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The identification of 8,9-dimethoxy-5-(2-aminoalkoxy-pyridin-3-yl)-benzo[c][2,7]naphthyridin-4-ylamines as potent inhibitors of 3-phosphoinositide-dependent kinase-1 (PDK-1)

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ABSTRACT

A series of 8,9-dimethoxy-5-(2-aminoalkoxy-pyridin-3-yl)-benzo[c][2,7]naphthyridin-4-ylamine-based inhibitors of 3-phosphoinositide-dependent kinase-1 (PDK-1) has been identified. Several examples appear to be potent and relatively selective inhibitors of PDK-1 over the related AGC kinases PKA, PKB/AKT, and p70S6K. The introduction of a stereochemical center beside the amino substituent on the aminoalkoxy-side chain had little effect upon the inhibitory activity against these enzymes, and X-ray crystallographic analyses of a representative pair of enantiomeric inhibitors bound to the active site of PDK-1 revealed comparable binding modes for each enantiomer.

1. Introduction

Phosphoinositide-dependent kinase-1 (PDK-1), a 63 kDa serine/threonine kinase, is a major player in the PI3-kinase signaling pathway that regulates gene expression, cell cycle, growth, and proliferation [1–8]. PDK-1 has been termed the "master kinase" because it phosphorylates highly conserved serine or threonine residues in the T-loop (or activation loop) of numerous AGC kinases, including PKB/AKT, PKC, p70S6K, SGK, and PDK-1 itself [9]. Although the precise regulatory mechanisms vary, in the case of PKB/AKT, activation by PDK-1 is critically dependent upon prior PI3 kinase activation and the presence of phosphatidylinositol-(3,4,5)-triphosphate (PIP3). A significant proportion (40–50%) of all tumors involve mutations in PIP3-3-phosphatase (PTEN) [10–12], which results in elevated levels of PIP3 and enhanced activation of PKB/AKT, p70S6K, and SGK; inhibitors of PDK-1 could potentially provide valuable therapeutic agents for the treatment of cancer.

In our initial efforts to identify inhibitors of PDK-1, high-throughput screening (HTS) was used to discover the tetracyclic dibenzo[c,f][2,7]-naphthyridine derivative **1** (Fig. 1) as a relatively potent PDK-1 inhibitor ($IC_{50} = 60$ nM) [13]. An X-ray crystal structure of **1** complexed to PDK-1 revealed key hydrogen bonding interactions between the N8 nitrogen in **1** and the backbone NH of Ala162, and between the C6-amino group in **1** and the backbone carbonyl oxygen of Ser160. An additional hydrogen-bonding interaction was noted between the N5 nitrogen in **1** and the side chain hydroxyl group of Thr222. Subsequent to this work, we reported that the truncated 2-heteroaryl-substituted 8,9-dialkoxy-benzo[c][2,7]naphthyridines [14], exemplified by the imidazole-substituted derivative **2** ($IC_{50} = 70$ nM) and the pyridyl-substituted derivative **3** ($IC_{50} = 35$ nM), were also potent inhibitors of PDK-1. An X-ray crystal structure of compound **2** bound to PDK-1 revealed, in addition to all the interactions observed between **1** and PDK-1, that this compound formed a hydrogen-bonding interaction between N3 of the imidazole headpiece and the Lys111 ε-amino group in PDK-1. This conserved catalytic lysine residue mediates the binding of the α-phosphate of ATP and facilitates the phosphate transfer to the protein substrate [15]. This additional hydrogen bonding interaction was predicted on the basis of molecular modeling and was also thought to be relevant in binding of the compounds containing the 5-imidazolyl and 3-pyridyl-headpiece substituents, of which several examples were presented. We noted that an

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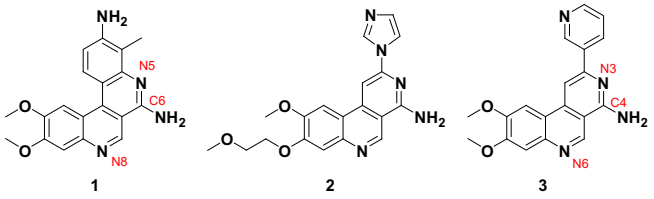


Fig. 1. PDK-1 inhibitors from our previously reported studies (**1** $IC_{50} = 60$ nM, **2** $IC_{50} = 70$ nM, **3** $IC_{50} = 35$ nM).

analogous interaction involving a pyridyl-substituent and the conserved lysine residue was reported to occur with a series of PKB/AKT inhibitors containing a 5-aminoalkoxy-3-pyridyl group placed upon a different kinase-active core structure [16]. The PKB/AKT inhibitors possessed additional beneficial interactions between the protonated amino-group on the aminoalkoxy-substituent and conserved asparagine and aspartate residues normally involved in magnesium chelation. Having established the hydrogen bonding interaction between our pyridyl- and imidazolyl-nitrogens and the conserved lysine residue, we next explored the effect of incorporating various aminoalkoxy-substituents onto the 5-position of a 3-pyridyl headpiece installed on the novel 8,9-dimethoxy-benzo[c][2,7]naphthyridine core. Herein are reported the results of those efforts.

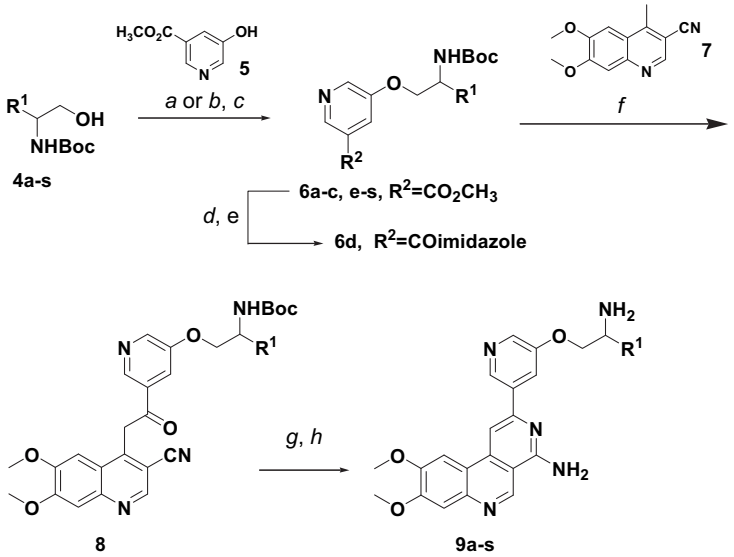
2. Synthesis

The intermediates **6a–s** were prepared either by performing a Mitsunobu reaction between the Boc-protected aminoalcohols **4a**, **d–i**, **k–s** and methyl-5-hydroxy nicotinate, **5** or by alkylation of **5** with the mesylates derived from the aminoalcohols (**4b**,**c**,**j**) (Scheme 1). The key step in the synthesis, as we have shown previously [14], is the condensation of the functionalized alkoxy-nicotinates **6a–c**, **e–s** or the acyl imidazole derivative **6d** with 6,7-dimethoxy-4-methyl-3-cyanoquinoline **7** to yield the intermediate ketones **8**. Without purification, these ketones were heated in acetic acid in the presence of ammonium acetate to promote cyclization which, after removal of the Boc protecting group with acid, furnished the inhibitors **9a–s**.

3. Results and discussion

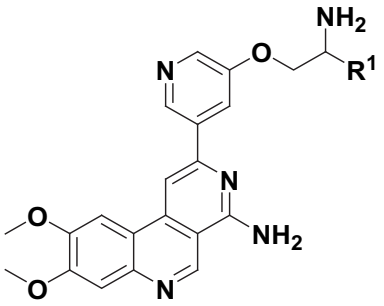
As noted above, previous work disclosed by the Abbott group coupled with our molecular modeling studies on this series of inhibitors suggested that we could establish additional beneficial hydrogen bonding interactions by incorporating an aminoalkoxy substituent at the 5-position of the pyridyl headpiece. We anticipated that this type of modification would result in enhanced potency. Indeed, the compounds prepared in this study each showed potent PDK-1 inhibitory activity ($IC_{50} < 22$ nM). Within this series, the SAR observed for the R^1 substituents was relatively flat (Table 1). For example, a compound with a small R^1 group (**9a**, R^1=H, $IC_{50} = 5$ nM) showed about the same activity as a compound having a much larger substituent (**9r**, R^1=CH_2-3,4-Cl_2–Ph, $IC_{50} = 6$ nM). In addition, for the inhibitors that are enantiomeric pairs (**9b** vs. **9c**, **9d** vs. **9e**, **9f** vs. **9g**, **9h** vs. **9i**, **9j** vs. **9k**, **9l** vs. **9m**, and **9n** vs. **9o**), the difference in potency between enantiomers was minimal with the largest difference observed between **9j** and **9k**, having IC_{50}s of 3 and 15 nM, respectively. In contrast, some members of this series of PDK-1 inhibitors did display a measure of selectivity for PDK-1 relative to some of the other AGC kinases such as PKA, PKB/AKT, and p70S6K. The largest selectivities were observed for compounds **9b**, **9c**, **9e** and **9s** over PKB/AKT, a kinase that acts downstream of PDK-1 and which is also a valid target for cancer therapy [17–22] (AKT/PDK-1 = 119, 144, 159, and 194, respectively). Compared to PKB/AKT, the compounds were less selective for PKA, a ubiquitous kinase that performs numerous useful functions [23–25], or p70S6K, another multifunctional kinase [26–29].

In order to derive further insights into the SAR, we obtained the X-ray crystal structures for one pair of entantiomers, **9h** [30] (PDK-1 $IC_{50} = 8$ nM) and **9i** [31] (PDK-1 $IC_{50} = 17$ nM), bound to the catalytic domain of PDK-1. For both enantiomers **9h** and **9i,** the interactions made by the tricyclic core to PDK-1 were analogous to those found for **1** and **2** (Fig. 2). Notably, the interactions between the ligand and the hinge region of PDK-1 were mediated by hydrogen



Scheme 1. Reagents and conditions: a) DEAD, PPh_3, THF; b) MsCl, TEA; c) $CsCO_3$, DMF; d) NaOH, THF; e) CDI, THF; f) LiHMDS, THF, −78–0 °C; g) NH_4OAc, DMF, 100 °C; h) HCl, THF, 60 °C.

Table 1
Inhibition of PDK-1 with Naphthyridines.[a,b]



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Compound #	*R*/*S*	R^1	IC50 (nM) PDK-1	IC50 (nM) PKA	IC50 (nM) AKT	IC50 (nM) p70S6K	PKA/PDK1	AKT/PDK1	p70S6K/PDK1
9a	–	H	5	66	402	80	13	80	16
9b	*S*	Me	6	123	712	235	21	119	39
9c	*R*	Me	3	86	377	97	33	144	37
9d	*S*	Et	6	59	422	216	11	77	39
9e	*R*	Et	3	45	318	72	23	159	36
9f	*S*	*i* -Bu	14	113	905	219	8	65	16
9g	*R*	*i* -Bu	18	385	1395	443	21	78	25
9h	*S*	CH_2Ph	8	77	261	107	10	33	13
9i	*R*	CH_2Ph	17	<31	259	88	<2	15	5
9j	*S*	CH_2-4-F–Ph	3	32	183	21	11	61	7
9k	*R*	CH_2-4-F–Ph	15	36	251	93	2	17	6
9l	*S*	CH_2-3-CF_3–Ph	13	68	209	182	5	16	14
9m	*R*	CH_2-3-CF_3–Ph	21	142	889	763	7	43	37
9n	*S*	CH_2-3-indolyl	6	54	302	77	10	55	14
9o	*R*	CH_2-3-indolyl	15	120	1324	254	8	88	17
9p	*S*	CH_2-2-Cl–Ph	8	79	793	106	10	99	13
9q	*S*	CH_2-3-Cl–Ph	8	18	78	76	2	10	10
9r	*S*	CH_2-3,4-Cl_2–Ph	6	41	433	19	7	72	3
9s	*S*	CH_2-4-pyridyl	9	138	1750	343	15	194	38

[a] See reference [4] for assay procedure.
[b] 100 uM ATP used in all assays.

bonds between the N6 nitrogen to the NH of Ala162 and the C4 amino group in **9h** or **9i** to the backbone carbonyl oxygen of Ser160. An additional hydrogen–bond interaction was also present between the N3 nitrogen in **9h** or **9i** and the side chain hydroxyl of Thr222. The pyridyl headpiece of **9h** or **9i** interacts with Lys111 through a hydrogen bond in a similar fashion to our observation earlier for the imidazole headpiece of **2** on the 8,9-dialkoxy-benzo[c][2,7]naphthyridine core.

Significantly, we observed new hydrogen bonding and electrostatic interactions between the protonated primary amine of the side chain of **9h** with the Asn210 and Asp223 residues of PDK-1, completely analogous to those observed by the Abbott group with their inhibitors of PKB/AKT [16]. Similar interactions were observed for **9i** with the Asn210 and Glu209 residues of PDK-1. An overlay of crystal structures obtained for **9h** and **9i** complexed to PDK-1 is shown in Fig. 3 where it is apparent that the amino groups of **9h** and **9i** make an electrostatic interaction with Asp223 and Glu209, respectively. In both structures the benzyl-side chains are oriented in a very similar manner even though they are derived from different enantiomers. Apparently, the degree to which the

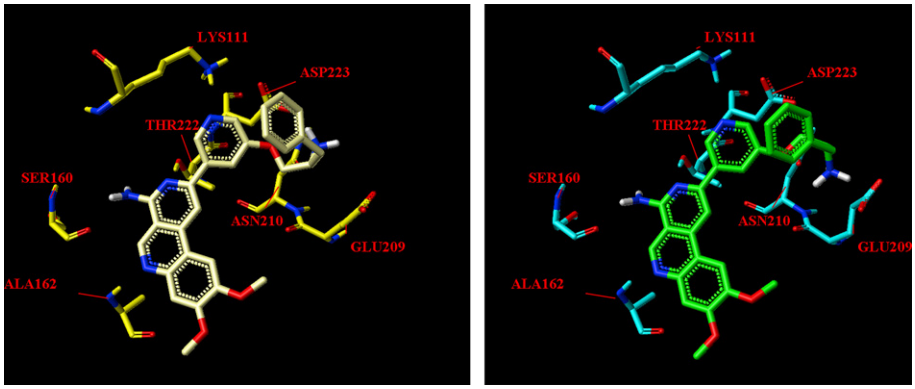

Fig. 2. X-ray crystallographic structures of **9h** (yellow) and **9i** (green) complexed with PDK-1. Comparable interactions made by the tricyclic core and the pyridyl headpiece were similar to those observed for **1** and **2**. (For interpretation of the reference to colour in this figure legend, the reader is referred to the web version of this article.)

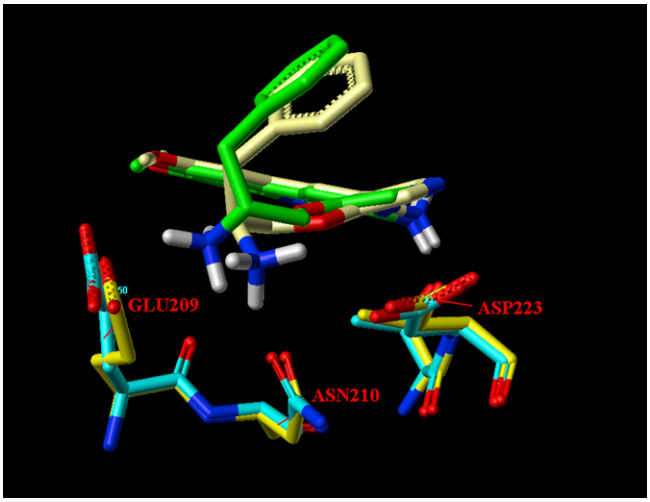

Fig. 3. An overlay of X-ray crystallographic structures **9h** (tan ligand, protein in yellow) and **9i** (green ligand, protein in cyan) complexed with PDK-1 showing the interactions of the aminoalkoxy side-chains with the protein. The amino-group on this side chain in either enantiomer interacts with Asn210 and a carboxylate residue; **9h** with Asp223 and **9i** with Glu209. (For interpretation of the reference to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Statistics from crystallographic analysis of PDK-1 with inhibitors.

	9h	9i
Space group	$P3_221$	$P3_221$
Unit cell (Å)	123.37, 123.37, 47.27	122.87, 122.87, 47.16
Resolution (Å) (last shell)	50 – 2.4 (2.49 – 2.40)	50 – 2.2 (2.28 – 2.20)
Total Observations	172,842	215,428
Unique Observations	16,389	20,849
Completeness (%)	99.9 (100.0)	99.5 (96.6)
R_{sym}[a]	10.1 (70.0)	17.1 (57.6)
I/σI	26.3 (3.8)	13.7 (2.8)
Refinement		
Resolution (Å)	20 – 2.4	20 – 2.2
R_{work}/R_{free}[b] (%)	24.5/28.2	23.8/27.8
RMSd[c] bonds (Å)	0.007	0.007
RMSd[c] angles (°)	1.03	0.964

[a] $R_{sym} = \Sigma\ |I - <I>|/I$, where I is the observed intensity, $<I>$ is the average intensity of multiple observations of symmetry- related reflections.
[b] $R_{work} = \Sigma||F_{obs}| - |F_{calc}|/\Sigma|F_{obs}|$, R_{free} is equivalent to R_{work}, but calculated for a randomly chosen 5% of reflections omitted from the refinement process.
[c] RMSd is the root mean square deviation from ideal geometry.

interactions of each enantiomer contribute to compound binding is comparable since the difference in potency in inhibiting PDK-1 is minimal ($IC_{50} = 8$ vs. 17 nM for **9h** vs. **9i**, respectively). We believe that these new interactions contribute to the superior potency of either enantiomer relative to the more simple derivatives **1** and **2**.

4. Conclusions

We have described in this report our efforts to identify additional potent PDK-1 inhibitors by expanding upon our previously reported series of 2-heteroaryl-substituted 8,9-dialkoxy-benzo[c][2,7]naphthyridines. The introduction of aminoalkoxy-substituents onto the 5-position of the 3-pyridyl headpieces present on the benzo[c][2,7]naphthyridine scaffold has resulted in significant increases in PDK-1 inhibitory potency. X-Ray crystallographic analysis of a PDK-1 complexed with the enantiomers **9h** and **9i** has revealed that these inhibitors bind to the ATP site of PDK-1 in a manner that is completely analogous to that observed for compounds **1** and **2**, and that these two compounds each establish additional beneficial polar interactions with the protein through hydrogen-bonding and ionic interactions involving the amino-alkoxy-substituent.

5. Experimental section

5.1. Biological assays

The details of the PDK-1 assay procedures have been published previously [13] using 100 uM ATP. The "Z′-LYTE" kinase assays for PKA, PKB/AKT, and p70S6K were performed according to the manufacturer's protocols (Invitrogen Cat#: PV3174, PV3179, and PV3180) using 100 uM ATP.

5.2. X-ray crystallography

An N-terminally truncated version of PDK-1 was purified and crystallized with ATP as previously described [32]. Crystals were harvested and transferred to a fresh drop of soaking solution containing 3 M ammonium sulfate, 0.5 M NaCl, 0.1 M Tris–HCl pH 7.0, 10 mM Mg sulfate, 5% DMSO and 0.3 mM inhibitor. Crystals were soaked for approximately one week then briefly transferred into a solution of 25% glycerol and 75% soaking solution before being flash cooled in a nitrogen stream at 100 K. Diffraction data were recorded in house with a Saturn92 CCD mounted on an FR-E CuK_α rotating anode X-ray source (Rigaku, Japan). Intensities were integrated and scaled using HKL2000 [33]. The structures were phased by molecular replacement with the CCP4 suite of software [34]. The search model used was based on a previously determined structure of PDK-1 in complex with ATP. Refinement and model building were performed in iterative cycles using the programs REfmac5 (CCP4 1994) and COOT [35]. See Table 2 for refinement statistics.

5.3. Chemistry

^{1}H NMR spectra were determined with a Bruker DRX400 spectrometer at 400 MHz. Chemical shifts, δ, are in parts per million relative to the internal standard tetramethylsilane. Electrospray (ES) mass spectra were recorded in positive mode on a Micromass Platform spectrometer. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT-90 or on a Bruker 9.4T FTMS spectrometer. Chromatographic purifications were by flash chromatography using EMD 0.04–0.06 mm silica gel. The following describes the syntheses and spectral data of non-commercial or non-published compounds.

5.3.1. Methyl 5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(2-chlorophenyl)propyl]oxy}nicotinate (**6p**)

To a solution of tert-butyl [(1S)-1-(2-chlorobenzyl)-2-hydroxyethyl]carbamate (4.01 g, 14.0 mmol), triphenylphosphine (4.42 g, 14.0 mmol), and 5-hydroxynicotinic acid methyl ester (2.12 g, 14.0 mmol) in anhydrous THF (60 mL) was added DEAD (2.65 mL, 16.9 mmol) in anhydrous THF (12 mL) over a 10 min period. The solution was stirred at room temperature for 3 h then concentrated in vacuo. The residue was dissolved in Et_2O and stirred for 1 h then filtered. The filtrate was washed with 3 × 200 mL 0.5 N NaOH and the organic layer dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography using a gradient elution of 10–50% EtOAc/Hexanes to give methyl 5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(2- chlorophenyl)propyl]oxy}nicotinate (1.8 g, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, 1H), 8.52 (d, 1H), 7.78 (m, 1H), 7.40 (m, 1H), 7.35 (m, 1H), 7.25 (m, 2H), 7.02 (d, 1H), 4.13 (s, 2H), 3.89 (s, 3H), 3.09 (m, 1H), 2.80 (s, 1H), 1.28 (s, 9H), 1.07 (s, 1H); MS 421.2 [M + H].

The following compounds were made using the above procedure:

*5.3.2. Methyl 5-{2-[(tert-butoxycarbonyl)amino]ethoxy}nicotinate (**6a**) WYE-120860*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, 1H), 8.47 (d, 1H), 7.76 (m, 1H), 5.01 (bs, 1H), 4.11 (t, 2H), 3.95 (s, 3H), 3.58 (m, 2), 1.45 (s, 9). MS (ESI) *m*/*z* 297.2.

*5.3.3. Methyl 5-({(2R)-2-[(tert-butoxycarbonyl)amino]-butyl}oxy)nicotinate (**6e**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, 1H), 8.52 (d, 1H), 7.76 (m, 1H), 6.68 (d, 1H), 4.03 (m, 2H), 3.89 (s, 3H), 3.66 (m, 1H), 1.59 (m, 1H), 1.46 (m, 1H), 1.37 (s, 9), 0.88 (t, 3H). MS (ESI) *m*/*z* 325.2.

*5.3.4. Methyl 5-({(2R)-2-[(tert-butoxycarbonyl)amino]-4-methylpentyl}oxy)nicotinate (**6f**)*

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.78 (d, 1H), 8.43 (d, 1H), 7.86 (s, 1H), 5.47 (m, 1H), 4.25 (m, 2H), 4.06 (m, 1H), 3.97 (s, 3H), 1.72 (m, 1H), 1.54 (m, 1H), 1.44 (s, 9H), 1.34 (m, 1H), 0.96 (t, 6H). MS (ESI) *m*/*z* 353.3.

*5.3.5. Methyl 5-({(2S)-2-[(tert-butoxycarbonyl)amino]-4-methylpentyl}oxy)nicotinate (**6g**)*

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.78 (d, 1H), 8.43 (d, 1H), 7.86 (s, 1H), 5.47 (m, 1H), 4.25 (m, 2H), 4.06 (m, 1H), 3.97 (s, 3H), 1.72 (m, 1H), 1.54 (m, 1H), 1.44 (s, 9H), 1.34 (m, 1H), 0.96 (t, 6H). MS (ESI) *m*/*z* 353.3.

*5.3.6. Methyl-5-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl}oxy)nicotinate (**6h**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, 1H), 8.52 (d, 1H), 7.75 (m, 1H), 7.24 (m, 5H), 7.01 (d, 1H), 4.07 (m, 2H), 3.98 (m, 1H), 3.89 (s, 3H), 2.89 (m, 1H), 2.76 (m, 1H), 1.31 (s, 9H). MS (ESI) *m*/*z* 387.1.

*5.3.7. Methyl 5-({(2R)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl}oxy)nicotinate (**6i**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.53 (d, 1H), 7.76 (m, 1H), 7.24 (m, 5H), 7.02 (d, 1H), 4.07 (m, 2H), 3.99 (m, 1H), 3.89 (s, 3H), 2.89 (m, 1H), 2.77 (m, 1H), 1.32 (s, 9H). MS (ESI) *m*/*z* 387.3.

*5.3.8. Methyl-5-{[(2R)-2-[(tert-butoxycarbonyl)amino]-3-(4-fluorophenyl)propyl]oxy}nicotinate (**6k**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, 1H), 8.53 (d, 1H), 7.76 (m, 1H), 7.26 (m, 2H), 7.10 (m, 2H), 7.00 (d, 1H), 4.07 (m, 2H), 3.96 (m, 1H), 3.89 (s, 3H), 2.89 (m, 1H), 2.73 (m, 1H), 1.30 (s, 9H). MS (ESI) *m*/*z* 405.3.

*5.3.9. Methyl-5-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-[3-(trifluoromethyl)phenyl]propyl}oxy)nicotinate (**6l**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, 1H), 8.54 (d, 1H), 7.78 (m, 1H), 7.55 (m, 3H), 7.05 (d, 2H), 4.12 (m, 2H), 4.03 (m, 1H), 3.90 (s, 3H), 3.04 (m, 1H), 2.82 (m, 1H), 1.26 (s, 9H). MS (ESI) *m*/*z* 455.3.

*5.3.10. Methyl-5-({(2R)-2-[(tert-butoxycarbonyl)amino]-3-[3-(trifluoromethyl)phenyl]propyl}oxy)nicotinate (**6m**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, 1H), 8.54 (d, 1H), 7.78 (m, 1H), 7.55 (m, 3H), 7.05 (d, 2H), 4.12 (m, 2H), 4.03 (m, 1H), 3.89 (s, 3H), 3.04 (m, 1H), 2.82 (m, 1H), 1.27 (s, 9H). MS (ESI) *m*/*z* 455.3.

*5.3.11. Methyl 5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(1H-indol-3-yl)propyl]oxy}nicotinate (**6n**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.98 (s, 1H), 8.67 (s, 1H), 8.53 (d, 1H), 7.72 (m, 1H), 7.56 (d, 1H), 7.33 (d, 1H), 7.15 (s, 1H), 7.01 (m, 2H), 4.07 (m, 3H), 3.88 (s, 3H), 2.94 (m, 2H), 1.36 (s, 9H). MS (ESI) *m*/*z* 426.3.

*5.3.12. Methyl-5-{[(2R)-2-[(tert-butoxycarbonyl)amino]-3-(1H-indol-3-yl)propyl]oxy}nicotinate (**6o**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.98 (s, 1H), 8.68 (s, 1H), 8.51 (d, 1H), 7.72 (m, 1H), 7.56 (d, 1H), 7.33 (d, 1H), 7.15 (s, 1H), 7.01 (m, 2H), 4.07 (m, 3H), 3.88 (s, 3H), 2.94 (m, 2H), 1.36 (s, 9H). MS (ESI) *m*/*z* 426.4.

*5.3.13. Methyl-5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3-chlorophenyl)propyl]oxy}nicotinate (**6q**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, 1H), 8.54 (d, 1H), 7.77 (m, 1H), 7.26 (m, 4H), 7.03 (d, 1H), 4.10 (m, 2H), 3.99 (m, 1H), 3.89 (s, 3H), 2.93 (m, 1H), 2.74 (m, 1H), 1.30 (s, 9H). MS (ESI) *m*/*z* 421.1.

*5.3.14. Methyl-5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,4-dichlorophenyl)propyl]oxy}nicotinate (**6r**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.54 (d, 1H), 7.77 (m, 1H), 7.53 (m, 2H), 7.24 (d, 1H), 7.02 (d, 1H), 4.10 (m, 2H), 3.99 (m, 1H), 3.89 (s, 3H), 2.94 (m, 1H), 2.72 (m, 1H), 1.29 (s, 9H). MS (ESI) *m*/*z* 455.

*5.3.15. Methyl 5-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-pyridin-4-ylpropyl}oxy)nicotinate (**6s**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.54 (d, 1H), 8.46 (d, 2H), 7.78 (m, 1H), 7.26 (d, 2H), 7.06 (d, 1H), 4.11 (m, 2H), 4.06 (m, 1H), 3.89 (s, 3H), 2.94 (m, 1H), 2.78 (m, 1H), 1.29 (s, 9H). MS (ESI) *m*/*z* 388.2.

*5.3.16. tert-Butyl [(1S)-1-({[5-(1H-imidazol-1-ylcarbonyl)pyridin-3-yl]oxy}methyl)propyl]carbamate (**6d**)*

To a solution of Boc-*S*-2-aminobutanol (8.05 g, 42.5 mmol), triphenylphosphine (33.5 g, 127.6 mmol), and 5-hydroxynicotinic acid methyl ester (6.51 g, 42.5 mmol) in anhydrous THF (200 mL) was added DEAD (20.1 mL, 127.6 mmol). The solution was stirred at room temperature for 16 h then concentrated in vacuo. The crude residue was dissolved in EtOAc then washed with a cold aqueous NaOH solution (0.5 N). The organic layer was then concentrated and dissolved in 200 mL of THF. The solution was then treated with aqueous NaOH solution (3 N, 150 mL) and stirred for 17 h. The mixture was concentrated in vacuo until only the aqueous layer remained. The aqueous layer was extracted with DCM then acidified until the pH was ~3 with concentrated HCl and the resulting white solid was collected by filtration to give 5-(({(2*S*)-2-[(tert-butoxycarbonyl)-amino]butyl}oxy)nicotinic acid (5.74 g, 44% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.44 (s, 1H), 8.66 (d, 1H), 8.48 (d, 1H), 7.73 (m, 1H), 6.83 (d, 1H), 4.02 (d, 2H), 3.67 (m, 1H), 1.59 (m, 1H), 1.48 (m, 1H), 1.37 (s, 9H), 0.88 (t, 3H). MS (ESI) *m*/*z* 309.2.

To a stirred solution of 5-({{(2*S*)-2-[(tert-butoxycarbonyl)-amino]butyl}oxy)nicotinic acid (560 mg, 1.80 mmol) in anhydrous THF (9 mL) was added 1,1′-carbonyldiimidazole (585 mg, 3.60 mmol). The reaction was stirred for 21 h and then diluted with EtOAc. The mixture was washed with water and brine, then dried over anhydrous $MgSO_4$ and concentrated in vacuo to give tert-butyl [(1S)-1-(({[5-(1H-imidazol-1-ylcarbonyl)pyridin-3- yl]oxy)methyl)propyl]carbamate (650 mg, 100% yield) as a white semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.6 (m, 2H), 8.1 (m, 1H), 7.62 (m, 1H), 7.56 (m, 1H), 7.22 (m, 1H), 4.68 (m, 1H), 4.12 (m, 2H), 3.91 (bs, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.45 (s, 9H), 1.02 (t, 3H). MS (ESI) *m*/*z* 361.3.

*5.3.17. Methyl-5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(4-fluorophenyl)propyl]oxy}nicotinate (**6j**)*

To a stirred solution of tert-butyl{(1S)-2-hydroxy-1-[3-(trifluoromethyl)benzyl]ethyl}carbamate (1.00 g, 3.13 mmol) in anhydrous DCM was added triethylamine (0.65 mL, 4.70 mmol) followed by dropwise addition of methanesulfonyl chloride (0.26 mL,

3.29 mmol). The reaction was stirred 30 min and concentrated in vacuo. The residue was dissolved in EtOAc (150 mL) and washed with water, saturated aqueous $NaHCO_3$, brine (100 mL of each), and then dried over Na_2SO_4. The organic layer was passed through a pad of silica gel with EtOAc and concentrated in vacuo. To a stirred solution of the residue and 5-hydroxynicotinic acid methyl ester (479 mg, 3.13 mmol) in anhydrous DMF (10 mL) was added Cs_2CO_3 (2.04 g, 6.26 mmol) and heated to 60 °C for 18 h. The mixture was concentrated in vacuo and the residue was dissolved in Et_2O (200 mL), washed with 0.1 N NaOH (150 mL), dried over Na_2SO_4, and purified by silica gel chromatography using a gradient elution of 20–100% EtOAc/Hexanes to give methyl 5-(({(2S)-2-[(tert-butoxycarbonyl)amino]-3-[3-trifluoromethyl)phenyl]propyl}oxy)nicotinate (0.34 mg, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, 1H), 8.53 (d, 1H), 7.76 (m, 1H), 7.26 (m, 2H), 7.10 (m, 2H), 7.00 (d, 1H), 4.07 (m, 2H), 3.96 (m, 1H), 3.89 (s, 3H), 2.89 (m, 1H), 2.73 (m, 1H), 1.30 (s, 9H). MS (ESI) *m*/*z* 405.2.

The following compounds were made using the above procedure:

*5.3.18. 2-(5-{[(2S)-2-Aminopropyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7- naphthyridin-4-amine (**6b**)*

^{1}H NMR (DMSO-d_6) δ 8.83 (d, 1H), 8.47 (d,1H), 7.75 (m, 1H), 4.75 (bs, 1H), 4.09 (m, 1H), 4.01 (d, 2H), 3.95 (s, 3H), 1.44 (s, 9H), 1.31 (d, 3H). MS (ESI) *m*/*z* 406.3.

*5.3.19. 2-(5-{[(2R)-2-Aminopropyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7- naphthyridin-4-amine (**6c**)*

^{1}H NMR (DMSO-d_6) δ 8.83 (d, 1H), 8.47 (d, 1H), 7.75 (m, 1H), 4.75 (bs, 1H), 4.09 (m, 1H), 4.01 (d, 2H), 3.95 (s, 3H), 1.44 (s, 9H), 1.31 (d, 3H). MS (ESI) *m*/*z* 406.3.

*5.3.20. 2-(5-{[(2S)-2-Amino-3-(3,4-dichlorophenyl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9r**)*

To a stirred solution of methyl-5-{[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,4-dichlorophenyl)propyl]oxy}nicotinate (0.50 g, 1.10 mmol) and 6,7-dimethoxy-4-methyl-quinoline-3-carbonitrile (0.25 g, 1.10 mmol) in anhydrous THF (5 mL) at −78 °C was added dropwise LiHMDS (3.52 mL, 1.0 M solution in THF, 3.52 mmol). The reaction was stirred at −78 °C for 1 h, slowly warmed to room temperature over 2 h, then stirred an additional 30 min and quenched by addition of crushed dry ice and water. The mixture was extracted with 3 × 150 mL EtOAc, dried over Na_2SO_4, and concentrated in vacuo. The residue was further dried by concentrating in vacuo with toluene.

The residue was dissolved in 20 mL of anhydrous DMF and sublimed NH_4OAc (1.70 g, 22.0 mmol) was added and the reaction mixture was heated at 100 °C for 2 h. The DMF was then removed by concentrating in vacuo and 15 mL of 2 N HCl in 40 ml of THF was added. The reaction was stirred at 60 °C for 6 h, concentrated in vacuo to removed the bulk amount of THF, cooled and poured into 10 N NaOH. This aqueous solution was extracted with 3 × 150 mL EtOAc, the pooled extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using 90:10:1 DCM/MeOH/Et_3N to give 2-(5-{[(2S)-2-Amino-3-(3,4-dichlorophenyl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (280 mg, 46% for 3 steps). 1H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.19 (d, 1H), 8.37 (s, 2H), 8.17 (m, 2H), 7.58 (d, 1H), 7.56 (s, 1H), 7.54 (s, 1H), 7.51 (s, 2H), 7.36 (bs, 2H), 7.30 (d, 1H), 7.28 (d, 1H), 4.08 (s, 3H), 4.02 (m, 2H), 3.98 (s, 3H), 2.92 (m, 1H), 2.67 (m, 1H). HRMS: calcd for $C_{28}H_{25}Cl_2N_5O_3 + H+$, 550.14072; found (ESI-FTMS, $[M + H]^{1+}$), 550.14001.

The following compounds were made using the above procedure:

*5.3.21. 2-[5-(2-Aminoethoxy)pyridin-3-yl]-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9a**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.24 (s, 1H), 8.48 (m, 1H), 8.42 (s, 1H), 8.22 (m, 2H), 8.11 (bs, 2H), 7.58 (s, 1H), 4.49 (t, 2), 4.09 (s, 3), 4.00 (s, 3H), 3.33 (m, 2H). HRMS: calcd for $C_{21}H_{21}N_5O_3 + H+$, 392.17172; found (ESI-FTMS, $[M + H]^{1+}$), 392.17316.

*5.3.22. 2-(5-{[(2S)-2-Aminopropyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9b**)*

^{1}H NMR (DMSO-d_6) δ 9.47 (s, 1H), 9.18 (d,1H), 8.38 (m, 2H), 8.17 (s, 2H), 7.50 (s, 1H), 7.37 (bs, 2H), 4.07 (s, 3H), 3.97 (s, 3H), 3.94 (m, 2H), 3.25 (m, 1H), 1.82 (bs, 2H), 1.11 (d, 3H). HRMS: calcd for $C_{22}H_{23}N_5O_3 + H+$, 406.18737; found (ESI-FTMS, $[M + H]^{1+}$), 406.18804.

*5.3.23. 2-(5-{[(2R)-2-Aminopropyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9c**)*

^{1}H NMR (DMSO-d_6) δ 9.47 (s, 1H), 9.18 (d, 1H), 8.38 (m, 2H), 8.17 (s, 2H), 7.50 (s, 1H), 7.37 (bs, 2H), 4.07 (s, 3H), 3.97 (s, 3H), 3.94 (m, 2H), 3.25 (m, 1H), 1.82 (bs, 2H), 1.11 (d, 3H). HRMS: calcd for $C_{22}H_{23}N_5O_3 + H+$, 406.18737; found (ESI-FTMS, $[M + H]^{1+}$), 406.18805.

*5.3.24. 2-(5-{[(2S)-2-Aminobutyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9d**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.25 (s, 1H), 8.49 (m, 1H), 8.42 (s, 1H), 8.23 (m, 2H), 8.14 (bs, 2H), 7.57 (s, 1H), 4.41 (m, 1H), 4.24 (m, 1H), 4.09 (s, 3H), 4.00 (s, 3H), 3.54 (bs, 1H), 1.75 (m, 2H), 1.03 (t, 3H). HRMS: calcd for $C_{23}H_{25}N_5O_3 + H+$, 420.20302; found (ESI-FTMS, $[M + H]^{1+}$), 420.20377.

*5.3.25. 2-(5-{[(2R)-2-Aminobutyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9e**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.25 (s, 1H), 8.49 (m, 1H), 8.42 (s, 1H), 8.23 (m, 2H), 8.14 (bs, 2H), 7.57 (s, 1H), 4.41 (m, 1H), 4.24 (m, 1H), 4.09 (s, 3), 4.00 (s, 3H), 3.54 (bs, 1H), 1.75 (m, 2H), 1.03 (t, 3H). HRMS: calcd for $C_{23}H_{25}N_5O_3 + H+$, 420.20302; found (ESI-FTMS, $[M + H]^{1+}$), 420.2031.

*5.3.26. 2-(5-{[(2S)-2-Amino-4-methylpentyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9f**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.30 (s, 1H), 8.64 (s, 1H), 8.54 (s, 1H), 8.47 (m, 2H), 8.32 (s, 1H), 7.70 (s, 1H), 4.56 (m, 2H), 4.40 (m, 2H), 4.14 (s, 3H), 4.01 (s, 3H), 3.62 (m, 2H), 1.83 (m, 1H), 1.62 (m, 2H), 0.95 (d, 6H). HRMS: calcd for $C_{25}H_{29}N_5O_3 + H+$, 448.23432; found (ESI-FTMS, $[M + H]^{1+}$), 448.23354.

*5.3.27. 2-(5-{[(2R)-2-Amino-4-methylpentyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9g**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.30 (s, 1H), 8.64 (s, 1H), 8.54 (s, 1H), 8.47 (m, 2H), 8.32 (s, 1H), 7.70 (s, 1H), 4.56 (m, 2H), 4.40 (m, 2H), 4.14 (s, 3H), 4.01 (s, 3H), 3.62 (m, 2H), 1.83 (m, 1H), 1.62 (m, 2H), 0.95 (d, 6H). HRMS: calcd for $C_{25}H_{29}N_5O_3 + H+$, 448.23432; found (ESI-FTMS, $[M + H]^{1+}$), 448.23614.

*5.3.28. 2-(5-{[(2S)-2-Amino-3-phenylpropyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7- naphthyridin-4-amine (**9h**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.19 (s, 1H), 8.37 (m, 2H), 8.18 (m, 2H), 7.51 (s, 1H), 7.36 (bs, 2H), 7.29 (m, 4H), 7.21 (m, 2H), 4.08 (s, 3H), 4.00 (m, 2H), 3.98 (s, 3H), 2.90 (m, 1H), 2.66 (m, 1H). HRMS: calcd for $C_{28}H_{27}N_5O_3 + H+$, 482.21867; found (ESI, $[M + H]^+$ Obs'd), 482.2186.

*5.3.29. 2-(5-{[(2R)-2-Amino-3-phenylpropyl]oxy}pyridin-3-yl)-8,9-dimethoxybenzo[c]-2,7- naphthyridin-4-amine (**9i**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.19 (s, 1H), 8.38 (m, 2H), 8.18 (m, 2H), 7.51 (s, 1H), 7.36 (bs, 2H), 7.30 (m, 4H), 7.22 (m,

2H), 4.08 (s, 3H), 4.03 (m, 2H), 3.97 (s, 3H), 2.93 (m, 1H), 2.73 (m, 1H). HRMS: calcd for $C_{28}H_{27}N_5O_3 + H+$, 482.21867; found (ESI-FTMS, $[M + H]^{1+}$), 482.22024.

*5.3.30. 2-(5-{[(2S)-2-Amino-3-(4-fluorophenyl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9j**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.18 (d, 1H), 8.37 (m, 2H), 8.17 (m, 2H), 7.51 (s, 1H), 7.36 (bs, 2H), 7.31 (m, 2H), 7.12 (m, 2H), 4.08 (s, 3H), 3.99 (m, 2H), 3.97 (s, 3H), 2.89 (m, 1H), 2.65 (m, 1H). HRMS: calcd for $C_{28}H_{26}FN_5O_3 + H+$, 500.20924; found (ESI-FTMS, $[M + H]^{1+}$), 500.20938.

*5.3.31. 2-(5-{[(2R)-2-Amino-3-(4-fluorophenyl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine*HCl (**9k**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 9.25 (d, 1H), 8.44 (m, 2H), 8.38 (s, 1H), 8.24 (bs, 2H), 8.18 (m, 1H), 7.53 (s, 1H), 7.44 (bs, 1H), 7.38 (m, 2H), 7.20 (m, 2H), 4.31 (m, 1H), 4.13 (m, 1H), 4.08 (s, 3H), 3.98 (s, 3H), 3.06 (d, 2H). HRMS: calcd for $C_{28}H_{26}FN_5O_3 + H+$, 500.20924; found (ESI-FTMS, $[M + H]^{1+}$), 500.20747.

*5.3.32. 2-[5-({(2S)-2-Amino-3-[3-(trifluoromethyl)phenyl]propyl}oxy)pyridin-3-yl]-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9l**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.96 (s, 1H), 8.40 (s, 1H), 8.01 (s, 2H), 7.78 (s, 1H), 7.58 (s, 1H), 7.53 (m, 2H), 7.46 (m, 2H), 5.49 (bs, 2H), 4.17 (s, 3H), 4.10 (s, 3H), 4.03 (m, 2H), 3.56 (m, 1H), 3.08 (m, 1H), 2.83 (m, 1H). HRMS: calcd for $C_{29}H_{26}F_3N_5O_3 + H+$, 550.20605; found (ESI-FTMS, $[M + H]_{1+}$), 550.20615.

*5.3.33. 2-[5-({(2R)-2-Amino-3-[3-(trifluoromethyl)phenyl]propyl}oxy)pyridin-3-yl]-8,9-dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9m**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.02 (d, 1H), 8.38 (d, 1H), 8.36 (s, 1H), 8.18 (s, 2H), 7.58 (m, 5H), 7.36 (s, 1H), 4.08 (s, 3H), 4.04 (m, 2H), 4.03 (m, 2H), 3.98 (s, 3H), 3.04 (m, 1H), 2.80 (m, 1H). HRMS: calcd for $C_{29}H_{26}F_3N_5O_3 + H+$, 550.20605; found (ESI-FTMS, $[M + H]^{1+}$), 550.20631.

*5.3.34. 2-(5-{[(2S)-2-Amino-3-(1H-indol-3-yl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9n**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (bs, 1H), 9.47 (s, 1H), 9.18 (d, 1H), 8.37 (d, 2H), 8.18 (s, 2H), 7.57 (d, 1H), 7.51 (s, 1H), 7.37 (bs, 2H), 7.34 (d, 1H), 7.21 (d, 1H), 7.05 (t, 1H), 6.94 (t, 1H), 4.07 (s, 3H), 4.03 (m, 2H), 3.98 (s, 3H), 3.41 (m, 1H), 3.01 (m, 1H), 2.80 (m, 1H). HRMS: calcd for $C_{30}H_{28}N_6O_3 + H+$, 521.22957; found (ESI-FTMS, $[M + H]^{1+}$), 521.22985.

*5.3.35. 2-(5-{[(2R)-2-Amino-3-(1H-indol-3-yl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9o**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (bs, 1H), 9.47 (s, 1H), 9.20 (s, 1H), 8.37 (m, 2H), 8.18 (s, 2H), 7.60 (d, 1H), 7.51 (s, 1H), 7.35 (m, 3H), 7.24 (s, 1H), 7.07 (t, 1H), 6.96 (t, 1H), 4.11 (m, 2H), 4.07 (s, 3H), 3.96 (s, 3H), 3.57 (m, 1H), 3.07 (m, 1H), 2.92 (m, 1H). HRMS: calcd for $C_{30}H_{28}N_6O_3 + H+$, 521.22957; found (ESI-FTMS, $[M + H]^{1+}$), 521.22842.

*5.3.36. 2-(5-{[(2S)-2-Amino-3-(2-chlorophenyl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9p**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.23 (s, 1H), 8.37 (m, 2H), 8.17 (s, 2H), 7.48 (m, 4H), 7.33 (m, 4H), 4.22 (m, 1H), 4.11 (m, 2H), 4.08 (s, 3H), 3.98 (s, 3H), 3.70 (m, 1H), 3.18 (m, 1H), 3.02 (m,1H). HRMS: calcd for C28H26ClN5O3 + H+, 516.17969; found (ESI-FTMS, [M + H]1+), 516.1801.

*5.3.37. 2-(5-{[(2S)-2-Amino-3-(3-chlorophenyl)propyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9q**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 9.25 (s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.18 (m, 2H), 7.52 (s, 1H), 7.46 (s, 1H), 7.35 (m, 4H), 4.32 (m, 1H), 4.14 (m, 1H), 4.08 (s, 3H), 3.98 (s, 3H), 3.90 (m, 2H), 3.07 (d, 2H). HRMS: calcd for $C_{28}H_{26}ClN_5O_3 + H+$, 516.17969; found (ESI-FTMS, $[M + H]^{1+}$), 516.1806.

*5.3.38. 2-(5-{[(2S)-2-Amino-3-pyridin-4-ylpropyl]oxy}pyridin-3-yl)-8,9- dimethoxybenzo[c]-2,7-naphthyridin-4-amine (**9s**)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.26 (s, 1H), 8.72 (d, 2H), 8.49 (d, 1H), 8.43 (s, 1H), 8.38 (bs, 2H), 8.25 (s, 1H), 8.18 (s, 1H), 7.68 (d, 2H), 7.59 (s, 1H), 4.38 (m, 1H), 4.21 (m, 1H), 4.11 (s, 3H), 4.08 (m, 3H), 4.01 (s, 3H), 3.22 (d, 2H). HRMS: calcd for $C_{27}H_{26}N_6O_3 + H+$, 483.21391; found (ESI-FTMS, $[M + H]^{1+}$), 483.21474.

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