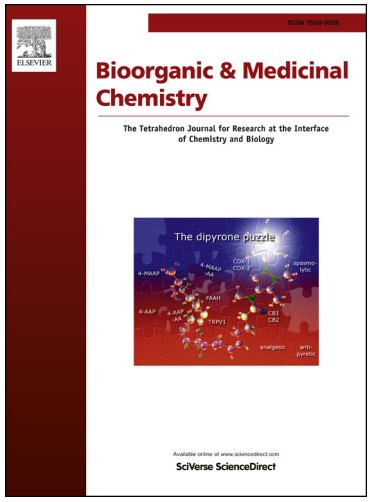

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PII: S0968-0896(15)30172-3
DOI: http://dx.doi.org/10.1016/j.bmc.2015.12.004
Reference: BMC 12697

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 8 October 2015
Revised Date: 18 November 2015
Accepted Date: 2 December 2015

Please cite this article as: Achary, R., Yun, J.I., Park, C.M., Mathi, G.R., Lee, J.Y., Ha, J.D., Chae, C.H., Ahn, S., Park, C.H., Lee, C.O., Hwang, J.Y., Yun, C-S., Jung, H.J., Cho, S.Y., Kim, H.R., Kim, P., Discovery of novel tetrahydroisoquinoline-containing pyrimidines as ALK inhibitors, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.12.004

Discovery of novel tetrahydroisoquinoline-containing pyrimidines as ALK inhibitors

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Abstract

Exploration of the 2-position side chain of pyrimidine in LDK378 with tetrahydroisoquinolines (THIQs) led to discovery of **8** and **17** as highly potent ALK inhibitors. THIQs **8** and **17** showed encouraging *in vitro* and *in vivo* xenograft efficacies, comparable with those of LDK378. Although THIQ analogs (**8a-o** and **17a-i**) prepared were not as active as their parent compounds, both **8** and **17** have significant inhibitory activities against various ALK mutant enzymes including G1202R, indicating that this series of compounds could be further optimized as useful ALK inhibitors overcoming the resistance issues found from crizotinib and LDK378.

1. Introduction

Anaplastic lymphoma kinase (ALK) is one of the receptor tyrosine kinases (RTK) belonging to the insulin receptor family [1]. Among various oncogenic fusion genes, ALK has obtained tremendous attention due to ALK-positive tumors found in various cancer types, such as anaplastic large cell lymphoma (ALCL) [2], diffuse large B-cell lymphoma (DLBCL) [1], and non-small-cell lung cancer (NSCLC) [3]. Nucleophosmin (NPM)-ALK and echinoderm microtubule-associated protein-like-4 (EML4)-ALK are most abundant fusion genes identified in ALCL and NSCLC, respectively. In 2011, crizotinib was first approved as an ALK inhibitor drug to treat ALK-positive NSCLC (Figure 1). Since the advent of crizotinib in clinics, crizotinib resistant mutants have been developed among patients treated with crizotinib within one to two years [4]. Thus, discovery efforts for second-generation ALK inhibitors which could overcome crizotinib-resistant issues have been pursued comprehensively, resulting in development of a few cornerstone compounds, such as TAE684, LDK378 (ceritinib), and CH5424802 (alectinib). Although TAE684 was discovered as a potent NPM-ALK inhibitor [5], labile nature of TAE684 under metabolic oxidation rendered its clinical trials discontinued. It was speculated that the toxicity profiles of TAE684 could be structurally originated from 1,4-diaminophenyl substitutent at the 2-position of pyrimidine [6]. To circumvent this issue, extensive modification efforts of the 2-position substituent of pyrimidine eventually produced LDK378, where metabolically unfavorable 1,4-diaminophenyl was modified by introducing 4-piperidinyl substituent [6]. LDK378 is known to be 3 to 6-fold more active than crizotinib in cell cytotoxicity assays. In terms of crizotinib resistance issues, LDK378 turned out to be active against most of the resistant mutants, such as L1196M, G1269A, I1171T, and S1206Y, but ineffective against G1202R and F1174C [4].

Recently, various discovery programs of ALK inhibitors have focused on modification of the 2-position substituent of pyrimidine in LDK378. For example, replacement of the 2-position substituent of pyrimidine in LDK378 with mono- or bicyclic 2-aminothiazole was investigated as **A** in Figure 1, leading

into discovery of highly selective tetrahydro-4*H*-thiazolo[4,5-*d*]azepine analogs [7]. Wang *et al*. reported phosphamides and carbamate analogs constructed by modifying the secondary amine of terminal piperidine in LDK378 [8]. One of the carbamates (**B**) showed efficacies as potent as LDK378 in a rat xenograft H2228 model, suggesting that modification of the terminal secondary amine could be tolerable to maintain ALK inhibitory efficacies. Analogs of 1,3-diaminophenyl connected with flexible amino acids at the terminal amine such as **C** showed potencies against both wild-type and mutant ALK kinases [9].

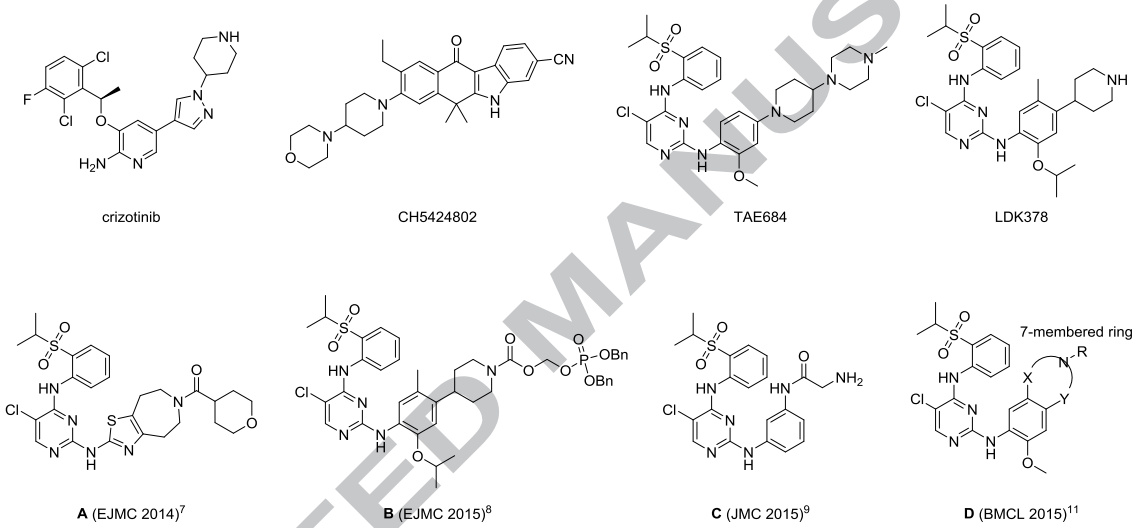


Figure 1. Known ALK inhibitors.

As our ongoing efforts to discover novel ALK inhibitors, our exploration started from modification of the 2-position substituent of pyrimidine in LDK378. Among diverse structural options, we opted to investigate bicyclic amines as the 2-position substituent of pyrimidine [10]. Thus, the bicyclic amines we designed have the following structural features: i) non-1,4-diaminophenyl, ii) more compact structure than that of LDK, and iii) alkyl groups at the para position of alkoxy groups [6]. Lately, we have reported that discovery of aminobenzazepines (**D**), one of the bicyclic amines we explored, as ALK inhibitors [11]. In the same context, our research also focused on THIQ analogs, which are non-1,4-diaminophenyl, at the 2-postion of pyrimidine rather than the lengthy substituents as in TAE684 or LDK378. THIQ could be considered a cyclized form of the 2-position substituent of LDK378, specifically, ring formation between

the methyl group and the terminal amine of piperidine (Figure 2). Interestingly, alkoxy substituted THIQs have been reported in just a few precedent reports such as for discovery of IGF-1R and IR receptor tyrosine kinase [12] and ALK inhibitors [13], the former coupled with pyrrolo[2,3-*d*]pyrimidine, the latter with pyrido[2,3-*d*]pyridazin-5-one. Herein, we report synthesis and structure-activity relationships of **KRCA** compounds as in Figure 2, bearing alkoxy substituted THIQ groups at the 2-position of pyrimidine.

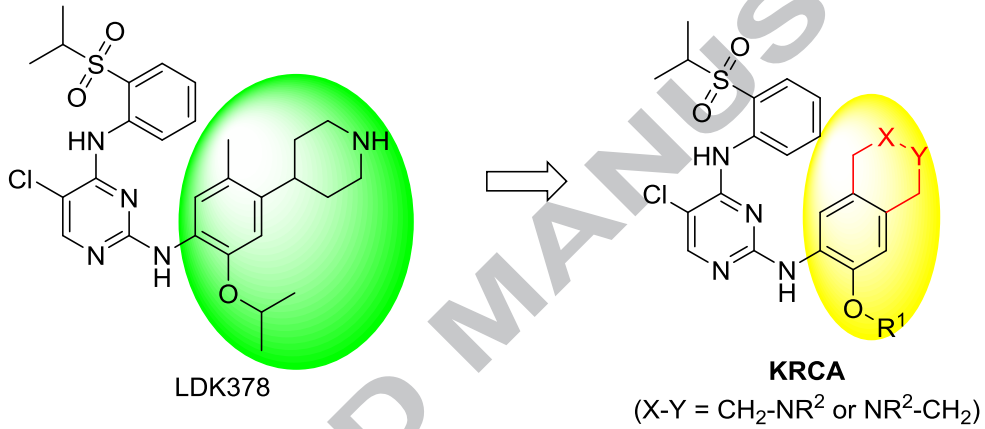
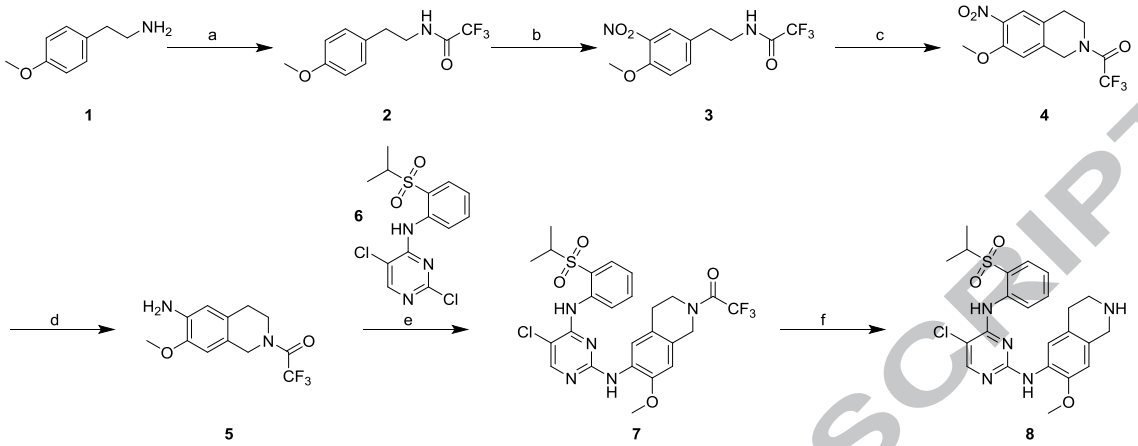


Figure 2. Design strategies.

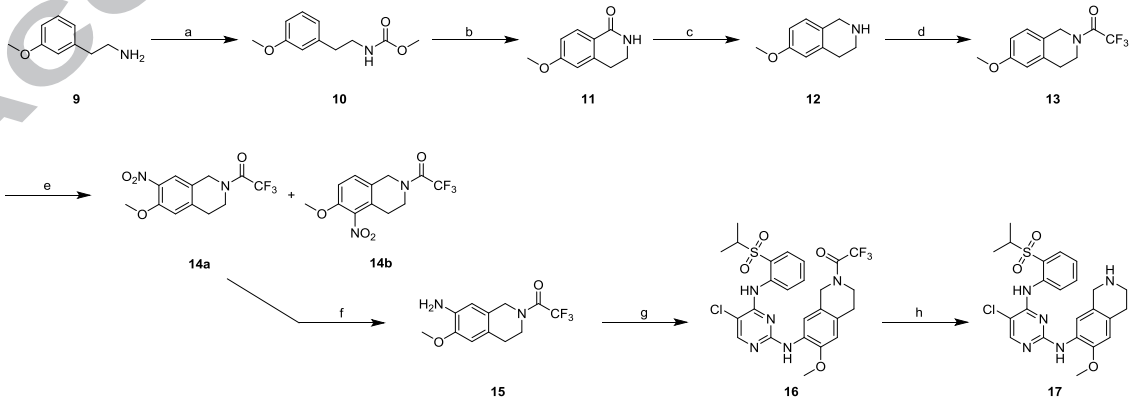
2. Chemistry

With a view to obtaining compound **8**, preparation of THIQ **5** started from commercially available 4-methoxyphenethylamine **1** (Scheme 1). Amine of **1** was protected with trifluoroacetyl to give amide **2**. Nitration of **2** gave rise to nitroamide **3** regioselectively [14]. Cyclization of **3** with paraformaldehyde under acidic heating conditions afforded *N*-protected THIQ **4** [15]. Reduction of nitro group in **4** was accomplished with Pd/C hydrogenation to facilitate amine **5**. While **5** was prepared in four steps in our hands, synthesis of Boc-protected version of **5**, instead of trifluoroacetyl, was reported in six steps starting from conversion of **1** to carbamate [13]. Coupling of **5** and commercially available compound **6** was achieved under acidic heating conditions to furnish **7** [16]. Subsequent deprotection of trifluoroacetyl group in **7** under $LiOH{\cdot}H_2O$ conditions gave rise to **8**.



Scheme 1. Reagents and conditions: (a) TFAA, Et_3N, DCM, 0 ^oC to rt, 3 h (97%); (b) HNO_3, TFA, 0 ^oC, 2 h (81%); (c) $(CH_2O)_n$, AcOH, H_2SO_4, 50 ^oC, 3.5 h (58%); (d) Pd/C, H_2 (g), MeOH, rt, 12 h (78%); (e) **6**, 0.08 M HCl in EtOEtOH, 80 ^oC, 12 h (65%); (f) $LiOH{\cdot}H_2O$, THF/H_2O/MeOH, rt, 2 h (60%).

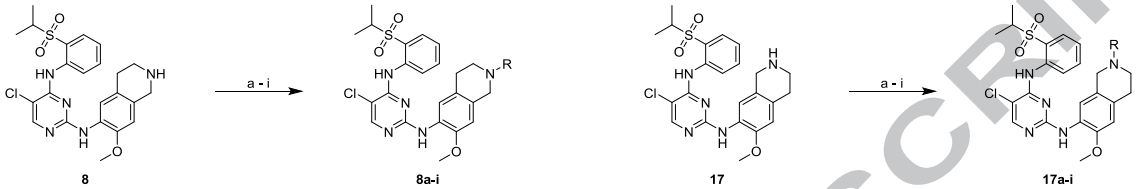
Compound **17**, tetrahydroisoquinolin-7-yl version of **8**, was synthesized with similar methods as described in Scheme 1. 3-Methoxyphenethylamine **9** was protected with methyl chloroformate to give carbamate **10** (Scheme 2). Bicyclic lactam **11** [17] was obtained by heating **10** in polyphosphoric acid [16]. Lactam carbonyl reduction of **11** was achieved in the presence of $LiAlH_4$ to facilitate THIQ **12** [18, 19]. Amine of **12** was protected with trifluoroacetyl to provide **13**. Nitration of **13** gave rise to **14a** as a major product and **14b** as a minor. Subsequently, nitro reduction of **14a**, coupling, and deprotection afforded **15**, **16,** and **17**, respectively [13].



Scheme 2. Reagents and conditions: (a) $ClCO_2Me$, K_2CO_3, DCM, 0 ^oC to rt, 4 h (87%); (b) PPA, 120 ^oC to rt, 6 h (76%); (c) $LiAlH_4$, THF, 0 ^oC to 70 ^oC, 12 h (86%); (d) TFAA, Et_3N, DCM, rt, 3 h (65%); (e)

HNO_3, TFA, 0 °C, 3 h, **14a** (55%), **14b** (24%); (f) Pd/C, H_2 (g), MeOH, rt, 12 h (80%); (g) **6**, 0.08 M HCl in EtOEtOH, 80 °C, 12 h (68%); (h) $LiOH·H_2O$, $THF/H_2O/MeOH$, rt, 2 h (64%).

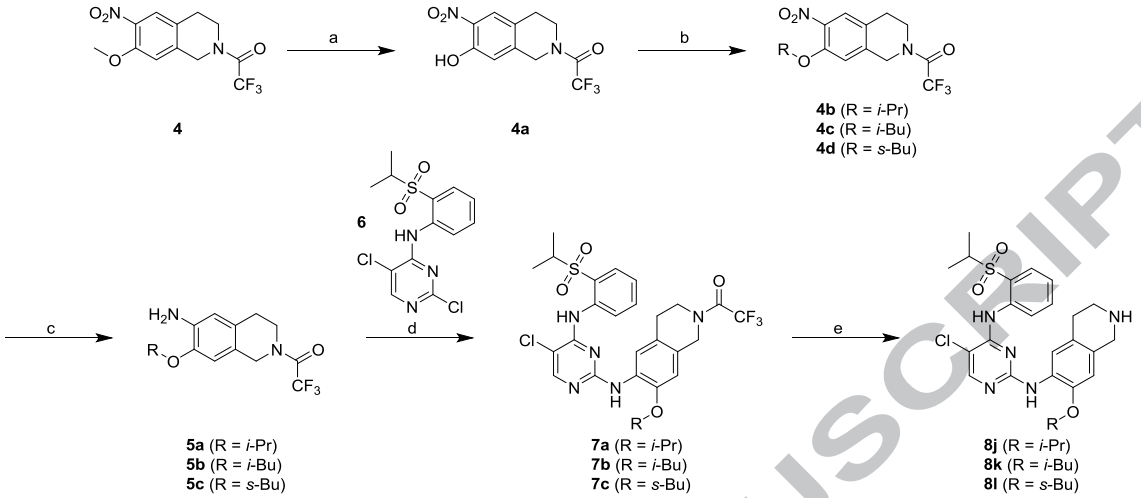
With tetraisoquinolines **8** and **17** in hand, the terminal secondary amines of THIQs were transformed to various functional groups to give **8a-i** and **17a-i** (Scheme 3).



Scheme 3. Reagents and conditions:

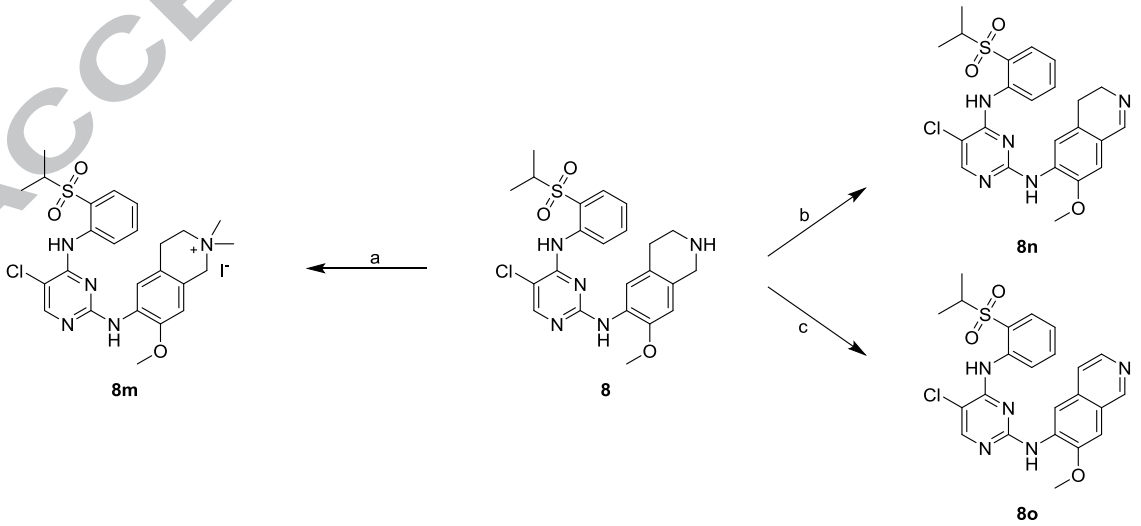
	conditions	R	Yield (%)	
			8	**17**
a	MeI, DIPEA, EtOH, rt, 18 h	Me	**8a** (75%)	**17a** (84%)
b	EtI, DIPEA, EtOH, rt, 18 h	Et	**8b** (45%)	**17b** (30%)
c	$Br(CH_2)_2OH$, Cs_2CO_3, DMF, rt, 18 h	$(CH_2)_2OH$	**8c** (94%)	**17c** (75%)
d	$Cl(CH_2)_2N(Me)_2·HCl$, Et_3N, DMF, 60 °C, 16 h	$(CH_2)_2N(Me)_2$	**8d** (9%)	**17d** (11%)
e	$ClCH_2CON(Me)_2$, K_2CO_3, CH_3CN, reflux, 18 h	$CH_2CON(Me)_2$	**8e** (13%)	**17e** (20%)
f	Ac_2O, Et_3N, DCM, rt, 18 h	Ac	**8f** (43%)	**17f** (89%)
g	$HOCH_2CO_2H$, EDCI, DMAP, Et_3N, DCM, rt, 18 h	$COCH_2OH$	**8g** (51%)	**17g** (17%)
h	EtNCO, Et_3N, DCM, rt, 18 h	CONHEt	**8h** (61%)	**17h** (55%)
i	$NH_2SO_2NH_2$, Et_3N, 1,4-dioxane, reflux, 18 h	SO_2NH_2	**8i** (48%)	**17i** (56%)

In order to study substitution effects of various alkoxy groups in **8**, at first methoxy group of **4** was transformed to alcohol **4a** under heating conditions with TfOH (Scheme 4) [20]. Compound **4a** was subsequently alkylated under Mitsunobu conditions with three different alcohols to give **4b-d** [21]. Typical nitro group reduction, coupling, and deprotection gave rise to **5a-c**, **7a-c**, and **8j-l**, respectively.



Scheme 4. Reagents and conditions: (a) TfOH, DCM, 70 °C, 10 h (42%); (b) ROH, DIAD, PPh_3, DCM, rt, 12 h (47-55%); (c) Pd/C, H_2 (g), MeOH, rt, 2 h (55-98%); (d) **6**, 0.08 M HCl in EtOEtOH, 80 °C, 12 h (53-83%); (e) K_2CO_3, EtOH/H_2O, 90 °C, 2 h (55-79%).

To investigate modification effects of the secondary amine in THIQ **8**, compounds **8m-o** were designed and synthesized (Scheme 5). Quaternary ammonium salt **8m** was prepared from **8** under heating conditions with MeI. Dihydroisoquinoline **8n** was obtained by tandem bromination and dehydrobromination using NBS and NaOH conditions, respectively [22]. Oxidation of **8** with Fremy's salt gave rise to isoquinoline **8o** [23].



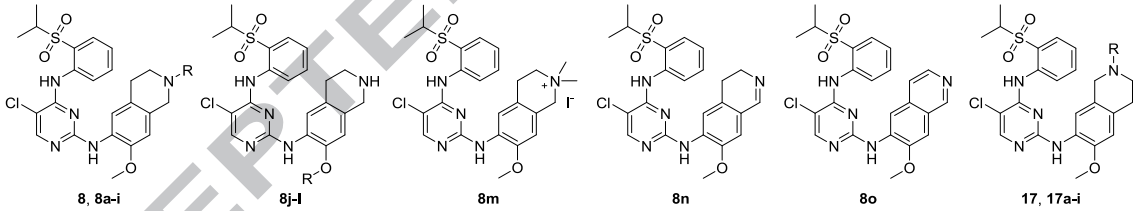
Scheme 5. Reagents and conditions: (a) MeI, THF, 70 °C, 18 h (35%); (b) i) NBS, DCM, rt, 1 h; ii) 30% NaOH (aq), rt, 1 h (51%); (c) $(KSO_3)_2NO$, 4% Na_2CO_3 (aq), rt, 48 h (10%).

3. Biological results and discussion

3.1. *In vitro* biological evaluations

All the compounds prepared were screened against not only ALK wild type and crizotinib-resistant L1196M mutant enzymes, but also three different cells having EML4-ALK fusion genes (Table 1). While THIQs **8** and **17** exhibit similar activities each other, overall, they are more active than LDK378 based on both enzyme and cell assay results. However, attempts were unfruitful to improve activities by constructing THIQ *N*-analogs, such as **8a-i** and **17a-i**. Replacing the methoxy group of **8** with bulky alkoxy groups as in **8j-l** results in almost similar enzyme activities as those of **8**, but cell activities tend to be getting lower. In case of quaternary ammonium salt **8m**, although enzyme activities are seemingly maintained, cell activities are abolished. While dihydroisoquinoline **8n** is slightly less active than **8** in enzyme assays, isoquinoline **8o** turns out to be completely inactive.

Table 1. ALK inhibitory activities against enzymes and cells.



compounds	R	enzymes		cells		
		ALK (wt) IC_{50} (μM)	ALK L1196M IC_{50} (μM)	H2228 CC_{50} (μM)	H3122 CC_{50} (μM)	Ba/F3 L1196M CC_{50} (μM)
LDK378	-	0.014	0.029	0.025	0.038	0.075
8	H	0.001	0.01	0.01	0.008	0.036
8a	Me	0.04	0.71	ND[a]	>10	>10
8b	Et	0.003	0.02	0.03	0.06	0.07
8c	$(CH_2)_2OH$	0.001	0.01	0.24	0.53	1.1
8d	$(CH_2)_2N(Me)_2$	0.018	1.18	0.41	0.24	0.28
8e	$CH_2CON(Me)_2$	0.003	0.054	0.22	0.54	0.12
8f	Ac	0.002	0.03	0.03	0.09	0.09
8g	$COCH_2OH$	0.001	0.01	0.009	0.03	0.04

8h	CONHEt	0.002	0.05	0.05	0.13	0.1
8i	SO_2NH_2	0.007	0.07	0.04	0.1	0.1
8j	*i*-Pr	0.00054	0.013	0.053	0.05	0.023
8k	*i*-Bu	0.0012	0.0012	1.71	0.54	0.12
8l	*s*-Bu	0.0012	0.0023	0.63	0.27	0.1
8m	-	0.0015	0.0033	ND[a]	2.2	>10
8n	-	0.0078	0.039	ND[a]	0.15	1.5
8o	-	0.13	ND[a]	ND[a]	1.1	>10
17	H	0.001	0.007	0.010	0.0047	0.010
17a	Me	0.003	0.03	ND	1.5	8
17b	Et	0.001	0.01	0.01	0.02	0.04
17c	$(CH_2)_2OH$	0.002	0.01	0.007	0.04	0.03
17d	$(CH_2)_2N(Me)_2$	0.016	0.072	0.58	0.21	0.17
17e	$CH_2CON(Me)_2$	0.003	0.034	0.04	0.11	0.26
17f	Ac	0.005	0.05	0.03	0.08	0.08
17g	$COCH_2OH$	0.004	0.03	0.01	0.04	0.05
17h	CONHEt	0.01	0.15	0.08	0.23	0.3
17i	SO_2NH_2	0.008	0.05	0.02	0.1	0.11

[a]ND: not determined

The activities of highly active compounds **8** and **17** were further evaluated using crizotinib-resistant ALK mutant enzymes (Table 2). Compound **8** showed similar activities as those of LDK378 against the mutants tested, except G1202R where **8** appeared to be 3-fold more active. In case of **17**, activities were 5-15 times better than those of LDK378 against all the mutant enzymes tested. In particular, both **8** and **17** apparently exhibited high activity against G1202R, which is known to be an essential mutant to overcome among patients treated with crizotinib or LDK378 [4, 24].

Table 2. Inhibitory activities against ALK mutant enzymes.

compounds	G1202R (μM)	G1269A (μM)	T1151-L1152 insT (μM)	F1174L (μM)	C1156Y (μM)
LDK378	0.020	0.0021	0.0017	0.0024	0.0042
8	0.0059	0.0017	0.0023	0.0021	0.0030
17	0.0013	0.00024	0.00033	0.00046	0.00045

3.2. Docking studies

Docking studies were performed to elucidate binding modes of **8**, **17**, and LDK378, to ALK. Binding modes of **8** and **17** turned out to be similar to that of LDK378 as shown in Figure 3 [4]. In particular, protonated secondary amines on THIQs of **8** and **17** have an identical electrostatic interaction with Asp1203 despite their different puckers of THIQ (Figures 3a and 3b), which mimics a charge-charge interaction between protonated piperidine of LDK378 and Glu1210 (Figure 3c) [6]. These key interactions could provide a rationale to comprehend similar ALK activity results between THIQs (**8** and **17**) and LDK378. On the other hand, the G1202R mutation leads to bulkier residues around the binding pocket, which could cause more steric interference in binding modes of ALK inhibitors (Figures 3d and 3e) [25]. As **8** and **17** have more compact THIQ side chains than that of LDK378, **8** and **17** could be affected by less steric interference than LDK378, consistent with high activities of THIQs against G1202R mutant.

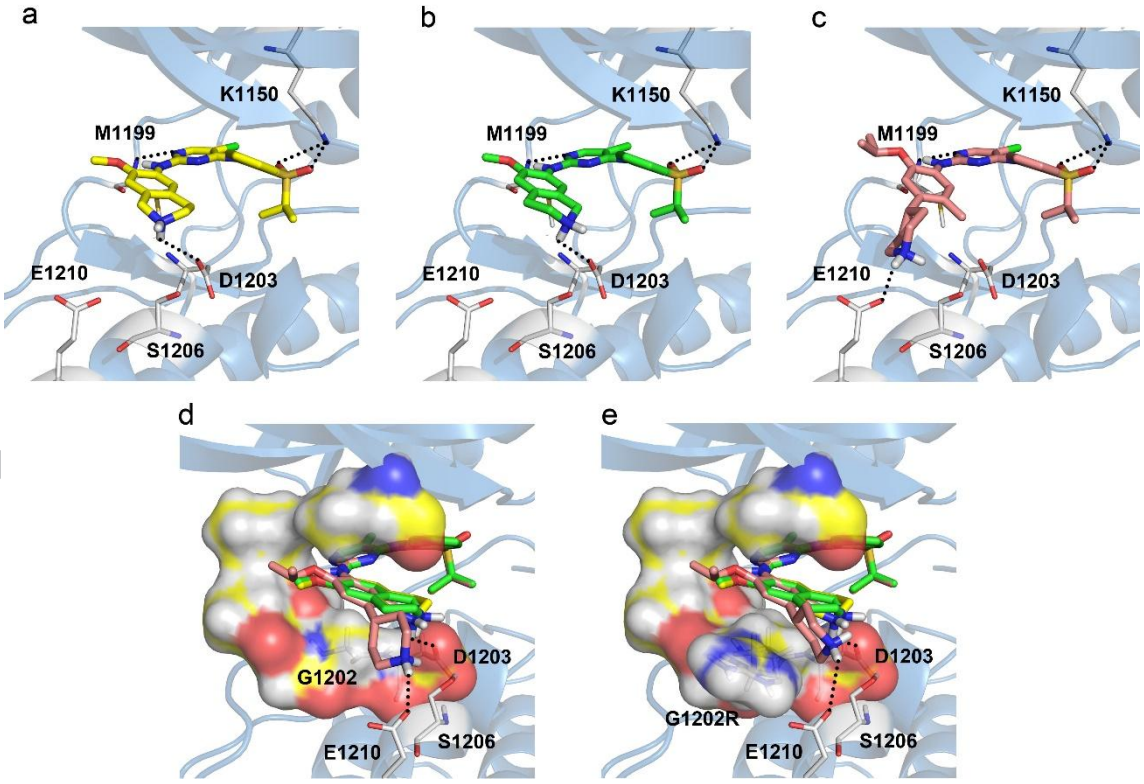


Figure 3. Binding modes of **8** (a), **17** (b), and LDK378 (c) in wild-type ALK and surface delineation of wild-type (d) and G1202R mutant (e) ALKs with ALK inhibitors. ALK is represented by ribbons with the

interacting residues as sticks. Hydrogen bonds and electrostatic interactions are drawn as dashed black lines. Blue and red colors on surface represent positively charged and negatively charged residues, respectively.

3.3. Stability and pharmacokinetic profiles

NADPH-dependent oxidative metabolism of compounds **8** and **17** in liver microsomes of different species were evaluated after 30 min incubation of each sample at 30 ^{o}C (Table 3). Compared with LDK378, **8** and **17** seem to be slightly less stable. *In vivo* pharmacokinetics (PK) of compounds **8** and **17** was examined in male rats with a dose of 10 or 20 mpk. C_{max} and AUC of **8** and **17** are significantly improved, compared with those of LDK378.

Table 3. Metabolic stability and PK data.

compounds	rat liver microsomes % remaining	human liver microsomes % remaining	rat PO C_{max} (μg/mL) (10 mpk)	rat PO AUC (μg·h/mL) (10 mpk)
LDK378	98	88	0.090	1.400
8	81	79	1.120[a]	15.900[a]
17	81	59	0.325	4.63

[a]20 mpk

3.4. *In vivo* xenograft evaluations

For *in vivo* xenograft study, H3122 cells were implanted subcutaneously into the right flanks of female nude mice. Drug treatment was initiated right after tumor volumes reached about 190 mm^3. 50 mpk of each LDK378, **8**, and **17** was administered by oral administration for 14 days (Figure 4). Overall, it turned out that **8** and **17** were as active as LDK378, suggesting that *in vitro* assay results could be correlated with *in vivo* xenograft model data in this series of compounds. In addition, there are no significant body weight changes detected among LDK378, **8**, and **17** (Supplementary data).

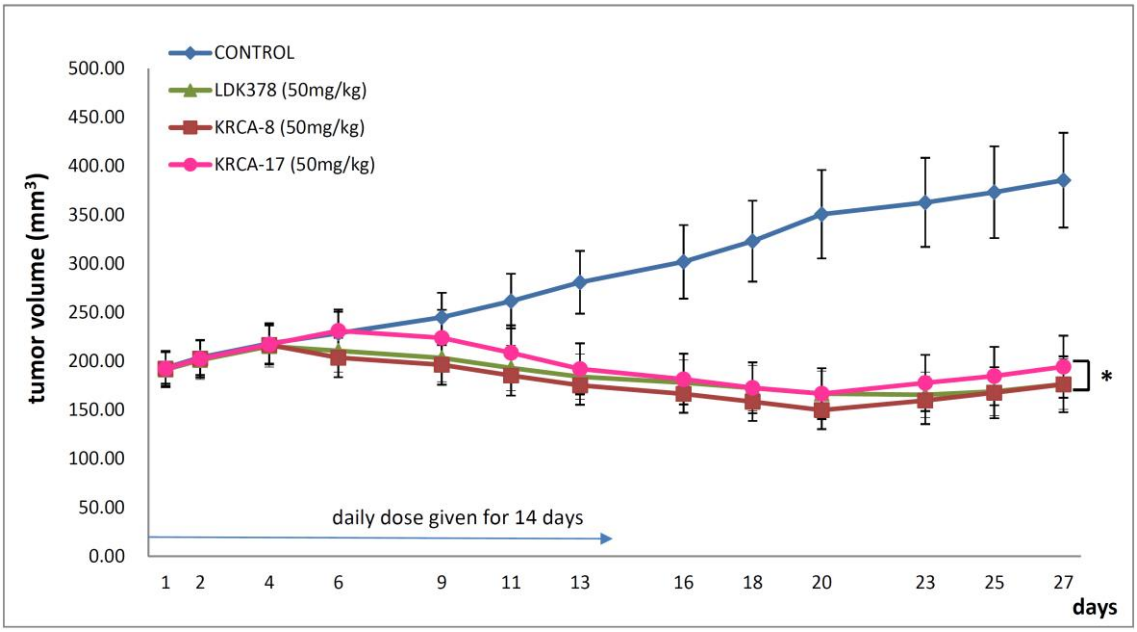


Figure 4. Antitumor activities of compounds in H3122 murine xenograft model.
*$p < 0.01$ versus control group on the final day using Student's *t*-test.

3.5. Kinase profiling

Out of the two promising THIQ compounds (**8** and **17**), the kinase profiling assay of compound **8** was performed against 96 kinases at 1 μM (Supplementary data). While LDK378 inhibits only 9 kinases at a level of over 90% inhibition, compound **8** apparently inhibits about one-third of 96 kinases tested, suggesting THIQ-containing ALK inhibitors could be multi-targeting kinase inhibitors.

4. Conclusion

THIQ-containing pyrimidine analogs **8** and **17** were discovered as highly potent ALK inhibitors, showing their *in vitro* and *in vivo* efficacies comparable with those of LDK378. However, in case of THIQ analogs (**8a**-**o** and **17a**-**i**), the activities were dramatically diminished, compared with their parent compounds. These data and docking results suggest that in this series of compounds the terminal secondary amine on THIQ may play a significant role in binding the ALK enzyme. This is also concurred with a recent docking study report where the terminal piperidine amine of LDK378 interacts with Glu1210 of ALK by forming a salt bridge [6]. It is notable to mention that compounds **8** and **17** have significant inhibitory activities against five different ALK mutant enzymes including G1202R. Since both crizotinib and LDK378 cannot overcome the resistance issues related to G1202R mutant, this THIQ scaffold could be useful to develop ALK inhibitors circumventing the resistance issues [4, 26]. Encouraged by these promising results, further optimization efforts of both **8** and **17** are underway and the progress will be reported in due course.

5. Experimental

5.1. Chemistry

Solvents and reagents were obtained from commercial vendors and used as received. Compound **6** was purchased from Chemlin (Nanjing, China). TLC was carried out on precoated silica gel F_{254} plate (Merck, art. 5715) and column chromatography was performed using silica gel (Merck, mesh 230-400 μm). ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance 300 and Bruker Avance, using TMS or

the solvent peak as an internal standard. LC/MS analysis was conducted on the Waters Acquity UPLC system with electrospray ionization in positive ion mode. EI/MS data was obtained with Varian 1200L. HRMS was conducted on the JMS-700 (JEOL**,** Tokyo**,** Japan).

5.1.1. 2,2,2-Trifluoro-*N*-(4-methoxyphenethyl)acetamide (2)

To a solution of 4-methoxyphenethylamine (**1**, 12.0 g, 79.4 mmol) in DCM (100 mL) was added trifluoroacetic anhydride (13.5 mL, 95.3 mmol) followed by dropwise addition of Et_3N (27.6 mL, 198 mmol) at 0 ^oC. The reaction mixture was allowed to stir at rt for 3 h, quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using EtOAc/Hexanes (1/2) as an eluent to afford **2** (19.0 g, 76.9 mmol, 97%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 3.71 (s, 3H), 3.39-3.35 (m, 2H), 2.72 (t, *J* = 7.2 Hz, 2H); LC/MS *m*/*z* 248.30 [M + H^+].

5.1.2. 2,2,2-Trifluoro-*N*-(4-methoxy-3-nitrophenethyl)acetamide (3)

To a solution of **2** (20.0 g, 80. 9 mmol) in TFA (206 mL) was added conc. HNO_3 (8.49 g, 80.89 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 2 h, concentrated under vacuum to remove TFA and extracted with EtOAc. The organic layers were washed with H_2O and saturated NaCl (aq), dried over Na_2SO_4, and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using EtOAc/Hexanes (1/2) as an eluent to afford **3** (19.2 g, 65.7 mmol, 81%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.49 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 3.42 (q, *J* = 6.9 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H); LC/MS *m*/*z* 293.28 [M + H^+], 585.44 [2M + H^+].

5.1.3. 2,2,2-Trifluoro-1-(7-methoxy-6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (4)

To a mixture of H_2SO_4 (150 mL) and AcOH (100 mL) was added **3** (25.0 g, 85.6 mmol) followed by paraformaldehyde (14.5 g, mmol). The reaction mixture was heated at 50 ^oC for 3.5 h, quenched with ice cold water, and extracted with EtOAc. The combined organic layers were dried over Na_2SO and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using EtOAc/Hexanes (1/1) as an eluent to afford **4** (15.1 g, 49.6 mmol, 58%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.38 (s, 0.4H), 7.33 (s, 0.6H), 4.85 (s, 0.7H), 4.81 (s, 1.3H), 3.88 (s, 3H), 3.80-3.78 (m, 2H), 2.86-2.92 (m, 2H); LC/MS *m*/*z* 305.40 [M + H^+].

5.1.4. 2,2,2-Trifluoro-1-(7-hydroxy-6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (4a)

To a solution of **4** (1.00 g, 3.29 mmol) in DCM (10 mL) was added triflic acid (3.00 mL, 32.9 mmol). The reaction mixture was heated at 70 ^oC for 10 h, allowed to cool rt, and quenched with ice cold water. This mixture was basified with $NaHCO_3$ (aq) and extracted with EtOAc (2 x 50 mL). The organic layers were washed with saturated NaCl (aq) followed by H_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography using EtOAc/Hexanes (1/1) as an eluent to afford **4a** (400 mg, 1.38 mmol, 42%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (br, s, 1H), 7.96 (s, 1H), 6.98 (s, 0.7H), 6.95 (s, 0.3H), 4.82 (s, 1.4H), 4.76 (s, 0.6H), 4.13-3.82 (m, 2H), 2.99-2.96 (m, 2H); LC/MS *m*/*z* 290.8 [M + H^+].

5.1.5. General procedure for the preparation of 4b-d

To a solution of **4a** (140 mg, 0.480 mmol) in DCM (2.0 mL) was added an appropriate alcohol (0.62 mmol). Ph_3P (194 mg, 0.720 mmol) and DIAD (146 mg, 0.720 mmol) were added to this mixture at 0 ^oC and the reaction mixture was stirred at rt for 12 h. The reaction mixture was quenched with H_2O and extracted with DCM. The organic layers were washed with brine solution followed by H_2O. The

combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using EtOAc/Hexanes (1/2) as an eluent to afford **4b-d**, respectively.

5.1.5.1. 2,2,2-Trifluoro-1-(7-isopropoxy-6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (4b)

Isopropanol (37 mg, 0.62 mmol) was used and **4b** (75.0 mg, 0.226 mmol, 47%) was obtained as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.85 (s, 0.7H), 6.81 (s, 0.3H), 4.81 (s, 1.4H), 4.75 (s, 0.6H), 4.63 (sept, *J* = 6.0 Hz, 1H), 3.93-3.85 (m, 2H), 2.96-2.92 (m, 2H), 1.39 (d, *J* = 6.0 Hz, 6H); LC/MS *m*/*z* 333.2 [M + H^+].

5.1.5.2. 2,2,2-Trifluoro-1-(7-isobutoxy-6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (4c)

Isobutanol (46 mg, 0.62 mmol) was used and **4c** (95.0 mg, 0.274 mmol, 53%) was obtained as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.86 (s, 0.6H), 6.83 (s, 0.4H), 4.82 (s, 1.3H), 4.77 (s, 0.7H), 3.91-3.83 (m, 4H), 2.95-2.94 (m, 2H), 2.19-2.11 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 6H); LC/MS *m*/*z* 345.9 [M + H^+].

5.1.5.3. 1-(7-(*sec*-Butoxy)-6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (4d)

2-Butanol (46 mg, 0.62 mmol) was used and **4d** (98.1 mg, 0.283 mmol, 55%) was obtained as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.85 (s, 0.7H), 6.82 (s, 0.3H), 4.82 (s, 1.3H), 4.76 (s, 0.7H), 4.43-4.39 (m, 1H), 3.93-3.86 (m, 2H), 2.97-2.93 (m, 2H), 1.82-1.65 (m, 2H), 1.35 (d, *J* = 5.70 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); LC/MS *m*/*z* 345.0 [M + H^+].

5.1.6. Representative procedure for the preparation of 5, 5a-c: 1-(6-Amino-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (5)

To a solution of **4** (3.04 g, 10.0 mmol) in MeOH (50 mL) was added Pd/C (304 mg, 10% wt/wt) and the mixture was stirred under H_2 (g) at rt for 12 h. The reaction mixture was filtered through a celite bed and washed with MeOH. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography using EtOAc/Hexanes (1/1) to afford **5** (2.14 g, 7.80 mmol, 78%) as a slightly yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.69 (s, 0.4H), 6.66 (s, 0.6H), 6.41 (s, 1H), 4.65 (br, s, 2H), 4.61-4.46 (m, 2H), 3.79-3.70 (m, 2H), 3.72 (s, 3H), 2.66-2.72 (m, 2H); LC/MS *m*/*z* 274.7 [M + H$^+$].

5.1.6.1. 1-(6-Amino-7-isopropoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (5a)

4b (50 mg, 0.15 mmol) in MeOH (1 mL), Pd/C (10 mg, 10% wt/wt), and 2 h reaction time were used and **5a** (41.2 mg, 0.136 mmol, 91%) was obtained as a slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55-6.49 (m, 2H), 4.67 (s, 1.3H), 4.62 (s, 0.7H), 4.81 (sept, *J* = 4.8 Hz, 1H), 3.85-3.79 (m, 2H), 3.63 (br, s, 2H), 2.80 (br, s, 2H), 1.34 (d, *J* = 4.8 Hz, 6H); LC/MS *m*/*z* 302.8 [M + H$^+$].

5.1.6.2. 1-(6-Amino-7-isobutoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (5b)

4c (90 mg 0.26 mmol) in MeOH (1 mL), Pd/C (9 mg, 10% wt/wt), and 2 h reaction time were used and **5b** (80 mg, 0.25 mmol, 98%) was obtained as a slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 1H), 6.48 (s, 1H), 4.67 (s, 1.2H), 4.62 (s, 0.8H), 3.83-3.79 (m, 4H), 3.72 (br, s, 2H), 2.79 (br, s, 2H), 2.14-2.09 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 6H); LC/MS *m*/*z* 316.7 [M + H$^+$], 631.2 [2M + H$^+$].

5.1.6.3. 1-(6-Amino-7-(*sec*-butoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1 (5c)

4d (90 mg 0.26 mmol) in MeOH (1 mL), Pd/C (9 mg, 10% wt/wt), and 2 h reaction time were used and **5c** (45.0 mg, 0.142 mmol, 55%) was obtained as a slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53-6.49 (m, 2H), 4.67 (s, 1.3H), 4.62 (s, 0.7H), 4.26-4.25 (m, 1H), 3.83-3.79 (m, 4H), 2.79-2.78 (m, 2H), 1.81-1.64 (m, 2H), 1.30 (d, *J* = 5.7 Hz, 3H), 0.99 (t, *J* = 6.9 Hz, 3H); LC/MS *m*/*z* 316.8 [M + H$^+$],

631.1 [2M + H^+].

5.1.7. Representative procedure for the preparation of 7, 7a-c: 1-(6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (7)

To a solution of **5** (100 mg, 0.37 mmol) in 0.08 M HCl in ethoxyethanol (1.0 mL) was added 2,5-dichloro-*N*-(2-(isopropylsulfonyl)phenyl)pyrimidin-4-amine (**6**, 152 mg, 0.44 mmol) and heated at 80 ^oC for 12 h. The reaction mixture was allowed to cool rt and solid precipitated was filtered, and washed with EtOH and dried under vacuum to afford **7** (138 mg, 0.236 mmol, 65%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.54 (t, *J* = 7.9 Hz, 1H), 8.19 (s, 1H), 8.10 (s, 0.4H), 8.13 (s, 0.6H), 7.95 (d, *J* = 6.6 Hz, 1H), 7.67-7.58 (m, 2H), 7.33-7.28 (m, 1H), 6.66 (s, 0.4H), 6.63 (s, 0.4H), 4.76 (s, 1.3H), 4.72 (s, 0.7H), 3.85 (s, 3H), 3.84-3.78 (m, 2H), 3.27 (sept, *J* = 6.9 Hz, 1H), 2.83-2.74 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 6H); LC/MS *m*/*z* 584.1 [M + H^+].

5.1.7.1. 1-(6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-isopropoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (7a)

The same method as **7** was used except replacing **5** with **5a** (50 mg, 0.17 mmol) to afford **7a** (61 mg, 0.10 mmol, 53%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.52 (t, J = 7.8 Hz, 1H), 8.18 (s, 1H), 8.09 (d, *J* = 9.9 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.62-7.58 (m, 2H), 7.32-7.26 (m, 1H) 6.65 (s, 0.4H), 6.62 (s, 0.6H), 4.73 (s, 1H), 4.68 (s, 1H), 4.58 (sept, *J* = 6.0 Hz, 1H), 3.88-3.79 (m, 2H), 3.26 (sept *J* = 6.9 Hz, 1H), 2.76-2.69 (m, 2H), 1.58 (d, *J* = 6.0 Hz, 6H), 1.32 (d, *J* = 6.9 Hz, 6H); LC/MS *m*/*z* 612.0 [M + H^+].

5.1.7.2. 1-(6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-isobutoxy-

3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (7b)

The same method as **7** was used except replacing **5** with **5b** (65 mg, 0.21 mmol) to afford **7b** (97 mg, 0.16 mmol, 83%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.57-8.52 (m, 1H), 8.19 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.62-7.58 (m, 2H), 7.31-7.26 (m, 1H) 6.64 (s, 0.6H), 6.61 (s, 0.4H), 4.73 (s, 1H), 4.69 (s, 1H), 3.79-3.86 (m, 4H), 3.25 (sept, *J* = 6.9 Hz, 1H), 2.77 (br, s, 2H), 2.21-2.14 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 6H), 1.08 (d, *J* = 6.6 Hz, 6H); LC/MS *m*/*z* 626.0 [M + H^+].

5.1.7.3. 1-(7-(*sec*-Butoxy)-6-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (7c)

The same method as **7** was used except replacing **5** with **5c** (45 mg, 0.14 mmol) to afford **7c** (50 mg, 0.079 mmol, 62%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.55-8.52 (m, 1H), 8.18 (s, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.66-7.61 (m, 2H), 7.31-7.26 (m, 1H) 6.64 (s, 0.7H), 6.61 (s, 0.3H), 4.72 (s, 1H), 4.68 (s, 1H), 4.35-4.34 (m, 1H), 3.85-3.81 (m, 2H), 3.26 (sept, *J* = 6.6 Hz, 1H), 2.75 (br, s, 2H), 1.82-1.69 (m, 2H), 1.34 (d, *J* = 5.4 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 6H), 1.02 (t, *J* = 7.5 Hz, 3H); LC/MS *m*/*z* 626.0 [M + H^+].

5.1.8. 5-Chloro-N^4-(2-(isopropylsulfonyl)phenyl)-N^2-(7-methoxy-1,2,3,4-tetrahydroisoquinolin-6-yl)pyrimidine-2,4-diamine (8)

To a solution of **7** (130 mg, 0.220 mmol) in THF (1.0 mL) was added a solution of $LiOH·H_2O$ (47.0 mg, 1.11 mmol) in H_2O (0.5 mL) followed by MeOH (0.25 mL). The reaction mixture was stirred at rt for 2 h. The solvents were evaporated under vacuum and extracted with EtOAc. The organic layers were washed with H_2O and saturated NaCl (aq). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to get a crude product which was purified through silica gel column chromatography using MeOH/DCM (1:9) as an eluent to afford **8** (64 mg, 0.13 mmol, 60%) as a white

solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.94 (dd, 1.5, 8.1 Hz, 1H), 7.66 (dt, *J* = 1.5, 8.7 Hz, 1H), 7.55 (s, 1H), 7.32-7.26 (m, 1H), 6.55 (s, 1H), 4.04 (br, s, 2H), 3.88 (s, 3H), 3.25 (sept, *J* = 6.9 Hz, 1H), 3.18 (br, s, 2H), 2.67 (br, s, 2H), 2.45 (br, s, 1H), 1.33 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 155.4, 155.3, 146.5, 138.4, 134.6, 131.3, 128.9, 127.0, 126.3, 124.9, 123.6, 123.2, 119.2, 107.7, 106.0, 55.8, 55.5, 48.0, 44.0, 28.8, 15.4; LC/MS *m*/*z* 488.2 [M + H^+]; HRMS (EI) calcd for $C_{23}H_{26}ClN_5O_3S$ [M^+] 487.1445, found 487.1432.

5.1.9. 5-Chloro-*N*^{4}-(2-(isopropylsulfonyl)phenyl)-*N*^{2}-(7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)pyrimidine-2,4-diamine (8a)

To a solution of **8** (50 mg, 0.10 mmol) in EtOH (1 mL) was added DIPEA (0.040 mL, 0.25 mmol) and MeI (0.010 mL, 0.15 mmol) at 0 ^{o}C. The reaction mixture was stirred at rt for 18 h, quenched with water, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8a** (38 mg, 0.075 mmol, 75%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 8.14 (s, 1H), 7.95-7.80 (m, 2H), 7.53 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.28-7.27 (m, 1H), 6.75 (s, 1H), 4.60 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.92 (s, 3H), 3.30-3.15 (m, 6H), 1.30 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 502.1 [M + H^+].

5.1.10. 5-Chloro-*N*^{2}-(2-ethyl-7-methoxy-1,2,3,4-tetrahydroisoquinolin-6-yl)-*N*^{4}-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (8b)

The same method as **8a** was used except replacing MeI with EtI (0.020 mL, 0.15 mmol) to afford **8b** (23 mg, 0.045 mmol, 45%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.15 (s, 1H), 7.99-7.90 (m, 2H), 7.73-7.59 (m, 1H), 7.53 (s, 1H), 7.34-7.22 (m, 1H), 6.54 (s, 1H), 3.85 (s, 3H), 3.68-3.54 (m, 2H), 3.23-3.08 (m, 1H), 2.90 (dd, *J* = 15.9, 5.1 Hz, 4H), 2.59 (q, *J* = 6.8 Hz, 2H), 1.38-1.16 (m, 9H); LC/MS *m*/*z* 516.2 [M + H^+].

5.1.11. 2-(6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-ol (8c)

To a solution of **8** (50 mg, 0.10 mmol) in DMF (1 mL) was added 2-bromoethanol (0.010 mL, 0.15 mmol) and Cs_2CO_3 (81 mg, 0.25 mmol) at 0 ^oC. The reaction mixture was stirred at rt for 18 h, quenched with water, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8c** (50 mg, 0.094 mmol, 94%) as a slightly yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.48 (q, *J* = 3.8 Hz, 1H), 8.15 (d, *J* = 10.1 Hz, 2H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.36-7.28 (m, 1H), 6.71 (s, 1H), 4.21 (s, 2H), 4.21 (s, 4H), 4.05-3.77 (m, 8H), 3.31-3.16 (m, 1H), 3.06 (s, 1H), 1.30 (d, *J* = 6.6 Hz, 6H); LC/MS *m*/*z* 532.1 [M + H^+].

5.1.12. 5-Chloro-*N*^{2}-(2-(2-(dimethylamino)ethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-6-yl)-*N*^{4}-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (8d)

To a solution of **8** (50 mg, 0.10 mmol) in DMF (1 mL) was added Et_3N (0.030 ml, 0.22 mmol) at rt. The mixture was stirred for 15 min at rt, and then 2-chloro-*N*,*N*-dimethylethanamine hydrochloride (18 mg, 0.13 mmol) was added to the mixture at rt. The reaction mixture was stirred at 60 ^oC for 16 h, quenched with water, acidified with 1 N HCl (aq), and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/7) as an eluent to afford **8d** (5.0 mg, 0.0090 mmol, 9%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.56-8.50 (m, 1H), 8.27-8.18 (m, 2H), 8.07 (d, *J* = 6.9 Hz, 1H), 7.95-7.93 (m, 1H), 7.66-7.55 (m, 2H), 6.62 (d, *J* = 6.9 Hz, 1H), 4.64-4.51 (m, 2H), 3.89 (s, 3H), 3.79-3.74 (m, 1H), 3.68-3.63 (m, 4H), 3.28-3.23 (m, 1H), 3.13-3.10 (m, 1H), 2.73-2.67 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.26 (s, 6H); LC/MS *m*/*z* 559.1 [M + H^+].

5.1.13. 2-(6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-dimethylacetamide (8e)

To a solution of **8** (50 mg, 0.10 mmol) in CH_3CN (1 mL) was added 2-chloro-*N*,*N*-dimethylacetamide (0.02 mL, 0.15 mmol) and K_2CO_3 (35 mg, 0.35 mmol) at rt. The reaction mixture was refluxed for 18 h, quenched with water, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8e** (7.6 mg, 0.013 mmol, 13%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) 9.58 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 6.66 (s, 1H), 5.47-5.23 (m, 4H), 5.10 (d, *J* = 16.1 Hz, 2H), 4.78-4.60 (m, 2H), 3.91 (s, 3H), 3.35-3.20 (m, 1H), 3.09 (s, 3H), 2.98 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 573.1 [M + H^+].

5.1.14. 1-(6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (8f)

To a solution of **8** (50 mg, 0.10 mmol) in DCM (1 mL) was added Et_3N (0.030 ml, 0.22 mmol) and acetic anhydride (0.020 mL, 0.15 mmol) at 0 ^{o}C. The mixture was stirred for 18 h at rt, quenched with water, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8f** (23 mg, 0.043 mmol, 43%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.56-8.49 (m, 1H), 8.17 (s, 1H), 8.06 (s, 0.4H), 8.05 (s, 0.6H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.70-750 (m, 2H), 7.35-7.26 (m, 1H), 6.65 (s, 0.6H), 6.61 (s, 0.4H), 4.68 (s, 1H), 4.58 (s, 1H), 3.89 (s, 1.2H), 3.87 (s, 1.8H), 3.79 (t, *J* = 5.6 Hz, 1H), 3.65 (t, *J* = 5.6 Hz, 1H), 3.25 (sept, *J* = 6.8 Hz, 1H), 2.73 (t, *J* = 5.4 Hz, 1H), 2.64 (t, *J* = 5.4 Hz, 1H), 2.18 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 530.2 [M + H^+].

5.1.15. 1-(6-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-hydroxyethan-1-one (8g)

To a solution of **8** (50 mg, 0.10 mmol) in DCM (1 mL) was added glycolic acid (11 mg, 0.15 mmol),

EDCI (23 mg, 0.15 mmol), DMAP (20 mg, 0.15 mmol), and Et_3N (0.010 ml, 0.072 mmol) at rt. The mixture was stirred for 18 h at rt, quenched with water, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8g** (28 mg, 0.051 mmol, 51%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.53 (t, *J* = 8.5 Hz, 1H), 8.17 (s, 1H), 8.08 (d, *J* = 3.6 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.68-7.3 (m, 2H), 7.35-7.34 (m, 1H), 6.62 (d, *J* = 18.1 Hz, 1H), 4.73 (s, 1H), 4.39 (s, 1H), 4.25 (s, 2H), 3.89 (s, 3H), 3.80-3.56 (m, 2H), 3.48 (t, *J* = 5.6 Hz, 1H), 3.24 (q, *J* = 6.9 Hz, 1H), 2.80-2.62 (m, 2H), 1.31 (d, *J* = 6.0 Hz, 6H); LC/MS *m*/*z* 546.1 [M + H^+].

5.1.16. 6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-*N*-ethyl-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (8h)

To a solution of **8** (50 mg, 0.10 mmol) in DCM (1 mL) was added ethylisocyanate (0.010 mL, 0.15 mmol) and Et_3N (0.010 ml, 0.072 mmol) at 0 ^oC. The mixture was stirred for 18 h at rt, quenched with water, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8h** (34 mg, 0.061 mmol, 61%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.56 (s, 1H), 7.36-7.20 (m, 1H), 6.64 (s, 1H), 4.55-4.37 (m, 2H), 3.87 (s, 3H), 3.70-3.53 (m, 2H), 3.40-3.16 (m, 3H), 2.67 (t, *J* = 5.5 Hz, 2H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.18 (t, *J* = 7.2 Hz, 3H); LC/MS *m*/*z* 559.1 [M + H^+].

5.1.17. 6-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-7-methoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (8i)

To a solution of **8** (50 mg, 0.10 mmol) in 1,4-dioxane (1 mL) was added sulfamide (14 mg, 0.15 mmol) and Et_3N (0.010 ml, 0.072 mmol) at rt. The mixture was refluxed for 18 h, quenched with water, and

extracted with DCM. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography using MeOH/DCM (1/10) as an eluent to afford **8i** (27 mg, 0.048 mmol, 48%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.52 (d, *J* = 8.3 Hz, 1H), 8.17 (s, 1H), 8.06(s, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 6.58 (s, 1H), 4.48 (s, 2H), 4.37 (s, 2H), 3.87 (s, 3H), 3.50 (t, *J* = 5.8 Hz, 2H), 3.26 (sept, *J* = 6.8 Hz, 1H), 2.80 (t, *J* = 5.8 Hz, 2H), 1.31 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 567.1 [M + H^+].

5.1.18. 5-Chloro-N^2-(7-isopropoxy-1,2,3,4-tetrahydroisoquinolin-6-yl)-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (8j)

To a solution of **7a** (50 mg, 0.08 mmol) in EtOH (2.0 mL) was added a solution of K_2CO_3 (45 mg, 0.33 mmol) in H_2O (1.0 mL) and heated at 100 ^{o}C for 1 h. The reaction mixture was evaporated, extracted with EtOAc, and washed with saturated NaCl (aq). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using MeOH/DCM (1:9) as an eluent to afford **8j** (16 mg, 0.032 mmol, 55%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (br, s, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 8.16 (s, 1H), 7.96-7.92 (m, 1H), 7.66-7.59 (m, 2H), 7.29-7.24 (m, 1H), 6.54 (s, 1H), 4.54 (sept, *J* = 6.3 Hz, 1H), 3.95 (s, 2H), 3.26 (sept, *J* = 6.9 Hz, 1H), 3.13-3.08 (m, 2H), 2.59-2.55 (m, 2H), 1.93 (br, s, 1H), 1.37 (d, *J* = 6.3 Hz, 6H), 1.31 (d, *J* = 6.9 Hz, 6H); LC/MS *m*/*z* 516.0 [M + H^+].

5.1.19. 5-Chloro-N^2-(7-isobutoxy-1,2,3,4-tetrahydroisoquinolin-6-yl)-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (8k)

The same method as **8j** was used except replacing **7a** with **7b** (75 mg, 0.12 mmol) to afford **8k** (44 mg, 0.083 mmol, 70%) as a white solid. ^{1}HNMR (300 MHz, $CDCl_3$) δ 9.49 (br, s, 1H), 8.56 (d, *J* = 8.4 Hz,

1H), 8.16 (s, 1H), 7.94-7.91 (m, 2H), 7.64-7.56 (m, 2H), 7.26-7.24 (m, 1H), 6.52 (s, 1H), 3.96 (s, 2H), 3.76 (d, *J* = 6.3 Hz, 2H), 3.26 (sept, *J* = 6.6 Hz, 1H), 3.10 (br, s, 2H), 2.59 (br, s, 2H), 2.18-2.14 (m, 1H), 1.71 (br, s, 1H), 1.31 (d, *J* = 6.6 Hz, 6H), 1.06 (d, *J* = 6.6 Hz, 6H); LC/MS *m*/*z* 530.0 [M + H^+].

5.1.20. N^2-(7-(*sec*-Butoxy)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-chloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (8l)

The same method as **8j** was used except replacing **7a** with **7c** (35 mg, 0.06 mmol) to afford **8l** (23 mg, 0.043 mmol, 79%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (br, s, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 7.95-7.90 (m, 2H), 7.64-7.59 (m, 2H), 7.28-7.23 (m, 1H), 6.52 (s, 1H), 4.31-4.29 (m, 1H), 3.95 (s, 2H), 3.24 (sept, *J* = 6.6 Hz, 1H), 3.10 (br, s, 2H), 2.57 (br, s, 2H), 2.25 (br, s, 1H), 1.83-1.61 (m, 2H), 1.30 (d, *J* = 6.6 Hz, 9H), 0.99 (t, *J* = 7.2 Hz, 3H); LC/MS *m*/*z* 530.0 [M + H^+].

5.1.21. 5-Chloro-N^4-(2-(isopropylsulfonyl)phenyl)-N^2-(7-methoxy-2,2-dimethyl-1,2,3,4-tetrahydro-2λ^4-isoquinolin-6-yl)pyrimidine-2,4-diamine, iodide salt (8m)

A solution of **8** (50 mg, 0.10 mmol) and MeI (0.031 mL, 0.50 mmol) in THF (1 mL) was stirred at 70 ^{o}C for 18 h. The reaction mixture was concentrated and purified by silica gel column chromatography using MeOH/DCM (1/9) as an eluent to afford **8m** (23 mg, 0.036 mmol, 35%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.62 (s, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 6.68 (s, 1H), 4.85 (s, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 3.91 (s, 3H), 3.61 (s, 6H), 3.32-3.16 (m, 1H), 3.08 (t, *J* = 6.5 Hz, 2H), 1.32 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 516.2 [M - I^-].

5.1.22. 5-Chloro-N^4-(2-(isopropylsulfonyl)phenyl)-N^2-(7-methoxy-3,4-dihydroisoquinolin-6-yl)pyrimidine-2,4-diamine (8n)

To a solution of **8** (50 mg, 0.10 mmol) in DCM (0.5 mL) was added NBS (20 mg, 0.11 mmol) and stirred at rt for 1 h. To the mixture was added 30% NaOH (aq) and stirred for 1h. The reaction mixture was extracted with EtOAc and organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography using MeOH/DCM (1/9) as an eluent to afford **8n** (25 mg, 0.051 mmol, 51%) as a dark orange gel. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.28 – 8.10 (m, 3H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.75 (s, 1H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.79 (s, 1H), 3.91 (s, 3H), 3.71 (t, *J* = 7.7 Hz, 2H), 3.31-3.16 (m, 1H), 2.55 (t, *J* = 7.7 Hz, 2H), 1.29 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 486.3 [M + H^+].

5.1.23. 5-Chloro-*N*^{4}-(2-(isopropylsulfonyl)phenyl)-*N*^{2}-(7-methoxyisoquinolin-6-yl)pyrimidine-2,4-diamine (8o)

To a solution of $(KSO_3)_2NO$ (304 mg, 1.13 mmol) in 4% Na_2CO_3 (aq) (4.6 mL) was added **8** (50 mg, 0.102 mmol) and stirred at rt for 48 h. The reaction mixture was extracted with DCM and organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography using MeOH/DCM (1/9) as an eluent to afford **8o** (6.3 mg, 0.13 mmol, 10%) as a yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.64 (s, 1H), 9.05 (s, 1H), 8.75 (s, 1H), 8.65 (d, *J* = 8.0 Hz, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 8.22 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.88-7.76 (m, 1H), 7.58-7.46 (m, 2H), 7.43-7.31 (m, 1H), 4.13 (s, 3H), 3.57-3.39 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 484.1 [M + H^+].

5.1.24. Methyl 3-methoxyphenethylcarbamate (10)

To a solution of 3-methoxyphenethylamine (**9**, 50.0 g, 331 mmol) in DCM (500 mL) was added Na_2CO_3 (70.1 g, 661 mmol) and methyl chloroformate (18.6 mL, 238.08 mmol) at 0 ^{o}C. The reaction mixture was stirred at rt for 4 h, quenched with water, and extracted with DCM. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by silica gel column

chromatography using EtOAc/hexanes (1/1) as an eluent to afford the title compound **10** (60.0 g, 287 mmol, 87 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.20 (m, 1H), 6.79-6.74 (m, 3H), 4.69 (br, s, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.41 (q, *J* = 6.6 Hz, 2H), 2.76 (t, *J* = 6.9 Hz, 2H); EI/MS *m*/*z* 209.1 [M^+].

5.1.25. 6-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (11)

To a preheated polyphosphoric acid (184 mL, 183.99 mmol) at 120 °C was added **10** (35.0 g, 167.26 mmol) slowly at 120 °C. The reaction mixture was stirred at rt for 6 h, quenched with ice water, basified with K_2CO_3, and extracted with DCM. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography using EtOAc/hexanes (1/1) as an eluent to afford the title compound **11** (38.5 g, 218 mmol, 76 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H), 3.56 (td, *J* = 6.6, 2.8 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H); EI/MS *m*/*z* 177.1 [M^+].

5.1.26. 6-Methoxy-1,2,3,4-tetrahydroisoquinoline (12)

To a solution of $LiAlH_4$ (8.17 g, 215 mmol) in THF (250 mL) was added a solution of **11** (38.0 g, 214 mmol) in THF (250 mL) at 0 ℃. The reaction mixture was stirred at 70 °C for 12 h, cooled down to rt, quenched with water and 15% NaOH (aq), and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography using EtOAc/hexanes (2/1) as an eluent to afford the title compound **12** (30.0 g, 184 mmol, 86 %) as a yellow oil.^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.62 (s, 1H), 3.95 (s, 2H), 3.77 (s, 3H), 3.11 (t, *J* = 5.6 Hz, 2H), 2.78 (t, *J* = 5.4 Hz, 2H), 2.20 (br, s, 1H); EI/MS *m*/*z* 163.1 [M^+].

5.1.27. 2,2,2-Trifluoro-1-(6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone (13)

To a solution of **12** (29.0 g, 178 mmol) in DCM (250 mL) was added Et_3N (49.6 mL, 356 mmol) and trifluoroacetic anhydride (29.7 mL, 213 mmol) at 0 ^oC. The reaction mixture was stirred at rt for 3 h, quenched with water, and extracted with DCM. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography using EtOAc/hexanes (1/1) as an eluent to afford the title compound **13** (30.0 g, 115.7 mmol, 65 %) as a yellow solid.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08-7.02 (m, 1H), 6.82 -6.76 (m, 1H), 6.73-6.68 (m, 1H), 4.73-4.68 (m, 2H), 3.88-3.82 (m, 2H), 3.80 (s, 3H), 2.95-2.93 (m, 2H); EI/MS m/z 259.0 [M^+].

5.1.28. 2,2,2-Trifluoro-1-(6-methoxy-7-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone (14a) and 2,2,2-trifluoro-1-(6-methoxy-5-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (14b)

To a solution of **13** (5.00 g, 30.6 mmol) in TFA (50 mL) was slowly added a solution of HNO_3 (3.5 g, 33.7 mmol) in TFA (10 mL) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 3 h, The solvent was evaporated under reduced pressure, neutralized with $NaHCO_3$ (aq), and extracted with DCM. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography using EtOAc/hexanes (1/2) as an eluent to afford the title compound **14a** (3.50 g, 16.8 mmol, 55%) as slightly yellow solid and **14b** (1.50 g, 7.20 mmol, 24%) as slightly yellow solid. **14a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 6.91 (s, 0.4H), 6.88 (s, 0.6H), 4.77 (s, 1.3H), 4.73 (s, 0.7H), 3.95 (s, 3H), 3.89-3.86 (m, 2H), 3.02-3.00 (m, 2H); LC/MS *m/z* 305.1 [M + H^+]. **14b:** ^{1}H NMR (300 MHz, $CDCl_3$) 7.25 (d, *J* = 9.2 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.78 (s, 1.4H), 4.73 (s, 0.6H), 3.90 (s, 3H), 3.87-3.85 (m, 2H), 2.90-2.86 (m, 2H); LC/MS *m/z* 305.1 [M + H^+].

5.1.29. 1-(7-Amino-6-methoxy-3,4-dihydisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (15)

To a solution of **14a** (1.52 g, 5.00 mmol) in MeOH (25 mL) was added Pd/C (152 mg, 10% wt/wt) and the mixture was stirred under H_2 (g) at rt for 12 h. The reaction mixture was filtered through a celite pad and washed with MeOH. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography using EtOAc/Hexanes (1/1) to afford **15** (1.10 g, 4.00 mmol, 80%) as a slightly yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (s, 0.4H), 6.53 (s, 0.6H), 6.47 (s, 0.6H), 6.44 (s, 0.4H), 4.64 (s, 1.4H), 4.59 (s, 0.6H), 3.83 (s, 3H), 3.83-3.77 (m, 2H), 2.86-2.81 (m, 2H); LC/MS *m*/*z* 274.7 [M + H^+].

5.1.30. 1-(7-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one (16)

To a solution of **15** (100 mg, 0.370 mmol) in 0.08 M HCl in ethoxyethanol (1.0 mL) was added **6** (152 mg, 0.44 mmol) and heated at 80 ^{o}C for 12 h. The reaction mixture was allowed to cool rt and solid precipitated was filtered, and washed with EtOH and dried under vacuum to afford **16** (145 mg, 0.248 mmol, 68%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 0.6H), 9.43 (s, 0.4H), 8.44 (t, *J* = 8.2 Hz, 1H), 8.18 (s, 0.4H), 8.16 (s, 0.6H), 8.18 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 7.3 Hz, 0.6H), 7.69-7.61 (m, 1.4H), 7.38 (t, *J* = 7.9 Hz, 0.6H), 7.31 (t, *J* = 7.9 Hz, 0.4H), 6.66 (s, 0.4H), 6.63 (s, 0.6H), 4.57 (s, 1.3H), 4.51 (s, 0.7H), 3.89 (s, 3H), 3.86-3.81 (m, 2H), 3.24 (sept, *J* = 6.9 Hz, 1H), 2.85-2.92 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 3H); LC/MS *m*/*z* 584.2 [M + H^+].

5.1.31. 5-Chloro-N^4-(2-(isopropylsulfonyl)phenyl)-N^2-(6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)pyrimidine-2,4-diamine (17)

To a solution of **16** (150 mg, 0.26 mmol) in THF (1.0 mL) was added a solution of $LiOH·H_2O$ (54 mg, 1.25 mmol) in H_2O (0.5 mL) followed by MeOH (0.25 mL). The reaction mixture was stirred at rt for 2 h. The solvents were evaporated under vacuum and extracted with EtOAc. The organic layers were washed

with H_2O and saturated NaCl (aq). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to get a crude product which was purified through silica gel column chromatography using MeOH/DCM (1:9) as an eluent to afford **17** (80 mg, 0.164 mmol, 64%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (br, s, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.16 (s, 1H), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.91 (s, 1H), 7.67 (dt, *J* = 8.7, 1.5 Hz, 1H), 7.56 (s, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 6.61 (s, 1H), 3.88 (s, 3H), 3.86 (br, s, 2H), 3.26 (sept, *J* = 6.9 Hz, 1H), 3.17 (br, s, 2H), 2.79 (br, s, 2H), 2.55 (br, s, 1H), 1.32 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 155.3, 155.2, 146.7, 138.4, 134.6, 131.3, 128.9, 127.8, 126.9, 125.0, 123.7, 123.3, 116.2, 110.5, 106.0, 55.8, 55.5, 47.8, 43.7, 28.7, 15.4; LC/MS 488.2 *m*/*z* [M + H$^+$]; HRMS (EI) calcd for $C_{23}H_{26}ClN_5O_3S$ [M$^+$] 487.1445, found 487.1429.

5.1.32. 5-Chloro-*N*^{4}-(2-(isopropylsulfonyl)phenyl)-*N*^{2}-(6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)pyrimidine-2,4-diamine (17a)

The same method as **8a** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17a** (42 mg, 0.084 mmol, 84%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.14 (s, 2H), 7.95-7.81 (m, 2H), 7.54 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.75 (s, 1H), 4.60 (s, 2H), 4.14 (t, *J* = 6.1 Hz, 2H), 3.92 (s, 3H), 3.99-3.78 (m, 1H), 3.30-3.15 (m, 2H), 3.22 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 502.1 [M + H$^+$].

5.1.33. 5-Chloro-*N*^{2}-(2-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)-*N*^{4}-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (17b)

The same method as **8b** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17b** (15 mg, 0.030 mmol, 30%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.49 (d, *J* = 8.3 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.92 (s, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.32-7.26 (m, 1H), 6.61 (s, 1H), 3.87 (s, 3H), 3.57 (s, 2H), 3.33-3.16 (m, 1H), 2.90 (dd, *J* = 15.9, 5.1 Hz, 4H), 2.71 (q, *J* = 6.9 Hz,

2H), 1.38-1.21 (m, 9H); LC/MS *m*/*z* 516.2 [M + H^+].

5.1.34. 2-(7-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-ol (17c)

The same method as **8c** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17c** (40 mg, 0.075 mmol, 75%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.51 (d, *J* = 8.3 Hz, 1H), 8.15 (s, 2H), 7.93 (s, 2H), 7.67 (t, *J* = 7.67 Hz, 1H), 7.54 (s, 1H), 6.62 (s, 1H), 4.59-4.43 (m, 5H), 3.97-3.79 (m, 3H), 3.79-3.66 (m, 2H), 3.58-3.45 (m, 2H), 2.93-2.67 (m, 3H)1.30 (d, *J* = 6.6 Hz, 6H); LC/MS *m*/*z* 532.2 [M + H^+].

5.1.35. 5-Chloro-N^2-(2-(2-(dimethylamino)ethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (17d)

The same method as **8d** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17d** (6.2 mg, 0.011 mmol, 11%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.80 (s, 1H), 8.69-8.66 (m, 1H), 8.18 (s, 1H), 7.89-7.87 (s, 1H), 7.73-7.70 (m, 1H), 7.39 (s, 1H), 6.71 (s, 1H), 5.84 (s, 1H), 3.95 (s, 3H), 3.89 (m, 2H), 3.73-3.49 (m, 6H), 3.26-3.21 (m, 1H), 2.99-2.95 (m, 2H), 1.32 (d, *J* = 6.9 Hz, 6H), 1.25 (s, 6H); LC/MS *m*/*z* 559.1 [M + H^+].

5.1.36. 2-(7-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*,*N*-dimethylacetamide (17e)

The same method as **8e** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17e** (11 mg, 0.020 mmol, 20%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.15 (s, 1H), 8.00-7.88 (m, 2H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 6.62 (s, 1H), 7.08 (s, 2H), 3.87 (s, 3H), 3.84 (s, 2H), 3.69-3.53 (m, 4H), 3.33-3.17 (m, 1H), 3.10 (s, 3H), 2.99 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 573.1 [M + H^+].

5.1.37. 1-(7-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-one (17f)

The same method as **8f** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17f** (47 mg, 0.089 mmol, 89%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, *J* = 6.6 Hz, 1H), 8.50 (dd, *J* = 8.4, 17.7 Hz, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.81-7.58 (m, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 6.2 Hz, 1H), 4.53 (s, 1H), 3.88 (s, 3H), 3.81 (t, *J* = 5.1 Hz, 1H), 3.73-3.62 (m, 2H), 3.33-3.16 (m, 1H), 2.84 (dt, *J* = 5.8, 13.4 Hz, 2H), 2.19 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 6H); LC/MS *m*/*z* 530.1 [M + H^+].

5.1.38. 1-(7-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-hydroxyethan-1-one (17g)

The same method as **8g** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17g** (9.1 mg, 0.017 mmol, 17%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.53-8.48 (m, 1H), 8.18 (s, 0.6H), 8.16 (s, 0.4H), 8.08 (s, 1H), 7.95(d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 7.4 Hz, 0.6H), 7.67 (t, *J* = 7.4 Hz, 0.4H), 7.58 (s, 1H), 7.39-7.31 (m, 1H), 6.66 (s, 0.4H), 6.64 (s, 0.6H), 4.59 (s, 1H), 4.24 (s, 1.6H), 4.19 (s, 0.4H), 3.88 (s, 3H), 3.59-3.47 (m, 4H), 3.24 (sept, *J* = 6.8 Hz, 1H), 2.87-2.82 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 6H); LC/MS *m*/*z* 546.1 [M + H^+].

5.1.39. 7-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-*N*-ethyl-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (17h)

The same method as **8h** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17h** (31 mg, 0.055 mmol, 55%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 8.15 (s, 1H), 8.04 (s, 1H), .7.93 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.32 (d, *J* = 11.3 Hz, 1H), 6.65 (s, 1H), 4.43 (s, 1H), 4.36 (s, 2H), 3.88 (s, 3H), 3.60 (t, *J* = 5.5 Hz, 2H), 3.42-3.15 (m, 3H), 2.81 (t, *J* = 5.3 Hz, 2H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); LC/MS *m*/*z* 559.1 [M +

H^+].

5.1.40. 7-((5-Chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-6-methoxy-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (17i)

The same method as **8i** was used except replacing **8** with **17** (50 mg, 0.10 mmol) to afford **17i** (32 mg, 0.056 mmol, 56%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.55 (s, 1H), 7.40-7.28 (m, 1H), 6.62 (s, 1H), 5.00-4.75 (m, 2H), 4.20 (s, 2H), 3.87 (s, 3H), 3.47 (t, *J* = 5.6 Hz, 2H), 3.30-3.16 (m, 1H), 2.94 (t, *J* = 5.5 Hz, 2H), 1.30 (d, *J* = 6.9 Hz, 6H); LC/MS *m/z* 567.1 [M + H^+].

5.2. *In vitro* enzyme assays

Experimental procedure was followed by the manufactured instruction (Cisbio, France). The reaction was initiated by ATP addition to a mixture containing the kinases, peptide substrates, and inhibitors. After 30 minutes, EDTA containing solution was added to stop the reaction. EDTA containing solution has europium conjugated anti-phospho residue antibody and streptavidin-XL665 (SA-XL665) for the detection of the phosphorylated peptide product. After 1 hour incubation, fluorescence was measured with excitation at 337 nm and dual emission at 665 and 620 nm of the Envision reader. IC_{50} was calculated using GraphPad Prism version 5 for Windows. The curves were fit using a nonlinear regression model with a log (inhibitor) versus response formula.

5.3. Cell cytotoxicity assays

For viability experiments, Ba/F3 cells were tested by WST-1 assay. Cells were seeded in 96-well plates at 30% confluency and exposed to chemicals the next day. After 72 h, WST-1 reagent was added and absorbance at 450nm was measured on a Spectramax spectrophotometer (Molecular Devices, US) according to the manufacturer's instructions. H3122, H2228, and A549 cells were tested by SRB

(SulfoRhodamine B) assay. Cells were seeded in 96-well plates at 30% confluency and exposed to chemicals the next day. After 72 h, cells were fixed with 10% CCl_3CO_2H. Then, cells were stained with 0.05% SRB solutions, and 10 mM Tris base was added to solubilize the protein-bound SRB dye. Absorbance at 564 nm was measured on each well. IC_{50} and curve fitting were performed at the methods described above.

5.4. Docking studies

Molecular docking was performed using the Maestro v10.2 (Schrödinger, Inc.) [27] with the crystal structure of ALK (PDB ID: 2XB7) [28] deposited in the PDB. Structural defects of ALK were fixed by the Protein Preparation Wizard module and low-energy 3D structures of ALK inhibitors were generated by the LigPrep. Based on a grid box of 30 × 30 × 30 $Å^3$ centered on ligands, each inhibitor was then docked into the binding site using the Glide module in Standard Precision (SP) mode. We also carried out modeling the G1202R mutated ALK starting from 2XB7 and predicted binding modes of ALK inhibitors in the mutated ALK by the Prime. The protein-ligand interactions were analyzed using the Discovery Studio Modeling Environment v4.0 [29]. The molecular models of docked compounds and surfaces of wild-type and mutant ALK were displayed using the PyMOL software [30].

5.5. Liver microsomal metabolic stability

NADPH-dependent oxidative metabolism of the test compounds in liver microsomes of different species was evaluated. The reaction mixture was composed of liver microsomes (0.5 mg protein /mL) in 100 mM PBS (pH 7.4) and the final concentration of a test compound was 1 μM. The metabolic reaction was initiated by the addition of NADPH-regenerating solution, containing 1.3 mM $NADP^+$, 3.3 mM glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, and 3.3 mM $MgCl_2$. After the 30 min

incubation of sample at 30'C with mild shaking, the reaction was stopped by the addition of ice-cold CH_3CN containing an internal standard (5 ng/mL imipramine) for quantification. Subsequently, the samples were then centrifuged at 13000 g for 10 min and supernatant was stored at -20℃ until the analysis. The concentrations of test compounds were determined by LC/MS/MS on an Agilent 1200 HPLC system coupled to an Agilent 6460 triple quadrupole mass spectrometer equipped with ESI source (Agilent, Santa Clara, CA, USA) using imipramine as an internal standard (IS). The peak areas for all components were automatically integrated using Agilent 6460 Quantitative Analysis processing software.

5.6. PK studies in rats

In vivo PK of compounds was examined in male rats (6-7 weeks, 250-280 g). The rats were cannulated with polyethylene tubing (PE-50, Intramedic, BD Bioscience, MD) in the femoral vein under anesthesia by a mixture of zoletil and rompun solution (3:1, 1 mL/kg). Animals were fasted overnight after the cannulation surgery. Then, the test compound was administered orally using oral gavage. Dosing vehicles were composed of 5% DMSO and 40% PEG400 in water and dosing volume was 2 mL/kg in p.o. administration. Blood samples were collected at different time points (n = 3 rats per time point) from the femoral vein. After centrifugation (13000 g, 3 min, 37℃), the plasma samples were obtained and were stored at -20℃ until the analysis. The area under the plasma concentration-time curve (AUC_{inf}) was calculated by the trapezoidal rule with extrapolation to time infinity. The maximum plasma concentration (C_{max}) was obtained by visual inspection of the plasma concentration-time curve. The sample analysis was performed by LC/MS/MS as described in the above section.

Acknowledgements

This work was supported by Korea Research Institute of Chemical Technology (KK-1503-A00 and

SI-1512-01) and by the National Research Foundation of Korea (NRF-2012M3A9A9054902).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxxx.

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Graphical Abstract:

Discovery of novel tetrahydroisoquinoline-containing pyrimidines as ALK inhibitors

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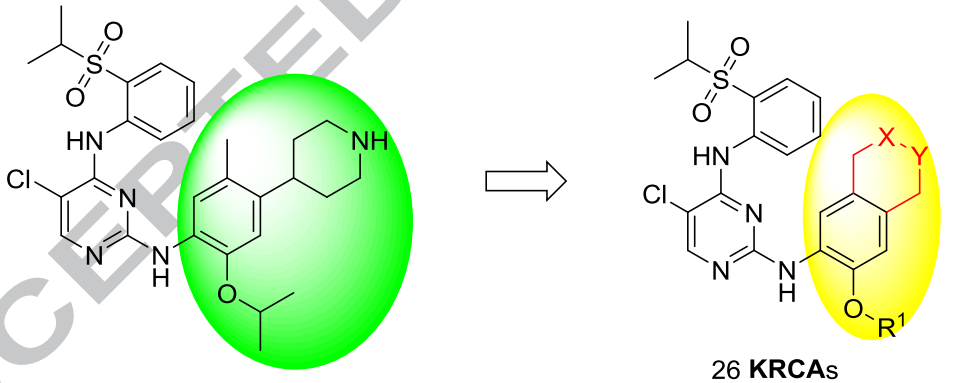

LDK378		26 **KRCA**s (X-Y = CH_2-NR^2 or NR^2-CH_2)	
		8	**17**
25 nM	H2228 CC_{50}	10 nM	10 nM
38 nM	H3122 CC_{50}	8 nM	4.7 nM
75 nM	Ba/F3 L1196M CC_{50}	36 nM	10 nM