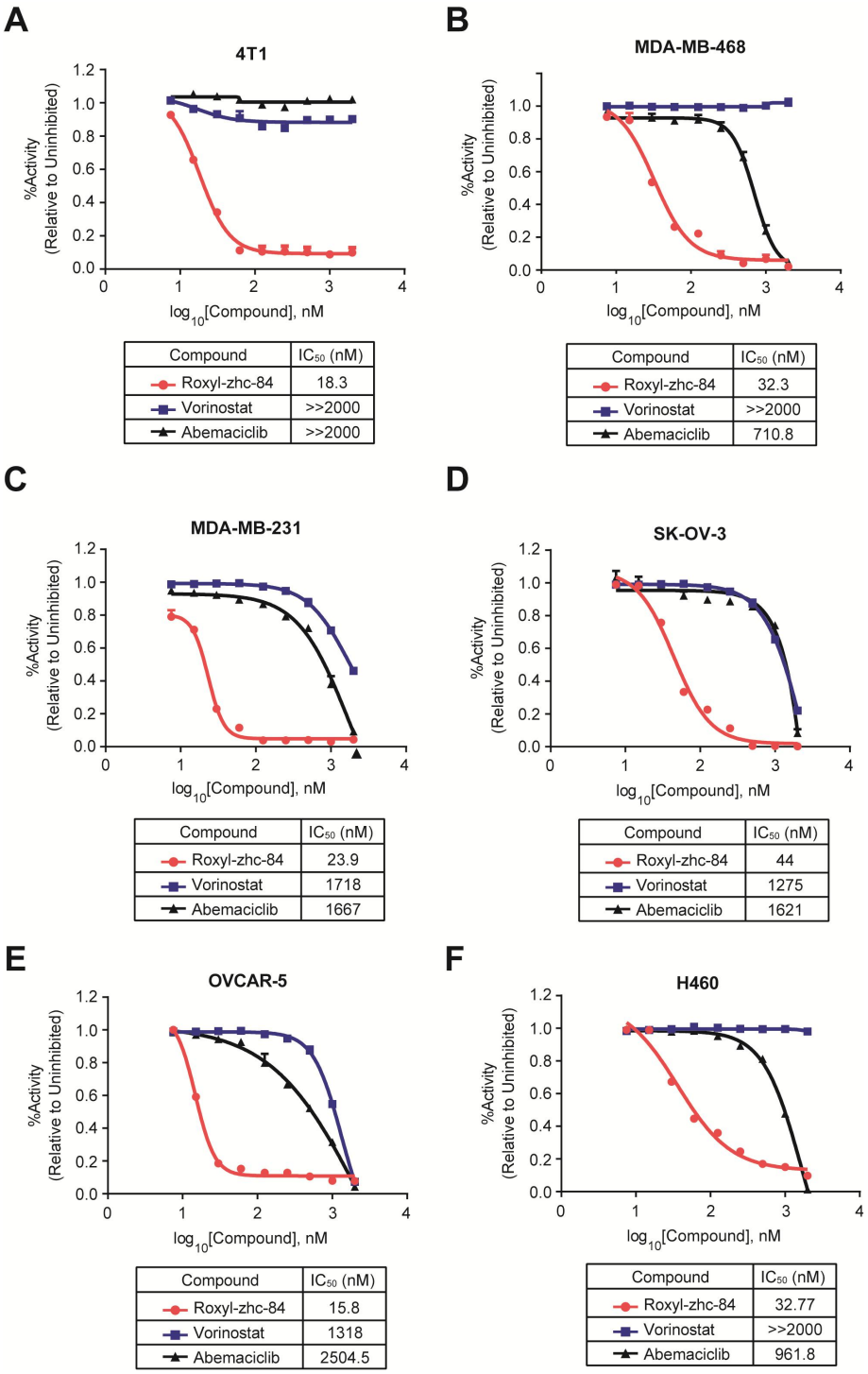


Figure S3. The cytotoxic effect of Roxyl-zhc-84, Vorinostat and Abemaciclib. A-F. Six solid tumor cell lines were assayed using CCK-8 assay (**A**. Breast cancer 4T1, **B**. MDA-MB-468, **C**. MDA-MB-231**,** Ovarian cancer **D**. SK-OV-3, **E**. OVCAR-5 and **F**. Non-small cell lung cancer H460). The IC_{50} values are shown in the bottom forms.

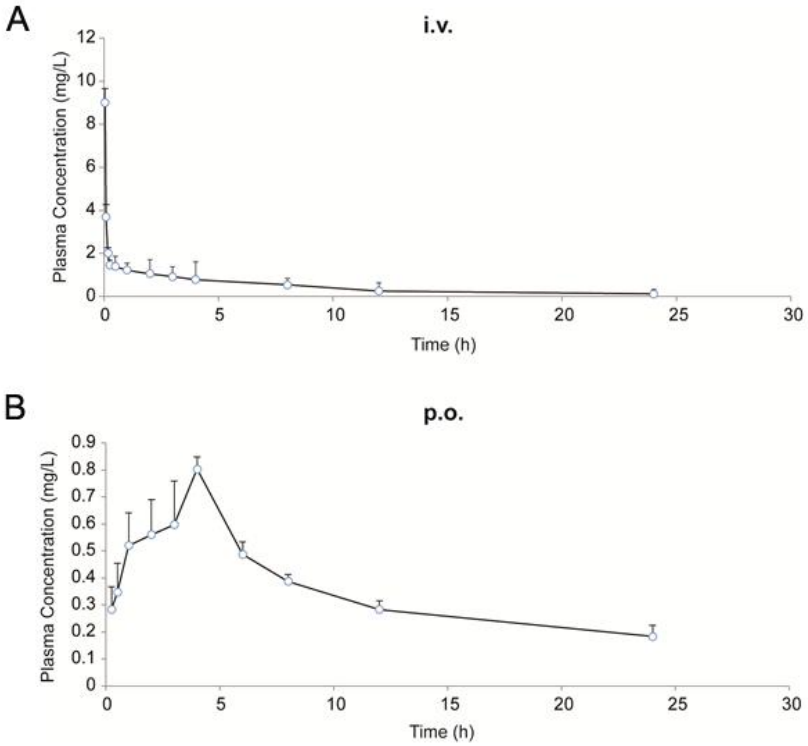


Figure S4. Pharmacokinetic characteristics of compound Roxyl-zhc-84. (A) Plasma concentration−time curve of **Roxyl-zhc-84** in SD rats after a single intravenous dose of 10 mg/kg. Blood was collected at indicated time points (0.05, 0.083, 0.17, 0.25, 0.5, 1, 2, 3, 4, 12, 24 h), and the plasma concentrations were determined by LC-MS. Points, mean; bars, SEM; n = 5. (B) Plasma concentration−time curve of **Roxyl-zhc-84** in SD rats after a single oral dose of 10 mg/kg. Blood was collected at indicated time points (0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h), and the plasma concentrations were determined by LC-MS. Points, mean; bars, SEM; n = 5.

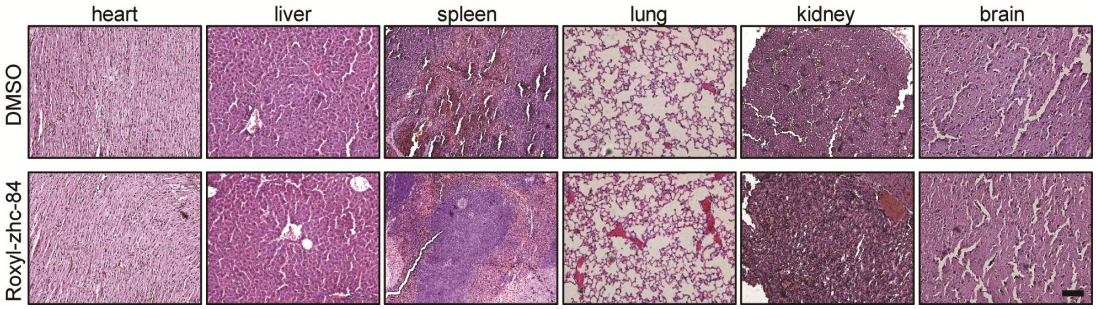


Figure S5. HE staining micrograph of the heart, liver, spleen, lung, kidney and brain sections after Roxyl-zhc-84 (60 mg/kg) or DMSO in the intraoral administration. The scale bar represents 100 μm.

SAR study

To understand the HDAC1 activities, several substituents, such as hydroxamic acids, methyl ester, alkyl and carbonyl group, were designed as a zinc binding group. Among these compounds, the ester group and alkyl group were completely inactive against HDAC1 at the highest concentration tested (1 μM) in Table S1, due to the weak chelating effect to the zinc cation in the HDAC1 active site. Hydroxamic acid is essential for good zinc binding and activity. Thus, the hydroxamic derivatives showed significant inhibition of HDAC1 activity in Table S1. 22 compounds with hydroxamic acid groups were synthesized. Once we identified suitable substituents for chelation position, we then investigated whether connecting unit or the length of the linker was important for potent inhibition of HDAC1. We tried to use the -NH-(C=O)- moiety (compounds Roxyl-zhc-76 to 80), -CH_2-NH-(C=O)- moiety (compounds Roxyl-zhc-81 to 85) , -(C=O)-NH- moiety (compounds Roxyl-zhc-86 to 90) and -CH_2-(C=O)-NH- moiety (compounds Roxyl-zhc-91 to 95) to the *para*-position of phenyl as the connecting unit. When the connecting unit was -CH_2-NH-(C=O)- moiety, this series of compounds Roxyl-zhc-81 to 85 afforded strong HDAC1 inhibition, regardless the length of the linker. Besides, the SAR appears to mirror that in other series of homologues, the length of the linker with four and five carbon atoms were optimal, such as Roxyl-zhc-78 and 79, Roxyl-zhc-88 and 89, Roxyl-zhc-93 and 94. What's more, we introduced the carboxyl group to study the SAR. According to compound Roxyl-zhc-101, we found the carboxyl group was acceptable for the activity of HDAC1. Interestingly, all 22 compounds with hydroxmic acid groups had very good activities on CDK4 enzyme, which indicated that the 2-aminopyrimidine moiety that we selected from CDK inhibitor for the hybrid molecule design was reasonable.

In order to find the most promising lead compound, 15 compounds were chosen to test their cellular cytotoxic activity based on the enzyme inhibitory results. Two Breast cancer cell lines (MDA-MB-468, MDA-MB-231) and one ovarian cancer cell

line (SK-OV-3) inhibition profiling assay with a concentration of 300 nM were first carried out. According to **Figure 1A**, we found that excellent enzymatic inhibition compounds were not all translated to overall cancer cell inhibition, except compounds Roxyl-zhc-81, 83-85 and 88. Other compounds displayed poor in cancer cell inhibition. It was probably due to methylene group of the -CH_2-NH-(C=O)- connecting unit with a comfortable and optimal merged pharmacophore for cell uptake. We further selected candidate compounds in six cancer cell lines based on the inhibitory rate (**Table S2**). Compound Roxyl-zhc-84 displayed almost excellent activity on all kinds of cancer cell lines. As a result, compound Roxyl-zhc-84 deserved a deeper look and further evaluation.

Synthesis of compounds

General Methods.

All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise indicated. Melting points (mp) were taken in open capillaries on a Mettler MP 50 melting-point system. All reactions were monitored by thin-layer chromatography (TLC), and silica gel plates with fluorescence F-254 were used and visualized with UV light. ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F NMR(376 MHz) spectra were taken on a Bruker AV-400 MHz spectrometer and chemical shifts were reported in ppm downfield from internal Me4Si. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-HS mass spectrometer under electron spray ionization (ESI). All of the solvents were purified and distilled according to the standard procedure. The commercially obtained materials were used directly without further purification unless otherwise noted.

The purity of tested compound was assessed to be ≥ 95% by HPLC analysis on a Shimadzu Prominence-i LC-2030C 3D system (column, InertSustain C_{18}, 4.6 mm × 250 mm, 5 μM; mobile phase, gradient elution of methanol/H_2O; low rate, 1.0 mL/min; UV wavelength, 190−800 nm; temperature, 40 °C; injection volume, 10 μL).

Synthesis of the intermediate compounds 24-26.

*methyl 8-((6-((tert-butoxycarbonyl)amino)pyridin-3-yl)amino)-8-oxooctanoate***(22).**

To a two-necked flask, suberic acid monomethyl ester (**14**) (531 mg, 2.82 mmol), tert-butyl (5-aminopyridin-2-yl)carbamate (**1**) (590 mg, 2.82 mmol), EDCI (649 mg, 3.38 mmol), DMAP (35 mg, 0.28 mmol), DIEA (437 mg, 3.38 mmol) and DMF (10

mL) were charged. The mixture was stirred at room temperature for 12 hours, then quenched by water. The mixture was extracted by ethyl acetate, and the combined organic layer was washed with brine solution and dried by anhydrous magnesium sulphate. The solvent was evaporated, and the residue was purified by silica gel column chromatography to obtain 570 mg (53 %) of **22** as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (s, 1H), 8.01 (s, 1H), 7.96-7.86 (m, 2H), 7.55 (s, 1H), 3.66 (s, 3H), 2.46-2.09 (m, 4H), 1.77-1.67 (m, 2H), 1.66-1.57 (m, 2H), 1.51 (s, 9H), 1.41-1.30 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.32, 171.55, 152.45, 148.25, 139.21, 130.63, 130.13, 112.27, 81.09, 51.55, 37.12, 33.91, 28.70, 28.64, 28.29, 25.23, 24.63.

methyl 8-((5-nitropyridin-2-yl)amino)-8-oxooctanoate (**23**). To a suspension of suberic acid monomethyl ester (**14**) (5.65 g, 30 mmol) in 50 mL THF were added $SOCl_2$ (8.41 g, 66 mmol) and heated for 3 h at 60℃. The reaction was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 50 mL THF, 50 mL pyridine and 5-nitropyridin-2-amine (**2**) (4.17 g, 30 mmol). The mixture was heated for 3 h at 60℃. The reaction was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added water 200 mL, and extracted by ethyl acetate. The combine organic was washed by water and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography to obtain 913.2 mg (10%) of **23** as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.16 (d, J = 2.8 Hz, 1H), 8.59 (dd, J = 9.3, 2.9 Hz, 1H), 8.30 (d, J = 9.3 Hz, 1H), 3.57 (s, 3H), 2.45

(t, *J* = 7.4 Hz, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.64-1.47 (m, 4H), 1.28 (p, *J* = 3.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.80, 173.57, 156.63, 145.21, 140.12, 134.67, 112.86, 51.64, 36.57, 33.66, 28.63, 24.94, 24.72.

methyl 8-((6-aminopyridin-3-yl)amino)-8-oxooctanoate (**24**). To a suspension of compound (**22**) (570 mg, 1.5 mmol) in 10 mL THF were was added concentrated HCl 10 mL, and the mixture was stirred for 1 hour. This solvent was basified to pH > 8 with aqueous Na_2CO_3 solution and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography to obtain 275 mg (66%) of **24** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.04 (d, *J* = 2.6 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 5.65 (s, 2H), 3.57 (s, 3H), 2.29 (t, *J* = 7.4 Hz, 2H), 2.22 (t, *J* = 7.4 Hz, 2H), 1.59 -1.47 (m, 4H), 1.32 -1.23 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.80, 171.13, 156.64, 139.98, 130.74, 126.18, 107.84, 51.62, 36.37, 33.70, 28.78, 28.68, 25.47, 24.78.

methyl 8-((5-aminopyridin-2-yl)amino)-8-oxooctanoate (**25**). To a suspension of methyl 8-((5-nitropyridin-2-yl)amino)-8-oxooctanoate (**23**) (913 mg, 2.94 mmol) in 10 mL ethanol and 10 mL ethyl acetate were added Palladium 10% on Carbon (91 mg, wetted with ca. 55% Water) and ammonium formate (927 mg, 14.7 mmol) and the flask was purged with N_2. Then the flask was sealed and the mixture was heated for 12 h at 80℃. The reaction was cooled to room temperature, and added 200 mL ethyl acetate. The organic was washed by water and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column

chromatography to obtain 728.6 mg (88%) of **25** as a brown solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 2.8 Hz, 1H), 7.08-7.02 (m, 1H), 3.63 (s, 3H), 2.36-2.21 (m, 4H), 1.71-1.52 (m, 4H), 1.37-1.23 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.25, 171.29, 143.85, 139.46, 133.91, 124.89, 115.00, 51.51, 37.37, 33.96, 28.82, 28.79, 25.27, 24.72.

methyl 8-((3-aminophenyl)amino)-8-oxooctanoate (**26**). To a two-necked flask, suberic acid monomethyl ester (**14**) (5.65 g, 30 mmol), *m*-Phenylenediamine (**3**) (6.49 g, 60 mmol), EDCI (8.27 g, 45 mmol), HOBt (4.87 g, 36 mmol), DIEA (7.76 g, 60 mmol) and DMF (60 mL) were charged. The mixture was stirred at room temperature for 12 hours, then quenched by water. The mixture was extracted by ethyl acetate, and the combined organic layer was washed with brine solution and dried by anhydrous magnesium sulphate. The solvent was evaporated, and the residue was purified by silica gel column chromatography to obtain 6.48 g (78%) of **26** as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52-7.41 (m, 1H), 7.17 (t, *J* = 2.2 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.40 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.65 (s, 3H), 2.32-2.26 (m, 4H), 1.65 (dt, *J* = 30.0, 7.1 Hz, 4H), 1.40-1.28 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.31, 171.42, 147.22, 139.08, 129.63, 110.90, 109.63, 106.56, 51.53, 37.63, 33.96, 28.78, 28.76, 25.38, 24.71.

Synthesis of the intermediate compounds 27-35.

General produce: To a two-necked flask, acid (**11-21**) (30 mmol), *p*-Phenylenediamine **4** (60 mmol), EDCI (45 mmol), HOBt (36 mmol), DIEA (60 mmol) and DMF (60 mL) were charged. The mixture was stirred at room temperature

for 12 hours, then quenched by water. The mixture was extracted by ethyl acetate, and the combined organic layer was washed with brine solution and dried by anhydrous magnesium sulphate. The solvent was evaporated, and the residue was purified by silica gel column chromatography to obtain intermediate compounds **27-35** as a solid.

*methyl 5-((4-aminophenyl)amino)-5-oxopentanoate***(27).**

Yield: 87%, light-brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.26-7.14 (m, 2H), 6.56-6.42 (m, 2H), 4.82 (s, 2H), 3.59 (s, 3H), 2.35 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 1.82 (p, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.07, 169.51, 144.56, 128.46, 120.89, 113.77, 51.19, 35.03, 32.66, 20.57.

methyl 6-((4-aminophenyl)amino)-6-oxohexanoate(**28**).

Yield: 39%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26-7.20 (m, 2H), 6.59 (dt, J = 8.8, 2.0 Hz, 2H), 3.65 (s, 3H), 2.35-2.23 (m, 4H), 1.74-1.61 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.14, 170.90, 143.28, 129.35, 122.14, 115.34, 51.63, 36.86, 33.71, 25.08, 24.39.

methyl 7-((4-aminophenyl)amino)-7-oxoheptanoate(**29**).

Yield: 77%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26-7.19 (m, 2H), 6.62-6.54 (m, 2H), 3.63 (s, 3H), 3.57 (br, 2H), 2.33-2.21 (m, 4H), 1.74-1.55 (m, 4H), 1.39-1.29 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.28, 171.23, 143.18, 129.42, 122.08, 115.37, 51.56, 37.05, 33.84, 28.65, 25.32, 24.55.

methyl 8-((4-aminophenyl)amino)-8-oxooctanoate(**30**).

Yield: 63%, light-brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.47 (d, J = 8.5 Hz, 2H), 4.82 (s, 2H), 3.57 (s, 3H), 2.29 (t, J = 7.4 Hz,

2H), 2.19 (t, *J* = 7.4 Hz, 2H), 1.53 (h, *J* = 7.4 Hz, 4H), 1.35 – 1.19 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.83, 170.65, 144.99, 129.06, 121.32, 114.24, 51.61, 36.61, 33.69, 28.84, 28.73, 25.62, 24.80.

methyl 9-((4-aminophenyl)amino)-9-oxononanoate(**31**).

Yield: 80%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 7.4 Hz, 2H), 3.63 (s, 3H), 2.31 – 2.19 (m, 4H), 1.68 – 1.50 (m, 4H), 1.34 – 1.24 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.41, 171.45, 143.20, 129.46, 122.02, 115.31, 51.52, 37.37, 34.03, 29.03, 28.97, 28.92, 25.67, 24.85.

N-(4-aminophenyl)hexanamide (**32**).

Yield: 60%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (s, 1H), 7.26 – 7.21 (m, 2H), 6.58 – 6.53 (m, 2H), 3.57 (s, 2H), 2.31 – 2.19 (m, 2H), 1.75 – 1.59 (m, 2H), 1.36 – 1.26 (m, 4H), 0.90 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.74, 143.17, 129.50, 122.16, 115.33, 37.41, 31.48, 25.53, 22.47, 14.00.

N-(4-aminophenyl)heptanamide (**33**).

Yield: 40%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.23 (m, 2H), 7.15 (s, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 3.67 – 3.37 (m, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.69 (p, *J* = 7.5 Hz, 2H), 1.42 – 1.22 (m, 6H), 0.91 – 0.86 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.25, 143.19, 129.39, 122.01, 115.39, 37.63, 31.59, 28.99, 25.75, 22.53, 14.06.

N-(4-aminophenyl)octanamide (**34**).

Yield: 82%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (s, 1H), 7.26 – 7.21 (m, 2H), 6.60 – 6.54 (m, 2H), 3.57 (br, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.66 (t, *J* =

7.3 Hz, 2H), 1.37 – 1.18 (m, 8H), 0.86 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.63, 143.17, 129.47, 122.13, 115.34, 37.51, 31.73, 29.30, 29.11, 25.85, 22.64, 14.12.

N-(4-aminophenyl)nonanamide (**35**)

Yield: 66%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 3.6 Hz, 2H), 7.10 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 3.59 (s, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.71 (p, *J* = 7.4 Hz, 2H), 1.41 – 1.21 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.22, 143.19, 129.38, 122.00, 115.39, 37.65, 31.84, 29.37, 29.32, 29.17, 25.78, 22.66, 14.11.

Synthesis of the intermediate compounds 36-40.

General produce: To a two-necked flask, acid (**11-15**) (25.63 mmol), 4-(Aminomethyl)anilinedihydrochloride **5** (25.63 mmol), EDCI (38.45 mmol), HOBt (30.76 mmol), DIEA (102.54 mmol) and DMF (50 mL) were charged. The mixture was stirred at room temperature for 12 hours, then quenched by water. The mixture was extracted by ethyl acetate, and the combined organic layer was washed with brine solution and dried by anhydrous magnesium sulphate. The solvent was evaporated, and the residue was purified by silica gel column chromatography to obtain intermediate compounds **36-40** as a solid.

methyl 5-((4-aminobenzyl)amino)-5-oxopentanoate (**36**).

Yield: 60%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (t, *J* = 5.9 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 2H), 6.50 (d, *J* = 7.9 Hz, 2H), 4.95 (s, 2H), 4.06 (d, *J* = 5.7 Hz, 2H), 3.58 (d, J = 1.6 Hz, 3H), 2.35 – 2.20 (m, 2H), 2.12 (t, J = 7.3 Hz, 2H), 1.82 – 1.56 (m, 2H).

^{13}C NMR (101 MHz, DMSO) δ 173.05, 171.09, 147.45, 128.20, 126.39, 113.65, 51.20, 41.77, 34.24, 32.66, 20.67.

methyl 6-((4-aminobenzyl)amino)-6-oxohexanoate (**37**).

Yield: 61%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 6.8 Hz, 1H), 6.90 (t, J = 7.9 Hz, 2H), 6.50 (t, J = 7.9 Hz, 2H), 4.94 (d, J = 7.6 Hz, 2H), 4.07 (dd, J = 8.7, 5.4 Hz, 2H), 3.59 (d, J = 8.0 Hz, 3H), 2.35 – 2.24 (m, 2H), 2.10 (d, J = 7.1 Hz, 2H), 1.59 – 1.45 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.22, 171.46, 147.42, 128.17, 126.43, 113.66, 51.14, 41.75, 34.92, 32.99, 24.74, 24.05.

methyl 7-((4-aminobenzyl)amino)-7-oxoheptanoate (**38**).

Yield: 62%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (t, J = 5.2 Hz,1H), 6.89 (d, J = 7.9 Hz, 2H), 6.50 (d, J = 7.8 Hz, 2H), 4.93 (s, 2H), 4.06 (d, J = 5.7 Hz, 2H), 3.58 (s, 3H), 2.28 (t, J = 7.4 Hz, 2H), 2.08 (t, J = 7.4 Hz, 2H), 1.50 (p, J = 7.2 Hz, 4H), 1.24 (p, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.29, 171.64, 147.41, 128.16, 126.48, 113.65, 51.12, 41.74, 35.15, 33.16, 28.10, 24.97, 24.17.

methyl 8-((4-aminobenzyl)amino)-8-oxooctanoate (**39**).

Yield: 67%, brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.04 (dt, J = 8.8, 2.5 Hz, 2H), 6.62 (dt, J = 7.2, 2.6 Hz, 2H), 4.28 (dt, J = 6.2, 3.0 Hz, 2H), 3.64 (d, J = 2.6 Hz, 3H), 2.27 (dd, J = 9.2, 6.2 Hz, 2H), 2.15 (dd, J = 9.4, 6.3 Hz, 2H), 1.69 – 1.52 (m, 4H), 1.30 (p, J = 3.7 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.23, 172.69, 145.88, 129.17, 128.15, 115.19, 51.50, 43.24, 36.66, 33.97, 28.87, 28.79, 25.54, 24.75.

methyl 9-((4-aminobenzyl)amino)-9-oxononanoate (**40**).

Yield: 59%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (t, J = 5.9 Hz, 1H), 6.89 (d,

J = 8.0 Hz, 2H), 6.49 (d, *J* = 8.0 Hz, 2H), 4.93 (s, 2H), 4.06 (d, *J* = 5.8 Hz, 2H), 3.58 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.07 (t, *J* = 7.4 Hz, 2H), 1.50 (q, *J* = 7.0 Hz, 4H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.34, 171.73, 147.40, 128.15, 126.54, 113.65, 51.11, 41.72, 35.30, 33.23, 28.46, 28.37, 28.33, 25.24, 24.36.

Synthesis of the intermediate compounds 41-50.

General produce: To a two-necked flask, amine (**6-10**) (38.45 mmol), acid (**16** or **17**) (38.45 mmol), EDCI (57.7 mmol), HOBt (46.14 mmol), DIEA (115.4 mmol) and DMF (80 mL) were charged. The mixture was stirred at room temperature for 12 hours, then quenched by saturated aqueous $NaHCO_3$ solution. The mixture was extracted by ethyl acetate, and the combined organic layers were dried by magnesium sulphate. The solvent was evaporated, and the residue was purified by silica gel column chromatography to obtain intermediate compounds **41-50** as an(a) oil or solid.

methyl 4-(4-aminobenzamido)butanoate (**41**).

Yield: 70%, gray. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (t, *J* = 5.7 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 8.5 Hz, 2H), 5.59 (s, 2H), 3.57 (s, 3H), 3.22 (q, *J* = 6.5 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.74 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.19, 166.27, 151.43, 128.61, 121.28, 112.50, 51.18, 38.24, 30.83, 24.70.

methyl 5-(4-aminobenzamido)pentanoate (**42**).

Yield: 63%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.56 (m, 2H), 6.69 – 6.61 (m, 2H), 6.21 (s, 1H), 3.66 (s, 3H), 3.41 (q, J = 6.6 Hz, 2H), 2.36 (t, J = 7.1 Hz, 2H), 1.76 – 1.52 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.10, 167.28, 149.44, 128.60, 124.22, 114.17, 51.63, 39.34, 33.53, 29.15, 22.12.

methyl 6-(4-aminobenzamido)hexanoate (**43**).

Yield: 66%, light-brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (t, J = 5.5 Hz, 1H), 7.67 – 7.48 (m, 2H), 6.62 – 6.47 (m, 2H), 5.57 (s, 2H), 3.69 – 3.51 (m, 3H), 3.18 (q, J = 6.6 Hz, 2H), 2.29 (t, J = 7.2 Hz, 2H), 1.50 (dp, J = 23.1, 7.5 Hz, 4H), 1.28 (td, J = 8.6, 4.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.30, 166.08, 151.39, 128.57, 121.40, 112.46, 51.11, 38.71, 33.20, 29.03, 25.94, 24.20.

methyl 7-(4-aminobenzamido)heptanoate (**44**).

Yield: 87%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dd, J = 8.5, 2.4 Hz, 2H), 6.72 – 6.49 (m, 2H), 6.40 – 6.05 (m, 1H), 4.03 (s, 2H), 3.70 – 3.60 (m, 3H), 3.40 – 3.27 (m, 2H), 2.35 – 2.22 (m, 2H), 1.56 (dp, J = 15.5, 7.4 Hz, 4H), 1.41 – 1.24 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.27, 167.38, 149.62, 128.59, 124.09, 114.09, 51.50, 39.79, 33.96, 29.58, 28.78, 26.61, 24.79.

methyl 8-(4-aminobenzamido)octanoate (**45**).

Yield: 73%, light-brown. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.55 (m, 2H), 6.63 (dd, J = 8.7, 2.4 Hz, 2H), 3.64 (s, 3H), 3.37 (td, J = 7.2, 5.8 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.58 (dt, J = 14.2, 7.2 Hz, 4H), 1.37 – 1.27 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.31, 167.26, 149.36, 128.56, 124.36, 114.18, 51.49, 39.87, 34.03, 29.73, 29.01, 28.95, 26.80, 24.83.

methyl 4-(2-(4-aminophenyl)acetamido)butanoate (**46**).

Yield: 68%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (t, J = 5.7 Hz, 1H), 6.96 – 6.81 (m, 2H), 6.51 – 6.41 (m, 2H), 4.89 (s, 2H), 3.58 (s, 3H), 3.17 (s, 2H), 3.03 (q, J = 6.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.63 (p, J = 7.1 Hz, 2H). ^{13}C NMR (101 MHz,

DMSO) δ 173.08, 170.95, 146.97, 129.29, 123.33, 113.76, 51.22, 41.72, 37.81, 30.62, 24.50.

methyl 5-(2-(4-aminophenyl)acetamido)pentanoate (**47**).

Yield: 69%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (t, J = 5.8 Hz, 1H), 6.89 (d, J = 7.9 Hz, 2H), 6.48 (d, J = 8.1 Hz, 2H), 4.88 (s, 2H), 3.58 (s, 3H), 3.18 (s, 2H), 3.02 (q, J = 6.5 Hz, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.50 (p, J = 7.2 Hz, 2H), 1.38 (p, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.23, 170.78, 146.94, 129.28, 123.40, 113.76, 51.14, 41.74, 38.05, 32.87, 28.51, 21.83.

methyl 6-(2-(4-aminophenyl)acetamido)hexanoate (**48**).

Yield: 66%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (t, J = 5.7 Hz, 1H), 6.89 (d, J = 8.3 Hz,2H), 6.48 (d, J = 8.3 Hz, 2H), 4.89 (s, 2H), 3.58 (s, 3H), 3.17 (s, 2H), 3.00 (td, J = 7.0, 5.6 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 1.51 (p, J = 7.5 Hz, 2H), 1.44 – 1.32 (m, 2H), 1.28 – 1.18 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.28, 170.74, 146.94, 129.28, 123.41, 113.74, 51.14, 41.75, 38.31, 33.19, 28.76, 25.81, 24.11.

methyl 7-(2-(4-aminophenyl)acetamido)heptanoate (**49**).

Yield: 76%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (t, J = 5.6 Hz, 1H), 6.97 – 6.78 (m, 2H), 6.57 – 6.38 (m, 2H), 4.89 (s, 2H), 3.58 (s, 3H), 3.17 (s, 2H), 3.00 (td, J = 7.0, 5.6 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 1.50 (t, J = 7.3 Hz, 2H), 1.36 (t, J = 6.8 Hz, 2H), 1.24 (q, J = 4.4 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.33, 170.72, 146.94, 129.28, 123.44, 113.74, 51.14, 41.76, 38.43, 33.17, 28.90, 28.12, 25.99, 24.34.

methyl 8-(2-(4-aminophenyl)acetamido)octanoate (**50**).

Yield: 55%, brown. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (t, J = 5.6 Hz, 1H), 6.89 (d, J = 8.1 Hz, 2H), 6.55 – 6.35 (m, 2H), 4.88 (s, 2H), 3.58 (s, 3H), 3.00 (q, J = 6.6 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 1.50 (t, J = 7.2 Hz, 2H), 1.36 (t, J = 6.8 Hz, 2H), 1.27 – 1.17 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.34, 170.70, 146.94, 129.27, 123.45, 113.73, 51.12, 41.76, 38.46, 33.22, 29.02, 28.38, 28.34, 26.17, 24.34.

6-(2-chloro-5-fluoropyrimidin-4-yl)-4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazole (**51**). Intermediate compound 51 as a light yellow solid was obtained from commercial supplier Jinan heropharma pharmaceutical Co., Ltd. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, J = 3.4 Hz, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.77 (dt, J = 11.5, 0.9 Hz, 1H), 4.74 (p, J = 7.0 Hz, 1H), 2.68 (s, 3H), 1.68 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.19, 155.43 (d, J = 3.3 Hz), 154.56, 154.26, 153.97 (d, J = 8.6 Hz), 152.80 (d, J = 150.4 Hz), 148.43 (d, J = 27.2 Hz), 136.95–134.29 (m), 125.93–124.89 (m), 108.90 (dd, J = 8.7, 3.4 Hz), 108.31 (dd, J = 20.3, 8.1 Hz), 48.71, 21.53, 15.23.

Synthesis of the final compounds Roxyl-zhc-(52-73).

General produce: To a suspension of 6-(2-chloro-5-fluoropyrimidin-4-yl)-4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazole **51** (2 mmol) in 20 mL 1,4-dioxane were added compound **25-50** (2 mmol), $Pd(OAc)_2$ (0.05 mmol), BINAP (0.1 mmol) and Cs_2CO_3 (4.2 mmol) and the flask was purged with N_2. Then the flask was sealed and the mixture was heated for 12 h at 100℃. The reaction was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography

to obtain final compounds **Roxyl-zhc-(52-72)** as a solid.

methyl

8-((5-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidi

n-2-yl)amino)pyridin-2-yl)amino)-8-oxooctanoate **(Roxyl-zhc-52).**

Yield: 73%, light yellow, mp 66.3 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.84 (s, 1H), 8.69 – 8.49 (m, 2H), 8.24 – 8.12 (m, 2H), 8.08 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 12.1 Hz, 1H), 4.84 (p, J = 6.8 Hz, 1H), 3.57 (s, 3H), 2.64 (s, 3H), 2.32 (dt, J = 26.1, 7.4 Hz, 4H), 1.72 – 1.44 (m, 10H), 1.28 (t, J = 3.7 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.34, 171.57, 156.24, 154.53, 153.52, 151.23 (d, J = 35.5 Hz), 150.03, 148.89, 147.87 (d, J = 25.8 Hz), 146.54, 138.66, 136.30 (d, J = 9.9 Hz), 133.16 (d, J = 16.7 Hz), 130.71 (d, J = 465.1 Hz), 126.59 (t, J = 6.6 Hz), 113.02, 108.85 (d, J = 7.1 Hz), 106.87 (dd, J = 20.1, 7.4 Hz), 51.14, 48.08, 35.87, 33.19, 28.24, 28.18, 24.83, 24.27, 20.90, 14.53. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.58(s, 1F), -150.19 (s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2689 $[M + H]^+$. HPLC purity 96%.

methyl

8-((3-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidi

n-2-yl)amino)phenyl)amino)-8-oxooctanoate **(Roxyl-zhc-53).**

Yield: 70%, light yellow, mp 139.4 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.77 (s, 1H), 8.62 (d, J = 3.8 Hz, 1H), 8.21 (d, J = 1.2 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 12.0 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.35 (dt, J = 14.1, 5.9 Hz, 1H), 7.22 (d, J = 1.7 Hz, 1H), 4.82 (p, J = 6.9 Hz, 1H), 3.57 (s, 3H), 2.63 (s, 3H), 2.29

(td, *J* = 7.4, 3.4 Hz, 4H), 1.64 – 1.46 (m, 10H), 1.31 – 1.24 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.81, 171.58, 156.87, 154.90, 154.06, 151.68 (d, *J* = 19.8 Hz), 150.56 (d, *J* = 8.0 Hz), 149.27, 148.07 (d, *J* = 26.1 Hz), 140.63 (d, *J* = 117.1 Hz), 136.79 (d, *J* = 10.0 Hz), 133.63 (d, *J* = 16.9 Hz), 128.93, 127.21 (t, *J* = 6.5 Hz), 114.30, 113.40, 110.58, 109.33, 107.57 (dd, *J* = 19.8, 7.3 Hz), 51.63, 48.54, 36.79, 33.69, 28.83, 28.72, 25.45, 24.80, 21.40, 15.06. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.63(s, 1F), -150.33(s, 1F). ESI-HRMS m/z calcd for $C_{30}H_{35}F_2N_6O_3^+$ 565.2733, found 565.2739 $[M + H]^+$. HPLC purity 99%.

methyl

5-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)amino)-5-oxopentanoate **(Roxyl-zhc-54).**

Yield: 75%, light yellow, mp 204.4 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.70 (s, 1H), 8.61 (d, *J* = 3.9 Hz, 1H), 8.28 (d, *J* = 1.3 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 2H), 7.66 (dd, *J* = 11.9, 1.2 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 4.86 (p, *J* = 6.9 Hz, 1H), 3.62 (s, 3H), 2.65 (s, 3H), 2.37 (dt, *J* = 14.3, 7.4 Hz, 4H), 1.86 (p, *J* = 7.4 Hz, 2H), 1.64 (d, *J* = 6.9 Hz, 6H).^{13}C NMR (101 MHz, DMSO) δ 173.54, 170.57, 156.85 (d, *J* = 2.9 Hz), 154.96, 153.98, 151.57 (d, *J* = 12.8 Hz), 150.35 – 149.94 (m), 149.13, 148.30 (d, *J* = 26.8 Hz), 136.79 (d, *J* = 10.4 Hz), 136.30, 134.01, 133.63 (d, *J* = 17.3 Hz), 127.29 (t, *J* = 6.5 Hz), 119.73 (d, *J* = 24.2 Hz), 109.17 (dd, *J* = 6.5, 3.2 Hz), 107.46 (dd, *J* = 20.2, 9.0 Hz), 51.73, 48.58, 35.65, 33.15, 21.40, 20.93, 15.01.^{19}F NMR (376 MHz, DMSO-d_6) δ -128.65(s, 1F), -150.81(s, 1F). ESI-HRMS m/z calcd for $C_{27}H_{29}F_2N_6O_3^+$ 523.2264, found 523.2260 $[M + H]^+$. HPLC purity 98%.

methyl

6-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidi

n-2-yl)amino)phenyl)amino)-6-oxohexanoate **(Roxyl-zhc-55)**.

Yield: 69%, light yellow, mp 224.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.68 (s, 1H), 8.59 (d, *J* = 4.0 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.64 (dd, *J* = 12.0, 1.2 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 3.59 (s, 3H), 2.63 (s, 3H), 2.32 (dt, *J* = 16.8, 7.0 Hz, 4H), 1.66 – 1.53 (m, 10H). ^{13}C NMR (101 MHz, DMSO) δ 173.72, 170.97, 156.84, 154.94, 153.97, 151.57 (d, *J* = 12.6 Hz), 150.14, 149.13, 148.30 (d, *J* = 26.5 Hz), 136.78 (d, *J* = 9.8 Hz), 136.28, 134.07, 133.63 (d, *J* = 17.2 Hz), 127.29 (t, *J* = 6.5 Hz), 119.72 (d, *J* = 20.6 Hz), 109.20, 107.45 (dd, *J* = 19.9, 8.8 Hz), 51.67, 48.58, 36.43, 33.52, 25.11, 24.57, 21.40, 15.00. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.68(s, 1 F), -150.82(s, 1 F). ESI-HRMS m/z calcd for $C_{28}H_{31}F_2N_6O_3^+$ 537.2420, found 537.2423 $[M + H]^+$. HPLC purity 99%.

methyl

7-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidi

n-2-yl)amino)phenyl)amino)-7-oxoheptanoate **(Roxyl-zhc-56)**.

Yield: 65%, light yellow, mp 210.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.68 (s, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.71 (d, *J* = 9.1 Hz, 2H), 7.65 (dd, *J* = 12.0, 1.2 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 4.85 (p, *J* = 6.8 Hz, 1H), 3.58 (s, 3H), 2.64 (s, 3H), 2.31 (t, *J* = 7.6 Hz, 4H), 1.60 (dd, *J* = 24.2, 7.4 Hz, 10H), 1.32 (dd, *J* = 7.0, 3.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.28, 170.63, 156.36, 154.42, 153.48, 151.07 (d, J = 11.3 Hz), 149.64, 148.62, 147.78 (d, *J* = 26.5

Hz), 136.28 (d, *J* = 9.8 Hz), 135.75, 133.61, 133.13 (d, *J* = 16.6 Hz), 126.80 (t, *J* = 6.7 Hz), 119.21 (d, *J* = 20.8 Hz), 108.69 (d, *J* = 4.2 Hz), 106.95 (dd, *J* = 20.1, 8.9 Hz), 51.11, 48.08, 36.14, 33.14, 28.12, 24.83, 24.19, 20.89, 14.49. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.68 (s, 1F), -150.83 (s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{29}H_{33}F_2N_6O_3^+$ 551.2577, found 551.2576 $[M + H]^+$. HPLC purity 99%.

methyl 8-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)amino)-8-oxooctanoate **(Roxyl-zhc-57).**

Yield: 70%, light yellow, mp 190.8 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.69 (s, 1H), 8.58 (d, *J* = 3.9 Hz, 1H), 8.26 (d, *J* = 1.3 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.67 – 7.60 (m, 1H), 7.56 (d, *J* = 8.9 Hz, 2H), 4.90 – 4.75 (m, 1H), 3.57 (s, 3H), 2.63 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 4H), 1.78 – 1.44 (m, 10H), 1.29 (t, *J* = 3.8 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.80, 171.21, 156.83 (d, *J* = 2.6 Hz), 154.93, 153.97, 151.56 (d, *J* = 11.7 Hz), 150.11, 149.11, 148.29 (d, *J* = 26.4 Hz), 136.77 (d, *J* = 9.9 Hz), 136.24, 134.12, 133.62 (d, *J* = 17.0 Hz), 127.29 (t, *J* = 6.6 Hz), 119.69 (d, *J* = 20.6 Hz), 109.16, 107.45 (dd, *J* = 19.9, 8.8 Hz), 51.61, 48.58, 36.75, 33.68, 28.83, 28.72, 25.50, 24.80, 21.38, 14.98. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.69 (s, 1F), -150.84 (s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{30}H_{35}F_2N_6O_3^+$ 565.2733, found 565.2733 $[M + H]^+$. HPLC purity 97%.

methyl 9-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)amino)-9-oxononanoate **(Roxyl-zhc-58)**.

Yield: 63%, light yellow, mp 170.7 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.69 (s, 1H), 8.58 (d, J = 3.9 Hz, 1H), 8.31 – 8.20 (m, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.66 – 7.61 (m, 1H), 7.56 (d, J = 9.0 Hz, 2H), 4.84 (p, J = 7.0 Hz, 1H), 3.56 (s, 3H), 2.63 (s, 3H), 2.27 (td, J = 7.4, 2.9 Hz, 4H), 1.66 – 1.46 (m, 10H), 1.26 (d, J = 9.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.81, 171.24, 156.83, 154.93, 153.97, 151.56 (d, J = 11.3 Hz), 150.11, 149.11, 148.29 (d, J = 26.8 Hz), 136.77 (d, J = 9.7 Hz), 136.24, 134.12, 133.63 (d, J = 17.2 Hz), 127.29 (t, J = 6.6 Hz), 119.69 (d, J = 20.7 Hz), 109.48 – 108.59 (m), 107.45 (dd, J = 20.0, 8.8 Hz), 51.60, 48.58, 36.80, 33.70, 29.01, 28.94, 28.84, 25.61, 24.87, 21.38, 14.98. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.68 (s, 1F), -150.83(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{31}H_{37}F_2N_6O_3^+$ 579.2890, found 579.2893 $[M + H]^+$. HPLC purity 99%.

methyl 5-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)amino)-5-oxopentanoate **(Roxyl-zhc-59)**.

Yield: 65%, light yellow, mp 210.3 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.62 (dd, J = 4.0, 2.3 Hz, 1H), 8.37 – 8.18 (m, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 12.1 Hz, 1H), 7.19 (d, J = 8.3 Hz, 2H), 4.85 (p, J = 6.9 Hz, 1H), 4.22 (d, J = 5.8 Hz, 2H), 3.58 (s, 3H), 2.64 (s, 3H), 2.33 (t, J = 7.4 Hz, 2H), 2.18 (t, J = 7.4 Hz, 2H), 1.80 (q, J = 7.4 Hz, 2H), 1.63 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.52, 171.80, 156.80, 154.98, 153.99, 151.62 (d, J = 19.7 Hz), 150.32 (d, J = 7.6 Hz), 149.21, 148.28 (d, J = 26.6 Hz), 139.73, 136.80 (d, J = 9.8 Hz), 133.63 (d, J = 17.3 Hz), 133.19, 127.97, 127.26 (t, J = 6.6 Hz), 119.07, 109.23 (d, J = 6.9 Hz),

107.45 (dd, *J* = 19.8, 8.6 Hz), 51.69, 48.59, 42.13, 34.76, 33.17, 21.40, 21.16, 15.01. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.64(s, 1F), -150.49(s, 1F) . ESI-HRMS m/z calcd for Chemical Formula: $C_{28}H_{31}F_2N_6O_3^+$ 537.2420, found 537.2424 $[M + H]^+$. HPLC purity 99%.

methyl 6-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)amino)-6-oxohexanoate **(Roxyl-zhc-60)**.

Yield: 64%, light yellow, mp 134.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 8.61 (d, *J* = 3.9 Hz, 1H), 8.36 – 8.15 (m, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.69 – 7.60 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 4.22 (d, *J* = 5.8 Hz, 2H), 3.57 (s, 3H), 2.64 (s, 3H), 2.31 (t, *J* = 5.5 Hz, 2H), 2.13 (d, *J* = 6.6 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 6H), 1.52 (d, *J* = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.72, 172.19, 156.79, 154.97, 153.98, 151.61 (d, *J* = 19.3 Hz), 150.28 (d, *J* = 8.2 Hz), 149.20, 148.27 (d, *J* = 26.2 Hz), 139.72, 138.43, 136.78 (d, *J* = 9.7 Hz), 133.63 (d, *J* = 16.9 Hz), 133.20, 127.96, 127.24 (t, *J* = 6.5 Hz), 119.04, 109.21 (d, *J* = 5.4 Hz), 107.45 (dd, *J* = 20.0, 8.3 Hz), 51.64, 48.58, 42.12, 35.45, 33.48, 25.25, 24.57, 21.39, 15.00. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.74 – -135.01 (m, 1F), -150.45(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{29}H_{33}F_2N_6O_3^+$ 551.2577, found 551.2578 $[M + H]^+$. HPLC purity 99%.

methyl 7-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)amino)-7-oxoheptanoate **(Roxyl-zhc-61)**.

Yield: 69%, light yellow, mp 161 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.61 (d, J = 3.9 Hz, 1H), 8.38 – 7.98 (m, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.65 (dd, J = 12.0, 1.2 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 4.23 (d, J = 5.8 Hz, 2H), 3.56 (s, 3H), 2.64 (s, 3H), 2.28 (t, J = 7.4 Hz, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.62 (d, J = 6.8 Hz, 6H), 1.52 (ddq, J = 11.3, 7.5, 3.8 Hz, 4H), 1.26 (qd, J = 7.1, 5.9, 4.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.76, 172.35, 156.78, 154.96, 153.99, 151.61 (d, J = 18.6 Hz), 150.38 – 150.21 (m), 149.20, 148.25 (d, J = 26.2 Hz), 139.71, 136.78 (d, J = 9.8 Hz), 133.64 (d, J = 17.1 Hz), 133.26, 127.95, 127.25 (t, J = 6.5 Hz), 119.05, 110.42 – 108.61 (m), 107.44 (dd, J = 19.9, 8.6 Hz), 51.60, 48.58, 42.12, 35.68, 33.63, 28.62, 25.48, 24.66, 21.39, 15.00. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.66(s, 1F), -150.46(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{30}H_{35}F_2N_6O_3^+$ 565.2733, found 565.2730 $[M + H]^+$. HPLC purity 100%.

methyl 8-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)amino)-8-oxooctanoate **(Roxyl-zhc-62)**.

Yield: 67%, light yellow, mp 161.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.61 (d, J = 3.9 Hz, 1H), 8.34 – 8.20 (m, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.66 (dd, J = 11.9, 1.2 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 4.85 (p, J = 6.9 Hz, 1H), 4.23 (d, J = 5.8 Hz, 2H), 3.56 (s, 3H), 2.64 (s, 3H), 2.26 (t, J = 7.4 Hz, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.63 (d, J = 6.8 Hz, 6H), 1.55 – 1.46 (m, 4H), 1.25 (t, J = 3.8 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.77, 172.43, 156.79 (d, J = 3.1 Hz), 154.96, 153.99, 151.61 (d, J = 18.5 Hz), 150.31 – 150.20 (m), 149.20, 148.25 (d, J = 26.5 Hz), 139.71, 136.78

(d, *J* = 9.9 Hz), 133.64 (d, *J* = 16.6 Hz), 133.29, 127.95, 127.25 (t, *J* = 6.6 Hz), 119.05, 109.19 (t, *J* = 4.4 Hz), 107.44 (dd, *J* = 20.1, 8.4 Hz), 51.59, 48.58, 42.11, 35.79, 33.67, 28.81, 28.67, 25.64, 24.79, 21.39, 15.00. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -128.24(s, 1F), -150.03(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{31}H_{37}F_2N_6O_3^+$ 579.2890, found 579.2888 $[M + H]^+$. HPLC purity 99%.

methyl 9-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)amino)-9-oxononanoate **(Roxyl-zhc-63)**.

Yield: 66%, light yellow, mp 163.8 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.75 (s, 1H), 8.60 (d, *J* = 4.0 Hz, 1H), 8.25 (s, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 12.1 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 4.22 (d, *J* = 5.8 Hz, 2H), 3.55 (s, 3H), 2.63 (s, 3H), 2.24 (t, *J* = 7.4 Hz, 2H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 6H), 1.49 (dt, *J* = 14.5, 7.2 Hz, 4H), 1.23 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.28, 171.95, 156.30, 154.45, 153.50, 151.11 (d, *J* = 18.0 Hz), 149.77 (d, *J* = 5.8 Hz), 148.70, 147.75 (d, *J* = 26.6 Hz), 139.21, 136.29 (d, *J* = 9.6 Hz), 133.15 (d, *J* = 17.3 Hz), 132.80, 127.45, 126.75 (t, *J* = 6.7 Hz), 118.53, 108.82 – 108.37 (m), 106.93 (dd, *J* = 19.9, 8.6 Hz), 51.07, 48.08, 41.60, 35.32, 33.18, 28.48, 28.39, 28.34, 25.25, 24.34, 20.89, 14.50. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -128.24(s, 1F) , -150.04(s, 1F) . ESI-HRMS m/z calcd for Chemical Formula: $C_{32}H_{39}F_2N_6O_3^+$ 593.3046, found 593.3040 $[M + H]^+$. HPLC purity 99%.

methyl

4-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzamido)butanoate **(Roxyl-zhc-64)**.

Yield: 72%, light yellow, mp 184.6 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.66 (d, J = 3.8 Hz, 1H), 8.35 (t, J = 5.6 Hz, 1H), 8.22 (d, J = 1.3 Hz, 1H), 7.88 (d, J = 8.9 Hz, 2H), 7.82 (d, J = 8.9 Hz, 2H), 7.66 (dd, J = 11.9, 1.2 Hz, 1H), 4.84 (p, J = 6.9 Hz, 1H), 3.59 (s, 3H), 3.28 (q, J = 6.6 Hz, 2H), 2.63 (s, 3H), 2.38 (t, J = 7.4 Hz, 2H), 1.80 (p, J = 7.2 Hz, 2H), 1.62 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.65, 166.32, 156.42 (d, J = 3.2 Hz), 154.99, 154.04, 151.78 (d, J = 42.4 Hz), 150.63 (d, J = 9.3 Hz), 149.47, 148.18 (d, J = 26.5 Hz), 143.66, 136.81 (d, J = 9.8 Hz), 133.69 (d, J = 17.2 Hz), 128.35, 127.56, 127.06 (t, J = 6.5 Hz), 117.78, 109.35 (dd, J = 7.7, 3.1 Hz), 107.40 (dd, J = 20.1, 7.2 Hz), 51.70, 48.57, 38.91, 31.31, 25.09, 21.40, 15.02. ^{19}F NMR (376 MHz, DMSO-d_6) δ -125.35 – -136.14 (m, 1 F), -146.28 – -153.85 (m, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{27}H_{29}F_2N_6O_3^+$ 523.2264, found 523.2263 $[M + H]^+$. HPLC purity 100%.

methyl

5-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzamido)pentanoate **(Roxyl-zhc-65)**.

Yield: 67%, light yellow, mp 202.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.66 (d, J = 3.7 Hz, 1H), 8.32 (t, J = 5.7 Hz, 1H), 8.23 (s, 1H), 7.88 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 12.0 Hz, 1H), 4.84 (p, J = 6.9 Hz, 1H), 3.58 (s, 3H), 3.26 (q, J = 6.2 Hz, 2H), 2.63 (s, 3H), 2.34 (t, J = 6.9 Hz, 2H), 1.58 (dd,

J = 27.3, 6.8 Hz, 10H). ^{13}C NMR (101 MHz, DMSO) δ 173.27, 165.68, 155.93 (d, *J* = 2.8 Hz), 154.50, 153.54, 151.28 (d, *J* = 41.7 Hz), 150.13 (d, *J* = 8.6 Hz), 148.97, 147.70 (d, *J* = 26.6 Hz), 143.11, 136.31 (d, *J* = 9.8 Hz), 133.19 (d, *J* = 16.6 Hz), 127.82, 127.19, 126.57 (t, *J* = 6.2 Hz), 117.30, 109.19 – 108.55 (m), 106.90 (dd, *J* = 19.8, 7.5 Hz), 51.14, 48.08, 38.60, 32.92, 28.66, 21.95, 20.91, 14.52. ^{19}F NMR (376 MHz, DMSO-d_6) δ -127.48 – -130.25 (m, 1F), -149.24(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{28}H_{31}F_2N_6O_3^+$ 537.2420, found 537.2424 $[M + H]^+$. HPLC purity 100%.

methyl

6-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzamido)hexanoate **(Roxyl-zhc-66)**.

Yield: 68%, light yellow, mp 182.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.66 (d, *J* = 3.7 Hz, 1H), 8.30 (t, *J* = 5.8 Hz, 1H), 8.22 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 12.0 Hz, 1H), 4.84 (p, *J* = 6.9 Hz, 1H), 3.57 (s, 3H), 3.24 (d, *J* = 6.5 Hz, 2H), 2.63 (s, 3H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.68 – 1.43 (m, 10H), 1.31 (q, *J* = 8.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.28, 165.64, 155.94 (d, *J* = 2.4 Hz), 154.50, 153.55, 151.28 (d, *J* = 41.5 Hz), 150.14 (d, *J* = 8.4 Hz), 148.97, 147.69 (d, *J* = 26.4 Hz), 143.09, 136.31 (d, *J* = 9.8 Hz), 133.20 (d, *J* = 16.9 Hz), 127.81, 127.24, 126.57 (t, *J* = 6.5 Hz), 117.29, 109.40 – 108.20 (m), 106.90 (dd, *J* = 20.1, 7.4 Hz), 51.11, 48.07, 33.20, 28.90, 25.94, 24.18, 20.91, 14.52. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.55(s, 1F), -149.26(s, 1F). ESI-HRMS m/z

calcd for Chemical Formula: $C_{29}H_{33}F_2N_6O_3^+$ 551.2577, found 551.2571 $[M + H]^+$. HPLC purity 100%.

methyl

7-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzamido)heptanoate **(Roxyl-zhc-67)**.

Yield: 71%, light yellow, mp 158.4 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.67 (d, J = 3.8 Hz, 1H), 8.29 (t, J = 5.6 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 7.88 (d, J = 8.9 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.66 (dd, J = 11.8, 1.2 Hz, 1H), 4.84 (p, J = 6.9 Hz, 1H), 3.57 (s, 3H), 3.24 (q, J = 6.6 Hz, 2H), 2.64 (s, 3H), 2.29 (t, J = 7.4 Hz, 2H), 1.62 (d, J = 6.9 Hz, 6H), 1.52 (q, J = 6.9 Hz, 4H), 1.35 – 1.26 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.81, 166.14, 156.45 (d, J = 3.1 Hz), 155.00, 154.05, 151.78 (d, J = 41.4 Hz), 150.64 (d, J = 8.3 Hz), 149.47, 148.21 (d, J = 26.5 Hz), 143.57, 136.82 (d, J = 9.8 Hz), 133.70 (d, J = 17.3 Hz), 128.31, 127.78 , 127.07 (t, J = 6.5 Hz), 117.79, 109.83 – 108.93 (m), 107.41 (dd, J = 20.2, 7.3 Hz), 51.60, 48.57, 33.69, 29.56, 28.71, 26.66, 24.88, 21.41, 15.02. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.54(s, 1F), -149.26(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{30}H_{35}F_2N_6O_3^+$ 565.2733, found 565.2730 $[M + H]^+$. HPLC purity 98%.

methyl

8-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzamido)octanoate **(Roxyl-zhc-68)**.

Yield: 60%, light yellow, mp 171.4 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.66 (d, J = 3.8 Hz, 1H), 8.30 (t, J = 5.7 Hz, 1H), 8.22 (d, J = 1.3 Hz, 1H), 7.88

(d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 12.0 Hz, 1H), 4.83 (p, *J* = 6.9 Hz, 1H), 3.56 (s, 3H), 3.23 (q, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H), 1.49 (t, *J* = 7.0 Hz, 4H), 1.27 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.80, 166.11, 156.43 (d, *J* = 2.8 Hz), 154.99, 154.04, 151.77 (d, *J* = 40.8 Hz), 150.60 (d, *J* = 7.0 Hz), 149.46, 148.20 (d, *J* = 26.6 Hz), 143.57, 136.80 (d, *J* = 10.0 Hz), 133.70 (d, *J* = 17.0 Hz), 128.31, 127.75, 127.25–126.27 (m), 117.76, 109.36 (d, *J* = 7.0 Hz), 107.40 (dd, *J* = 19.9, 7.4 Hz), 51.59, 48.57, 33.70, 29.69, 28.94, 26.85, 24.86, 21.40, 15.01. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -128.54(s, 1F), -149.26(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{31}H_{37}F_2N_6O_3^+$ 579.2890, found 579.2887 $[M + H]^+$. HPLC purity 95%.

methyl 4-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)butanoate **(Roxyl-zhc-69)**.

Yield: 75%, light yellow, mp 210.5 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.73 (s, 1H), 8.60 (d, *J* = 3.9 Hz, 1H), 8.25 (s, 1H), 8.04 (t, *J* = 5.7 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 12.0 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 3.57 (s, 3H), 3.35 (s, 2H), 3.06 (q, *J* = 6.6 Hz, 2H), 2.64 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.64 (dd, *J* = 18.8, 7.1 Hz, 8H). ^{13}C NMR (101 MHz, DMSO) δ 173.03, 170.35, 156.32, 154.45, 153.48, 151.10 (d, *J* = 17.4 Hz), 149.77 (d, *J* = 6.0 Hz), 148.68, 147.74 (d, *J* = 26.8 Hz), 138.85, 136.29 (d, *J* = 9.8 Hz), 133.12 (d, *J* = 17.1 Hz), 129.55, 128.92, 126.75 (t, *J* = 6.6 Hz), 118.60, 108.69 (d, *J* = 6.4 Hz), 106.94 (dd, *J* = 20.4, 8.5 Hz), 51.20, 48.08, 41.83, 37.89, 30.64, 24.50, 20.89, 14.52. ^{19}F NMR (376

MHz, DMSO-d_6) δ -128.23(s, 1F), -150.13(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{28}H_{31}F_2N_6O_3^+$ 537.2420, found 537.2421 $[M + H]^+$. HPLC purity 96%.

methyl 5-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)pentanoate **(Roxyl-zhc-70)**.

Yield: 70%, light yellow, mp 176.7 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.60 (d, J = 3.9 Hz, 1H), 8.44 – 8.10 (m, 1H), 8.03 (d, J = 5.7 Hz, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.19 (d, J = 8.2 Hz, 2H), 4.83 (p, J = 6.9 Hz, 1H), 3.56 (s, 3H), 3.35 (s, 2H), 3.04 (q, J = 6.5 Hz, 2H), 2.63 (s, 3H), 2.29 (t, J = 7.3 Hz, 2H), 1.62 (d, J = 6.9 Hz, 6H), 1.52 (d, J = 7.6 Hz, 2H), 1.44 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.72, 170.70, 156.81, 154.94, 153.98, 151.59 (d, J = 17.4 Hz), 150.25 (d, J = 6.2 Hz), 149.17, 148.24 (d, J = 26.0 Hz), 139.33, 136.77 (d, J = 9.6 Hz), 133.62 (d, J = 17.0 Hz), 130.11, 129.41, 127.25 (t, J = 6.5 Hz), 119.08 , 109.21, 107.44 (dd, J = 20.1, 8.6 Hz), 51.63, 48.58, 42.35, 38.63, 33.34, 29.01, 22.34, 21.38, 15.00. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.27(s, 1F), -150.13(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{29}H_{33}F_2N_6O_3^+$ 551.2577, found 551.2575 $[M + H]^+$. HPLC purity 99%.

methyl 6-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)hexanoate **(Roxyl-zhc-71)**.

Yield: 71%, light yellow, mp 170.4 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.60 (d, J = 3.9 Hz, 1H), 8.28 – 8.15 (m, 1H), 7.99 (t, J = 5.7 Hz, 1H), 7.71 (d, J

= 8.3 Hz, 2H), 7.65 (d, *J* = 12.1 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.83 (p, *J* = 6.9 Hz, 1H), 3.55 (s, 3H), 3.34 (s, 2H), 3.03 (q, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 6H), 1.49 (p, *J* = 7.5 Hz, 2H), 1.39 (p, *J* = 7.2 Hz, 2H), 1.24 (td, *J* = 8.4, 4.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.74, 170.67, 156.81, 155.49 – 154.47 (m), 153.98, 151.60 (d, *J* = 17.6 Hz), 150.25 (d, *J* = 6.0 Hz), 149.18, 148.24 (d, *J* = 26.3 Hz), 139.33, 136.78 (d, *J* = 10.0 Hz), 133.62 (d, *J* = 16.9 Hz), 130.15, 129.41, 127.25 (t, *J* = 6.5 Hz), 119.08, 109.21 (t, *J* = 4.8 Hz), 107.44 (dd, *J* = 20.0, 8.5 Hz), 51.61, 48.58, 42.37, 38.87, 33.66, 29.26, 26.32, 24.60, 21.38, 15.00. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.22(s, 1F), -150.11(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{30}H_{35}F_2N_6O_3^+$ 565.2733, found 565.2735 $[M + H]^+$. HPLC purity 100%.

methyl

7-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)heptanoate **(Roxyl-zhc-72)**.

Yield: 64%, light yellow, mp 166.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.59 (d, *J* = 3.9 Hz, 1H), 8.25 (d, *J* = 1.3 Hz, 1H), 7.96 (t, *J* = 5.6 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.64 (dd, *J* = 12.0, 1.2 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 4.83 (p, J = 6.9 Hz, 1H), 3.54 (s, 3H), 3.34 (s,2H), 3.02 (q, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H), 1.47 (dd, *J* = 8.9, 5.1 Hz, 2H), 1.40 – 1.32 (m, 2H), 1.26 – 1.18 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.77, 170.65, 156.82, 154.95, 153.99, 151.60 (d, *J* = 16.4 Hz), 150.26 (d, *J* = 6.9 Hz), 149.18, 148.24 (d, *J* = 26.3 Hz), 139.33, 136.79 (d, *J* = 10.0 Hz), 133.63 (d, *J* = 17.3 Hz), 130.18, 129.40,

127.26 (t, *J* = 6.3 Hz), 119.09, 109.21 (d, *J* = 6.4 Hz), 107.44 (dd, *J* = 20.1, 8.2 Hz), 51.58, 48.58, 42.38, 38.99, 33.64, 29.40, 28.61, 26.49, 24.83, 21.39, 15.01. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.23(s, 1F), -150.13(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{31}H_{37}F_2N_6O_3^+$ 579.2890, found 579.2891 $[M + H]^+$. HPLC purity 98%.

methyl

8-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)octanoate **(Roxyl-zhc-73)**.

Yield: 69%, light yellow, mp 171.3 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.60 (d, *J* = 3.9 Hz, 1H), 8.25 (d, *J* = 1.3 Hz, 1H), 7.98 (t, *J* = 5.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.68 – 7.57 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.83 (p, *J* = 6.9 Hz, 1H), 3.54 (s, 3H), 3.34 (s, 2H), 3.02 (q, *J* = 6.6 Hz, 2H), 2.63 (s,3H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 6H), 1.46 (t, *J* = 7.2 Hz, 2H), 1.40 – 1.34 (m, 2H), 1.23 – 1.15 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 173.78, 170.64, 156.80 (d, *J* = 2.7 Hz), 154.95, 153.99, 151.60 (d, *J* = 16.4 Hz), 150.25 (d, *J* = 7.2 Hz), 149.18, 148.25 (d, *J* = 26.8 Hz), 139.33, 136.78 (d, *J* = 10.0 Hz), 133.63 (d, *J* = 17.2 Hz), 130.18, 129.39, 127.25 (t, *J* = 6.6 Hz), 119.06, 109.59 – 108.61 (m), 107.44 (dd, *J* = 20.0, 8.5 Hz), 51.58, 48.57, 42.39, 39.00, 33.66, 29.51, 28.88, 28.85, 26.68, 24.82, 21.38, 15.01. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.26(s, 1F), -150.14(s, 1F). ESI-HRMS m/z calcd for Chemical Formula: $C_{32}H_{39}F_2N_6O_3^+$ 593.3046, found 593.3047 $[M + H]^+$. HPLC purity 99%.

Synthesis of the final compounds Roxyl-zhc-(74-95).

General produce: To a stirred solution of the compound **52-73** (0.5 mmol) in methanol (10 mL) was added a solution of hydroxylamine (50% in water, 3 mL). The resulting solution was stirred for 18 h under reflux. The solvent was removed under vacuum and the crude residue purified by chromatography on a silica gel column to obtain the final compounds **Roxyl-zhc-(74-95)** as a solid,

N^1-(5-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-2-yl)-N^8-hydroxyoctanediamide **(Roxyl-zhc-74)**.

Yield: 58%, light yellow, mp 169.3 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (d, *J* = 3.6 Hz, 2H), 9.84 (s, 1H), 8.78 – 8.46 (m, 3H), 8.19 (d, *J* = 13.6 Hz, 2H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 12.1 Hz, 1H), 4.96 – 4.62 (m, 1H), 2.64 (s, 3H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.94 (t, *J* = 7.3 Hz, 2H), 1.69 – 1.34 (m, 10H), 1.27 (d, *J* = 6.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 171.58, 169.07, 156.27, 154.54, 153.53, 151.24 (d, *J* = 35.0 Hz), 150.11, 148.91, 147.87 (d, *J* = 26.8 Hz), 146.56, 138.70, 136.32 (d, *J* = 9.9 Hz), 133.17 (d, *J* = 17.2 Hz), 130.73 (d, *J* = 460.9 Hz), 126.59 (t, *J* = 6.4 Hz), 113.04, 108.88, 107.04 – 106.69 (m), 48.08, 35.92, 32.22, 28.36, 25.00, 24.92, 20.92, 14.54. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.88(s, 1F), -145.53(s, 1F). ESI-HRMS m/z calcd for $C_{28}H_{33}F_2N_8O_3^+$ 567.2638, found 567.2637 $[M + H]^+$. HPLC purity 96%.

N^1-(3-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)-N^8-hydroxyoctanediamide **(Roxyl-zhc-75)**.

Yield: 62%, light yellow, mp 190 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.86 (s, 1H), 9.76 (s, 1H), 8.69 (s, 1H), 8.62 (d, *J* = 3.7 Hz, 1H), 8.21 (s, 1H), 7.98 (s, 1H), 7.71 (d, *J* = 12.0 Hz, 1H), 7.51 (d, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 4.83

(t, J = 6.9 Hz, 1H), 2.64 (s, 3H), 2.29 (t, J = 7.4 Hz, 2H), 1.94 (t, J = 7.3 Hz, 2H), 1.71 – 1.43 (m, 10H), 1.32 – 1.18 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 171.60, 169.55, 156.80, 154.94, 153.96, 151.71 (d, J = 21.3 Hz), 150.52 (d, J = 8.4 Hz), 149.24, 148.04 (d, J = 27.2 Hz), 141.20, 140.05, 136.77 (d, J = 20.8 Hz), 133.60 (d, J = 23.2 Hz), 128.94, 127.37 – 126.90 (m), 113.86 (d, J = 91.8 Hz), 110.58, 109.34 (d, J = 20.7 Hz), 107.86 – 107.16 (m), 48.55, 36.84, 32.72, 28.94, 28.90, 25.53, 21.41, 15.07. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.93(s, 1F), -145.63(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2685 $[M + H]^+$. HPLC purity 100%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)-N^5-hydroxyglutaramide **(Roxyl-zhc-76).**

Yield: 59%, light yellow, mp 159.9 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.86 (s, 1H), 9.70 (s, 1H), 8.60 (d, J = 3.8 Hz, 2H), 8.27 (s, 1H), 7.76 – 7.47 (m, 5H), 4.85 (p, J = 6.9 Hz, 1H), 2.64 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 2.02 (t, J = 7.4 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.63 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 170.77, 169.22, 156.85 (d, J = 2.4 Hz), 154.95, 153.87, 151.52 (d, J = 22.4 Hz), 150.12 (d, J = 7.4 Hz), 149.12, 148.33 (d, J = 26.6 Hz), 136.69 (d, J = 9.8 Hz), 136.25, 134.10, 133.30 (d, J = 17.0 Hz), 127.41 (t, J = 6.5 Hz), 119.71 (d, J = 23.6 Hz), 109.24 (dd, J = 6.5, 3.2 Hz), 107.57 (dd, J = 19.9, 8.7 Hz), 48.66, 36.05, 32.16, 21.40, 14.96. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.15(s, 1F), -150.36(s, 1F). ESI-HRMS m/z calcd for $C_{26}H_{28}F_2N_7O_3^+$ 524.2216, found 524.2221 $[M + H]^+$. HPLC purity 98%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)-N^6-hydroxyadipamide **(Roxyl-zhc-77)**.

Yield: 55%, light yellow, mp 188.8 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.84 (s, 1H), 9.68 (s, 1H), 8.78 (d, J = 3.5 Hz, 1H), 8.57 (d, J = 3.9 Hz, 1H), 8.26 (s, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 12.1 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 4.99 – 4.72 (m, 1H), 2.63 (s, 3H), 2.31 (d, J = 6.5 Hz, 2H), 2.00 (t, J = 6.6 Hz, 2H), 1.59 (dd, J = 23.4, 6.0 Hz, 10H). ^{13}C NMR (101 MHz, DMSO) δ 171.12, 169.45, 156.83, 154.95, 153.96, 151.55 (d, J = 13.8 Hz), 150.10 (d, J = 8.3 Hz), 149.11, 148.29 (d, J = 26.5 Hz), 136.76 (d, J = 9.8 Hz), 136.26, 134.09, 133.60 (d, J = 17.2 Hz), 127.28 (t, J = 6.4 Hz), 119.72 (d, J = 20.3 Hz), 109.19, 107.46 (dd, J = 20.0, 8.6 Hz), 48.59, 36.62, 32.65, 25.40, 21.39, 14.98. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.20(s, 1F), -150.35(s, 1F). ESI-HRMS m/z calcd for $C_{27}H_{30}F_2N_7O_3^+$ 538.2373, found 538.2372 $[M + H]^+$. HPLC purity 98%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)-N^7-hydroxyheptanediamide **(Roxyl-zhc-78)**.

Yield: 54%, light yellow, mp 210.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.81 (s, 1H), 9.70 (s, 1H), 8.71 (d, J = 1.7 Hz, 1H), 8.58 (d, J = 3.9 Hz, 1H), 8.26 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 12.1 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 2.63 (s, 3H), 2.28 (t, J = 7.3 Hz, 2H), 1.96 (t, J = 7.3 Hz, 2H), 1.68 – 1.47 (m, 10H), 1.29 (q, J = 8.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 171.19, 169.54, 156.84, 155.54 – 154.55 (m), 153.96, 151.55 (d, J = 12.6 Hz), 150.07 (d, J = 10.3 Hz), 149.11, 148.30 (d, J = 26.2 Hz), 136.76 (d, J = 10.1 Hz), 136.24, 134.11, 133.60 (d, J = 17.2 Hz), 127.28 (t, J = 6.5 Hz), 119.70 (d, J = 19.0 Hz), 109.17, 107.46 (dd, J = 19.8, 8.8 Hz), 48.58, 36.69, 32.64, 28.76, 25.43, 21.40, 15.00.

^{19}F NMR (376 MHz, DMSO-d_6) δ -128.24(s, 1F), -150.39(s, 1F). ESI-HRMS m/z calcd for $C_{28}H_{32}F_2N_7O_3^+$ 552.2529, found 552.2521 $[M + H]^+$. HPLC purity 100%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidi n-2-yl)amino)phenyl)-N^8-hydroxyoctanediamide **(Roxyl-zhc-79)**.

Yield: 52%, light yellow, mp 238.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.79 (s, 1H), 9.68 (s, 1H), 8.69 (s, 1H), 8.58 (d, *J* = 3.9 Hz, 1H), 8.26 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 12.1 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 2.63 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.95 (t, *J* = 7.3 Hz, 2H), 1.66 – 1.47 (m, 10H), 1.32 – 1.24 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 170.75, 169.08, 156.34, 154.46, 153.47, 151.06 (d, *J* = 12.4 Hz), 149.59 (d, *J* = 12.7 Hz), 148.62, 147.79 (d, *J* = 26.2 Hz), 136.27 (d, *J* = 9.8 Hz), 135.73, 133.62, 133.11 (d, *J* = 17.3 Hz), 126.79 (t, *J* = 6.6 Hz), 119.23 (d, *J* = 19.5 Hz), 108.68 (d, *J* = 5.8 Hz), 106.96 (dd, *J* = 20.2, 8.9 Hz), 48.08, 36.29, 32.23, 28.43, 28.39, 25.09, 25.03, 20.90, 14.49. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.98(s, 1F), -146.14(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2690 $[M + H]^+$. HPLC purity 98%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidi n-2-yl)amino)phenyl)-N^9-hydroxynonanediamide **(Roxyl-zhc-80)**.

Yield: 61%, light yellow solid, mp 215 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.78 (s, 1H), 9.69 (s, 1H), 8.66 (s, 1H), 8.60 (d, *J* = 3.9 Hz, 1H), 8.28 – 8.24 (m, 1H), 7.67 (dd, *J* = 17.3, 10.3 Hz, 3H), 7.55 (d, *J* = 8.5 Hz, 2H), 4.85 (p, *J* = 6.9, 6.2 Hz, 1H), 2.64 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.94 (t, *J* = 7.3 Hz, 2H), 1.63 (d, *J* = 6.8 Hz, 8H), 1.48 (t, *J* = 7.1 Hz, 2H), 1.28 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz,

DMSO) δ 171.27, 169.57, 156.87, 155.00, 153.98, 151.57 (d, *J* = 13.3 Hz), 150.20 (d, *J* = 7.6 Hz), 149.13, 148.34 (d, *J* = 26.4 Hz), 136.79 (d, *J* = 9.8 Hz), 136.23, 134.14, 133.62 (d, *J* = 16.4 Hz), 127.29 (t, *J* = 6.5 Hz), 119.73 (d, *J* = 17.5 Hz), 109.20 (d, *J* = 5.3 Hz), 107.47 (dd, *J* = 19.9, 8.6 Hz), 48.58, 36.82, 32.73, 29.08, 29.02, 28.96, 25.64, 25.57, 21.41, 15.02. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.94(s, 1F), -146.14(s, 1F). ESI-HRMS m/z calcd for $C_{30}H_{36}F_2N_7O_3^+$ 580.2842, found 580.2832 $[M + H]^+$. HPLC purity 95%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)-N^5-hydroxyglutaramide **(Roxyl-zhc-81)**.

Yield: 55%, light yellow, mp 190.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.75 (s, 1H), 8.60 (d, *J* = 3.8 Hz, 1H), 8.30 (t, *J* = 5.9 Hz, 1H), 8.25 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 12.0 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 4.23 (d, *J* = 5.7 Hz, 2H), 2.63 (s, 3H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.99 (t, *J* = 7.5 Hz, 2H), 1.77 (q, *J* = 7.6 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 171.51, 168.75, 156.29, 154.47, 153.47, 151.10 (d, *J* = 20.5 Hz), 149.77 (d, *J* = 7.8 Hz), 148.69, 147.75 (d, *J* = 26.3 Hz), 139.21, 136.28 (d, *J* = 9.8 Hz), 133.12 (d, *J* = 16.8 Hz), 132.70, 127.45, 126.74 (t, *J* = 6.5 Hz), 118.58, 108.70 (t, *J* = 4.8 Hz), 106.96 (dd, *J* = 20.1, 8.5 Hz), 48.09, 41.63, 34.72, 31.81, 21.51, 20.90, 14.50. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.94(s, 1F), -145.75(s, 1F). ESI-HRMS m/z calcd for $C_{27}H_{30}F_2N_7O_3^+$ 538.2373, found 538.2375 $[M + H]^+$. HPLC purity 97%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)-N^6-hydroxyadipamide **(Roxyl-zhc-82)**.

Yield: 58%, light yellow, mp 177 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.75 (s, 1H), 8.71 (s, 1H), 8.59 (d, J = 3.8 Hz, 1H), 8.36 – 8.17 (m, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.68 – 7.56 (m, 1H), 7.19 (d, J = 8.3 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 4.23 (d, J = 5.8 Hz, 2H), 2.63 (s, 3H), 2.21 – 2.05 (m, 2H), 2.03 – 1.89 (m, 2H), 1.62 (d, J = 6.8 Hz, 6H), 1.51 (p, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 172.30, 169.45, 156.75, 154.97, 153.96, 151.59 (d, J = 20.6 Hz), 150.23 (d, J = 7.1 Hz), 149.18, 148.24 (d, J = 26.7 Hz), 139.70, 136.76 (d, J = 9.8 Hz), 133.61 (d, J = 17.3 Hz), 133.20, 127.95, 127.22 (t, J = 6.6 Hz), 119.08, 109.19 (d, J = 6.7 Hz), 107.45 (dd, J = 20.0, 8.7 Hz), 48.58, 42.14, 35.66, 32.63, 25.45 (d, J = 7.6 Hz), 21.39, 14.99. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.94(s, 1F), -145.73(s, 1F). ESI-HRMS m/z calcd for $C_{28}H_{32}F_2N_7O_3^+$ 552.2529, found 552.2523 $[M + H]^+$. HPLC purity 100%.

*N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)-N^7-hydroxyheptanediamide***(Roxyl-zhc-83)**.

Yield: 57%, light yellow, mp 178.5 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.75 (s, 1H), 8.70 (s, 1H), 8.60 (d, J = 3.8 Hz, 1H), 8.26 (d, J = 7.0 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 12.0 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 4.84 (p, J = 7.0 Hz, 1H), 4.22 (d, J = 5.8 Hz, 2H), 2.64 (s, 3H), 2.13 (t, J = 7.4 Hz, 2H), 1.95 (t, J = 7.4 Hz, 2H), 1.56 (dd, J = 44.1, 7.2 Hz, 10H), 1.25 (q, J = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 171.91, 169.04, 156.28 (d, J = 1.9 Hz), 154.49, 153.48, 151.11 (d, J = 19.8 Hz), 149.77 (d, J = 5.9 Hz), 148.70, 147.76 (d, J = 26.4 Hz), 139.20, 136.28 (d, J = 9.8 Hz), 133.12 (d, J = 17.3 Hz), 132.76, 127.46, 126.74 (t, J = 6.5 Hz), 118.60, 108.70 (d, J = 6.0 Hz), 106.96 (dd, J = 20.2, 8.7 Hz), 48.08, 41.63, 35.25,

32.13, 28.30, 25.06, 24.91, 20.90, 14.51. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.93 (s, 1F), -145.74(s, 1F) . ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2684 $[M + H]^+$. HPLC purity 99%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)-N^8-hydroxyoctanediamide **(Roxyl-zhc-84)**.

Yield: 64%, light yellow, mp 174.9 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.74 (s, 1H), 8.70 (s, 1H), 8.59 (d, *J* = 3.8 Hz, 1H), 8.26 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 12.0 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.91 – 4.76 (m, 1H), 4.22 (d, *J* = 5.7 Hz, 2H), 2.63 (s, 3H), 2.13 (t, *J* = 7.4 Hz, 2H), 1.94 (t, *J* = 7.4 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H), 1.50 (dt, *J* = 15.0, 7.3 Hz, 4H), 1.29 – 1.10 (m,4H). ^{13}C NMR (101 MHz, DMSO) δ 171.98, 169.10, 156.28 (d, *J* = 2.6 Hz), 154.48, 153.48, 151.11 (d, *J* = 19.6 Hz), 149.76 (d, *J* = 8.0 Hz), 148.70, 147.74 (d, *J* = 26.4 Hz), 139.20, 136.27 (d, *J* = 9.9 Hz), 133.12 (d, *J* = 16.7 Hz), 132.78, 127.44, 126.75 (t, *J* = 6.5 Hz), 118.58, 108.69 (d, *J* = 8.2 Hz), 106.95 (dd, *J* = 19.9, 8.6 Hz), 48.08, 41.62, 35.36, 32.23, 28.45, 28.36, 25.25, 25.02, 20.89, 14.49. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.91(s, 1F), -145.71(s, 1F). ESI-HRMS m/z calcd for $C_{30}H_{36}F_2N_7O_3^+$ 580.2842, found 580.2839 $[M + H]^+$. HPLC purity 100%.

N^1-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)benzyl)-N^9-hydroxynonanediamide **(Roxyl-zhc-85)**.

Yield: 63%, light yellow, mp 173.8 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.76 (s, 1H), 8.71 (s, 1H), 8.60 (d, *J* = 3.8 Hz, 1H), 8.26 (d, *J* = 12.6 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 12.0 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.83 (p, *J*

= 6.9 Hz, 1H), 4.22 (d, *J* = 5.5 Hz, 2H), 2.63 (s, 3H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.93 (t, *J* = 7.3 Hz, 2H), 1.62 (d, *J* = 6.7 Hz, 6H), 1.49 (dt, *J* = 20.5, 6.9 Hz, 4H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 172.48, 169.57, 156.75 (d, *J* = 2.6 Hz), 154.96, 153.96, 151.59 (d, *J* = 19.8 Hz), 150.23 (d, *J* = 6.5 Hz), 149.18, 148.25 (d, *J* = 26.3 Hz), 139.69, 136.75 (d, *J* = 9.8 Hz), 133.60 (d, *J* = 17.0 Hz), 133.26, 127.93, 127.23 (t, *J* = 6.6 Hz), 119.03, 109.19, 107.44 (dd, *J* = 20.0, 8.3 Hz), 48.58, 42.10, 35.85, 32.70, 29.09, 28.97, 28.96, 25.80, 25.57, 21.39, 15.00. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.89(s, 1F), -145.71(s, 1F). ESI-HRMS m/z calcd for $C_{31}H_{38}F_2N_7O_3^+$ 594.2999, found 594.2998 $[M + H]^+$. HPLC purity 99%.

4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)-N-(4-(hydroxyamino)-4-oxobutyl)benzamide **(Roxyl-zhc-86)**.

Yield: 64%, light yellow, mp 160.4 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.44 (s, 1H), 10.06 (s, 1H), 8.76 (s, 1H), 8.65 (d, *J* = 3.8 Hz, 1H), 8.38 (t, *J* = 5.6 Hz, 1H), 8.22 (d, *J* = 1.3 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 8.9 Hz, 2H), 7.65 (dd, *J* = 11.8, 1.2 Hz, 1H), 4.84 (p, *J* = 6.9 Hz, 1H), 3.27 (q, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 2.05 (t, *J* = 7.5 Hz, 2H), 1.78 (q, *J* = 7.3 Hz, 2H), 1.62 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 169.44, 166.27, 156.42, 155.00, 154.03, 151.77 (d, *J* = 43.3 Hz), 150.63 (d, *J* = 8.4 Hz), 149.46, 148.18 (d, *J* = 26.5 Hz), 143.65, 136.80 (d, *J* = 9.8 Hz), 133.68 (d, *J* = 16.6 Hz), 128.35, 127.61, 127.06 (t, *J* = 6.5 Hz), 117.79, 109.37 (d, *J* = 7.1 Hz), 107.41 (dd, *J* = 19.8, 7.5 Hz), 48.58, 30.54, 25.92, 21.41, 15.02. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.84(s, 1F), -144.51(s, 1 F). ESI-HRMS m/z calcd for $C_{26}H_{28}F_2N_7O_3^+$ 524.2216, found 524.2212 $[M + H]^+$. HPLC purity 100%.

4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)-N-(5-(hydroxyamino)-5-oxopentyl)benzamide **(Roxyl-zhc-87)**.

Yield: 66%, light yellow, mp 222.2 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 10.05 (s, 1H), 8.71 (s, 1H), 8.65 (d, *J* = 3.8 Hz, 1H), 8.33 (t, *J* = 5.7 Hz, 1H), 8.22 (s, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 12.0 Hz, 1H), 4.83 (p, *J* = 6.9 Hz, 1H), 3.25 (d, *J* = 6.2 Hz, 2H), 2.63 (s, 3H), 2.00 (t, *J* = 6.8 Hz, 2H), 1.57 (dd, *J* = 34.4, 6.4 Hz, 10H). ^{13}C NMR (101 MHz, DMSO) δ 169.04, 165.67, 155.93, 154.50, 153.53, 151.27 (d, *J* = 42.4 Hz), 150.12 (d, *J* = 8.6 Hz), 148.97, 147.69 (d, *J* = 26.5 Hz), 143.10, 136.30 (d, *J* = 9.8 Hz), 133.18 (d, *J* = 17.1 Hz), 127.82, 127.21, 126.57 (t, *J* = 6.3 Hz), 117.31, 108.86 (d, *J* = 7.6 Hz), 106.91 (dd, *J* = 20.0, 7.4 Hz), 48.08, 32.03, 28.90, 22.76, 20.91, 14.52. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.84(s, 1F), -144.52(s, 1F). ESI-HRMS m/z calcd for $C_{27}H_{30}F_2N_7O_3^+$ 538.2373, found 538.2368 $[M + H]^+$. HPLC purity 99%.

4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)-N-(6-(hydroxyamino)-6-oxohexyl)benzamide **(Roxyl-zhc-88)**.

Yield: 62%, light yellow, mp 155.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 10.07 (s, 1H), 8.77 – 8.59 (m, 2H), 8.32 (t, *J* = 5.6 Hz, 1H), 8.22 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 12.0 Hz, 1H), 4.84 (p, *J* = 6.9 Hz, 1H), 3.24 (q, *J* = 6.5 Hz, 2H), 2.63 (s, 3H), 1.96 (t, *J* = 7.3 Hz, 2H), 1.57 (dd, *J* = 39.5, 6.9 Hz, 10H), 1.30 (dt, *J* = 14.8, 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.54, 166.13, 156.43 (d, *J* = 2.4 Hz), 155.03, 154.03, 151.98, 151.55, 150.64 (d, *J* = 6.2 Hz), 149.47, 148.22 (d, *J* = 26.7 Hz), 143.59, 136.80 (d, *J* = 10.0 Hz), 133.67 (d, *J*

= 16.9 Hz), 128.33, 127.71, 127.06 (t, *J* = 6.6 Hz), 117.79, 109.36 (d, *J* = 6.5 Hz), 107.41 (dd, *J* = 20.1, 7.3 Hz), 48.58, 32.72, 29.53, 26.63, 25.43, 21.41, 15.03. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.84(s, 1F), -144.56(s, 1F). ESI-HRMS m/z calcd for $C_{28}H_{32}F_2N_7O_3^+$ 552.2529, found 552.2523 $[M + H]^+$. HPLC purity 99%.

4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)-N-(7-(hydroxyamino)-7-oxoheptyl)benzamide **(Roxyl-zhc-89)**.

Yield: 59%, light yellow, mp 171.1 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.39 (s, 1H), 10.06 (s, 1H), 8.70 (s, 1H), 8.66 (d, *J* = 3.7 Hz, 1H), 8.32 (t, *J* = 5.7 Hz, 1H), 8.22 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 12.0 Hz, 1H), 4.84 (p, *J* = 7.0 Hz, 1H), 3.24 (d, *J* = 6.5 Hz, 2H), 2.63 (s, 3H), 1.95 (t, *J* = 7.3 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H), 1.50 (q, *J* = 6.1 Hz, 4H), 1.36 – 1.18 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 169.11, 165.66, 155.93 (d, *J* = 2.4 Hz), 154.52, 153.53, 151.27 (d, *J* = 42.7 Hz), 150.13 (d, *J* = 8.0 Hz), 148.96, 147.70 (d, *J* = 27.0 Hz), 143.07, 136.30 (d, *J* = 9.8 Hz), 133.17 (d, *J* = 16.6 Hz), 127.83, 127.26, 126.57 (t, *J* = 6.5 Hz), 117.31, 108.85 (d, *J* = 7.5 Hz), 106.92 (dd, *J* = 20.0, 7.6 Hz), 48.08, 32.23, 29.14, 28.36, 26.24, 25.10, 20.91, 14.52. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.85(s, 1F), -144.57(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2692 $[M + H]^+$. HPLC purity 96%.

4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)-N-(8-(hydroxyamino)-8-oxooctyl)benzamide **(Roxyl-zhc-90)**.

Yield: 61%, light yellow, mp 123.6 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.36 (s, 1H), 10.05 (s, 1H), 8.69 (s, 1H), 8.65 (d, *J* = 3.8 Hz, 1H), 8.30 (t, *J* = 5.6 Hz, 1H),

8.22 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 12.0 Hz, 1H), 4.84 (p, *J* = 7.0 Hz, 1H), 3.24 (q, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 1.94 (t, *J* = 7.3 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H), 1.50 (q, *J* = 7.3 Hz, 4H), 1.32 – 1.19 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 170.31, 166.84, 157.13, 155.71, 154.73, 152.47 (d, *J* = 41.8 Hz), 151.32 (d, *J* = 8.2 Hz), 150.16, 148.90 (d, *J* = 26.7 Hz), 144.27, 137.50 (d, *J* = 9.8 Hz), 134.38 (d, *J* = 16.6 Hz), 129.01, 128.46, 128.11 – 127.53 (m), 118.50, 110.05 (d, *J* = 6.3 Hz), 108.11 (dd, *J* = 20.1, 7.5 Hz), 49.28, 33.44, 30.43, 29.76, 29.70, 27.62, 26.27, 22.11, 15.72. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.87 (s, 1F), -144.58(s, 1F). ESI-HRMS m/z calcd for $C_{30}H_{36}F_2N_7O_3^+$ 580.2842, found 580.2842 $[M + H]^+$. HPLC purity 100%.

4-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)-N-hydroxybutanamide **(Roxyl-zhc-91)**.

Yield: 56%, light yellow solid, mp 188 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.42 (s, 1H), 9.73 (s, 1H), 8.76 (s, 1H), 8.57 (d, *J* = 3.8 Hz, 1H), 8.24 (s, 1H), 8.07 (t, *J* = 5.5 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 11.7 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.82 (p, *J* = 7.0 Hz, 1H), 3.36 (s, 2H), 3.05 (q, *J* = 6.6 Hz, 2H), 2.62 (s, 3H), 1.98 (t, *J* = 7.5 Hz, 2H), 1.63 (dd, *J* = 17.8, 7.1 Hz, 8H). ^{13}C NMR (101 MHz, DMSO) δ 170.85, 169.31, 156.78 (d, *J* = 2.02 Hz), 154.94, 153.96, 151.58 (d, *J* = 18.6 Hz), 150.24, 149.17, 148.21 (d, *J* = 26.7 Hz), 139.35, 136.76 (d, *J* = 9.7 Hz), 133.60 (d, *J* = 17.0 Hz), 130.04, 129.44, 127.24 (t, *J* = 6.5 Hz), 119.12, 109.18, 107.45 (dd, *J* = 20.0, 8.6 Hz), 48.59, 42.33, 38.82, 30.38, 25.88, 21.38, 14.99. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.96(s, 1F), -145.84(s, 1F). ESI-HRMS m/z calcd for $C_{27}H_{30}F_2N_7O_3^+$ 538.2373,

found 538.2370 $[M + H]^+$. HPLC purity 100%.

5-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)-N-hydroxypentanamide **(Roxyl-zhc-92)**.

Yield: 56%, light yellow, mp 188.6 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.72 (s, 1H), 8.71 (s, 1H), 8.60 (d, J = 3.9 Hz, 1H), 8.25 (d, J = 1.3 Hz, 1H), 8.02 (t, J = 5.6 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.65 (dd, J = 11.9, 1.2 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 3.36 (s, 2H), 3.04 (q, J = 6.6 Hz, 2H), 2.64 (s, 3H), 1.96 (t, J = 7.2 Hz, 2H), 1.62 (d, J = 6.9 Hz, 6H), 1.56 – 1.45 (m, 2H), 1.43 – 1.32 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.67, 169.43, 156.79, 154.95, 153.96, 151.58 (d, J = 18.4 Hz), 150.26 (d, J = 7.1 Hz),149.17, 148.22 (d, J = 26.7 Hz), 139.31, 136.77 (d, J = 9.8 Hz), 133.60 (d, J = 17.3 Hz), 130.13, 129.42, 127.24 (t, J = 6.4 Hz), 119.13, 109.19 (d, J = 6.1 Hz), 107.44 (dd, J = 19.8, 8.6 Hz), 48.58, 42.32, 38.87, 32.40, 29.21, 23.12, 21.40, 15.01. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.95(s, 1F), -145.83(s, 1F). ESI-HRMS m/z calcd for $C_{28}H_{32}F_2N_7O_3^+$ 552.2529, found 552.2526 $[M + H]^+$. HPLC purity 100%.

6-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)-N-hydroxyhexanamide **(Roxyl-zhc-93)**.

Yield: 60%, light yellow, mp 222.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.72 (s, 1H), 8.70 (s, 1H), 8.59 (d, J = 3.9 Hz, 1H), 8.25 (d, J = 1.3 Hz, 1H), 7.99 (t, J = 5.6 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.65 (dd, J = 12.0, 1.2 Hz, 1H), 7.19 (d, J = 8.3 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 3.36 (s, 2H), 3.03 (q, J = 6.6 Hz, 2H), 2.64 (s, 3H), 1.94 (t, J = 7.4 Hz, 2H), 1.62 (d, J = 6.9 Hz, 6H), 1.49 (p, J = 7.5 Hz, 2H), 1.40

(p, *J* = 7.2 Hz, 2H), 1.24 (qd, *J* = 9.4, 8.9, 6.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.66, 169.54, 156.82, 154.96, 153.98, 151.60 (d, *J* = 17.7 Hz), 150.26 (d, *J* = 8.5 Hz), 149.18, 148.23 (d, *J* = 26.3 Hz), 139.32, 136.78 (d, *J* = 10.3 Hz), 133.61 (d, *J* = 17.3 Hz), 130.16, 129.43, 127.26 (t, *J* = 6.5 Hz), 119.14, 109.21 (d, *J* = 6.2 Hz), 107.45 (dd, *J* = 20.0, 8.2 Hz), 48.58, 42.34, 39.03, 32.68, 29.36, 26.52, 25.34, 21.39, 15.01. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -123.98(s, 1F), -145.86(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2682 $[M + H]^+$. HPLC purity 100%.

7-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)-N-hydroxyheptanamide **(Roxyl-zhc-94)**.

Yield: 53%, light yellow, mp 177.7 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.36 (s, 1H), 9.71 (s, 1H), 8.69 (d, *J* = 1.5 Hz, 1H), 8.58 (d, *J* = 3.9 Hz, 1H), 8.24 (d, *J* = 1.3 Hz, 1H), 7.98 (t, *J* = 5.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.58 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.83 (p, *J* = 6.9 Hz, 1H), 3.35 (s, 2H), 3.03 (q, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 1.93 (t, *J* = 7.3 Hz, 2H), 1.61 (d, *J* = 6.8 Hz, 6H), 1.47 (t, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 2H), 1.23 (p, *J* = 4.1, 3.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 170.68, 169.60, 156.80 (d, *J* = 1.9 Hz), 154.95, 153.98, 151.59 (d, *J* = 18.2 Hz), 150.24 (d, *J* = 8.1 Hz), 149.18, 148.22 (d, *J* = 26.5 Hz), 139.32, 136.77 (d, *J* = 9.8 Hz), 133.61 (d, *J* = 16.6 Hz), 130.17, 129.41, 127.26 (t, *J* = 6.5 Hz), 119.12, 109.20 (d, *J* = 6.6 Hz), 107.45 (dd, *J* = 20.4, 8.5 Hz), 48.58, 42.36, 39.07, 32.70, 29.49, 28.77, 26.61, 25.55, 21.39, 15.00. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -124.00(s, 1F), -145.88(s, 1F). ESI-HRMS m/z calcd for $C_{30}H_{36}F_2N_7O_3^+$ 580.2842, found 580.2842 $[M + H]^+$. HPLC

purity 99%.

8-(2-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)acetamido)-N-hydroxyoctanamide **(Roxyl-zhc-95)**.

Yield: 56%, light yellow, mp 166.6 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.72 (s, 1H), 8.68 (s, 1H), 8.60 (d, J = 3.9 Hz, 1H), 8.25 (s, 1H), 7.98 (t, J = 5.6 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 12.1 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 5.03 – 4.61 (m, 1H), 3.36 (d, J = 10.1 Hz, 2H), 3.03 (q, J = 6.5 Hz, 2H), 2.63 (s, 3H), 1.92 (t, J = 7.3 Hz, 2H), 1.62 (d, J = 6.8 Hz, 6H), 1.46 (t, J = 6.9 Hz, 2H), 1.37 (d, J = 6.4 Hz, 2H), 1.22 (d, J = 4.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 170.64, 169.57, 156.81 (d, J = 1.9 Hz),154.94, 153.97, 151.59 (d, J = 18.1 Hz), 150.26 (d, J = 8.1 Hz), 149.17, 148.23 (d, J = 26.3 Hz), 139.31, 136.77 (d, J = 9.8 Hz), 133.60 (d, J = 17.3 Hz), 130.17, 129.40, 127.25 (t, J = 6.5 Hz), 119.10, 109.21 (d, J = 6.4 Hz), 107.44 (dd, J = 20.1, 8.3 Hz), 48.58, 42.36, 39.06, 32.70, 29.56, 26.77, 25.53, 21.38, 15.01. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.94 (s, 1F), -145.82(s, 1F). ESI-HRMS m/z calcd for $C_{31}H_{38}F_2N_7O_3^+$ 594.2999, found 594.2994 $[M + H]^+$. HPLC purity 99%.

methyl 8-((6-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)pyridin-3-yl)amino)-8-oxooctanoate **(Roxyl-zhc-96)**. To a suspension of 6-(2-chloro-5-fluoropyrimidin-4-yl)-4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazole **51** (645 mg, 2 mmol) in 20 mL 1,4-dioxane were added compound **24** (559 mg, 2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), BINAP (62 mg, 0.1 mmol) and Cs_2CO_3 (1.37 g, 4.2 mmol) and the flask was purged with N_2. Then the flask was sealed and the

mixture was heated for 12 h at 100℃. The reaction was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to obtain 747 mg (66%) of **Roxyl-zhc-96,** yellow solid, mp 231.1 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) ^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 9.99 (s, 1H), 8.66 (d, *J* = 3.8 Hz, 1H), 8.60 – 8.50 (m, 1H), 8.30 (s, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 8.04 – 7.91 (m, 1H), 7.67 (d, *J* = 12.0 Hz, 1H), 4.84 (p, *J* = 7.1 Hz, 1H), 3.57 (s, 3H), 2.64 (s, 3H), 2.30 (d, *J* = 6.7 Hz, 4H), 1.80 – 1.48 (m, 10H), 1.34 – 1.24 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.83, 171.70, 155.49 (d, *J* = 83.6 Hz), 153.97, 151.80 (d, *J* = 61.9 Hz), 150.41 (d, *J* = 8.7 Hz), 149.59, 148.95, 148.23 (d, *J* = 26.2 Hz), 139.29, 136.80 (d, *J* = 10.2 Hz), 133.73 (d, *J* = 16.9 Hz), 131.13, 128.91, 127.05 (t, *J* = 6.6 Hz), 112.71, 109.35 (d, *J* = 4.8 Hz), 107.56 (dd, *J* = 20.2, 9.3 Hz), 51.65, 48.59, 33.69, 28.78, 28.69, 25.36, 24.78, 21.40, 15.02. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.94 (s, 1F), -144.57(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{34}F_2N_7O_3^+$ 566.2686, found 566.2681 $[M + H]^+$. HPLC purity 95%.

Synthesis of the final compounds Roxyl-zhc-(97-100).

General produce: To a suspension of 6-(2-chloro-5-fluoropyrimidin-4-yl)-4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazole **51** (2 mmol) in 20 mL 1,4-dioxane were added compound **32-35** (2 mmol), $Pd(OAc)_2$ (0.05 mmol), BINAP (0.1 mmol) and Cs_2CO_3 (4.2 mmol) and the flask was purged with N_2. Then the flask was sealed and the mixture was heated for 12 h at 100℃. The reaction was cooled to room temperature, the solvent was removed under

reduced pressure, and the residue was purified by silica gel column chromatography to obtain the final compounds **Roxyl-zhc-(97-100)** as a solid.

N-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)hexanamide **(Roxyl-zhc-97)**.

Yield: 78%, light yellow, mp 232 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 9.68 (s, 1H), 8.58 (d, J = 3.9 Hz, 1H), 8.26 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 12.1 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 2.63 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.62 (d, J = 6.9 Hz, 8H), 1.30 – 1.28 (m, 4H), 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.27, 156.85, 154.93, 153.98, 151.57 (d, J = 11.0 Hz), 150.16, 149.12, 148.28 (d, J = 26.6 Hz), 136.78 (d, J = 9.9 Hz), 136.23, 134.15, 133.63 (d, J = 16.6 Hz), 127.29 (t, J = 6.8 Hz), 119.71 (d, J = 19.4 Hz), 109.14 (d, J = 6.1 Hz), 107.45 (dd, J = 20.4, 8.8 Hz), 48.58, 36.81, 31.42, 25.37, 22.39, 21.40, 15.00, 14.34. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.67 (s, 1F), -150.83(s, 1F). ESI-HRMS m/z calcd for $C_{27}H_{31}F_2N_6O^+$ 493.2522, found 493.2518 $[M + H]^+$. HPLC purity 98%.

N-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)heptanamide **(Roxyl-zhc-98)**.

Yield: 70%, light yellow, mp 242.7 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 9.68 (s, 1H), 8.57 (d, J = 3.8 Hz, 1H), 8.26 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 12.2 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 4.84 (p, J = 6.9 Hz, 1H), 2.63 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.66 – 1.53 (m, 10H), 1.34 – 1.22 (m, 4H), 0.97 – 0.79 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.76, 156.35, 154.40, 153.48, 151.06 (d, J = 10.8 Hz), 149.61 (d, J = 8.3 Hz), 148.61, 147.75 (d, J = 26.1 Hz), 136.27 (d, J = 10.2 Hz),

135.74, 133.63, 133.13 (d, *J* = 16.5 Hz), 126.80 (t, *J* = 6.6 Hz), 119.20 (d, *J* = 20.5 Hz), 108.62 (d, *J* = 6.5 Hz), 106.94 (dd, *J* = 19.8, 8.8 Hz), 48.07, 36.35, 31.03, 28.36, 25.14, 21.98, 20.88, 14.48, 13.87. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -128.69(s, 1F), -150.84(s, 1F). ESI-HRMS m/z calcd for $C_{28}H_{33}F_2N_6O^+$ 507.2678, found 507.2671 $[M + H]^+$. HPLC purity 100%.

N-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)octanamide **(Roxyl-zhc-99)**.

Yield: 65%, light yellow, mp 241.4 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.78 (s, 1H), 9.68 (s, 1H), 8.59 (d, *J* = 3.9 Hz, 1H), 8.27 (d, *J* = 1.3 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 2H), 7.67 – 7.62 (m, 1H), 7.56 (d, *J* = 8.9 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 2.64 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.67 – 1.54 (m, 8H), 1.32 – 1.19 (m, 8H), 0.89 – 0.79 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.26, 156.86, 154.92, 153.98, 151.57 (d, J = 11.0 Hz), 150.16, 149.12, 148.28 (d, *J* = 26.1 Hz), 136.78 (d, *J* = 9.8 Hz), 136.23, 134.15, 133.63 (d, *J* = 16.8 Hz), 127.30 (t, *J* = 6.5 Hz), 119.70 (d, *J* = 19.2 Hz), 109.17 (d, *J* = 5.4 Hz), 107.45 (dd, *J* = 20.1, 9.0 Hz), 48.58, 36.84, 31.67, 29.15, 28.97, 25.69, 22.55, 21.39, 15.00, 14.39. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -128.68(s, 1F), -150.85(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{35}F_2N_6O^+$ 521.2835, found 521.2836 $[M + H]^+$. HPLC purity 100%.

N-(4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)nonanamide **(Roxyl-zhc-100)**.

Yield: 72%, light yellow, mp 222.9 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.78 (s, 1H), 9.68 (s, 1H), 8.59 (d, *J* = 3.9 Hz, 1H), 8.27 (d, *J* = 1.3 Hz, 1H), 7.71 (d, *J* = 9.0 Hz,

2H), 7.65 (dd, *J* = 12.0, 1.2 Hz, 1H), 7.59 – 7.53 (m, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 2.63 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.82 – 1.46 (m, 8H), 1.25 (dt, *J* = 16.0, 4.8 Hz, 10H), 0.90 – 0.69 (m,3H). ^{13}C NMR (101 MHz, DMSO) δ 171.26, 156.86, 154.92, 153.98, 151.57 (d, *J* = 10.9 Hz), 150.18, 149.12, 148.28 (d, *J* = 26.9 Hz), 136.78 (d, *J* = 9.8 Hz), 136.23, 134.14, 133.63 (d, *J* = 17.0 Hz), 127.30 (t, *J* = 6.6 Hz), 119.70 (d, *J* = 19.9 Hz), 109.17 (d, *J* = 5.3 Hz), 107.44 (dd, *J* = 19.9, 8.9 Hz), 48.57, 36.84, 31.73, 29.26, 29.20, 29.10, 25.68, 22.56, 21.39, 14.99, 14.39. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -128.66(s, 1F), -150.83(s, 1F). ESI-HRMS m/z calcd for $C_{30}H_{37}F_2N_6O^+$ 535.2991, found 535.2988 $[M + H]^+$. HPLC purity 98%.

*8-((4-((5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-yl)amino)phenyl)amino)-8-oxooctanoic acid***(Roxyl-zhc-101)**. To a suspension of compound (**Roxyl-zhc-57**) (565 mg, 1 mmol) in THF/CH_3OH/H_2O (5 mL/5 mL /5 mL) were added NaOH (60 mg, 4.5 mmol) and the mixture was stirred for 12 hours at room temperature. The reaction added saturated ammonium chloride aqueous solution (20 mL) and extracted by ethyl acetate. The organic phase was washed by water and brine. The organic phase was dried over $MgSO_4$, evaporated and the residue was purified by recrystallization (ethanol/ toluene) to obtain 446 mg (81%) of **Roxyl-zhc-101,** light yellow, mp 236.5 ℃. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.79 (s, 1H), 9.68 (s, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 8.26 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 12.1 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 4.84 (p, *J* = 6.9 Hz, 1H), 3.43 (s, 1H), 2.63 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.19 (t, *J* = 7.4 Hz, 2H), 1.70 – 1.43 (m, 10H), 1.37 – 1.24 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.62, 170.75, 156.34, 154.44,

153.47, 151.06 (d, J = 12.3 Hz), 149.62 (d, J = 6.4 Hz), 148.62, 147.79 (d, J = 26.0 Hz), 136.27 (d, J = 9.8 Hz), 135.73, 133.63, 133.11 (d, J = 17.0 Hz), 126.80 (t, J = 6.6 Hz), 119.23 (d, J = 19.5 Hz), 108.66 (d, J = 5.1 Hz), 106.96 (dd, J = 19.9, 8.9 Hz), 48.08, 36.28, 33.73, 28.41, 28.34, 25.05, 24.43, 20.90, 14.49. ^{19}F NMR (376 MHz, DMSO-d_6) δ -124.00(s, 1F), -146.15(s, 1F). ESI-HRMS m/z calcd for $C_{29}H_{33}F_2N_6O_3^+$ 551.2577, found 551.2572 $[M + H]^+$. HPLC purity 95%.