Journal of Medicinal Chemistry

Article

Discovery of (R)-8-(6-Methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-b]pyrrol-2-yl)-3-(1-methylcyclopropyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3H)-one, a Potent and Selective Pim- 1/2 Kinase Inhibitor for Hematological Malignancies

Hui-Ling Wang, Kristin Andrews, Shon K. Booker, Jude Canon, Victor J. Cee, Frank Chavez Jr., Yuping Chen, Heather Eastwood, Nadia Guerrero, Bradley Herberich, Dean Hickman, Brian A Lanman, Jimmy Laszlo III, Matthew R Lee, J. Russell Lipford, Bethany Mattson, Christopher Mohr, Yen Nguyen, Mark H Norman, Liping H. Pettus, David Powers, Anthony B. Reed, Karen Rex, Christine Sastri, Nuria A. Tamayo, Paul Wang, Jeffrey T. Winston, Bin Wu, Qiong Wu, Tian Wu, Ryan P. Wurz, Yang Xu, Yihong Zhou, and Andrew S Tasker

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.8b01733 • Publication Date (Web): 09 Jan 2019

Discovery of (*R*)-8-(6-Methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(1-methylcyclopropyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one, a Potent and Selective Pim-1/2 Kinase Inhibitor for Hematological Malignancies

Hui-Ling Wang,*† Kristin L. Andrews,‡ Shon K. Booker,† Jude Canon,‖ Victor J. Cee,† Frank Chavez, Jr.,† Yuping Chen,§ Heather Eastwood,‡ Nadia Guerrero,‖ Brad Herberich,† Dean Hickman,§ Brian A. Lanman,† Jimmy Laszlo, III,# Matthew R. Lee,‡ J. Russell Lipford,‖ Bethany Mattson,‖ Christopher Mohr,‡ Yen Nguyen,# Mark H. Norman,† Liping H. Pettus ,† David Powers,# Anthony B. Reed,† Karen Rex,‖ Christine Sastri,‖ Nuria Tamayo,† Paul Wang,# Jeffrey T. Winston,‖ Bin Wu,† Qiong Wu,⊥ Tian Wu,⊥ Ryan P. Wurz,† Yang Xu,§ Yihong Zhou,§ and Andrew S. Tasker†

† Department of Therapeutic Discovery-Medicinal Chemistry, ‡ Molecular Structure, § Pharmacokinetics and Drug Metabolism, ‖ Oncology Research, ⊥ Pharmaceutics, # Discovery Technologies, Amgen Research, One Amgen Center Drive, Thousand Oaks, California 91320, United States

KEYWORDS Pim kinase inhibitor, multiple myeloma, KMS-12BM, oncogene, hematologic cancers

ABSTRACT: Pim kinases are a family of constitutively active serine/threonine kinases which are partially redundant and regulate multiple pathways important for cell growth and survival. In human disease, high expression of the three Pim isoforms has been implicated in the progression of hematopoietic and solid tumor cancers, which suggests that Pim kinase inhibitors could provide patients with therapeutic benefit. Herein, we describe the structure-guided optimization of a series of quinazolinone-pyrrolodihydropyrrolone analogs leading to the identification of potent pan-Pim inhibitor **28** with improved potency, solubility and drug-like properties. Compound **28** demonstrated on-target Pim activity in an *in vivo* pharmacodynamic assay with significant inhibition of BAD phosphorylation in KMS-12-BM multiple myeloma tumors for 16

hours post dose. In a 2-week mouse xenograft model, daily dosing of compound **28** resulted in 33% tumor regression at 100 mg/kg.

INTRODUCTION

Pim proteins were first identified as a preferred proviral integration site of Moloney (Pim) murine leukemia virus in mouse models of virus-induced lymphomas.[1] They are a family of serine/threonine kinases composed of three members (Pim-1, Pim-2, and Pim-3) that regulate oncogenesis,[2] survival pathways, drug resistance, and migration.[3] The three Pim isoforms are highly homologous, functionally redundant and often over expressed in subsets of B-cell malignancies[4,5] including lymphomas, leukemias, and multiple myeloma, as well as some solid tumors.[6] Pan-Pim kinase inhibitors have been shown to inhibit proliferation of multiple myeloma cell lines *in vitro* and in xenograft models, and are expected to provide the most clinical benefit in patients with this disease.[7,8]

The research for Pim kinase inhibitors has been very active in recent years,[9-18] resulting in three small molecules, SGI-1776,[19,20] AZD-1208[21] and PIM447,[8,22] which have reached clinical trials. In recent years, efforts at Amgen have also culminated in the identification of small molecule Pim kinase inhibitors. The structure–activity relationships (SAR) of numerous diverse scaffolds (Figure 1) have been disclosed including aminothiadiazole **1**,[23] aminooxadiazole **2**,[24] 3-(pyrazin-2-yl)-1*H*-indazole **3**,[25] and imidazopyridazine **4**.[26] Although imidazopyridazine **4** exhibited superior enzymatic and cellular potency over previously identified compounds (KMS-12 p-BAD IC_{50} = 28 nM), the moderate to high clearance of this class of compounds precluded their further advancement.

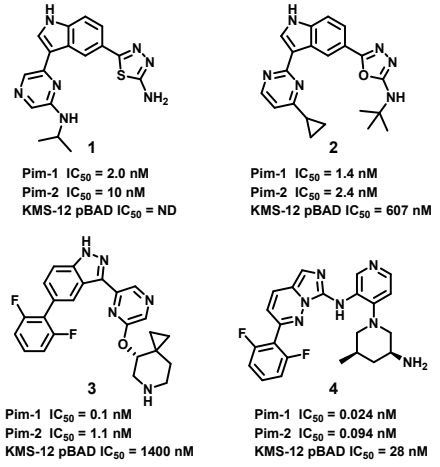


Figure 1. Pim kinase inhibitors previously reported by Amgen.

The naphthyridine pyrrolodihydropiperidinone **5** was another chemotype that was identified from our prior kinase programs (Figure 2).[27] Although this screening hit was a potent Pim-1/2 kinase inhibitor with modest cell potency, it exhibited poor kinase selectivity. The nitrogen at the 5-position of naphthyridine **5** has favorable H-bonding interactions with the backbone hydrogen bond donor presented by most kinase hinge residues. The replacement of the naphthyridine with a methylquinoxaline (**6**) resulted in not only improved Pim-1/2 potency, but also significantly improved kinase selectivity. Pim-

1/2 kinases are able to accommodate both the naphthyridine and quinoxaline cores because the hinge region of the Pim kinases contains a proline residue and therefore lacks the canonical hydrogen-bond donor of all other kinases. In an effort to diversify the aniline substituent of **5**, molecules containing *N*-alkyl groups (such as compound **6**) were found to be similarly potent. Consideration of the U-shape of these *N*-alkyl analogs led to the discovery of macrocyclic quinoxaline-pyrrolodihydropiperidinone **7** as potent Pim-1/2 inhibitors (Figure 2).[27]

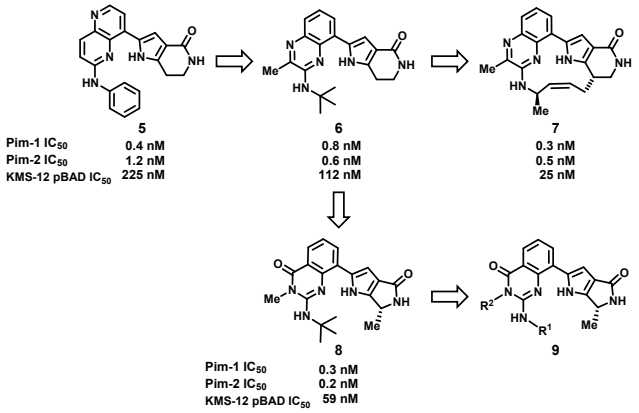


Figure 2. Hit-to-lead progression and optimization strategy toward macrocyclic quinoxaline **7** and non-macrocyclic quinazolinone **9**.

In parallel with the optimization efforts on the macrocyclic inhibitors, lead optimization efforts on non-macrocyclic analogs resulted in the discovery of quinazolinone-pyrrolodihydropyrrolone **8**.[28] This compound demonstrated improved metabolic stability over quinoxaline-pyrrolodihydropiperidinones. Although both **7** and **8** are potent and selective pan-Pim inhibitors and orally efficacious in mouse xenograft models (KMS-12-BM) of multiple myeloma, the limited solubility (compound **7**, PBS/FaSSIF, 40/295 μM; compound **8**, 23/104 μM respectively) became a potential barrier for further development. Thus, the challenge was to improve the solubility while maintaining the potency, selectivity and metabolic stability achieved with compound **8**.

The Pim hinge region is unusual in both sequence and conformation; a two-residue insertion gives rise to a wider ATP binding pocket, and a proline residue in the hinge removes a conserved hydrogen bond donor that can participate in inhibitor binding. Without this hydrogen bond, van der Waals interactions with the hinge serve to position the ligand. Based on the X-ray structure of **8** bound to Pim-1 protein (PDB ID: 5IPJ)[28] (Figure 3) the dihedral angle between the pyrrole and quinazolinone is 0° due to the intramolecular H-bond from the pyrrole-NH to the quinazolinone-N. This coplanarity between the two rings is required for potency but is likely a contributor to the low solubility of compound **8**. Because of the wider ATP binding pocket of Pim, replacement of the methyl group at the 3-position of quinazolinone with various larger substitutions R^2 is feasible to keep the potency and to prevent the molecule tight stacking in the crystalline lattice. Therefore, our strategy focused on modifying the substituent in structure **9** (Figure 2) to further improve drug-like properties suitable for development.

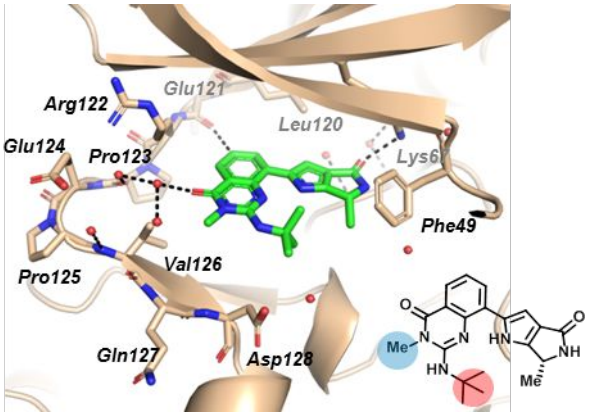
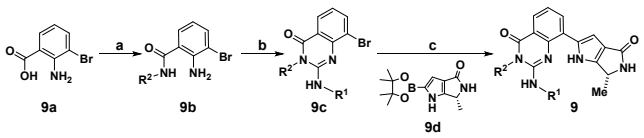


Figure 3. X-ray crystal structure of **8** bound to Pim-1 (PDB ID: 5IPJ).

CHEMISTRY

The general synthetic route used to prepare Pim inhibitors is described in Scheme 1. R^2 was introduced early in the sequence via amide coupling of various amines with commercially available *o*-aminobenzoic acid **9a** in the presence of T3P or HATU. The amino-quinazolinone scaffold could be accessed through three different routes. Method A: cyclization of amide **9b** using triphosgene afforded 2-hydroxyquinazolinone, which was then elaborated to 2-chloroquinazolinone by reacting with $POCl_3$. Displacement of the resulting chloride with amines furnished 2-amino-substituted-quinazolinones **9c**. Method B: following the cyclization of amide **9b** using triphosgene, 2-hydroxyquinazolinone was treated with BOP and DBU in the presence of amines to obtain the desired 2-amino-substitued-quinazolinone **9c**. Method C: amines **9b** were converted to azides under mild conditions with *tert*-butyl nitrite and azidotrimethylsilane.[29] The resulting aromatic azides were not isolated, but elaborated to iminophosphoranes by addition of trimethylphosphine. Subsequent heating of the iminophosphoranes with isocyanates resulted in formation of carbodiimide intermediate, which underwent intramolecular cyclization to furnish the desired 2-amino-substituted-quinazolinones **9c**.[30] Method A and B are good for the scale-up. Method C is a one-pot synthesis through 4 sequential steps and useful to quickly generate SAR. Installation of the pyrrolopyrrolone was accomplished with a Suzuki coupling between quinazolinones **9c** and chiral boronic ester **9d**, whose synthesis has been previously described.[28]



Scheme 1. Synthesis of compounds **9**. Reagents and conditions: (a) R^1-NH_2, T3P, DIPEA, EtOAc, rt or R^1-NH_2, HATU, Et_3N, dichloromethane, DMF, rt; (b) Method A: (1) triphosgene, (2) $POCl_3$, DIPEA, reflux, (3) R^2-NH_2, heat; Method B: (1) triphosgene, (2) R^2-NH_2, BOP, DBU; Method C: (1) *t*-BuONO,

$TMSN_3$, MeCN, 0 °C, (2) Me_3P, (3) R^2NCO, 60 °C, (4) DBU, 60 °C; (c) Pd_2dba_3, XPhos, K_3PO_4, dioxane/H_2O, 80 °C; or XPhos-Pd-G2, K_3PO_4, dioxane/H_2O, 45 °C.

RESULTS AND DISCUSSION

All analogs were evaluated in Pim biochemical and cellular assays. In the biochemical assays, compounds were assessed for their ability to inhibit the phosphorylation of a BAD peptide at serine 112 (S112) by full-length recombinant human Pim-1 and Pim-2 proteins. According to our experience across multiple scaffolds in the Pim program, the activity of Pim-3 was in general comparable to Pim-1. Therefore, the Pim-3 enzyme assay was not routinely performed. In cell-based assays, the compounds were assessed for their ability to inhibit the phosphorylation of BAD at S112 in KMS-12 BM cells in the presence of 20% fetal bovine serum (FBS) using flow cytometry. KMS-12 BM[31] is a multiple myeloma cell line with expression of Pim-1, -2, and -3 proteins, Pim-2 is expressed at a high level. For an initial assessment of metabolism, the compounds were evaluated in RLM and HLM, and the data, reported as intrinsic clearance (CL_{int}), were used to prioritize potent compounds for additional PK studies.

Initially, we systematically increased the size of the alkyl substituent at the 3-position of 2-*tert*-butylamino quinazolinone (Table 1). Replacement of the methyl group (**8**) with isopropyl (**10**), cyclopropyl (**11**), and 1-methylcyclopropyl (**12**) led to a slight improvement in Pim activity (enzymatic and cellular), but only the cyclopropyl derivative **11** maintained rat and human microsomal stability relative to the parent **8**. Introduction of a *tert*-butyl moiety (**13**) resulted in a 3-fold loss in cellular potency. Interestingly, installation of a cyclopropylmethyl group (**14**) restored enzymatic and cellular potency. However, none of these analogs demonstrated improved solubility relative to **8**. Attempting to increase solubility by introducing polar groups onto the cyclopropylmethyl moiety, both (1-hydroxycyclopropyl)methyl (**15**) and (1-aminocyclopropyl)methyl (**16**) exhibited comparable enzymatic and cellular potencies and compound **16** indeed had good solubility in acidic media. Opening the cyclopropyl ring of compound **16** to 2-amino-2-methylpropyl derivative **17** led to a greater than 10-fold loss in KMS-12 cell potency.

Next, we investigated heterocyclic substituents at the 3-position of the 2-*tert*-butylaminoquinazolinone. Replacement of the methyl group (**8**) with oxetan-3-ylmethyl (**18**), (tetrahydrofuran-2-yl)methyl (**19** and **20**) and (4-methylmorpholin-2-yl)methyl (**21** and **22**) were tolerated, especially **19** and **22** demonstrating significant improvements in KMS-12 cell potency. Unfortunately, their microsomal stability was unacceptable. Analogs equipped with (1-methyl-1*H*-imidazol-4-yl)methyl (**23**) and 1-(1-methyl-1*H*-imidazol-4-yl)ethyl (**24,** a racemic mixture) delivered comparable enzymatic and cellular potencies to the parent **8** with moderate microsomal stability. Compound **24** additionally exhibited improved solubility in all three media.

We had discovered previously that introduction of a (1-methylcyclopropyl)amino group (**25**) at the 2-position of quinazolinone improved Pim potency (KMS-12 IC_{50} = 11 nM) as well as solubility.[28] However, the rat PK profile of compound **25** was not ideal with high clearance (2.7 L/h/kg) and low bioavailability (%F = 5). We then turned our attention to optimization of the 2-(1-methylcyclopropyl)aminoquinazolinone scaffold with the SAR learned from 2-*tert*-

butylaminoquinazolinones (Table 1). Replacement of the methyl group (**25**) with cyclopropyl (**26**), cyclobutyl (**27**) and cyclopropylmethyl group (**30**) led to a slight improvement in Pim enzymatic activity but a 2- to 5-fold loss in cellular potency along with an increase in microsomal turnover. Introduction of the 1-methylcyclopropyl moiety (**28**) retained the excellent cellular potency with moderate microsomal stability. Installation of *t*-butyl group (**29**), as with compound **13**, resulted a 100-fold loss in cellular potency. Remarkably, the solubility of all these R^1 cyclopropylmethyl and R^2 C1-C4 alkyl analogs (**25**-**30**) were better than their corresponding 2-*tert*-butylamino quinazolinone analogs (**8**-**14**) (Figure 4). Appending a polar group to cyclopropylmethyl, both (1-hydroxycyclopropyl)methyl (**31**) and (1-aminocyclopropyl)methyl (**32**) in this scaffold resulted a large loss in cellular potency. A racemic mixture of 1-(1-methyl-1*H*-imidazol-4-yl)ethyl derivative **33** afforded a similar potency and solubility profile to compound **28**. After SFC chiral separation of **33**, we obtained two pure single isomers **34** and **35**. Compound **35** displayed a better profile than **34**. The isomer **35** demonstrated excellent enzymatic and cellular potency (KMS-12 IC_{50} = 8 nM) as well as good solubility and moderate microsomal stability.

Through these SAR efforts, we recognized that **26**, **28** and **35** exhibited the best cellular potency with reasonable microsomal stability and improved solubility. These three most promising analogues were selected for pharmacokinetic profiling (data presented in Table 2; Parent compounds **8** and **25** [28] are also included for comparison). In general, these molecules demonstrated moderate plasma protein binding, and good permeability. The *in vivo* PK in male Sprague-Dawley rats revealed significant differences in oral bioavailability (19-85%), but not in clearance (0.8-1.0 L/h/kg). Compound **28** possessed the most favorable profile (lowest clearance and highest oral bioavailability, even when dosed in a standard formulation) and was advanced to further evaluation.

A solubility comparison study between the most stable known crystalline form of compound **8** (T_m = 339 °C) and **28** (T_m = 294 °C) was established at 37 °C using water and three biologically relevant gastrointestinal media, FaSSGF, FaSSIF and FeSSIF.[32] Data for compound **8** are: 6, 62, 14, 118 μM and for compound **28** are: 12, 486, 30, 226 μM respectively. Compound **28** demonstrated a higher solubility than compound **8** in water and biological relevant media. This may be due in part to its lower melting point (294 °C) versus compound **8** (339 °C).[33] Comparison of eight matched pairs in Figure 4 shows that cyclopropylmethyl at R^1 is uniformly more soluble than *tert*-butyl. A dog PK study of compound **28** revealed low IV clearance (0.14 L/h/kg) with V_{ss} of 2.1 L/kg, $t_{1/2}$ of 11.2 h, and good oral bioavailability (56%). The plasma protein binding of **28** was also measured and its unbound fractions (f_u) were similar across the different species (rat/dog/mouse/human, 0.040/0.045/0.033/ 0.039, respectively). In a hERG binding assay, **28** had IC_{50} of >30 μM.

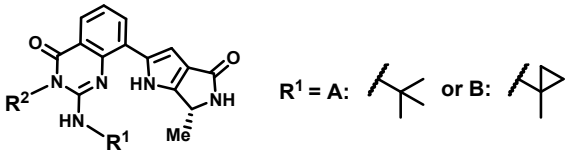


Table 1. SAR for substitutions at 2 & 3-position of quinazolinones

Cmpd	R^1	R^2	Pim-1 IC_{50} (nM) [a]	Pim-2 IC_{50} (nM) [a]	KMS-12 pBAD IC_{50} (nM) [a]	HLM/RLM (μL/min/mg) [b]	Solubility (μM) PBS (pH 7.4) [c]	Solubility (μM) FaSSIF (pH 6.8) [c]	Solubility (μM) 0.01 N HCl (pH 2.0) [c]
8	A		0.34	0.38	59	19 / 22	23	104	60
10	A		0.07*	0.13*	42	74 / 121	11	68	26
11	A		0.17	0.12	35	27 / 32	13	175	95
12	A		0.29	0.16	36	109 / 96	<5	36	<5
13	A		0.21	0.83	196	195 / 187	<5	58	<5
14	A		0.09*	0.08*	31	71 / 125	<5	12	<5
15	A		0.13*	0.23*	55	58 / 70	<5	<5	<5
16	A		0.11*	0.24*	48	67 / 77	<5	42	500
17	A		0.56*	2.2*	707	32 / 21	26	131	347
18	A		0.16*	0.60*	126	17 / 18	6	32	14
19	A		0.36*	0.13*	24	>399 / 319	19	60	<5
20	A		1.8*	1.1*	341	175 / 361	12	15	28
21[d]	A		1.2*	1.6*	224	50 / 80	<5	<5	256
22[d]	A		0.55*	0.41*	38	193 / 341	122	283	500
23	A		0.35*	0.16*	46	96 / 23	22	131	94
24	A		0.12	0.7	83	79 / 63	86	489	423
25	B		0.20	0.38	11	20 / 49	56	344	500
26	B		0.10	0.09	24	42 / 68	78	144	458
27	B		0.14*	0.18*	57	61 / 133	<5	379	441
28	B		0.05	0.05	12	54 / 81	31	185	490
29	B		20.3	3.50	1,239	107 / 177	<5	326	495
30	B		0.06*	0.12*	21	52 / 87	13	179	214
31	B		0.08*	0.18*	1,805	47 / 65	<5	15	43
32	B		0.02*	0.16*	99	46 / 72	134	280	454
33	B		0.03*	0.11*	19	54 / 80	52	500	500
34[d]	B		0.65*	3.2*	472	47 / 107	53	435	485
35[d]	B		0.03	0.15	8	35 / 92	60	469	464

[a] Average of at least two determinations unless indicated by *(n = 1); for full statistical information, see the supporting information. [b] Single experimental value; estimated clearance from percent parent compound (1 μM) remaining following a 30 min incubation in liver microsomes (0.25 mg/mL) and NADPH. [c] *n* = 1 for solubility data, PBS = phosphate-buffered saline, FaSSIF = fasted state simulated intestinal fluid. [d] The absolute structure was arbitrarily assigned.

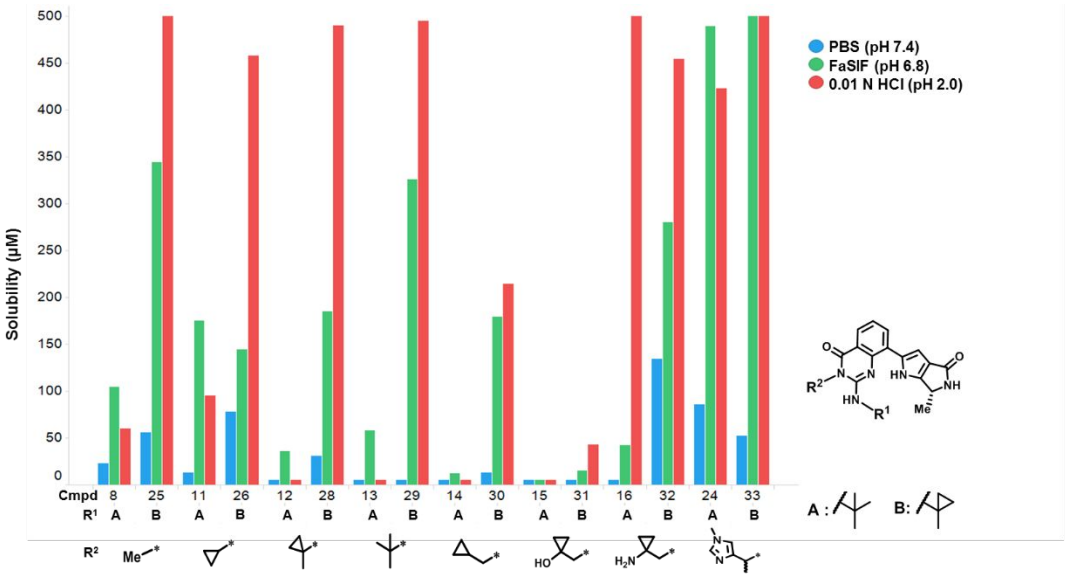


Figure 4. Solubility comparison for the selected compounds from Table 1

Table 2. Pharmacokinetic properties of most potent analogs

Cmpd	LLC-PK1 P_{app} (μcm/s) [a]	Rat PPB f_u [b]	CL (L/h/kg) [c]	V_{ss} (L/kg) [c]	$t_{1/2}$ (h) [c]	%F [c]
8	**46**	**0.061**	**0.3** [d]	**1.5**	**4.6**	**39** [f]
25	**31**	**0.061**	**2.7** [d]	**1.9**	**0.6**	**5** [f]
26	**23**	**0.047**	**1.2** [e]	**1.2**	**1.5**	**68** [g]
28	**32**	**0.040**	**0.8** [e]	**1.7**	**2.2**	**85** [g]
35	**35**	**0.032**	**1.0** [e]	**1.0**	**2.5**	**19** [g]

[a] Average of A–B and B–A diffusion rates across a single layer of LLC-PK1 cells determined at 5 μM compound. [b] Plasma protein binding determined by rapid equilibrium dialysis with 5 μM compound. [c] Pharmacokinetic parameters following administration to male Sprague Dawley rats; mean values from 3 animals per dosing route. [d] Dosed iv at 2 mg/kg as a solution in DMSO. [e] Dosed iv at 1 mg/kg as a solution in DMSO. [f] Dosed po at 5 mg/kg in 40.0% PEG 400, 60.0% water, adjusted to pH 2.2 with methanesulfonic acid. [g] Dosed po at 5 mg/kg in 1% Tween 80, 2% HPMC, 97% water adjusted to pH 2.2 with methanesulfonic acid.

The selectivity of **28** against a panel of 100 protein and lipid kinases was examined at 1 μM in the ScanMAX KINOMEscan panel offered by DiscoveRx. The S(35), S(10), S(1) selectivity scores, representing the fraction of tested kinases with percent-of-control (POC) values < 35, 10 and 1% were determined to be 0.04, 0.01 and 0, respectively. Four kinases exhibited POC < 35%: CLK4 (34%), MEK3 (31%), JNK3 (11%) and Pim-1 (2%).[34] Compound **28** demonstrated better kinase selectivity than **8,** which against the same panel exhibited S(35), S(10), S(1) selectivity scores of 0.07, 0.06 and 0.03, respectively.[28] This selectivity improvement is consistent with the additional hinge residues (two-residue insertion) of Pim-1 kinase resulting in a wider ATP binding pocket than other kinases. Therefore, the lager methylcyclopropyl group at the 3-position of the quinazolinone was accommodated by Pim-1 kinase, but not accommodated by other kinases. With the high kinase selectivity, we believe the *in vivo* efficacy of **28** is primarily driven by Pim kinase inhibition.

The X-ray crystal structure of **28** bound to Pim-1 protein (PDB ID: 6MT0) in Figure 5A revealed a similar binding mode to compound **8**. The carbonyl oxygen of the pyrrolone engages in a direct H-bonding (N to O distance 2.6 Å) interaction with the conserved catalytic Lys67. A water-mediated bridge between the carbonyl oxygen of Asn172 and Asp186, and the NH of pyrrolone was resolved. The pyrrolone is closely packed against the Asp186 side chain (N to O distance 2.8 Å). Another two water-mediated bridges between the carbonyl oxygen (C4=O) in quinazolinone and the carbonyl oxygen of Pro123, which are

5.0 Å apart was also observed. The presence of Pro123 in the ATP-binding hinge of the Pim kinases results in the absence of the canonical backbone NH found in other kinases, and this uniquely accommodates the C5-H of the quinazolinone. In addition, the favorable hydrophobic contacts between the two methylcyclopropyl groups well filled small lipophilic pockets under the glycine rich loop and lower hinge region of Pim-1 (shown in Figure 5B) which likely contribute to the excellent potency and kinase selectivity of **28**.

The antiproliferative activity of **8** and **28** across hematologic malignancies was assessed in the multiple cell lines listed in Table 3, including multiple myeloma and AML cell lines. In general, multiple myeloma cell lines exhibit higher Pim-2 expression, whereas AML cell lines show higher Pim-1 expression. Compound **28** with low double digit picomolar enzymatic potency in Pim-1/2 resulted in improved IC_{50} values in the proliferation assay across the panel relative to compound **8**.

Table 3. Proliferation activities of compounds 8 and 28 across hematologic malignancies

Cell Line	Proliferation IC_{50} (μM) Cmpd 8 [c]	Proliferation IC_{50} (μM) Cmpd 28 [c]	Basal Pim-1 levels (counts per 15 μg)[d]	Basal Pim-2 levels (counts per 15 μg)[d]
KMS-12-BM [a]	0.26	0.049	3547 ± 68.6	19,067 ± 1074.1
RPMI-8226 [a]	0.83	0.104	1188 ± 4.2	23,228 ± 413.7
OPM-2 (PTEN null) [a]	0.72	0.667	264 ± 16.3	10,289 ± 310.4
EOL-1 [b]	0.02	0.002	16,376 ± 243.2	1136 ± 59.4
OCI-M1 [b] (erythroleukemia)	1.5	0.093	22,004 ± 124.5	4008 ± 5.7

[a] Multiple myeloma cell line. [b] Acute myeloid leukemia cell line. [c] IC_{50} value corresponds to 72 h incubation of compounds in the CellTiter-Glo® proliferation assay. [d] Basal Pim-1 and Pim-2 protein levels as measured by MSD assays ($n = 2$ separate determinations) using electrochemiluminescence (ECL) per 15 μg protein[26]

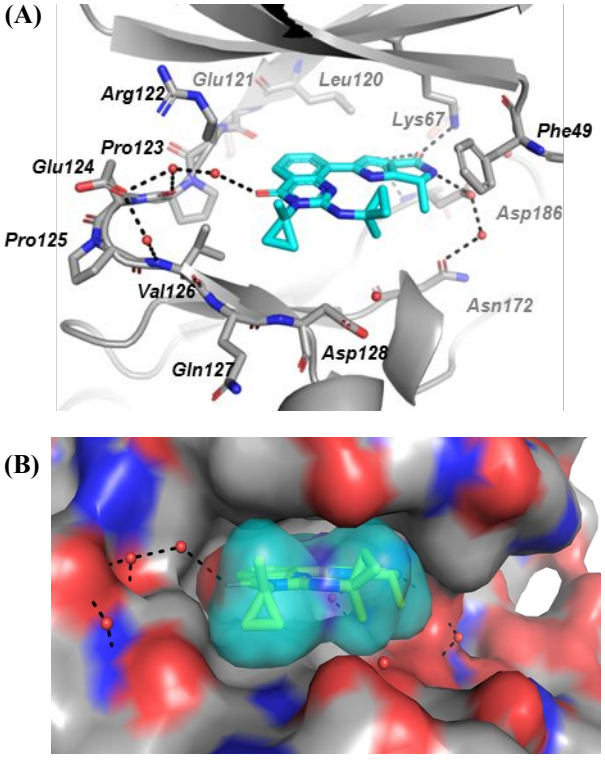


Figure 5. X-ray crystal structure of **28** bound to Pim-1 (PDB ID: 6MT0). (A) Inhibitor **28** occupies the ATP-binding site; hydrogen bond contacts are shown with dashed lines; the red dots represent water molecules; the top of the ATP-binding pocket is omitted for clarity. (B) CPK (Corey–Pauling–Koltun) rendering of **28** illustrating that the two methylcyclopropyl groups form a complementary hydrophobic surface under the P-loop and floor residues of Pim-1. The figures were generated with the PyMOL Molecular Graphics System, version 1.7.0.1 Schrödinger, LLC.

The *in vivo* activity of **28** on Pim-dependent phosphorylation of BAD (Ser 112) was further evaluated in the KMS-12-BM human multiple myeloma xenograft model in female SCID-beige mice (Figure 6). In this pharmacodynamics (PD) model, we typically observe a maximum inhibition of 60-70% BAD phosphorylation at Ser-112 for selective Pim kinase inhibitors; the remainder of BAD phosphorylation is attributed to other kinases, possibly PKB (AKT).[27, 28] Compound **28** dosed orally at 25, 50, or 100 mg/kg provided a dose-dependent increase in exposure and nearly all doses achieved a maximum inhibition of 60-70% p-BAD levels at 6 and 16 hours (Figure 6). We next tested the efficacy of compound **28**, choosing a dosing regimen of 10, 25, 50 or 100 mg/kg orally once per day for 14 days. A dose-dependent inhibition of tumor growth was observed with complete stasis achieved at 50 mg/kg QD and tumor regression observed at 100 mg/kg QD (Figure 7A). All doses were well tolerated, with minimal impact on body weight over the course of the study (Figure 7B). These data suggest that *in vivo* exposures above the *in vitro* IC_{50} for at least 16 h with greater than 50% p-BAD inhibition results in significant tumor growth inhibition (Figure 7C).

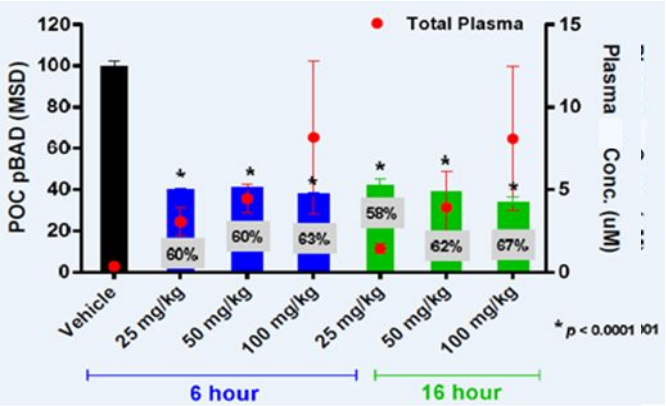


Figure 6. The *in vivo* activity of **28** to impact Pim-dependent phosphorylation of BAD (Ser 112) was evaluated in KMS-12-BM tumors in female SCID-beige mice. Bars represent %pBAD. Terminal total plasma concentration of 28 is indicated by red circles. Data represent the mean (n = 3) ± standard deviation, Statistical significance (* p < 0.0001) was evaluated by analysis of variance (ANOVA), followed by Dunnet's post hoc.

CONCLUSION

In summary, modifications at the 2- and 3-positions of quinazolinone **8** resulted in potent Pim-1/2 kinase inhibitors with improved properties. Compound **28,** bearing two methylcyclopropyl groups at the 2- and 3-positions of the quinazolinone, demonstrated not only improved Pim potency and kinase selectivity by leveraging more lipophilic interactions, but exhibited improved solubility over compound **8** in water and biologically relevant media. With the combination of cellular potency, solubility, good PK profile across species, and potent single agent antitumor activity in a KMS-12-BM mouse xenograft model (ED_{50} = 12 mg/kg), compound **28** emerged as a best in-series candidate. This compound has advanced into additional mouse

xenograft models of DLBCL and AML, combination studies with standard of care agents and toxicology studies, and the results will be reported in due course.

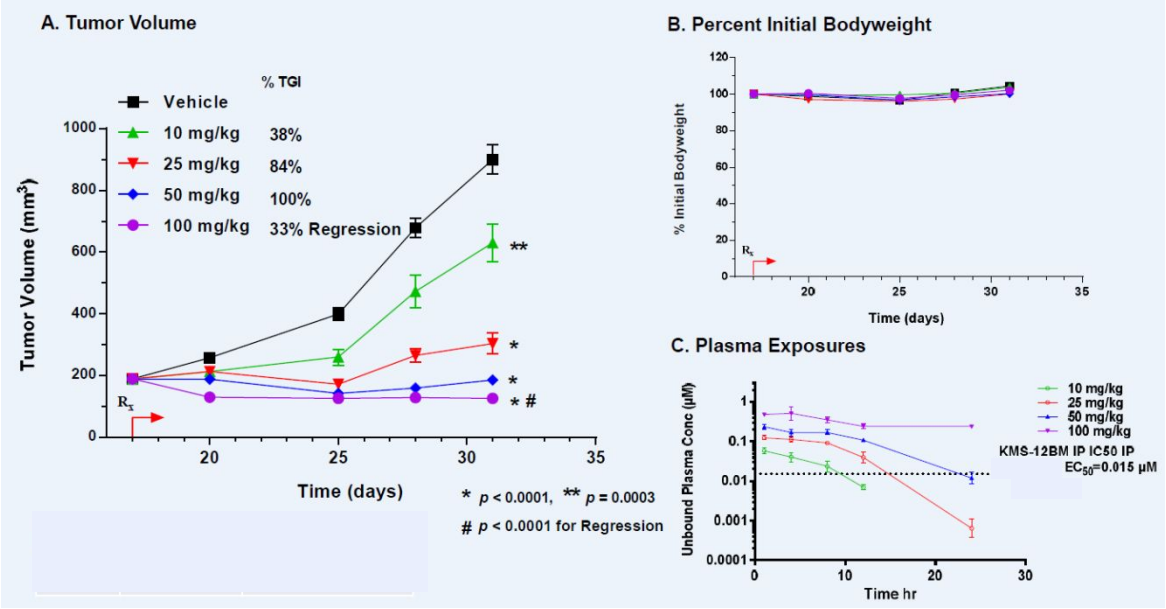


Figure 7. Pim inhibition suppresses MM growth in the KMS-12-BM mouse xenograft model. (A) Compound **28** (10, 25, 50, or 100 mg/kg p.o.) is associated with a dose-dependent inhibition of KMS-12-BM tumor growth. (B) All doses were well tolerated, with minimal impact on body weight over the course of the study. Data represent the mean (n = 10) ± SEM. (C) Unbound plasma concentration of **28**. Data represent the mean (n = 2 / timepoint) Statistical significance (*p < 0.0001) was determined by repeated measures analysis of variance (RMANOVA) followed by Dunnet's post hoc.

EXPERIMENTAL SECTION

Pim-1 and Pim-2 Enzyme Assays

The assay for the determination of Pim activity was based on the formation of phosphorylated biotinylated-BAD peptide at the serine 112 residue (S112) and employed homogeneous time-resolved fluorescence (HTRF) technology to detect the product in a 384-well plate format. The phosphorylation of biotinylated-BAD (S112) peptide by full length recombinant Pim-1 or Pim-2 protein was detected with streptavidin:allophycocyanin conjugate and an europium (Eu) labeled antibody directed against phosphorylated-BAD (S112). Excitation of Eu by a high energy laser light (337 nm) led to a transfer of energy to the APC molecule and resulted in an emission at 665 nm. The fluorescence was directly proportional to the amount of phosphorylated BAD peptide present in the reaction. Compounds were prepared in DMSO by conducting 3-fold serial dilutions to give a 22-point dosing curve having a high dose of 1 μM. A reference compound was included on each assay plate [Costar 3658] in order to validate that plate; on one plate of every assay run, two additional reference compounds were included. The reaction buffer consisted of 45 mM Hepes, pH 7.0, 15 mM NaCl, and 1 mM $MgCl_2$. The quench/detection buffer consisted of 50 mM Tris, 100 mM NaCl, 0.05% BSA, 0.1% Tween, and 3 mM EDTA, biotinylated BAD peptide (Biopeptide), 10 mM ATP (Sigma), labeled pBAD (S112) mAb (Cell Signaling and PerkinElmer) [with 0.05% BSA and 2 mM DTT added], and streptavidin:allophycocyanin [PerkinElmer], and final concentrations, either Pim-1 enzyme [5 pM] or Pim-2 enzyme [0.5 pM],

DMSO [1%], BAD-LANCE-conjugated BAD (S112) [0.5 μM], ATP [1.5 μM], streptavidin:allophycocyanin [0.002 mg/mL], and biotinylated-BAD (S112) mAb [100 pM]. Initial incubations were carried out at RT (22 °C) for 30 min for both Pim-1 and Pim-2. Pim enzyme was added to compound in buffer, and plates were incubated for 30 min. Biotinylated BAD and ATP were added, and plates were incubated for 1 h. A mixture of labeled pBAD (S112) mAb and quench/detection buffer were added and incubated for 2 h. Fluorescence was measured by an HTRF Envision microplate reader. For each plate, percent of control (POC) values were calculated for each well. Values for the IC_{50} were estimated using a standard three- or four-parameter logistic model.

KMS-12 BM pBAD Assay

The flow cytometry assay for determination of the Pim activity in the KMS-12 BM cell line (DSMZ catalogue no. ACC 551) measured levels of phospho-BAD normalized against total BAD protein levels. Protocols: compounds were initially diluted in DMSO by conducting 2-fold serial dilutions to give a 22-point dosing curve having a high dose of 30 μM. Exponentially growing KMS-12 BM cells (50 μL, between 0.5 and 1.5 × 10^6/mL, DSMZ) in assay media (RPMI/20% heat inactivated FBS/1× NaPyruvate/1× NEAA/1× PSG (pen/strep glutamine)) were added to a 384-well plate containing 200 nL of compound. The cell plates were then incubated with compound for 110 min at 37 °C, 5% CO_2. BD Phosflow Lyse/Fix (BD Biosciences) was diluted to 2× with assay media. Then 50 μL of the diluted BD Phosflow Lyse/Fix was added to each well. The cell plates were incubated for 15 min at RT. The plates were spun for 15 s at 2 K RPM then aspirated. Staining Media (1× PBS with 0.5% FBS) was added (80 μL). The plates again were spun for 15 s at 2 K RPM then aspirated. BD Perm/Wash Buffer (1×, 50 μL, BD Biosciences) was added. The cell plates were then incubated for >30 min at RT in the dark. The plates were spun for 15 s at 2 K RPM and then aspirated. Staining media (1× PBS with 0.5% FBS) was added (80 μL). The plates were spun for 15 s at 2 K RPM and then aspirated and additional staining media (1× PBS with 0.5% FBS) was added (80 μL). The plates were spun for 15 s at 2 K RPM and then aspirated. Rabbit antihuman pBAD Ser112 Ab (Cell Signaling) was diluted in staining media (1:120). The diluted pBAD Ab (10 μL) was added to each well. The cell plates were incubated for >1h at RT. The plates were spun for 15 s at 2 K RPM then aspirated. Staining media (1× PBS with 0.5% FBS) was added (80 μL). Goat anti-rabbit Alexa-647 (Invitrogen) was diluted in staining media (1:4000). The diluted goat anti-rabbit Alexa-647 (70 μL) was added to each well. The cell plates were then incubated for >30 min at RT in the dark. The plates were spun for 15 s at 2 K RPM and then aspirated. Staining media (1× PBS with 0.5% FBS) was added (80 μL). The plates were spun for 15 s at 2 K RPM and then aspirated and additional staining media (1× PBS with 0.5% FBS) was added (80 μL). The plates were spun for 15 s at 2 K RPM and then aspirated. Staining Media (1× PBS with 0.5% FBS) was added (30 μL). The plates were read on a BD LSRII, and results were calculated according to the assay protocols ((%Phosphoprotein = ((2 × Phospho signal)/(Phospho signal + Total signal)) × 100)).

KMS-12 BM Cell Viability Assay

KMS-12 BM cells were seeded into 96-well tissue culture plates at 5000 cells/well in full growth medium, RPMI1640/20% heat-inactivated FBS and were allowed to acclimate overnight in an incubator (37 °C; 5% CO_2) prior to treatment. The following day, cells were treated with compounds that had been serially diluted first in DMSO and then into full growth medium, which was then added onto the cells to achieve a dose–response curve with a final high dose of 10 μM. DMSO alone was used as a control in all viability assays. Cellular viability was assessed after 72 h of treatment using the CellTiter-Glo luminescent viability assay reagent (Promega Inc.). Plates were read on the EnVision Multilabel plate reader (PerkinElmer), and IC_{50} values were calculated using the statistical curve-fitting program XLFit (IDBS software).

KMS-12 BM Xenograft Efficacy

Animals were cared for in accordance to the *Guide for the Care and Use of Laboratory Animals* (eighth edition, National Research Council (US)). All research protocols were approved by the Institutional Animal Care and Use Committee. The effect of compound **28** on tumor growth inhibition (TGI) *in vivo* was evaluated in the KMS-12 BM human multiple myeloma xenograft model. Female SCID-beige mice were injected with 10^6 KMS-12 BM cells at a ratio of 1:1 cell culture media to Matrigel. Animals were randomized into treatment groups when tumors reached approximately 200 mm^3. Vehicle (25% PEG 400, 10% Kollidon VA 64, 0.1% ascorbic acid, pH 1.5 with MSA) or compound **28** was administered orally at 10, 25, 50, or 100 mg/kg once daily. Body weights and tumor volumes were measured twice per week. The tumor volume was calculated as $L \times W \times H$ and expressed in mm^3. Tumor volume data represent the mean volume (n = 10) ± standard error of the mean (SEM). Statistical significance was determined by repeated measures followed by Dunnett's post hoc analysis. Statistical calculations were made through the use of JMP software v8.0.2 interfaced with SAS v9.1 (SAS Institute, Inc., Cary, NC).

KMS-12 BM PD Studies

The ability of compound **28** to impact Pim-dependent phosphorylation of BAD (Ser-112) was evaluated *in vivo*. When average tumor size reached ~300 mm3, mice were randomized into treatment groups (n=3). Mice were treated with a single dose orally with vehicle or compound **28** at 25, 50, or 100 mg/kg. Tumors were harvested at 6 and 16 h post dose. Tumor lysates were generated and analyzed by MSD as per manufacturer's recommendation for levels of phosphorylated BAD. Bars represent levels of phosphorylated BAD and are expressed as percent of vehicle; circles represent total plasma concentration (μM).

Solubility Assays

Compounds as 10 mM DMSO stock solutions were dispensed into 96-deep-well plates at a volume of 10 μL per well. Four copies of identical plates were created. The DMSO was removed in a Genevac evaporator for 2.5 h, at 40 °C, under full vacuum. After drying down was complete, a Tecan Evo liquid handler was used to transfer 200 μL of each of the buffers/solvent to the corresponding plate copy. The buffers used were 1× PBS (pH 7.4), fasted state simulated intestinal fluid (FaSIF, pH 6.8) and 0.01 N HCl (pH 2.0), and the solvent DMSO was used to create the standard plate for comparison. The plates were sealed and

centrifuged at 1000 rpm for 1 min to push all liquid from walls to the bottom of the wells. The plates were shaken at 1500 rpm on a 3 mm radius orbital shaker for 1 h. The samples were equilibrated at RT for 72 h. The plates were centrifuged at 4000 rpm for 30 min. The supernatant was analyzed by LC/MS (at 215 nm, 2 μL injection volume). Peak area in PBS, fasted state simulated intestinal fluid and 0.01 N HCl aqueous were compared to DMSO standard to determine solubility, accurate within the range of 5–500 μM.

Chemistry

Unless otherwise noted, all reagents were commercially available and used as received. All final compounds possessed purity ≥95% as determined by high performance liquid chromatography (HPLC). The HPLC methods used the following conditions: Zorbax SB-C18 column (50 mm × 3.0 mm, 3.5 μm) at 40 °C with a 1.5 mL/min flow rate; solvent A of 0.1% TFA in water, solvent B of 0.1% TFA in MeCN; 0.0–3.0 min, 5–95% B in A; 3.0–3.5 min, 95% B in A; 3.5–3.51 min, 5% B in A. Flow from the UV detector was split (50:50) to the MS detector, which was configured with APIES as ionizable source. The UV detection wavelengths were 210 and 254 nm. ^{1}H NMR spectra were recorded on a 300 or 400 MHz Bruker NMR spectrometer at ambient temperature. Data are reported as follows: chemical shift (ppm, δ units) from an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (Hz), and integration. All microwave-assisted reactions were performed in sealed reaction vials using a Personal Chemistry Emrys Optimizer microwave synthesizer. Analytical thin-layer chromatography (TLC) was performed using JT Baker silica gel plates precoated with a fluorescent indicator. Silica gel chromatography was performed using either an ISCO Companion or Biotage medium pressure liquid chromatography system.

(*R*)-2-(*tert*-Butylamino)-3-isopropyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (10). (Method A) Step-1: 2-Amino-3-bromo-*N*-isopropylbenzamide. To a slurry of 2-amino-3-bromobenzoic acid (1.00 g, 4.63 mmol) in 10 mL of EtOAc in an ice bath was added T3P (1-propanephosphonic acid cyclic anhydride, 50 wt% in EtOAc, 3.00 mL, 5.09 mmol) followed by isopropylamine (1.19 mL, 13.89 mmol). The ice bath was removed, and the solution stirred rapidly at ambient temperature for 30 min. The reaction was partitioned between saturated $NaHCO_3$ and EtOAc. The organic layer was washed with saturated NaCl, and the organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 2-amino-3-bromo-*N*-isopropylbenzamide (1.00 g, 3.89 mmol, 84 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.25 (d, *J* = 1.4 Hz, 1H), 6.53 (t, *J* = 7.8 Hz, 1H), 5.72 - 6.15 (m, 3H), 4.15 - 4.33 (m, 1H), 1.27 (d, *J* = 6.7 Hz, 6H), *m/z* (ESI, +ve) 257.0/259.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-isopropylquinazoline-2,4(1*H*,3*H*)-dione. A slurry of 2-amino-3-bromo-*N*-isopropylbenzamide (1.00 g, 3.89 mmol) and tri-phosgene (0.46 g, 1.56 mmol) in 50 mL of dichloromethane was heated to reflux overnight. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to give 8-bromo-3-isopropylquinazoline-2,4(1*H*,3*H*)-dione (1.10 g, 3.89 mmol, 100%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 - 8.25 (m, 1H), 7.98 (br.

s., 1H), 7.78 (d, *J* = 7.8, 1.4 H z, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 5.27 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.56 (s, 6H). *m/z* (ESI, +ve) 282.9/284.9 (1:1) $(M+H)^+$

Step-3: 8-Bromo-2-chloro-3-isopropylquinazolin-4(3*H*)-one. A mixture of 8-bromo-3-isopropylquinazoline-2,4(1*H*,3*H*)-dione (1.11 g, 3.89 mmol), $POCl_3$ (1.79 mL, 19.60 mmol) and DIPEA (1.36 mL, 7.84 mmol) was heated to reflux for 2 h. The reaction reached 50% conversion. Additional DIPEA (1.36 mL, 7.84 mmol) was added and the reaction stirred overnight. The reaction was cooled, treated with ice, and agitated. The slurry was poured onto 20 mL of 10N NaOH aqueous solution in ice bath and stirred rapidly for 20 min. The fine precipitate was collected by filtration and rinsed with water (3 x 20 mL). The solid was dried *in vacuo* to give 8-bromo-2-chloro-3-isopropylquinazolin-4(3*H*)-one (0.978 g, 3.24 mmol, 83%) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.18 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.00 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 5.31 (br s, 1H), 1.67 (d, *J* = 7.0 Hz, 6H). *m/z* (ESI, +ve) 301.0/302.9 (4:5) $(M+H)^+$.

Step-4: 8-Bromo-2-(*tert*-butylamino)-3-isopropyl-quinazolin-4(3*H*)-one. A slurry of 8-bromo-2-chloro-3-isopropylquinazolin-4(3*H*)-one (0.40 g, 1.33 mmol) and *tert*-butylamine (4.18 mL, 39.8 mmol) was heated in a sealed tube at 80 °C overnight. The reaction was treated with ice water, and dichloromethane. The cloudy aqueous layer was extracted with dichloromethane and EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (eluted with 0-40% EtOAc/hexanes) to afford 8-bromo-2-(*tert*-butylamino)-3-isopropylquinazolin-4(3*H*)-one (0.39 g, 1.15 mmol, 87%) as an oil which slowly solidified. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 5.55 (br s, 1H), 4.68 (br s, 1H), 1.63 (s, 9H), 1.55 (d, *J* = 7.2 Hz, 6H). *m/z* (ESI, +ve) 338.0/340.0 (1:1) $(M+H)^+$.

Step-5: (*R*)-2-(*tert*-Butylamino)-3-isopropy-8-(6-methy4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrro2-yl)quinazolin-4(3*H*)-one. Argon was bubbled into a mixture of Pd_2dba_3 (7.45 mg, 0.008 mmol), XPhos (7.75 mg, 0.016 mmol), (*R*)-6-methy2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrro4(1*H*)-one (**9d**[28]; 85.0 mg, 0.33 mmol), 8-bromo-2-(*tert*-butylamino)-3-isopropylquinazolin-4(3*H*)-one (55.0 mg, 0.16 mmol), potassium phosphate (104 mg, 0.49 mmol) in 1 mL of dioxane and 0.2 mL of water for 1 min. The reaction was sealed and heated to 80 °C for 2 h. The reaction mixture was cooled and concentrated onto silica gel *in vacuo*. The material was purified by silica gel chromatography (using 0-100% 90/10 dichloromethane /MeOH in dichloromethane) to afford (*R*)-2-(*tert*-butylamino)-3-isopropy-8-(6-methy4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrro2-yl)quinazolin-4(3*H*)-one (44.0 mg, 0.112 mmol, 69 %) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.78 (s, 1H), 7.84 (ddd, *J* = 14.9, 7.6, 1.6 Hz, 2H), 7.59 (s, 1H), 7.15 (t, *J* = 6.7 Hz, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 5.72 (s, 1H), 4.94 (quin, *J* = 6.7 Hz, 1H), 4.51 (q, *J* = 6.8 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 6H), 1.48 (s, 9H), 1.36 (d, *J* = 6.7 Hz, 3H), LC–MS t_R = 2.09 min (>95%); *m/z* (ESI, +ve ion) 394.1 $(M+H)^+$.

(*R*)-2-(*tert*-Butylamino)-3-cyclopropyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (11). (Method A) Step-1: 2-Amino-3-bromo-*N*-cyclopropylbenzamide. To a heterogenous mixture of 2-amino-3-bromobenzoic acid (8.00 g, 37.0 mmol) in EtOAc (80 mL) at 0 °C was added 1-propanephosphonic acid

cyclic anhydride (T3P) (50 wt.% solution in ethyl acetate, 24.0 mL, 40.7 mmol) followed by cyclopropylamine (2.57 mL, 37.0 mmol). The ice bath was removed, and the reaction was allowed to stir at room temperature for 1 h. Saturated $NaHCO_3$ (aq.) was added and the mixture was stirred for 5 min. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layer was extracted with EtOAc (3 x 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford 2-amino-3-bromo-*N*-cyclopropylbenzamide (6.00 g, 23.5 mmol, 64% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (dd, *J* = 7.8, 1.37 Hz, 1H), 7.20 (dd, *J* = 7.9, 1.27 Hz, 1H), 6.50 (t, *J* = 7.8 Hz, 1H), 6.13 (br. s., 2H), 2.85 (tq, *J* = 7.0, 3.5 Hz, 1H), 0.83 - 0.91 (m, 2H), 0.57 - 0.64 (m, 2H). The -NH peak was not observed. *m/z* (ES, +ve) 255.1/257.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-cyclopropylquinazoline-2,4(1*H*,3*H*)-dione. Triphosgene (2.79 g, 9.41 mmol) was added to a solution of 2-amino-3-bromo-*N*-cyclopropylbenzamide (6.00 g, 23.5 mmol) in dichloromethane (235 mL) at room temperature. The mixture was heated to reflux and stirred for 17 h. The resulting cloudy reaction mixture was cooled and concentrated to afford 8-bromo-3-cyclopropylquinazoline-2,4(*1H,3H*)-dione (6.61 g, 23.5 mmol, 100% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09 (d, *J* = 8.0 Hz, 1H), 8.06 (br. s., 1H), 7.78 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 2.74 - 2.84 (m, 1H), 1.21 (q, *J* = 7.0 Hz, 2H), 0.83 - 0.91 (m, 2H). *m/z* (ES, +ve) 281.0/283.0 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-chloro-3-cyclopropylquinazolin-4(3*H*)-one. To A mixture of 8-bromo-3-cyclopropylquinazoline-2,4(*1H,3H*)-dione (5.00 g, 17.8 mmol), $POCl_3$ (8.3 mL, 89.0 mmol) and DIPEA (12.4 mL, 71.1 mmol) was stirred at reflux overnight. The reaction was then cooled and concentrated. The brown syrup was cooled in an ice bath and then ice (100 mL) was added to the reaction mixture. The brown sludge was added to 100 mL of 10M aqueous NaOH and stirred for 20 min. The mixture was filtered, and the brown solid was washed with water, and then dissolved in CH_2Cl_2 and filtered. The filtrate was dried over Na_2SO_4, filtered, and concentrated to afford 8-bromo-2-chloro-3-cyclopropylquinazolin-4(*3H*)-one (4.54 g, 15.16 mmol, 85% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 3.02 (tt, *J* = 7.1, 4.0 Hz, 1H), 1.33 - 1.43 (m, 2H), 0.94 - 1.04 (m, 2H). *m/z* (ES, +ve) 298.9/301.0 (4:5) $(M+H)^+$.

Step-4: 8-Bromo-2-(*tert*-butylamino)-3-cyclopropylquinazolin-4(3*H*)-one. 8-bromo-2-chloro-3-cyclopropyl-quinazolin-4(3*H*)-one (213 mg, 0.71 mmol) was mixed with *tert*-butylamine (0.90 mL, 8.56 mmol) and heated at 90 °C in a sealed tube for 24 h. The reaction mixture was concentrated to remove the excess *tert*-butylamine and the crude residue was purified by silica gel chromatography (using a gradient of 0-5% MeOH in dichloromethane) to afford 8-bromo-2-(*tert*-butylamino)-3-cyclopropylquinazolin-4(3*H*)-one (224 mg, 0.66 mmol, 94% yield) as an off-white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.82 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.94 (t, *J* = 7.7 Hz, 1H), 5.42 (s, 1H), 2.62 - 2.71 (m, 1H), 1.61 (s, 9H), 1.28 - 1.35 (m, 2H), 0.87 - 0.95 (m, 2H). *m/z* (ESI, +ve) 335.9/337.9 (1:1) $(M+H)^+$.

Step-5: (*R*)-2-(*tert*-Butylamino)-3-cyclopropyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. To a mixture of (R)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-

dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**; 1.69 g, 6.44 mmol) and 8-bromo-2-(*tert*-butylamino)-3-cyclopropylquinazolin-4(3*H*)-one (1.48 g, 4.39 mmol) in 1,4-dioxane (15 mL) and water (2.5 mL) was added potassium phosphate (2.80 g, 13.2 mmol). The reaction mixture was bubbled with Argon for 3 min, and then XPhos-Pd-G2 (0.17 g, 0.22 mmol) was added and the mixture was stirred at 40 °C for 1.5 h. The reaction mixture was diluted with EtOAc (50 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the filtrate was treated with Si-thiol (ca. 20 g) and stirred 48 h. The mixture was filtered and concentrated. The residue was purified by silica gel chromatography (using a gradient of 0-15% MeOH in dichloromethane) to afford the title compound (1.09 g, 2.78 mmol, 63.4%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.97 (s, 1H), 7.87 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.61 (s, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 1.4 Hz, 1H), 6.12 (s, 1H), 4.49 - 4.57 (m, 1H), 2.82 - 2.90 (m, 1H), 1.52 (s, 9H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 5.7 Hz, 2H), 0.73 - 0.82 (m, 2H). LC–MS t_R = 1.90 min (>95%); *m/z* (ESI, +ve) 392.0 $(M+H)^+$.

***(R)*-2-(*tert*-Butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-b]pyrrol-2-yl)-3-(1-methylcyclopropyl)quinazolin-4(3*H*)-one (12). (Method C) Step-1: 2-Amino-3-bromo-*N*-(1-methylcyclopropyl)benzamide**. 2-(3*H*-[1,2,3]-Triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (HATU; 1.94 g, 5.09 mmol) was added to a suspension of 2-amino-3-bromobenzoic acid (1.00 g, 4.63 mmol), 1-methylcyclopropanamine hydrochloride (0.55 g, 5.09 mmol), and triethylamine (1.6 mL, 12.04 mmol) in a mixture of DMF (3.5 mL) and dichloromethane (3.5 mL) and the resulting mixture was stirred at 23 °C for 2 h. The reaction mixture was then diluted with dichloromethane (50 mL), and the resulting solution was sequentially washed with water (2 × 40 mL), 0.5N aqueous NaOH (40 mL), and brine (40 mL), then concentrated *in vacuo* and purified by silica gel chromatography (using a gradient 0–80% EtOAc in hexanes) to yield 2-amino-3-bromo-*N*-(1-methylcyclopropyl)benzamide (960 mg, 3.57 mmol, 77% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.50 (t, *J* = 7.3 Hz, 1H), 6.31 (br. s., 1H), 6.10 (br. s., 2H), 1.47 (br. s., 3H), 0.84 (br. s., 2H), 0.74 (br. s., 2H). *m/z* (ESI, +ve) 268.9/271.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-2-(*tert*-butylamino)-3-(1-methylcyclopropyl)quinazolin-4(3*H*)-one. 2-(*tert*-Butyl nitrite (0.35 mL, 2.65 mmol) and azidotrimethylsilane (0.28 mL, 2.12 mmol) were sequentially added (dropwise) to a suspension of 2-amino-3-bromo-*N*-(1-methylcyclopropyl)benzamide (476 mg, 1.77 mmol) in MeCN (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 min, and then allowed to warm to 23 °C and stir for 15 min. Trimethylphosphine (1.0M in THF; 2.12 mL, 2.12 mmol) was added dropwise, and the resulting solution was stirred at 23 °C for 5 min. *tert*-Butyl isocyanate (0.23 mL, 2.03 mmol) was added, and the resulting mixture was stirred at 23 °C for 10 min, and then at 60 °C for 45 min. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU; 0.32 mL, 2.12 mmol) was added, and the resulting brown suspension was heated at 60 °C for 20 min. The reaction mixture was subsequently cooled to ambient temperature, half-saturated aqueous sodium bicarbonate (50 mL) was added, and the resulting mixture was extracted with dichloromethane (3 × 50 mL). The combined

organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated onto silica gel. The crude material was purified by silica gel chromatography (using a gradient 0–60% Et_2O/hexanes) to obtain 8-bromo-2-(*tert*-butylamino)-3-(1-methylcyclopropyl)-quinazolin-4(3*H*)-one (291 mg, 0.83 mmol, 47% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.94 (t, *J* = 7.8 Hz, 1H), 5.43 (br. s., 1H), 1.62 (s, 9H), 1.41 (s, 3H), 1.21 - 1.37 (m, 2H), 0.88 - 1.02 (m, 2H). *m/z* (ESI, +ve) 349.9/352.0 (1:1) $(M+H)^+$.

Step-3: (*R*)-2-(*tert*-Butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(1-methylcyclopropyl)quinazolin-4(3*H*)-one. A solution of 8-bromo-2-(tert-butylamino)-3-(1-methylcyclopropyl)quinazolin-4(3H)-one (129 mg, 0.37 mmol), (R)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1H)-one (**9d**; 135 mg, 0.51 mmol), potassium phosphate (234 mg, 1.10 mmol), and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (XPhos-Pd-G2; 14.5 mg, 0.02 mmol) in a mixture of 1,4-dioxane (1.3 mL) and water (0.3 mL) was stirred under argon at 45 °C for 1.5 h. Additional potassium phosphate (234 mg, 1.10 mmol), XPhos-Pd-G2 (14.5 mg, 0.02 mmol), and (R)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1H)-one (135 mg, 0.51 mmol) were added, and the resulting solution was stirred under argon at 45 °C for 1 h. The reaction mixture was then concentrated onto silica gel and purified by silica gel chromatography (using a gradient 50–100% EtOAc/hexanes). The collected product was triturated with MeOH (3 mL), and the resulting suspension was vacuum filtered. The collected solid was washed with ethyl ether (8 mL) and dried *in vacuo* to provide (*R*)-2-(tert-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(1-methylcyclopropyl)quinazolin-4(3*H*)-one (**12**) (65.2 mg, 0.16 mmol, 44% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.89 (br. s., 1H), 7.81 - 7.90 (m, 2H), 7.60 (s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 5.68 (d, *J* = 3.9 Hz, 1H), 4.52 (q, *J* = 6.7 Hz, 1H), 1.53 (s, 9H), 1.47 (s, 3H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.14 - 1.27 (m, 2H), 1.11 - 1.14 (m, 1H), 0.91 - 1.01 (m, 1H). LC–MS t_R = 2.48 min (>95%); *m/z* (ESI, +ve) 406.0 $(M+H)^+$.

***(R)*-3-(*tert*-Butyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (13). (Method C)** The title compound was prepared analogous to compound **12** (Method C). *Step-1: 2-Amino-3-bromo-N-(tert-butyl)benzamide.* The title compound (1.29 g, 4.76 mmol, 48.9 % yield) was prepared using 2-amino-3-bromobenzoic acid (2.10 g, 9.72 mmol), 2-methylpropan-2-amine (1.2 mL, 11.66 mmol), HATU (4.80 g, 12.64 mmol), DIPEA (2.5 mL, 14.58 mmol) and DMF (9.7 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.22 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.51 (t, *J* = 7.8 Hz, 1H), 5.95 (br. s., 2H), 5.82 (br. s., 1H), 1.46 (s, 9H). *m/z* (ESI, +ve) 271.0/273.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-(*tert*-butyl)-2-(*tert*-butylamino)quinazolin-4(3*H*)-one. The title compound (1.17 g, 3.32 mmol, 69.8 % yield) was prepared using 2-amino-3-bromo-*N*-(*tert*-butyl)benzamide (1.29 g, 4.76 mmol), *tert*-butyl nitrite (0.95 mL, 7.14 mmol), azidotrimethylsilane (0.76 mL, 5.71 mmol), trimethylphosphine (5.71 mL, 5.71 mmol), 2-isocyanato-2-methylpropane (0.63 mL, 5.47 mmol) and DBU (0.78 mL, 5.23 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (dd, *J* = 7.8, 1.4

Hz, 1H), 7.76 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.89 (t, *J* = 7.7 Hz, 1H), 4.42 (s, H), 1.75 (s, 9H), 1.59 (s, 9H). *m/z* (ESI, +ve) 352.1/354.0 (1:1) $(M+H)^+$.

Step-3: (*R*)-3-(*tert*-Butyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. The title compound (74 mg, 0,18 mmol, 12.2 % yield) was prepared using 8-bromo-3-(*tert*-butyl)-2-(*tert*-butylamino)quinazolin-4(3*H*)-one (525 mg, 1.49 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**, 781 mg, 2.98 mmol), XPhos-Pd-G2 (59 mg, 0.08 mmol), and potassium phosphate (949 mg, 4.47 mmol) in 1,4-dioxane (12.0 mL)/water (3.0 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.34 (br. s., 1H), 7.92 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 1.4 Hz, 1H), 6.32 (s, 1 H), 4.66 (q, *J* = 6.5 Hz, 1H), 4.59 (s, 1H), 1.77 (s, 9H), 1.64 (s, 9H), 1.52 (d, *J* = 6.7 Hz, 3H). LC–MS t_R = 2.35 min (>95%); *m/z* (ESI, +ve) 408.0 $(M+H)^+$.

***(R)*-2-(*tert*-Butylamino)-3-(cyclopropylmethyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (14). Step-1: 8-Bromoquinazoline-2,4(1*H*,3*H*)-dione.** Urea (3.78 g, 63.0 mmol) and 2-amino-3-bromo-benzoic acid (4.00 g, 18.52 mmol) were combined and heated at 170 °C, open to air, in an oil bath. After 3 h, additional urea (3.78 g, 63.0 mmol) was added and stirring continued. After 5 h, the reaction was judged complete and cooled, treated with water, filtered, and the solid dried overnight under vacuum to give 4.7 g. The material was treated with water and stirred rapidly for 3 h to give a fine suspension. The solid was collected by filtration and dried *in vacuo* overnight, to give 8-bromoquinazoline-2,4(1*H*,3*H*)-dione (4.30 g, 17.8 mmol, 96% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.50 (br. s., 1H), 10.25 (br. s., 1H), 7.93 (dq, *J* = 7.8, 1.4 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), *m/z* (ESI, +ve ion) 240.9/242.9 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-2,4-dichloroquinazoline. To a slurry of 8-bromoquinazoline-2,4-diol (4.30 g, 17.8 mmol) in $POCl_3$ (8.17 mL, 89.0 mmol) was added DIPEA (15.5 mL, 89.0 mmol) in small ~ 2 mL portions. The reaction became hot and was cooled in an ice bath for the rest of DIPEA addition. The slurry was fitted with a water-cooled reflux condenser and drying tube and heated to reflux. After 4 h, the reaction was nearly complete. The reaction was heated 1 h additional, cooled, and poured onto ice. While still cold the mixture was treated with 10N NaOH until pH >10. The resulting very fine orange solid was collected by filtration. The solid was rinsed water and dried *in vacuo* to give 8-bromo-2,4-dichloroquinazoline (4.30 g, 15.5 mmol, 87% yield) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.31 (m, 2H), 7.61 (dd, *J*=8.2, 7.6 Hz, 1H), *m/z* (ESI, +ve ion) 276.9/278.9/280.9 $(M+H)^+$.

Step-3: 8-Bromo-2-chloroquinazolin-4(3*H*)-one. To a biphasic mixture of NaOH 1 N aq. (10.8 mL, 10.8 mmol) and THF (11 mL) was added 8-bromo-2,4-dichloroquinazoline (1.50 g, 5.40 mmol) in one portion. The reaction became dark red. After 20 min the reaction mixture was cooled in an ice/water bath and acidified with AcOH until pH ~7. The resulting mixture was concentrated to 1/2 volume under vacuum (precipitate observed) and cooled in an ice/water bath. The slurry was filtered and the solid rinsed with water. The orange solid was collected and dried *in vacuo* to give 8-bromo-2-chloroquinazolin-4(3*H*)-

one (1.10 g, 4.24 mmol, 79% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.49 (br. s., 1H), 8.15 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H). *m/z* (ESI, +ve ion) 258.9/260.9 (1:1) $(M+H)^+$.

Step-4: 8-Bromo-2-chloro-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one. In a sealed tube, sodium hydride (60 % dispersion in mineral oil, 58 mg, 1.44 mmol) was added to a solution of 8-bromo-2-chloroquinazolin-4(3*H*)-one (0.34 g, 1.31 mmol) in DME (5.2 mL)/DMF (1.3 mL) at 0 °C. After stirring for 5 min, lithium bromide in THF (1.75 mL, 2.62 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After stirring for 5 min, (bromomethyl)cyclopropane (0.38 mL, 3.93 mmol) was added, and the reaction vessel was sealed and heated to 60 °C for 16 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous sodium bicarbonate (2 x 100 mL); the organic layer was separated, dried over sodium sulfate, and concentrated to give 8-bromo-2-chloro-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one (0.35 g, 1.12 mmol, 85 % yield) as a crude red oil, which was used for next step without purification. *m/z* (ESI, +ve) 312.9/314.9 (4:5) $(M+H)^+$.

Step-5: 8-Bromo-2-(*tert*-butylamino)-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one. A solution of 8-bromo-2-chloro-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one (0.35 g, 1.12 mmol) and 2-methylpropan-2-amine (0.59 mL, 5.58 mmol) in DMSO (2.79 mL) was stirred at 90 °C for 16 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous brine (2 x 100 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. The crude product was adsorbed onto silica and was purified by silica gel chromatography (using a gradient 0–30% EtOAc/hexanes) to give 8-bromo-2-(*tert*-butylamino)-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one (264 mg, 0.75 mmol, 67.5 % yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.37 Hz, 1H), 6.97 (t, *J*=7.8 Hz, 1H), 4.80 (s, 1H), 3.97 (d, *J* = 6.5 Hz, 2H), 1.62 (s, 9H), 1.00 - 1.12 (m, 1H), 0.62 - 0.69 (m, 2H), 0.44 - 0.52 (m, 2H). *m/z* (ESI, +ve) 350.0/352.0 (1:1) $(M+H)^+$.

Step-6: (*R*)-2-(*tert*-Butylamino)-3-(cyclopropylmethyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. A mixture of 8-bromo-2-(tert-butylamino)-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one (129 mg, 0.37 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**, 212 mg, 0.81 mmol), XPhos-Pd-G2 (14.5 mg, 0.02 mmol), and potassium phosphate (235 mg, 1.11 mmol) in 1,4-dioxane (2.9 mL)/water (0.7 mL) was stirred at 90 °C for 1 h. The reaction mixture was diluted with dichloromethane (75 mL) and washed with saturated aqueous brine (2 x 50 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. The crude product was adsorbed onto silica and purified by silica gel chromatography (using a gradient 0–6% 2 M ammonia in MeOH/dichloromethane) to give (*R*)-2-(*tert*-butylamino)-3-(cyclopropylmethyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (84 mg, 0.21 mmol, 56.2 % yield) as an yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.43 (br. s., 1H), 8.04 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 1.4 Hz, 1H), 5.91 (s, 1H), 5.01 (s, 1H), 4.66 (q, *J* = 6.7 Hz, 1H), 4.06 (dd, *J* = 6.4, 2.5 Hz, 2H), 1.67 (s, 9H), 1.53 (d,

J = 6.7 Hz, 3H), 1.04 - 1.14 (m, 1H), 0.66 - 0.75 (m, 2H), 0.49 - 0.56 (m, 2H). LC–MS t_R = 2.23 min (>95%); *m/z* (ESI, +ve) 406.1 $(M+H)^+$.

(*R*)-2-(*tert*-Butylamino)-3-((1-hydroxycyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (15). (Method C) Step-1: (1-((*tert*-Butyldimethylsilyl)oxy)cyclopropyl)methanamine. A mixture of 1-(aminomethyl)-cyclopropanol (1.00 g, 11.5 mmol) and DIPEA (6.0 mL, 34.4 mmol) in dichloromethane (25 mL) at 0 °C under nitrogen was treated with (*t*-butyldimethylsilyl trifluoromethanesulfonate (3.2 mL, 13.8 mmol). The reaction mixture was allowed to warm to ambient temperature over 1 h. The reaction was partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (using a gradient 0–10% 2M ammonia in MeOH/dichloromethane). The product-containing fractions (stained blue in CAM) were concentrated to afford 2.65 g of an orange solid. The material was treated with saturated aqueous sodium bicarbonate and dichloromethane. The aqueous layer was extracted with dichloromethane (2X), and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give (1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methanamine (1.14 g, 5.66 mmol, 49.3 % yield) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.70 (s, 2H), 1.95 - 2.49 (br. s, 2H), 0.88 (s, 9H), 0.73 - 0.79 (m, 2H), 0.50 - 0.55 (m, 2H), 0.12 (s, 6H).

Step-2: 2-Amino-3-bromo-*N*-((1-((*tert*-butyldimethylsilyl)-oxy)cyclopropyl)methyl)benzamide. The title compound (1.16 g, 2.90 mmol, 59.8 % yield, yellow solid) was prepared analogous to compound **10**, *Step-1* using T3P (50 wt.% solution in ethyl acetate, 3.4 mL, 5.35 mmol), DIPEA (1.3 mL, 7.29 mmol), 2-amino-3-bromobenzoic acid (1.05 g, 4.86 mmol), (1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methanamine (1.18 g, 5.83 mmol), and EtOAc (20 mL): ^{1}H NMR (400 MHz, CDC_3) δ ppm 7.49 - 7.56 (m, 1H), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.56 (t, *J* = 7.8 Hz, 1H), 6.44 (br. s., 1H), 6.01 (br. s., 2H), 3.48 (d, *J* = 5.1 Hz, 2H), 0.88 (s, 9H), 0.80 - 0.86 (m, 2H), 0.63 - 0.68 (m, 2H), 0.14 (s, 6H). *m/z* (ESI, +ve ion) 399.0/401.0 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-(*tert*-butylamino)-3-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)quinazolin-4(3*H*)-one. The title compound (300 mg, 0.62 mmol, 45.3 % yield, white solid) was prepared analogous to compound **12**, *Step-2* using 2-amino-3-bromo-*N*-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl) benzamide (550 mg, 1.38 mmol), MeCN (10 mL), *tert*-butyl nitrite, 90% (0.25 mL, 2.07 mmol), trimethylsilyl azide (0.22 mL, 1.65 mmol), trimethylphosphine (1.0 M in THF, 1.65 mL, 1.65 mmol), *tert*-butyl isocyanate (0.18 mL, 1.58 mmol), DBU (0.25 mL, 1.65 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (dd, *J*=7.8, 1.4 Hz, 1H), 7.85 (dd, *J*=7.6, 1.4 Hz, 1H), 6.96 (t, *J*=7.8 Hz, 1H), 5.61 (s, 1H), 4.36 (s, 2H), 1.64 (s, 9H), 0.90 - 0.95 (m, 2H), 0.88 (s, 9H), 0.70 - 0.75 (m, 2H), 0.20 (s, 6H). *m/z* (ESI, +ve ion) 480.0/482.0 (1:1) $(M+H)^+$.

Step-4: (*R*)-2-(*tert*-Butylamino)-3-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. The title compound (139 mg, 0.26 mmol, 83 % yield,

white foam) was prepared analogous to compound **12**, Step-3 using potassium phosphate tribasic (265 mg, 1.25 mmol), XPhos-Pd-G2 (12 mg, 0.02 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**; 164 mg, 0.62 mmol), 8-bromo-2-(*tert*-butylamino)-3-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)quinazolin-4(3*H*)-one (150 mg, 0.31 mmol) and dioxane (3 mL) / water (0.5 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.54 (br s, 1 H), 8.01 (br s, 2 H), 7.15 - 7.24 (m, 2 H), 6.83 (br s, 1 H), 5.75 (br s, 1 H), 4.67 (br d, *J*=6.7 Hz, 1 H), 4.40 (q, *J*=15.2 Hz, 2 H), 1.53 (br d, *J*=5.3 Hz, 3 H), 1.24 (br s, 9 H), 0.97 (br s, 2 H), 0.87 (br s, 9 H), 0.78 (br d, *J*=5.3 Hz, 2 H), 0.19 (br s, 6 H). *m/z* (ESI, +ve ion) 536.2 $(M+H)^+$.

Step-5: (R)-2-(*tert*-Butylamino)-3-((1-hydroxycyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. To a solution of (*R*)-2-(*tert*-butylamino)-3-((1-((tert-butyldimethylsilyl)oxy)cyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo-[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (139 mg, 0.26 mmol) in THF (3 mL) under nitrogen was added TBAF(1.0 M in THF, 0.39 mL, 0.39 mmol) at room temperature and stirred for 30 min. The resulting mixture was concentrated *in vacuo* and purified by silica gel chromatography (using a gradient 0–10% 2M ammonia in MeOH/dichloromethane) to afford the title compound (76 mg, 0.18 mmol, 69.5 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.00 (s, 1H), 7.76 - 8.04 (m, 2H), 7.62 (s, 1H), 7.36 (s, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 4.54 (q, *J* = 6.7 Hz, 1H), 4.20 (s, 2H), 1.50 (s, 9H), 1.37 (d, *J* = 6.7 Hz, 3H), 0.79 - 0.88 (m, 2H), 0.73 - 0.79 (m, 2H). LC–MS t_R = 1.87 min (>95%); m/z (ESI, +ve ion) 422.1 $(M+H)^+$.

***(R)*-3-((1-Aminocyclopropyl)methyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(*3H*)-one (16). (Method C) Step-1: *tert*-Butyl (1-((2-amino-3-bromobenzamido)methyl)cyclopropyl)carbamate.** The title compound (392 mg, 1.02 mmol, 76 % yield, white solid) was prepared analogous to compound **12**, *Step-1* using 2-amino-3-bromobenzoic acid (290 mg, 1.34 mmol), *tert*-butyl 1-(aminomethyl)cyclopropylcarbamate (0.30 g, 1.61 mmol), DIPEA (0.7 mL, 4.03 mmol), HATU (561 mg, 1.48 mmol), DMF (1.3 mL) and dichloromethane (1.3 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (br s, 1 H), 7.41 - 7.55 (m, 2 H), 6.53 (t, *J* = 7.9 Hz, 1 H), 6.26 (br s, 2 H), 5.11 (br s, 1 H), 3.42 (d, *J* = 3.9 Hz, 2 H), 1.43 (s, 9 H), 0.90 (br d, *J* = 8.2 Hz, 4 H). *m/z* (ESI, +ve ion) 384.0/386.0 (1 :1) $(M+H)^+$.

Step-2: *tert*-Butyl (1-((8-bromo-2-(tert-butylamino)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate. The title compound (70 mg, 0.15 mmol, 19.6 % yield, white solid) was prepared analogous to compound **12**, *Step-2* using *tert*-butyl (1-((2-amino-3-bromobenzamido)methyl)cyclopropyl)carbamate (295 mg, 0.77 mmol), MeCN (5.1 mL), tert-butyl nitrite, 90% (0.15 mL, 1.15 mmol), azidotrimethylsilane (0.12 mL, 0.92 mmol), trimethylphosphine (1.0 M in THF, 0.92 mL, 0.92 mmol), tert-butyl isocyanate (0.01 mL, 0.84 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 mL, 0.84 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.86 (br. s., 1H), 5.05 (br. s., 1H), 4.40 (br. s., 2H), 1.66 (s, 9H), 1.46 (s, 9H), 0.65 - 0.82 (m, 4H). *m/z* (ESI, +ve ion) 465.0/467.0 (1 :1) $(M+H)^+$.

Step-3: (R)-tert-Butyl (1-((2-(tert-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate. The title compound (55 mg, 0.11 mmol, 78 % yield, pale green solid) was prepared analogous to compound **12**, Step-3 using tert-butyl (1-((8-bromo-2-(*tert*-butylamino)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate (63 mg, 0.14 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1*H*)-one (71 mg, 0.27 mmol), X-Phos precatalyst generation II (5.33 mg, 6.77 µmol) and potassium phosphate (86 mg, 0.41 mmol) and 1,4-dioxane (3.2 mL)/water (0.8 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.50 (br s, 1 H), 7.99 (ddd, *J* = 7.8, 6.5, 1.6 Hz, 2 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 6.96 (br s, 1 H), 6.81 (d, *J* = 1.2 Hz, 1 H), 5.58 (s, 1 H), 5.11 (s, 1 H), 4.66 (q, *J* = 6.9 Hz, 1 H), 4.49 (br s, 2 H), 1.70 (s, 9 H), 1.53 (d, *J* = 6.7 Hz, 3 H), 1.46 (s, 9 H), 0.79 (br s, 2 H), 0.74 (br d, *J*=3.9 Hz, 2 H). *m/z* (ESI, +ve ion) 521.1 $(M+H)^+$.

Step-4: (R)-3-((1-Aminocyclopropyl)methyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo [3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. Trifluoroacetic acid (0.2 mL, 2.88 mmol) was added to a heterogenous solution of (*R*)-*tert*-butyl (1-((2-(tert-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate (50 mg, 0.10 mmol) in dichloromethane (0.5 mL) at room temperature. The solution turned clear and yellow upon addition of TFA. The reaction stirred for 2 h and then saturated $NaHCO_3$ (aq.) was added. The mixture was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered and concentrated to give (*R*)-3-((1-aminocyclopropyl)methyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (35 mg, 0.08 mmol, 87 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.12 (s, 1H), 7.92 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.84 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.62 (s, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 1.4 Hz, 1H), 4.55 (q, *J* = 6.5 Hz, 1H), 4.05 (s, 2H), 1.52 (s, 9H), 1.38 (d, *J* = 6.5 Hz, 3H), 0.83 - 0.89 (m, 2H), 0.61 - 0.69 (m, 2H). The peaks of -NH and -NH2 were not observed. LC–MS t_R = 1.32 min (>95%); *m/z* (ESI, +ve ion) 421.1 $(M+H)^+$.

(*R*)-3-(2-Amino-2-methylpropyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (17). (Method C) Step-1: *tert*-Butyl(1-(2-amino-3-bromobenzamido)-2-methylpropan-2-yl)carbamate. The title compound (1.57 g, 4.06 mmol, 88% yield, white solid) was prepared analogous to compound **16**, Step-1 using 2-amino-3-bromobenzoic acid (1.00 g, 4.63 mmol), 2-*N*-boc-2-methylpropane-1,2-diamine hydrochloride salt (1.25 g, 5.55 mmol), DIPEA (3.2 mL, 18.50 mmol), HATU (1.94 g, 5.09 mmol), DMF (4.5 mL) and dichloromethane (4.5 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79 (br s, 1 H), 7.50 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 6.55 (t, *J*=7.9 Hz, 1 H), 6.17 (br s, 2 H), 4.71 (br s, 1 H), 3.57 (d, *J* = 5.7 Hz, 2 H), 1.44 (s, 9 H), 1.34 (s, 6 H). *m/z* (ESI, +ve ion) 386.0/388.0 (1:1) $(M+H)^+$.

Step-2: *tert*-Butyl(1-(8-bromo-2-(*tert*-butylamino)-4-oxoquinazolin-3(4*H*)-yl)-2-methylpropan-2-yl)carbamate. The title compound (133 mg, 0.28 mmol, 35.3% yield, white solid) was prepared analogous to compound **16**, Step-2 using tert-butyl(1-(2-amino-3-bromobenzamido)-2-methylpropan-2-yl)carbamate (311 mg, 0.80 mmol), MeCN (5.2 mL), tert-butyl nitrite, 90% (0.16 mL, 1.21 mmol), azidotrimethylsilane (0.13 mL, 0.97 mmol), trimethylphosphine (1M in THF, 0.97 mL, 0.97

mmol), *tert*-butyl isocyanate (0.01 mL, 0.89 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 mL, 0.89 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 6.77 (br. s., 1H), 4.69 (s, 1H), 3.79 - 4.63 (m, 2H), 1.64 (s, 9H), 1.47 (s, 9H), 1.35 (br. s., 6H). *m/z* (ESI, +ve ion) 467.0/469.1 (1:1) $(M+H)^+$.

Step-3: (*R*)-*tert*-Butyl (1-(2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-4-oxoquinazolin-3(4*H*)-yl)-2-methylpropan-2-yl)carbamate. The title compound (125 mg, 0.24 mmol, 89 % yield, pale yellow solid) was prepared analogous to compound **16**, Step-3 using tert-butyl(1-(8-bromo-2-(tert-butylamino)-4-oxoquinazolin-3(4H)-yl)-2-methylpropan-2-yl)carbamate (125 mg, 0.27 mmol), (R)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1H)-one (175 mg, 0.67 mmol), X-Phos precatalyst generation II (10.5 mg, 0.01 mmol) and potassium phosphate (170 mg, 0.80 mmol) and 1,4-dioxane (2.2 mL)/water (0.6 mL): ^{1}H NMR (400 MHz, DMSO-d_6) 11.86 (s, 1 H), 7.89 (q, *J*=1.6 Hz, 1 H), 7.87 (q, *J*=1.6 Hz, 1 H), 7.63 (s, 1 H), 7.17 (t, *J*=7.6 Hz, 1 H), 7.11 (s, 1 H), 6.75 (s, 1 H), 6.69 (d, *J*=1.4 Hz, 1 H), 4.53 (q, *J*=6.4 Hz, 1 H), 3.97 (br. s., 2H), 1.51 (s, 9 H), 1.42 (s, 9 H), 1.37 (d, *J*=6.7 Hz, 3 H), 1.15 - 1.32 (m, 6 H). *m/z* (ESI, +ve ion) 523.1 $(M+H)^+$.

Step-4: (*R*)-3-(2-Amino-2-methylpropyl)-2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. The title compound (55 mg, 0.13 mmol, 61.8 % yield, off-white solid) was prepared analogous to compound **16**, Step-4 using trifluoroacetic acid (0.47 mL, 6.31 mmol), (*R*)-*tert*-butyl (1-(2-(*tert*-butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-4-oxoquinazolin-3(4*H*)-yl)-2-methylpropan-2-yl)carbamate (110 g, 0.21 mmol) and dichloromethane (2.0 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.14 (br. s., 1H), 7.91 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.85 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (s, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 1.4 Hz, 1H), 4.54 (q, *J* = 6.3 Hz, 1H), 3.97 (br. s., 2H), 1.50 (s, 9H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.15 (br. s., 6H). The peaks of -NH and -NH2 were not observed. LC–MS t_R = 1.32 min (>95%); *m/z* (ESI, +ve ion) 423.0 $(M+H)^+$.

(*R*)-2-(*tert*-Butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(oxetan-3-ylmethyl)-quinazolin-4(3*H*)-one (18). Step-1: 8-Bromo-2-chloro-3-(oxetan-3-ylmethyl)quinazolin-4(3*H*)-one. The title compound (132 mg, 0.40 mmol, 52 % yield, orange solid) was prepared analogous to compound **14**, *Step-4* using sodium hydride (60% dispersion in mineral oil, 34 mg, 0.85 mmol), 8-bromo-2-chloroquinazolin-4(3*H*)-one (200 mg, 0.77 mmol), lithium bromide (1.5M in THF, 1.0 mL, 1.54 mmol), 3-(iodomethyl)oxetane (168 mg, 0.85 mmol) and DME (0.5 mL)/ DMF (0.5 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.11 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 4.63 (dd, *J* = 7.9, 6.2 Hz, 2H), 4.42 - 4.53 (m, 4H), 3.47 (dt, *J* = 14.2, 7.3 Hz, 1H). *m/z* (ESI, +ve) 329.0/331.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-2-(tert-butylamino)-3-(oxetan-3-ylmethyl)-quinazolin-4(3*H*)-one. The title compound (86 mg, 0.24 mmol, 81 % yield, white solid) was prepared analogous to compound **14**, *Step-5* using 8-bromo-2-chloro-3-(oxetan-3-ylmethyl)quinazolin-4(3*H*)-one (95 mg, 0.29 mmol), *tert*-butylamine (0.45 mL, 4.32 mmol), and NMP (0.2 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.91 (d, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.15 (s, 1H), 4.59 (dd, *J* = 8.0, 6.1 Hz, 2H), 4.48 (d, *J* = 7.0 Hz, 2H), 4.42 (t, *J* = 6.3 Hz, 2H), 3.29 - 3.37 (m, 1H), 1.55 (s, 9H). *m/z* (ESI, +ve) 366.0/368.0 (1:1) $(M+H)^+$.

Step-3: (R)-2-(*tert*-Butylamino)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(oxetan-3-ylmethyl)-quinazolin-4(3*H*)-one. The title compound (45 mg, 0.11 mmol, 45% yield, off-white solid) was prepared analogous to compound **14**, Step-6 using 8-bromo-2-(*tert*-butylamino)-3-(oxetan-3-ylmethyl)quinazolin-4(3*H*)-one (86 mg, 0.24 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (62 mg, 0.24 mmol), XPhos-Pd-G2 (9.3 mg, 0.01 mmol), potassium phosphate (151 mg, 0.71 mmol), and 1,4-dioxane (0.8 mL)/water (0.2 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.79 (s, 1H), 7.82 - 7.92 (m, 2H), 7.59 (s, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 1.6 Hz, 1H), 6.00 (s, 1H), 4.60 (dd, *J* = 7.9, 6.0 Hz, 2H), 4.48 - 4.57 (m, 3H), 4.43 (t, *J* = 6.3 Hz, 2H), 4.08 (q, *J* = 5.3 Hz, 1H), 1.47 (s, 9H), 1.36 (d, *J* = 6.7 Hz, 3H). LC–MS t_R = 2.17 min (>95%); m/z (ESI, +ve ion) 422.5 $(M+H)^+$.

2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(((*R*)-tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one (19). (Method B) Step-1: (*R*)-2-Amino-3-bromo-*N*-((tetrahydrofuran-2-yl)methyl)benzamide. The title compound (1.35 g, 4.50 mmol, 88 % yield, light yellow solid) was prepared analogous to compound **10**, *Step-1* using 2-amino-3-bromobenzoic acid (1.10 g, 5.09 mmol) and *(R)*-(-)-tetrahydrofurfurylamine (0.57 g, 5.60 mmol), DIPEA (2.7 mL, 15.3 mmol) and T3P (50 wt% in EtOAc, 3.9 mL, 6.11 mmol) and EtOAc (20 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 (t, *J* = 6.1 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 6.53 (t, *J* = 7.8 Hz, 1H), 6.42 (s, 2H), 3.97 (quin, *J* = 6.3 Hz, 1H), 3.73 - 3.82 (m, 1H), 3.59 - 3.68 (m, 1H), 3.21 - 3.31 (m, 2H), 1.75 - 1.96 (m, 3H), 1.53 - 1.64 (m, 1H). *m/z* (ESI, +ve) 299.0/301.0 (1:1) $(M+H)^+$.

Step-2: (*R*)-8-Bromo-3-((tetrahydrofuran-2-yl)methyl)-quinazoline-2,4(1*H*,3*H*)-dione. The title compound (1.45 g, 4.46 mmol, 99 % yield, tan solid) was prepared analogous to compound **10**, *Step-2* using *(R)*-2-amino-3-bromo-*N*-((tetrahydrofuran-2-yl)methyl)benzamide (1.34 g, 4.49 mmol), triphosgene (0.47 g, 1.57 mmol) and dichloromethane (20 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.57 (s, 1H), 7.95 - 8.03 (m, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 4.14 - 4.23 (m, 1H), 4.04 - 4.12 (m, 1H), 3.72 - 3.87 (m, 2H), 3.58 - 3.65 (m, 1H), 1.87 - 1.98 (m, 2H), 1.75 - 1.86 (m, 1H), 1.60 - 1.70 (m, 1H). *m/z* (ESI, +ve) 325.0/327.0 (1:1) $(M+H)^+$.

Step-3: (*R*)-8-Bromo-2-(*tert*-butylamino)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one. A glass microwave reaction vessel was charged with *(R)*-8-bromo-3-((tetrahydrofuran-2-yl)methyl)quinazoline-2,4(1*H*,3*H*)-dione (221 mg, 0.68 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (451 mg, 1.02 mmol) in DMF (2 mL) followed by 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.20 mL, 1.36 mmol). The reaction mixture was stirred for 5 min and *tert*-butylamine (0.36 mL, 3.40 mmol) was added. The reaction was stirred at 40 °C for 30 min and allowed to cool to room temperature. The mixture was added ice water and stirred for 5 min. The resulting precipitate was collected by filtration, washed with water and MeOH to give *(R)*-8-bromo-2-(dimethylamino)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one (188 mg, 0.50 mmol, 73.0 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.88 - 7.98 (m, 2H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 4.07 - 4.29 (m, 3H), 3.69 - 3.89 (m, 2H), 2.01 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.79 - 1.93 (m, 2H), 1.55 - 1.66 (m, 1H), 1.54 (s, 9H). *m/z* (ESI, +ve) 380.0/382.0 (1:1) $(M+H)^+$.

Step-4: (2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(((*R*)-tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one. The title compound (154 mg, 0.35 mmol, 73.1 % yield, tan solid) was prepared analogous to compound **10**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d,** 206 mg, 0.63 mmol), (*R*)-8-bromo-2-(tert-butylamino)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one (184 mg, 0.48 mmol), potassium phosphate (308 mg, 1.45 mmol) and XPhos-Pd-G2 (19.0 mg, 0.02 mmol) and 1,4-dioxane (4 mL)/water (1.2 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.94 (s, 1H), 7.85 - 7.94 (m, 2H), 7.62 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.74 (d, *J* = 1.0 Hz, 1H), 4.50 - 4.58 (m, 1H), 4.13 - 4.32 (m, 3H), 3.72 - 3.88 (m, 2H), 2.05 (dq, *J* = 12.3, 6.1 Hz, 1H), 1.81 - 1.93 (m, 2H), 1.55 - 1.67 (m, 1H), 1.49 (s, 9H), 1.37 (d, J = 6.7 Hz, 3H). LC–MS t_R = 2.43 min (>95%); *m/z* (ESI, +ve) 436.0 $(M+H)^+$.

2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(((*S*)-tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one (20). (Method B) The title compound was prepared analogous to compound **19** using (*S*)-(+)-tetrahydrofurfurylamine (0.57 g, 5.60 mmol) in the *Step-1*: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.95 (s, 1H), 7.90 (ddd, *J* = 11.3, 7.6, 1.4 Hz, 2H), 7.62 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.74 (d, *J* = 1.2 Hz, 1H), 4.54 (q, *J* = 6.5 Hz, 1H), 4.11 - 4.34 (m, 3H), 3.70 - 3.90 (m, 2H), 2.00 - 2.13 (m, 1H), 1.81 - 1.94 (m, 2H), 1.55 - 1.68 (m, 1H), 1.49 (s, 9H), 1.38 (d, *J* = 6.7 Hz, 3H). LC–MS t_R = 2.43 min (>95%); *m/z* (ESI, +ve) 436.0 $(M+H)^+$.

Isomer 1 and isomer 2 of 2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-((4-methylmorpholin-2-yl)methyl)quinazolin-4(3*H*)-one (21 and 22). (Method B) Step-1: 2-Amino-3-bromo-*N*-((4-methylmorpholin-2-yl)methyl)benzamide. The title compound (*0.85 g, 2.59 mmol, 33.7 % yield*, white solid) was prepared analogous to compound **12**, *Step-1* using 2-amino-3-bromobenzoic acid (1.66 g, 7.68 mmol), (4-methylmorpholin-2-yl)methanamine (1.00 g, 7.68 mmol), HATU (3.21 g, 8.45 mmol), DIPEA (1.6 mL, 9.22 mmol) and DMF (5 mL): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.51 (br t, *J* = 5.3 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 6.54 (t, *J* = 7.8 Hz, 1H), 6.46 (br s, 2H), 3.87 (br d, *J* = 11.5 Hz, 1H), 3.67 (br d, *J* = 9.4 Hz, 1H), 3.55 (br t, *J* = 11.6 Hz, 1H), 3.31 (td, *J* = 13.5, 6.7 Hz, 2H), 3.17 (s, 2H), 2.97 (br d, *J* = 11.3 Hz, 1H), 2.84 (br d, *J* = 11.8 Hz, 1H), 2.40 (s, 3H). *m/z* (ESI, +ve) 327.9/329.9 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-((4-methylmorpholin-2-yl)methyl)-quinazoline-2,4(1*H*,3*H*)-dione. The title compound (300 mg, 0.85 mmol, 42.8 % yield, white solid) was prepared analogous to compound **10**, *Step-2* using 2-amino-3-bromo-*N*-((4-methylmorpholin-2-yl)methyl)benzamide (650 mg, 1.98 mmol) and tri-phosgene (206 mg, 0.69 mmol) and dichloromethane (16 mL): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.78 - 11.01 (m, 1H), 10.69 (br s, 1H), 7.99 (d, *J* = 7.7 Hz, 2H), 7.18 (t, *J*=7.8 Hz, 1H), 4.10 (br d, *J* = 8.9 Hz, 2H), 3.89 - 4.04 (m, 2H), 3.76 (br t, *J* = 11.6 Hz, 1H), 3.50 (br d, *J* = 11.1 Hz, 1H), 2.95 - 3.09 (m, 1H), 2.86 (br s, 1H), 2.72 (s, 3H). *m/z* (ESI, +ve) 353.9/355.8 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-(tert-butylamino)-3-((4-methylmorpholin-2-yl)methyl)quinazolin-4(3*H*)-one. The title compound (254 mg, 0.62 mmol, 73.3 % yield, white solid) was prepared analogous to compound **19**, *Step-3* using 8-bromo-3-((4-methylmorpholin-2-yl)methyl)quinazoline-2,4(1*H*,3*H*)-dione (300 mg, 0.85 mmol), (benzotriazol-1-

yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (562 mg, 1.27 mmol), and tert-butylamine (0.45 mL, 4.23 mmol) and DMF (5.2 mL): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.92 (t, *J* = 6.6 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.58 (s, 1H), 3.97 - 4.16 (m, 2H), 3.77 - 3.95 (m, 2H), 3.56 (br t, *J* = 11.1 Hz, 1H) 2.74, (br d, *J* = 11.4 Hz, 1H), 2.54 - 2.66 (m, 2H), 2.18 (s, 3H), 1.81 (br t, *J* = 10.4 Hz, 1H), 1.53 (s, 9H). *m/z* (ESI, +ve) 408.9/410.9 (1:1) $(M+H)^+$.

Step-4: 2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-((4-methylmorpholin-2-yl)methyl)quinazolin-4(3*H*)-one. The title compound (250 mg, 0.54 mmol, 87 % yield, yellow solid) was prepared analogous to compound **10**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d,** 325 mg, 1.24 mmol), potassium phosphate (527 mg, 2.48 mmol), XPhos-Pd-G2 (24 mg, 0.03 mmol), 8-bromo-2-(*tert*-butylamino)-3-((4-methylmorpholin-2-yl)methyl)quinazolin-4(3*H*)-one (254 mg, 0.62 mmol), and 1,4-dioxane (6 mL)/water (1.5 mL): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.91 (br s, 1H), 7.89 (t, *J* = 6.7 Hz, 2H), 7.61 (s, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 4.53 (q, *J* = 6.2 Hz, 1H), 4.16 (br s, 2H), 3.83 - 3.98 (m, 2H), 3.57 (br t, *J* = 10.8 Hz, 1H), 2.77 (br d, *J* = 11.5 Hz, 1H), 2.60 (br d, *J* = 12.0 Hz, 1H), 2.18 (s, 3H), 1.93 - 2.06 (m, 1H), 1.80 (br t, *J* = 10.8 Hz, 1H), 1.47 (s, 9H), 1.37 (d, *J* = 6.4 Hz, 3H). *m/z* (ESI, +ve) 465.2 $(M+H)^+$.

Step-5: Isomer 1 and isomer 2 of 2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-((4-methylmorpholin-2-yl)methyl)quinazolin-4(3*H*)-one (21 and 22). The above racemic mixture of 2-(*tert*-butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-((4-methylmorpholin-2-yl)methyl)quinazolin-4(3*H*)-one was purified by SFC for chiral separation (Chiralpak IDH, 250 x 20 mm, 5 µm, 25% MeOH (containing 20 mM Ammonia)/CO2, 70 mL/min, 165 bar) to obtain two isomers: Isomer 1 (**21**, Peak 1, 49.6 mg, >99% ee, white solid) and isomer 2 (**22**, Peak 2, 44.4 mg, >99% ee, light yellow solid). **Isomer 1 (21):** ^{1}H NMR (300 MHz, DMSO-d_6) 11.91 (br s, 1H), 7.89 (t, *J* = 6.8 Hz, 2H), 7.61 (s, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 4.53 (q, *J* = 6.7 Hz, 1H), 4.16 (br s, 2H), 3.79 - 3.98 (m, 2H), 3.57 (br t, *J* = 11.1 Hz, 1H), 2.77 (br d, *J* = 11.5 Hz, 1H), 2.60 (br d, *J* = 11.7 Hz, 1H), 2.18 (s, 3H), 1.99 (br t, *J* = 10.0 Hz, 1H), 1.80 (br t, *J* = 10.8 Hz, 1H), 1.47 (s, 9H), 1.37 (d, *J* = 6.4 Hz, 3H). LC–MS t_R = 1.48 min (>95%); *m/z* (ESI, +ve) 465.0 $(M+H)^+$. **Isomer 2 (22):** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.90 (s, 1H), 7.89 (t, *J* = 6.6 Hz, 2H), 7.62 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 6.61 (s, 1H), 4.43 - 4.60 (m, 1H), 4.08 - 4.27 (m, 2H), 3.80 - 4.01 (m, 2H), 3.58 (br t, *J* = 11.1 Hz, 1H), 2.79 (br d, *J* = 11.4 Hz, 1H), 2.62 (br d, *J* = 11.4 Hz, 1H), 2.20 (s, 3H), 1.96 - 2.12 (m, 1H), 1.73 - 1.91 (m, 1H), 1.47 (s, 9H), 1.37 (d, *J* = 6.6 Hz, 3H). LC–MS t_R = 1.48 min (>95%); *m/z* (ESI, +ve) 465.0 $(M+H)^+$.

2-(*tert*-Butylamino)-3-((1-methyl-1*H*-imidazol-4-yl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (23). (Method B) Step-1: 2-Amino-3-bromo-*N*-((1-methyl-1*H*-imidazol-4-yl)methyl)benzamide. The title compound (752 mg, 2.43 mmol, 52.5% yield, orange solid) was prepared analogous to compound **10**, *Step-1* using 2-amino-3-bromobenzoic acid (1.00 g, 4.63 mmol) and (1-methyl-1*H*-imidazol-4-yl)methylamine (514 mg, 4.63 mmol), DIPEA (2.4 mL, 13.89 mmol), T3P (50 wt% in EtOAc, 4.42 mL, 6.94 mmol) and EtOAc (20 mL): ^{1}H NMR

(400 MHz, DMSO-*d6*) δ ppm 8.87 (t, *J* = 5.5 Hz, 1 H), 7.54 (td, *J* = 8.1, 1.3 Hz, 2 H), 7.08 (d, *J* = 1.0 Hz, 1 H), 6.79 (d, *J* = 1.2 Hz, 1 H), 6.46 - 6.54 (m, 3 H), 4.48 (d, *J* = 5.5 Hz, 2 H), 3.65 (s, 3 H)*m/z* (ESI, +ve) 308.9/310.9 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-((1-methyl-1*H*-imidazol-4-yl)methyl)quinazoline-2,4(1*H*,3*H*)-dione*.*** The title compound (313 mg, 0.93 mmol, 38.4 % yield, white solid) was prepared analogous to compound **10**, *Step-2* using 2-amino-3-bromo-*N*-((1-methyl-1*H*-imidazol-4-yl)methyl)benzamide (752 mg, 2.43 mmol) and triphosgene (253 mg, 0.85 mmol) and dichloromethane (20 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.85 (s, 1H), 8.95 (s, 1H), 7.96 - 8.05 (m, 2H), 7.63 (s, 1H), 7.20 (t, *J*=7.8 Hz, 1H), 5.12 (s, 2H), 3.79 (s, 3H). *m/z* (ESI, +ve) 334.9/336.9 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-(*tert*-butylamino)-3-((1-methyl-1*H*-imidazol-4-yl)methyl)quinazolin-4(3*H*)-one. The title compound (164 mg, 0.42 mmol, 69.4% yield, yellow oil) was prepared analogous to compound **19**, *Step-3* using 8-bromo-3-((1-methyl-1*H*-imidazol-4-yl)methyl)quinazoline-2,4(1*H*,3*H*)-dione (203 mg, 0.61 mmol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 402 mg, 0.91 mmol), *tert*-butylamine (0.32 mL, 3.03 mmol) and DMF (2 mL): *m/z* (ESI, +ve) 389.9/391.9 (1:1) $(M+H)^+$.

Step-4: (2-(*tert*-Butylamino)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(((*R*)-tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one. The title compound (111 mg, 0.25 mmol, 59.3 % yield, white solid) was prepared analogous to compound **10**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1*H*)-one (**9d,** 132 mg, 0.50 mmol), (*R*)-8-bromo-2-(*tert*-butylamino)-3-((tetrahydrofuran-2-yl)methyl)quinazolin-4(3*H*)-one (164 mg, 0.42 mmol), potassium phosphate (268 mg, 1.26 mmol) and XPhos-Pd-G2 (16.5 mg, 0.02 mmol) and 1,4-dioxane (3 mL)/water (1 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.94 (br. s., 1H), 7.79 - 7.93 (m, 3H), 7.57 - 7.70 (m, 2H), 7.22 (s, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 5.08 (s, 2H), 4.53 (q, *J* = 6.1 Hz, 1H), 3.64 (s, 3H), 1.52 (s, 9H), 1.36 (d, *J* = 6.5 Hz, 3H). LC–MS t_R = 1.44 min (>95%); m/z (ESI, +ve) 446.0 $(M+H)^+$.

2-(*tert*-Butylamino)-3-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one (24). (Method B) Step-1: 2-amino-3-bromo-*N*-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)benzamide. The title compound (511 mg, 1.58 mmol, 56.2% yield, orange solid) was prepared analogous to compound **10**, *Step-1* using 2-amino-3-bromobenzoic acid (608 mg, 2.81 mmol) and 1-(1-methyl-1*H*-imidazol-4-yl)ethanamine (352 mg, 2.81 mmol), DIPEA (1.5 mL, 8.44 mmol), T3P (50 wt% in EtOAc, 2.7 mL, 4.22 mmol) and EtOAc (5 mL): *m/z* (ESI, +ve) 322.9/324.9 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-(1-(1-methyl-1H-imidazol-4-yl)ethyl) quinazoline-2,4(1H,3H)-dione. The title compound (561 mg, 1.58 mmol, 100 % yield, white solid) was prepared analogous to compound **10**, *Step-2* using 2-amino-3-bromo-*N*-((1-methyl-1*H*-imidazol-4-yl)ethyl)benzamide (511 mg, 1.58 mmol) and triphosgene (164 mg, 0.55 mmol) and dichloromethane (16 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.71 (br. s., 1H), 9.01 (s, 1H), 7.97 (dd, *J* = 18.6, 7.8 Hz, 2H), 7.70 (s, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.15 (q, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 1.76 (d, *J* = 6.8 Hz, 3H). *m/z* (ESI, +ve) 348.8/350.8 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-(*tert*-butylamino)-3-((1-methyl-1*H*-imidazol-4-yl)methyl)quinazolin-4(3*H*)-one. The title compound (298 mg, 0.74 mmol, 47.0 % yield, yellow solid) was prepared analogous to compound **19**, *Step-3* using 8-bromo-3-((1-methyl-1*H*-imidazol-4-yl)ethyl)quinazoline-2,4(1*H*,3*H*)-dione (548 mg, 1.57 mmol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.04 g, 2.35 mmol), *tert*-butylamine (0.8 mL, 7.85 mmol) and DMF (5.2 mL): *m/z* (ESI, +ve) 403.9/405.9 (1:1) $(M+H)^+$.

Step-4: 2-(*tert*-Butylamino)-3-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)quinazolin-4(3*H*)-one. The title compound (263 mg, 0.57 mmol, 78 % yield, yellow solid) was prepared analogous to compound **10**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d,** 300 mg, 1.03 mmol), (*R*)-8-bromo-2-(*tert*-butylamino)-3-((tetrahydrofuran-2-yl)ethyl)quinazolin-4(3*H*)-one (298 mg, 0.74 mmol), potassium phosphate (468 mg, 2.20 mmol) and XPhos-Pd-G2 (12.2 mg, 0.02 mmol) and 1,4-dioxane (3 mL)/water (1 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.87 (d, *J* = 6.3 Hz, 1H), 8.03 (d, *J* = 11.3 Hz, 1H), 7.88 - 7.94 (m, 1H), 7.85 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 7.26 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.71 (m, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 1.4 Hz, 1H), 4.46 - 4.56 (m, 1H), 3.65 (s, 3H), 1.72 (dd, *J* = 7.3, 1.5 Hz, 3H), 1.45 (s, 9H), 1.35 (dd, *J* = 6.6, 1.7 Hz, 3H). LC–MS t_R = 1.39 min (>95%); m/z (ESI, +ve) 460.0 $(M+H)^+$.

***(R)*-3-Cyclopropyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (26). (Method A) Step-1: 8-bromo-3-cyclopropyl-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one.** The title compound (170 mg, 0.51 mmol, 76 % yield, white solid) was prepared analogous to compound **11**, *Step-4.* A mixture of 8-bromo-2-chloro-3-cyclopropyl quinazolin-4(3*H*)-one (200 mg, 0.67 mmol), 1-methylcyclopropanamine hydrochloride (252 mg, 2.34 mmol), triethylamine (0.46 mL, 3.34 mmol) and DMSO (0.5 mL) in a sealed tube was heated in an oil bath at 80 °C. After 1 h, the reaction was cooled to room temperature. Water and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude material purified by silica gel chromatography (0-50 % EtOAc in hexanes) to provide the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 5.77 (s, 1H), 2.65 (tt, *J* = 6.8, 4.1 Hz, 1H), 1.61 (s, 3H), 1.27 - 1.34 (m, 2H), 0.85 - 0.92 (m, 4H), 0.80 - 0.85 (m, 2H). *m/z* (ESI, +ve) 334.0/336.0 (1:1) $(M+H)^+$.

Step-2: (*R*)-3-Cyclopropyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (117 mg, 0.30 mmol, 59.1 % yield, tan solid) was prepared analogous to compound **11**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrol-4(1*H*)-one (**9d,** 167 mg, 0.64 mmol), 8-bromo-3-cyclopropyl-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (170 mg, 0.51), potassium phosphate (324 mg, 1.53 mmol) and XPhos-Pd-G2 (20 mg, 0.03 mmol) and 1,4-dioxane (1.4 mL)/water (0.4 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.01 (s, 1H), 8.09 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.77 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 1.0 Hz, 1H), 4.63

(q, *J* = 6.5 Hz, 1H), 3.91 (s, 1H), 1.55 (s, 3H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.19 - 1.27 (m, 2H), 0.99 - 1.04 (m, 2H), 0.83 - 0.88 (m, 2H), 0.73 (dd, *J* = 3.9, 2.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 162.3, 151.1, 149.4, 143.7, 136.2, 129.4, 124.2, 121.8, 119.4, 118.2, 99.3, 47.9, 29.9, 24.9, 24.4, 21.7, 20.6, 14.7, 14.5, 10.4, 10.3. LC–MS t_R = 1.60 min (>95%); *m/z* (ESI, +ve) 390.0 $(M+H)^+$.

***(R)*-3-Cyclobutyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (27). (Method A) Step-1: 2-Amino-3-bromo-*N*-cyclobutylbenzamide.** The title compound (2.13 g, 7.90 mmol, 85% yield, light-yellow solid) was prepared analogous to compound **11**, *Step-1* using 2-amino-3-bromobenzoic acid (2.00 g, 9.26 mmol) and cyclobutylamine (2.4 mL, 27.8 mmol), DIPEA (1.5 mL, 8.44 mmol), T3P (50 wt% in EtOAc, 6.06 mL, 10.18 mmol) and EtOAc (20 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 6.52 (t, *J* = 7.8 Hz, 1H), 6.12 (br. s., 2H), 5.81 - 6.06 (m, 1H), 4.53 (sxt, *J* = 8.0 Hz, 1H), 2.35 - 2.53 (m, 2H), 1.90 - 1.98 (m, 2H), 1.74 - 1.82 (m, 2H). *m/z* (ESI, +ve) 268.9/271.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-cyclobutylquinazoline-2,4(1*H*,3*H*)-dione. The title compound (2.59 g, 8.78 mmol, light-yellow solid) was prepared analogous to compound **11**, *Step-2* using 2-amino-3-bromo-*N*-cyclobutylbenzamide (2.13 g, 7.90 mmol), triphosgene (0.80 g, 2.69 mmol) and dichloromethane (80 mL): *m/z* (ESI, +ve) 295.0/297.0 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-chloro-3-cyclobutylquinazolin-4(3*H*)-one. The title compound (1.89 g, 6.02 mmol, 76% yield, tan solid) was prepared analogous to compound **11**, *Step-3* using 8-bromo-3-cyclobutylquinazoline-2,4(1*H*,3*H*)-dione (2.33 g, 7.89 mmol), phosphorus oxychloride (3.7 mL, 39.5 mmol), and DIPEA (5.5 mL, 31.6 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 5.22 (quin, *J* = 8.8 Hz, 1H), 2.89 - 3.05 (m, 2H), 2.43 - 2.56 (m, 2H), 1.98 (q, *J* = 10.7 Hz, 1H), 1.74 - 1.90 (m, 1H). *m/z* (ESI, +ve) 313.0/314.9 (4:5) $(M+H)^+$.

Step-4: 8-Bromo-3-cyclobutyl-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (226 mg, 0.65 mmol, 100% yield, light-yellow solid) was prepared analogous to compound **26**, *Step-4* using 8-bromo-2-chloro-3-cyclobutylquinazolin-4(3*H*)-one (203 mg, 0.65 mmol), 1-methylcyclopropanamine hydrochloride (209 mg, 1.94 mmol), triethylamine (0.27 mL, 1.94 mmol) and DMSO (1.5 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.93 - 7.02 (m, 1H), 4.79 (br. s., 1H), 4.50 (br. s., 1H), 2.58 - 2.71 (m, 2H), 2.35 - 2.50 (m, 2H), 1.76 - 1.87 (m, 2H), 1.59 (s, 3H), 0.87 (br. s., 2H), 0.81 (br. s., 2H). *m/z* (ESI, +ve) 347.9/349.9 (1:1) $(M+H)^+$.

Step-5: (*R*)-3-Cyclobutyl-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino) quinazolin-4(3*H*)-one. The title compound (65.8 mg, 0.16 mmol, 53% yield, tan solid) was prepared analogous to compound **11**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d,** 203 mg, 0.39 mmol), 8-bromo-3-cyclobutyl-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (108 mg, 0.31 mmol), potassium phosphate (197 mg, 0.93 mmol) and XPhos-Pd-G2 (12 mg, 0.02 mmol) and 1,4-dioxane (1.2 mL)/water (0.3 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.92 (s, 1H), 8.09 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.76 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.68 (s, 1H), 7.31 (s, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 1.2

Hz, 1H), 4.63 (q, *J* = 6.5 Hz, 1H), 4.43 - 4.54 (m, 1H), 2.51 - 2.59 (m, 2H), 2.32 (sxt, *J* = 10.2 Hz, 2H), 1.56 - 1.74 (m, 2H), 1.51 (s, 3H), 1.36 (d, *J* = 6.7 Hz, 3H), 0.96 (br. s, 2H.), 0.78 - 0.87 (m, 2H). LC–MS t_R = 2.25 min (>95%); m/z (ESI, +ve) 404.0 $(M+H)^+$.

(*R*)-8-(6-Methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(1-methylcyclopropyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (28). (Method A) Step-1: 2-Amino-3-bromo-*N*-(1-methylcyclopropyl)benzamide. The title compound (10.5 g, 39.0 mmol, 78% yield, light-yellow solid) was prepared analogous to compound **11**, *Step-1* using 2-amino-3-bromobenzoic acid (10.8 g, 49.9 mmol) and 1-methylcyclopropanamine hydrochloride (6.44 g, 59.8 mmol), DIPEA (20.8 mL, 120 mmol), T3P (50 wt% in EtOAc, 32.6 mL, 54.8 mmol) and EtOAc (150 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.19 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.49 (t, *J* = 7.8 Hz, 1H), 6.31 (br. s., 1H), 6.10 (br. s., 2H), 1.47 (s, 3H), 0.81 - 0.87 (m, 2H), 0.71 - 0.77 (m, 2H). *m/z* (ESI, +ve) 268.9/270.8 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-(1-methylcyclopropyl)quinazoline-2,4(1*H*,3*H*)-dione. The title compound (22.5 g, 76 mmol, 99 % yield, light-yellow solid) was prepared analogous to compound **11**, *Step-2* using 2-amino-3-bromo-*N*-(1-methylcyclopropyl)benzamide (20.7 g, 77.0 mmol) and triphosgene (8.78 g, 29.6 mmol) and toluene (250 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09 (d, *J* = 7.8 Hz, 1H), 8.01 (br. s., 1H), 7.77 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 1.51 (s, 3H), 1.04 (d, *J*=3.5 Hz, 2H), 1.00 (d, *J*=3.1 Hz, 2H). *m/z* (ESI, +ve) 294.8/296.9 (1:1) $(M+H)^+$.

Step-3: 8-Bromo-2-chloro-3-(1-methylcyclopropyl)quinazolin-4(3*H*)-one. The title compound (16.0 g, 51.0 mmol, 97% yield, light-brown solid) was prepared analogous to compound **11**, *Step-3* using 8-bromo-3-(1-methylcyclopropyl)quinazoline-2,4(1*H*,3*H*)-dione (15.6 g, 52.9 mmol), $POCl_3$ (38.7 mL, 423 mmol), and DIPEA (36.8 mL, 211 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.18 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.99 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 1.61 (s, 3H), 1.09 - 1.29 (m, 4H). *m/z* (ESI, +ve) 312.8/314.7 (4:5) $(M+H)^+$.

Step-4: 8-Bromo-3-(1-methylcyclopropyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (9.63 g, 27.7 mmol, 59% yield, light-yellow solid) was prepared analogous to compound **26**, *Step-4* using 8-bromo-2-chloro-3-(1-methylcyclopropyl)quinazolin-4(3*H*)-one (14.6 g, 46.7 mmol), 1-methylcyclopropanamine hydrochloride (10.0 g, 93.3 mmol), and DIPEA (32.5 mL, 187 mmol) in DMSO (70 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 5.71 - 6.39 (m, 1H), 1.62 (s, 3H), 1.50 (s, 3H), 0.97 - 1.08 (m, 2H), 0.82 - 0.96 (m, 6H). *m/z* (ESI, +ve) 347.7/349.9 (1:1) $(M+H)^+$.

Step-5: (R)-8-(6-Methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-3-(1-methylcyclopropyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (10.2 g, 25.3 mmol, 90% yield, light-yellow solid) was prepared analogous to compound **11**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1*H*)-one (**9d,** 14.7 g, 56.1 mmol), 8-bromo-3-(1-methylcyclopropyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (9.77 g, 28.1 mmol, potassium phosphate (17.9 g, 84 mmol) and XPhos-Pd-G2 (0.51 g, 0.65 mmol) and 1,4-dioxane (105 mL)/water 35 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.83 - 13.10 (m, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 7.78 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.68 (s, 1H), 7.22 - 7.36 (m, 1H), 7.14 (t, J=7.7 Hz, 1H), 6.93 (dd, *J* = 5.8, 1.3

Hz, 1H), 4.63 (q, J=6.4 Hz, 1H), 1.56 (d, *J* = 7.6 Hz, 3H), 1.44 (d, *J* = 9.2 Hz, 3H), 1.36 (dd, *J* = 6.5, 2.7 Hz, 3H), 0.80 - 1.25 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.8, 162.2, 150.3, 149.9, 144.2, 136.7, 129.9, 124.8, 124.7, 122.4, 120.0, 118.8, 99.9, 48.4, 31.6, 30.5, 22.3, 21.1, 21.0, 17.9, 16.5, 15.4, 15.3. LC–MS t_R = 1.88 min (>95%); m/z (ESI, +ve) 403.9 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{23}H_{25}N_5O_2$ $(M+H)^+$: 403.2008; found: 404.2079.

***(R)*-3-(*tert*-Butyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (29). (Method C) Step-1: 2-Amino-3-bromo-*N*-(*tert*-butyl)benzamide.** The title compound (1.29 g, 4.76 mmol, 48.9 % yield) was prepared analogous to compound **12**, *Step-1* using 2-amino-3-bromobenzoic acid (2.10 g, 9.72 mmol), 2-methylpropan-2-amine (1.2 mL, 11.7 mmol), HATU (4.80 g, 12.6 mmol), DIPEA (2.5 mL, 14.6 mmol) and DMF (9.7 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 (dd, *J*=8.0, 1.37 Hz, 1H), 7.22 (dd, *J*=7.8, 1.2 Hz, 1H), 6.51 (t, *J*=7.8 Hz, 1H), 5.95 (br. s., 2H), 5.82 (br. s., 1H), 1.46 (s, 9 H). *m/z* (ESI, +ve) 271.0/273.0 (1:1) $(M+H)^+$.

Step-2: 8-Bromo-3-(*tert*-butyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (114 mg, 0.33 mmol, 9.1 % yield, white solid) was prepared analogous to compound **12**, *Step-2* using 2-amino-3-bromo-*N*-(*tert*-butyl)benzamide (0.97 g, 3.58 mmol), *tert*-butyl nitrite (0.64 mL, 5.37 mmol), azidotrimethylsilane (0.57 mL, 4.29 mmol), trimethylphosphine (1.0M in THF, 4.3 mL, 4.3 mmol), 1-isocyanato-1-methylcyclopropane in toluene (4.11 mL, 4.11 mmol) and DBU (0.59 mL, 3.94 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 (dd, *J*=7.9, 1.5 Hz, 1H), 7.62 (dd, *J*=7.8, 1.6 Hz, 1H), 6.86 (t, *J*=7.8 Hz, 1H), 5.26 (br. s, 1H), 1.51 (s, 3H), 1.41 (s, 9H), 0.87 - 0.94 (m, 2H), 0.72 - 0.77 (m, 2H). *m/z* (ESI, +ve) 350.1/352.1 (1:1) $(M+H)^+$.

Step-3: (*R*)-3-(*tert*-Butyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (78 mg, 0.19 mmol, 59.1 % yield, light-yellow solid) was prepared analogous to compound **12**, Step-3 using 8-bromo-3-(*tert*-butyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (114 mg, 0.33 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**, 128 mg, 0.49 mmol), XPhos-Pd-G2 (12.8 mg, 0.02 mmol), and potassium phosphate (207 mg, 0.98 mmol) in 1,4-dioxane (2.6 mL)/water (0.7 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.46 (s, 1 H), 8.14 - 8.24 (m, 1 H), 7.57 - 7.81 (m, 1 H), 7.16 - 7.32 (m, 1 H), 6.88 - 7.13 (m, 1 H), 6.64 - 6.84 (m, 1 H), 6.35 (s, 1 H), 4.92 - 5.26 (m, 1 H), 1.65 (dd, *J* = 16.8, 6.7 Hz, 3 H), 1.56 (s, 9 H), 1.49 (s, 3 H), 0.90 - 1.13 (m, 2 H), 0.67 - 0.88 (m, 2 H). LC–MS t_R = 1.79 min (>95%); m/z (ESI, +ve) 406.2 $(M+H)^+$.

***(R)*-3-(Cyclopropylmethyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (30). Step-1: 8-Bromo-3-(cyclopropylmethyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one.** The title compound (0.26 g, 0.73 mmol, 47.5 % yield, yellow solid) was prepared analogous to compound **14**, *Step-5* using 8-bromo-2-chloro-3-(cyclopropylmethyl)quinazolin-4(3*H*)-one (483 mg, 1.54 mmol), 1-methylcyclopropanamine hydrochloride (331 mg, 3.08 mmol), and DIPEA (0.8 mL, 4.62 mmol) and DMSO (3.9 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 5.31

(s, 1H), 3.93 (d, *J* = 6.7 Hz, 2H), 1.62 (s, 3H), 0.98 - 1.10 (m, 1H), 0.86 - 0.93 (m, 2H), 0.79 - 0.86 (m, 2H), 0.56 - 0.63 (m, 2H), 0.46 (q, *J* = 5.0 Hz, 2H). *m/z* (ESI, +ve) 348.0/350.0 (1:1) $(M+H)^+$.

Step-2: (R)-3-(Cyclopropylmethyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (197 mg, 0.49 mmol, 66.7 % yield, yellow solid) was prepared analogous to compound **14**, Step-6 using 8-bromo-3-(cyclopropylmethyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (255 mg, 0.73 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**, 480 mg, 1.83 mmol), XPhos-Pd-G2 (29 mg, 0.04 mmol), and potassium phosphate (466 mg, 2.20 mmol) in 1,4-dioxane (6.0 mL)/water (1.5 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.08 (s, 1H), 8.00 (ddd, *J* = 7.6, 5.9, 1.4 Hz, 2H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 1.2 Hz, 1H), 6.65 (s, 1H), 5.81 (s, 1H), 4.67 (q, *J* = 6.7 Hz, 1H), 3.95 - 4.11 (m, 2H), 1.65 (s, 3H), 1.53 (d, *J* = 6.7 Hz, 3H), 1.04 - 1.16 (m, 3H), 0.85 - 0.94 (m, 2H), 0.58 - 0.65 (m, 2H), 0.47 - 0.53 (m, 2H). LC–MS t_R = 1.99 min (>95%); m/z (ESI, +ve) 404.1 $(M+H)^+$.

(*R*)-3-((1-Hydroxycyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (31). (Method C) Step-1: 8-Bromo-3-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (320 mg, 0.67 mmol, 89 % yield) was prepared analogous to compound **15**, *Step-3* using 2-amino-3-bromo-*N*-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl) benzamide (from compound **15**, *Step-2,* 300 mg, 0.75 mmol), MeCN (7.5 mL), *tert*-butyl nitrite, 90% (0.13 mL, 1.13 mmol), trimethylsilyl azide (0.12 mL, 0.90 mmol), trimethylphosphine (1.0M in THF, 0.9 mL, 0.90 mmol), 1-isocyanato-1-methylcyclopropane (88 mg, 0.90 mmol), DBU (0.14 mL, 0.90 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.83 (br. s., 1H), 4.29 (s, 2H), 1.61 (s, 3H), 0.84 - 1.01 (m, 13H), 0.81 (s, 4H), 0.22 (s, 6H). *m/z* (ESI, +ve ion) 478.1/480.1 (1:1) $(M+H)^+$.

Step-2: (R)-3-((1-((tert-Butyldimethylsilyl)oxy)cyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (372 mg, 0.67 mmol, 100 % yield, yellow foam) was prepared analogous to compound **15**, Step-4 using potassium phosphate (568 mg, 2.68 mmol), XPhos-Pd-G2 (26 mg, 0.03 mmol), (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d**; 351 mg, 1.34 mmol), 8-bromo-3-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (320 mg, 0.67 mmol) and dioxane (4 mL) / water (0.8 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.90 (br. s., 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.68 (s, 1H), 7.50 (s, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 4.64 (d, *J* = 6.3 Hz, 1H), 4.39 - 4.49 (m, 1H), 4.27 - 4.39 (m, 1H), 1.54 (s, 3H), 1.36 (d, *J* = 6.5 Hz, 3H), 0.83 - 1.01 (m, 4H), 0.61 - 0.78 (m, 13H), 0.01 (br. s., 6H). m/z (ESI, +ve ion) 534.2 $(M+H)^+$.

Step-3: (R)-3-((1-Hydroxycyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (58 mg, 0.14 mmol, 19.8 % yield, off-white

solid) was prepared analogous to compound **15**, Step-5 using (*R*)-3-((1-((*tert*-butyldimethylsilyl)oxy)cyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (0.372 g, 0.697 mmol), THF (4 mL) and tetrabutylammonium fluoride (1.0 M in THF, 1.05 mL, 1.05 mmol): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.97 (br. s., 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 6.7 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 6.16 (s, 1H), 4.64 (d, *J* = 6.5 Hz, 1H), 4.20 (s, 2H), 1.55 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 3H), 0.97 (br. s., 2H), 0.85 (br. s., 2H), 0.77 (br. s., 2H), 0.69 (br. s., 2H). LC–MS t_R = 1.81 min (>95%); m/z (ESI, +ve ion) 420.2 $(M+H)^+$.

***(R)*-3-((1-Aminocyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(*3H*)-one (32). (Method B) Step-1: *tert*-Butyl (1-((8-bromo-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate.** To a mixture of *tert*-butyl (1-((2-amino-3-bromobenzamido)methyl)cyclopropyl)carbamate (from compound **16,** *Step-1*, 290 mg, 0.76 mmol) and triphosgene (90 mg, 0.30 mmol) in dichloromethane (2.8 mL) was stirred at reflux for 90 min. The reaction mixture was cooled and concentrated and *tert*-butyl (1-((8-bromo-2,4-dioxo-1,2-dihydroquinazolin-3(*4H*)-yl)methyl)cyclopropyl)carbamate was used without further purification. *m/z* (ESI, +ve) 310.0/311.9 (1:1) $(M-Boc+H)^+$.

Step-2: *tert*-Butyl (1-((8-bromo-2-((1-methylcyclopropyl)amino)-4-oxoquinazolin-3(4*H*)-yl)methyl)-cyclopropyl)carbamate. The title compound (170 mg, 0.37 mmol, 48.6 % yield, white solid) was prepared analogous to compound **19**, Step-3 using *tert*-butyl (1-((8-bromo-2,4-dioxo-1,2-dihydroquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate (310 mg, 0.756 mmol), BOP (668 mg, 1.51 mmol), 1-methylcyclopropanamine hydrochloride (244 mg, 2.27 mmol), DBU (0.57 mL, 3.78 mmol) and DMF (1.9 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.85 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.80 (br. s., 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 5.08 (br. s., 1H), 4.34 (br. s., 2H), 1.66 (s, 3H), 1.49 (s, 9H), 0.91 - 0.97 (m, 2H), 0.73 - 0.79 (m, 4H), 0.66 - 0.72 (m, 2H). m/z (ESI, +ve) 463.1/465.0 (1:1) $(M+H)^+$.

Step-3: (*R*)-*tert*-Butyl (1-((8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate. The title compound (180 mg, 0.35 mmol, 95 % yield, pale green solid) was prepared analogous to compound **10**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-b]pyrrol-4(1*H*)-one (**9d,** 192 mg, 0.73 mmol), *tert*-butyl (1-((8-bromo-2-((1-methylcyclopropyl)amino)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate (170 mg, 0.37 mmol), potassium phosphate (234 mg, 1.10 mmol) and XPhos-Pd-G2 (14 mg, 0.02 mmol) and 1,4-dioxane (3 mL)/water (0.75 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.17 (br. s., 1H), 8.28 (br. s., 1H), 8.03 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 1.2 Hz, 1H), 5.75 (s, 1H), 5.20 (s, 1H), 4.66 (q, *J* = 6.5 Hz, 1H), 4.27 - 4.57 (m, 2H), 1.53 (d, *J* = 6.7 Hz, 3H), 1.50 (s, 9H), 1.24 (s, 3H), 1.09 - 1.15 (m, 2H), 0.82 - 0.88 (m, 2H), 0.71 - 0.79 (m, 4H). m/z (ESI, +ve) 519.2 $(M+H)^+$.

Step-4: (*R*)-3-((1-Aminocyclopropyl)methyl)-8-(6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (85 mg, 0.20 mmol, 58.8 % yield, orange solid) was prepared analogous to compound **16**, Step-4 using trifluoroacetic acid (0.7 mL, 10.41 mmol), (*R*)-*tert*-butyl (1-((8-(6-

methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)-amino)-4-oxoquinazolin-3(4*H*)-yl)methyl)cyclopropyl)carbamate (180 mg, 0.35 mmol) and dichloromethane (2.0 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.07 (s, 1H), 8.13 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.72 (s, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 1.4 Hz, 1H), 4.64 (q, *J* = 6.7 Hz, 1H), 4.06 (s, 2H), 1.56 (s, 3H), 1.37 (d, *J* = 6.7Hz, 3H), 0.97 (br. s., 2H), 0.82 - 0.86 (m, 2H), 0.77 (s, 2H), 0.63 (s, 2H). The peaks of -NH and -NH2 were not observed. LC–MS t_R = 1.30 min (>95%); m/z (ESI, +ve ion) 419.1 $(M+H)^+$.

3-(1-(1-Methyl-1H-imidazol-4-yl)ethyl)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (33). (Method B) Step-1: 8-Bromo-3-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (790 mg, 1.96 mmol, 84 % yield, yellow solid) was prepared analogous to compound **19**, *Step-3* using 8-bromo-3-((1-methyl-1*H*-imidazol-4-yl)ethyl)quinazoline-2,4(1*H*,3*H*)-dione (from Compound **24**, *Step-2*, 819 mg, 2.35 mmol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 1.56 g, 3.52 mmol), 1-methylcyclopropanamine hydrochloride (757 mg, 7.04 mmol) and DBU (1.05 mL, 7.04 mmol) and DMF (7.7 mL): *m/z* (ESI, +ve) 401.9/403.9 (1:1) $(M+H)^+$.

Step-2: 3-(1-(1-Methyl-1*H*-imidazol-4-yl)ethyl)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one. The title compound (471 mg, 1.03 mmol, 53.2 % yield, yellow solid) was prepared analogous to compound **10**, Step-5 using (*R*)-6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyrrolo[3,4-*b*]pyrrol-4(1*H*)-one (**9d,** 790 mg, 2.71 mmol), 8-bromo-3-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (779 mg, 1.94 mmol), potassium phosphate (1233 mg, 5.81 mmol) and XPhos-Pd-G2 (12.2 mg, 0.02 mmol) and 1,4-dioxane (9 mL)/water (3 mL): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.76 - 12.95 (m, 1H), 9.02 - 9.26 (m, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H), 7.67 (s, 1H), 7.25 (s, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.94 (s, 1H), 6.63 (br. s., 1H), 4.61 (m, *J* = 6.7 Hz, 1H), 3.64 (s, 3H), 1.62 - 1.73 (m, 3H), 1.46 - 1.54 (m, 3H), 1.28 - 1.41 (m, 3H), 0.75 - 0.99 (m, 4H). LC–MS t_R = 1.39 min (>95%); *m/z* (ESI, +ve) 458.0 $(M+H)^+$.

Isomer 1 and isomer 2 of 3-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (34 and 35). The above racemic mixture of 3-(1-(1-methyl-1*H*-imidazol-4-yl)ethyl)-8-((*R*)-6-methyl-4-oxo-1,4,5,6-tetrahydropyrrolo[3,4-*b*]pyrrol-2-yl)-2-((1-methylcyclopropyl)amino)quinazolin-4(3*H*)-one (463 mg) was purified by SFC for chiral separation (Chiralpak AS, 250 x 30 mm, 5 µm, 20% MeOH (containing 20 mM Ammonia)/CO_2, 120 mL/min, 227 bar) to obtain two isomers: **Isomer 1** (**34**, Peak 1, 150.6 mg, >98% ee, light-yellow solid) and **isomer 2** (**35**, Peak 2, 145.7 mg, >98% ee, light-yellow solid). **Isomer 1** (**34**): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.87 (br. s., 1H), 9.19 (br. s., 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 7.26 (s, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.63 (br. s., 1H), 4.62 (q, *J* = 6.4 Hz, 1H), 3.65 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.48 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H), 0.79 - 1.00 (m, 4H). LC–MS t_R = 1.38 min (>95%); *m/z* (ESI, +ve) 458.0 $(M+H)^+$. **Isomer 2 (35)**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.85 (br. s., 1H), 9.13 (br. s., 1H), 8.10 (d, *J* = 7.4 Hz, 1H),

7.84 (d, J = 7.6 Hz, 1H), 7.76 (br. s., 1H), 7.67 (br. s., 1H), 7.25 (s, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.63 (br. s., 1H), 4.62 (d, J = 6.5 Hz, 1H), 3.64 (s, 3H), 1.69 (d, J = 7.0 Hz, 3H), 1.51 (s, 3H), 1.36 (d, J = 6.3 Hz, 3H), 0.79 - 0.98 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.7, 162.0, 150.0, 144.1, 139.0, 138.1, 138.0, 136.5, 130.1, 125.3, 124.8, 122.6, 120.2, 120.0, 118.1, 100.1, 48.4, 44.4, 33.6, 30.4, 22.2, 21.1, 17.4, 14.8, 14.2**.** LC–MS t_R = 1.38 min (>95%); m/z (ESI, +ve) 458.0 $(M+H)^+$.

ASSOCIATED CONTENT

Supporting Information

Molecular formula strings (CVS) and statistical analysis of the associated biochemical data.

KINOMEscan data of Compound **28**.

Atomic coordinates and experimental data of Compound **28**/Pim-1 (PDB ID: 6MT0). The atomic coordinates will be released upon article publication.

AUTHOR INFORMATION

Corresponding Author

* E-mail: huiw@amgen.com. Phone: 805-447-4735.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing for financial interest.

ACKNOWLEDGMENT

We thank Wes Barnhart, Kyung Gahm, and Sam Thomas for chiral SFC separation of intermediates and final compounds; Chris Wilde for NMR studies.

ABBREVIATIONS

BAD, Bcl-2-associated death promoter; BM, bone marrow; CL, clearance; CPK, Corey–Pauling–Koltun; FBS, fetal bovine serum; HLM, human liver microsome; RLM, rat liver microsome; PBS, phosphate-buffered saline; Pim, proviral insertion site of moloney murine leukemia; PK, pharmacokinetic; POC, percent of control; PPB, plasma protein binding; QD, once a day; SAR, structure– activity relationship; SFC, supercritical fluid chromatograph.

REFERENCES

(1) Cuypers, H. T.; Selten, G.; Quint, W.; Zijlstra, M.; Maandag, E. R.; Boelens, W.; van Wezenbeek, P.; Melief, C.; Berns, A. Murine Leukemia Virus-Induced T-Cell Lymphomagenesis: Integration of Proviruses in a Distinct Chromosomal Region. *Cell* **1984**, *37*, 141–150.

(2) Nawijn, M. C.; Alendar, A.; Berns, A. For Better or for Worse: The Role of Pim Oncogenes in Tumorigenesis. *Nat. Rev. Cancer* **2011**, *11*, 23–34.

(3) Blanco-Aparicio, C.; Carnero, A. Pim Kinases in Cancer: Diagnostic, Prognostic and Treatment Opportunities. *Biochem. Pharmacol.* **2013**, *85,* 629–643.

(4) Lu, J.; Zavorotinskaya, T.; Dai, Y.; Niu, X. H.; Castillo, J.; Sim, J.; Yu, J.; Wang, Y.; Langowski, J. L.; Holash, J.; Shannon, K.; Garcia, P. D. Pim2 Is Required for Maintaining Multiple Myeloma Cell Growth Through Modulating TSC2 Phosphorylation. *Blood* **2013**, *122*, 1610–1620.

(5) van der Lugt, N. M.; Domen, J.; Verhoeven, E.; Linders, K.; van der Gulden, H.; Allen, J.; Berns, A. Proviral Tagging in E mu-myc Transgenic Mice Lacking the Pim-1 Proto-Oncogene Leads to Compensatory Activation of Pim-2. *EMBO J.* **1995**, *14*, 2536–2544.

(6) Brault, L.; Gasser, C.; Bracher, F.; Huber, K.; Knapp, S.; Schwaller, J. PIM Serine/Threonine Kinases in the Pathogenesis and Therapy of Hematologic Malignancies and Solid cancers. *Haematologica* **2010**, *95*, 1004–1015.

(7) Hiasa, M.; Teramachi, J.; Oda, A.; Amachi, R.; Harada, T.; Nakamura, S.; Miki, H.; Fujii, S.; Kagawa, K.; Watanabe, K.; Endo, I.; Kuroda, Y.; Yoneda, T.; Tsuji, D.; Nakao, M.; Tanaka, E.; Hamada, K.; Sano, S.; Itoh, K.; Matsumoto, T.; Abe, M. Pim-2 Kinase is an Important Target of Treatment for Tumor Progression and Bone Loss in Myeloma. *Leukemia* **2015**, *29*, 207–217.

(8) Paíno, T.; Garcia-Gomez, A.; González-Méndez, L.; San-Segundo, L.; Hernández-Garcia, S.; López-Iglesias, A.; Algarin, E. M.; Martin-Sánchez, M.; Corbacho, D.; Ortiz-de-Solorzano, C.; Corchete, L. A.; Gutiérrez, N. C.; Maetos, M.-V.; Garayoa, M.; Ocio, E. M. The Novel Pan-PIM Kinase Inhibitor, PIM447, Displays Dual Antimyeloma and Bone-Protective Effects, and Potently Synergizes with Current Standards of Care. *Clin. Cancer. Res.* **2017**, *23*, 225–238.

(8) Mikkers, H.; Allen, J.; Knipscheer, P.; Romeijn, L.; Hart, A.; Vink, E.; Berns, A. High Throughput Retroviral Tagging to Identify Components of Specific Signaling Pathways in Cancer. *Nat. Genet.* **2002**, *32*, 153–159.

(9) Le, B. T.; Kumarasiri, M.; Adams, J. R.; Yu, M.; Milne, R.; Sykes, M. J.; Wang, S. Targeting Pim Kinases for Cancer Treatment: Opportunities and Challenges. *Future Med. Chem.* **2015**, *7*, 35–53.

(10) Warfel, N. A.; Kraft, A. S. PIM Kinase (and Akt) Biology and Signaling in Tumors. *Pharmacol. Ther.* **2015**, *151*, 41–49.

(11) Arunesh, G. M.; Shanthi, E.; Krishna, M. H.; Sooriya Kumar, J.; Viswanadhan, V. N. Small Molecule Inhibitors of PIM1 Kinase: July 2009 to February 2013 Patent Update. *Expert Opin. Ther. Pat.* **2014**, *24*, 5–17.

(12) Burger, M. T.; Han, W.; Lan, J.; Nishiguchi, G.; Bellamacina, C.; Lindval, M.; Atallah, G.; Ding, Y.; Mathur, M.; McBride, C.; Beans, E. L.; Muller, K.; Tamez, V.; Zhang, Y.; Huh, K.; Feucht, P.; Zavorotinskaya, T.; Dai, Y.; Holash, J.; Castillo, J.; Langowski, J.;

Wang, Y.; Chen, M. Y.; Garcia, P. D. Structure Guided Optimization, in Vitro Activity, and in Vivo Activity of Pan-PIM Kinase Inhibitors. *ACS Med. Chem. Lett.* **2013**, *4*, 1193–1197.

(13) More, K. N.; Jang, H. W.; Hong, V. S.; Lee, J. Pim Kinase Inhibitory and Antiproliferative Activity of a Novel Series of Meridianin C Derivatives. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2424–2428.

(14) Ishchenko, A.; Zhang, L.; Le Brazidec, J.-Y.; Fan, J.; Chong, J. H.; Hingway, A.; Raditsis, A.; Singh, L.; Elenbaas, B.; Hong, V. S.; Marcotte, D.; Silvian, L.; Enyedy, I.; Chao, J. Structure-Based Design of Low-Nanomolar PIM Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 474–480.

(15) Xu, Y.; Brenning, B. G.; Kultgen, S. G.; Foulks, J. M.; Clifford, A.; Lai, S.; Chan, A.; Merx, S.; McCullar, M. V.; Kanner, S. B.; Ho, K.- K. Synthesis and Biological Evaluation of Pyrazolo[1,5-*a*]Pyrimidine Compounds as Potent and Selective Pim-1 Inhibitors. *ACS Med. Chem. Lett.* **2015**, *6*, 63–67.

(16) Fan, Y.-B.; Li, K.; Huang, M.; Cao, Y.; Li, Y.; Jin, S.-Y.; Liu, W.- B.; Wen, J.-C.; Liu, D.; Zhao, L.-X. Design and Synthesis of Substituted Pyrido[3,2-*d*]-1,2,3-Triazines as Potential Pim-1 Inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1224–1228.

(17) Nishiguchi, G. A.; Burger, M. T.; Han, W.; Lan, J.; Atallah, G.; Tamez, V.; Lindvall, M.; Bellamacina, C.; Garcia, P.; Feucht, P.; Zavorotinskaya, T.; Dai, Y.; Wong, K. Design, Synthesis and Structure Activity Relationship of Potent Pan-PIM Kinase Inhibitors Derived from the Pyridyl Carboxamide Scaffold. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2328–2332.

(18) Wang, X.; Kolesnikov, A.; Tay, S.; Chan, G.; Chao, Q.; Do, S.; Drummond, J.; Ebens, A. J.; Liu, N.; Ly, J.; Harstad, E.; Hu, H.; Moffat, J.; Munugalavadla, V.; Murray, J.; Slaga, D.; Tsui, V.; Volgraf, M.; Wallweber, H.; Chang, J. H. Discovery of 5-Azaindazole (GNE-955) as a Potent Pan-Pim Inhibitor with Optimized Bioavailability. *J. Med. Chem.* **2017**, *60*, 4458–4473.

(19) Cervantes-Gomez, F.; Chen, L. S.; Orlowski, R. Z.; Gandhi, V. Biological Effects of the Pim Kinase Inhibitor, SGI-1776, in Multiple Myeloma. Clin. *Lymphoma Myeloma Leuk.* **2013**, *13* (Suppl 2), S317– S329.

(20) Yang, Q.; Chen, L. S.; Neelapu, S. S.; Miranda, R. N.; Medeiros, L. J.; Gandhi, V. Transcription and Translation Are Primary Targets of Pim Kinase Inhibitor SGI-1776 in Mantle Cell Lymphoma. *Blood* **2012**, *120*, 3491–3500.

(21) Keeton, E. K.; McEachern, K.; Dillman, K. S.; Palakurthi, S.; Cao, Y.; Grondine, M. R.; Kaur, S.; Wang, S.; Chen, Y.; Wu, A.; Shen, M.; Gibbons, F. D.; Lamb, M. L.; Zheng, X.; Stone, R. M.; DeAngelo, D. J.; Platanias, L. C.; Dakin, L. A.; Chen, H.; Lyne, P. D.; Huszar, D. AZD1208, a Potent and Selective Pan-Pim Kinase Inhibitor, Demonstrates Efficacy in Preclinical Models of Acute Myeloid Leukemia. *Blood* **2014**, *123*, 905–913.

(22) Burger, M. T.; Nishiguchi, G.; Han, W.; Lan, J.; Simmons, R.; Atallah, G.; Ding, Y.; Tamez, V.; Zhang, Y.; Mathur, M.; Muller, K.; Bellamacina, C.; Lindvall, M. K.; Zang, R.; Huh, K.; Feucht, P.; Zavorotinskaya, T.; Dai, Y.; Basham, S.; Chan, J.; Ginn, E.; Aycinena, A.; Holash, J.; Castillo, J.; Langowski, J. L.; Wang, Y.; Chen, M. Y.; Lambert, A.; Fritsch, C.; Kauffmann, A.; Pfister, E.; Vanasse, K. G.; Garcia, P. D. Identification of *N*-(4-((1*R*,3*S*,5*S*)-3-Amino-5- Methylcyclohexyl)Pyridin-3-yl)-6-(2,6-Difluorophenyl)-5-Fluoropicolinamide (PIM447), a Potent and Selective Proviral Insertion Site of Moloney Murine Leukemia (PIM) 1, 2, and 3 Kinase Inhibitor in Clinical Trials for Hematological Malignancies. *J. Med. Chem.* **2015**, *58*, 8373–8386.

(23) Wu, B.; Wang, H.-L.; Cee, V. J.; Lanman, B. A.; Nixey, T.; Pettus, L.; Reed, A. B.; Wurz, R. P.; Guerrero, N.; Sastri, C.; Winston, J.; Lipford, J. R.; Lee, M. R.; Mohr, C.; Andrews, K. L.; Tasker, A. S. Discovery of 5-(1*H*-Indol-5-yl)-1,3,4-Thiadiazol-2-Amines as Potent PIM Inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 775−780.

(24) Wurz, R. P.; Pettus, L. H.; Jackson, C.; Wu, B.; Wang, H.-L.; Herberich, B.; Cee, V.; Lanman, B. A.; Reed, A. B.; Chavez, F.; Nixey, T.; Laszlo, J.; Wang, P.; Nguyen, Y.; Sastri, C.; Guerrero, N.; Winston, J.; Lipford, J. R.; Lee, M. R.; Andrews, K. L.; Mohr, C.; Xu, Y.; Zhou, Y.; Reid, D. L.; Tasker, A. S. The Discovery and Optimization of Aminooxadiazoles as Potent Pim Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 847−855.

(25) Wang, H.-L.; Cee, V. J.; Chavez, F.; Lanman, B. A.; Reed, A. B.; Wu, B.; Guerrero, N.; Lipford, J. R.; Sastri, C.; Winston, J.; Andrews, K. L.; Huang, X.; Lee, M. R.; Mohr, C.; Xu, Y.; Zhou, Y.; Tasker, A. S. The Discovery of Novel 3-(Pyrazin-2-yl)-1*H*-Indazoles as Potent Pan-Pim Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 834−840.

(26) Wurz, R. P.; Sastri, C.; D'Amico, D. C.; Herberich, B.; Jackson, C. L. M.; Pettus, L. H.; Tasker, A. S.; Wu, B.; Guerrero, N.; Lipford, J. R.; Winston, J. T.; Yang, Y.; Wang, P.; Nguyen, Y.; Andrews, K. L.; Huang, X.; Lee, M. R.; Mohr, C.; Reid, D. L.; Xu, Y.; Zhou, Y.; Wang, H.-L. Discovery of Imidazopyridazines as Potent Pim-1/2 Kinase Inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5580−5590.

(27) Cee, V. J.; Chavez, F., Jr.; Herberich, B.; Lanman, B. A.; Pettus, L. H.; Reed, A. B.; Wu, B.; Wurz, R. P.; Andrews, K. L.; Chen, J.; Hickman, D.; Laszlo, J., III; Lee, M. R.; Guerrero, N.; Mattson, B. K.; Nguyen, Y.; Mohr, C.; Rex, K.; Sastri, C. E.; Wang, P.; Wu, Q.; Wu, T.; Xu, Y.; Zhou, Y.; Winston, J. T.; Lipford, J. R.; Tasker, A. S.; Wang, H.-L. Discovery and Optimization of Macrocyclic Quinoxaline-Pyrrolodihydropiperidinones as Potent Pim-1/2 Kinase Inhibitors. *ACS Med. Chem. Lett.* **2016**, *7*, 408−412.

(28) Pettus, L. H.; Andrews, K. L.; Booker, S. K.; Chen, J.; Cee, V. J.; Chavez, F.; Chen, Y.; Eastwood, H.; Guerrero, N.; Herberich, B.; Hickman, D.; Lanman, B. A.; Laszlo, J.; Lee, M. R.; Lipford, J. R.; Mattson, B.; Mohr, C.; Nguyen, Y.; Norman, M. H.; Powers, D.; Reed, A. B.; Rex, K.; Sastri, C.; Tamayo, N.; Wang, P.; Winston, J. T.; Wu, B.; Wu, T.; Wurz, R. P.; Xu, Y.; Zhou, Y.; Tasker, A. S.; Wang, H.-L. Discovery and Optimization of Quinazolinone-Pyrrolopyrrolones as Potent and Orally Bioavailable Pan-Pim Kinase Inhibitors. *J. Med. Chem.* **2016**, *59*, 6407−6430.

(29) Barral, K.; Moorhouse, A. D.; and Moses, J. E. Efficient Conversion of Aromatic Amines into Azides: A One-Pot Synthesis of Triazole Linkages. *Org. Lett.* **2007**, *9*, 1809−1811.

(30) Zhang, W.; Mayer, J. P.; Hall, S. E.; Weigel, J. A. A Polymer-Bound Iminophosphorane Approach for the Synthesis of Quinazolines. *J. Comb. Chem.* **2001**, *3*, 255−256.

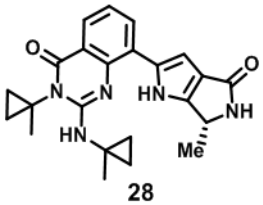
(31) Ohtsuki, T.; Yawata, Y.; Wada, H.; Sugihara, T.; Mori, M.; Namba, M. Two Human Myeloma Cell Lines, Amylase-Producing KMS-12-PE and Amylase-non-Nroducing KMS-12-BM, Were Established From a Patient, Having the Same Chromosome Marker, t(11;14)(q13;q32) *br J. Haematol.* **1989**, 73, 199− 204.

(32) Three biologically relevant gastrointestinal media: FaSSGF (fasted state simulated gastric fluid), FaSSIF (fasted state simulated intestinal fluid), and FeSSIF (fed state simulated intestinal fluid).

(33) Jain, N. and Yalkowsky, S. H. Estimation of the aqueous solubility I: Application to Organic Nonelectrolytes. *J. Pharm. Sci.* **2001**, *90*, 234-252.

(34) KINOMEscan data of **28** in Supporting Information. For kinase profiling protocols, please visit http://www.discoverx.com.

For Table of Contents Only



28

Pim-1 IC_{50} = 0.05 nM
Pim-2 IC_{50} = 0.05 nM
KMS-12 pBAD IC_{50} = 12 nM