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# Synthesis and biological evaluation of novel purinyl quinazolinone derivatives as PI3Kδ-specific inhibitors for the treatment of hematologic malignancies

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ABSTRACT

Phosphatidylinositol 3-kinases (PI3Ks) mediate intracellular signal transduction. Aberrant PI3K signaling is associated with oncogenesis and disease progression in solid tumors and hematologic malignancies. Idelalisib (**1**), a first-in-class PI3Kδ inhibitor for the treatment of hematologic malignancies, was developed, but its sales were limited by black box warnings due to unexpected adverse effects. Therefore, to overcome these adverse events, various quinazolinone derivatives were synthesized and evaluated *in vitro* based on their inhibitory activity against the PI3K enzyme and the viability of cell lines such as MOLT and SUDHL. Among them, **6f** ($IC_{50}$ = 0.39 nM) and **6m** ($IC_{50}$ = 0.09 nM) showed excellent enzyme activity, and **6m** displayed an approximately four-fold higher selectivity for PI3Kγ/δ compared with Idelalisib (**1**). Furthermore, *in vivo* PK experiments with 6f and **6m** revealed that **6f** ($AUC_{last}$ = 81.04 h*ng/mL, $C_{max}$ = 18.34 ng/mL, $T_{max}$ = 0.5 h, $t_{1/2}$ = 10.2 h in 1 mpk dose) had improved PK compared with **1**. Finally, further experiments will be conducted with **6f** selected as a candidate, and the potential for it to be developed as a treatment with good efficacy for hematologic malignancies will be determined.

## 1. Introduction

Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that catalyze the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) by phosphorylation and have been associated with an intracellular signaling pathway, including cell growth, proliferation, motility, survival, and intracellular trafficking [1–4]. The PI3K pathway is dysregulated in various cancers, and aberrant PI3K signaling is associated with oncogenesis and disease progression involving solid tumors and hematologic malignancies [5–10]. Therefore, PI3K inhibitors [11–14] are currently under investigation as potential cancer treatments. For example, pan-PI3K inhibitors [15–16] suppress all class I PI3K isoforms compared with isoform-selective PI3K inhibitors [17–22] and dual PI3K/mTOR inhibitors (Fig. 1) [23]. In addition, various PI3K inhibitors are still being studied and numerous clinical trials are in progress.[24–26]

Based on the catalytic and regulatory subunits, the class I PI3Ks family is divided into two categories.[20,27] Class IA PI3Ks are mainly activated by receptor tyrosine kinases (RTKs), which are heterodimeric enzymes and composed of an 85 $k_D$ regulatory subunit (p85) and a 110 $k_D$ catalytic subunit (p110α, p110β, p110δ[28]), whereas class IB PI3Ks, which are mainly activated by G-protein coupled receptors (GPCRs), include two different regulatory subunits (p101 or p87) and a single catalytic subunit (p110γ).[29] Among the catalytic subunits, p110α (PI3Kα) and p110β (PI3Kβ) are ubiquitous, whereas p110δ (PI3Kδ) and p110γ (PI3Kγ) are only expressed in leukocytes, neuroblastoma cells and hematopoietic cells, respectively. In particular, PI3Kδ regulates the signaling pathway to induce pathogenesis of CLL, rheumatoid arthritis, and allergic asthma mediated via B and T cells.[30–33]

Idelalisib (**1**),[34] a first-in-class PI3Kδ inhibitor for the treatment of

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hematologic malignancies such as chronic lymphocytic leukemia (CLL), and follicular lymphoma (FL), was approved by the United States Food and Drug Administration (FDA) in July 2014.[35] However, the U.S. prescribing information contains a black box warning for unexpected adverse effects, such as fatal and severe diarrhea or colitis, hepatotoxicity, pneumonitis, and intestinal perforation.[36–37] Nevertheless, **1** showed high response rates and extraordinary efficacy in patients with hematologic malignancies who were difficult to treat with conventional anticancer drugs[38] and demonstrated a tolerable safety profile in clinical trials.

To overcome these adverse effects of compound **1**, we developed a potent PI3Kδ inhibitor by specific structural modifications to lower the toxicity associated with enhanced PI3Kδ inhibition and expanded the target indications, such as *T*-ALL, which has yet to be treated with **1** (Fig. 2). These modifications including the substituent change of quinazolinone moiety at C-5 or 6 positions (region A) and alteration of chain (region B) into a hydrophobic pocket are mainly focused on developing potent PI3Kδ inhibitors since the purinyl group as the hinge binder and the phenyl group that affects the potency and selectivity across the PI3K class I family are key pharmacophores.[39]

## 2. Results and discussion

### 2.1. Pharmacological evaluation

#### 2.1.1. Cell viability and enzyme-based assays in vitro

Fifteen effective compounds were synthesized by structural modification of compound **1**. Among them, an *in vitro* kinase assay based on ATP site-dependent competitive binding of PI3Kδ was initially performed to select potent PI3Kδ inhibitors. The concentrations for half-maximal inhibition ($IC_{50}$) of each compound were calculated. As shown in Figure 3 and Table 1, the $IC_{50}$ values of the compounds were in the nanomolar (nM) range of 0.09–3.23. Among them, about half of the compounds (**6b**, **6f**, **6h**, **6i**, **6j**, **6m**, and **8a)** exhibited excellent efficiencies with sub-nanomolar functional potency when compared with the reference PI3Kδ inhibitor, **1**.

Cell viability was analyzed in two blood cancer cell lines such as SUDHL-5 and MOLT-4, to determine the anti-cancer effects of the compounds **6a-m** and **8a-c** (Fig. 3). Each compound showed a similar pattern in the two cell lines, but higher efficacy was detected in SUDHL-5, a DLBCL cell line that was used as a therapeutic target indication of **1**, while the efficacy was modest in MOLT-4, a *T*-ALL cell line. However, only compound **6m** showed the best anti-proliferative activity regardless of cell lines, which is consistent with results demonstrating the strongest PI3Kδ inhibitory effect. Specifically, the CelTiter-Glo assay showed a decrease in cell viability by approximately 14–20% after **6m** treatment of both cell lines, demonstrating that the anticancer effect of **6m** was approximately five-fold higher than **1** for SUDHL-5 as well as MOLT-4. In addition, we also found that several compounds, such as **6h** and **6j**, as well as **8c**, which showed excellent kinase activity, exhibit a stronger anticancer effect than **1**, although it was not completely consistent with their kinase efficacy. Taken together, these results demonstrated that most of the compounds showed enhanced efficacy *in vitro* compared with **1**. In particular, **6m** was identified as the strongest compound that inhibits the kinase activity of PI3Kδ, resulting in an anticancer effect of more than 80% *in vitro* in both DLBCL and *T*-ALL.

The four isoforms of the catalytic subunit of PI3K share the same domain composition, but PI3K α/β subunits are ubiquitously expressed, whereas PI3K δ/γ subunits are mainly restricted to the hematopoietic cell system. In particular, PI3Kδ and PI3Kγ are enriched in immune cells and regulate the development and function of innate and adaptive immunity. Recent reports[8,40] raise concerns about the risk of potential adverse effects such as autoimmune disease, a chronic inflammatory disorder, allergies, and immunodeficiency in the case of poor heterotropic specificity of inhibitors to pharmacological targets, due to the interaction between p110δ and p110γ. Therefore, appropriate isomeric selectivity (ratio of γ/δ) should be considered in developing small-molecule inhibitors of PI3Kδ. In addition, preceding studies showed that **1** has substantially higher selectivity for PI3Kδ than for PI3Kα and PI3Kβ, but not for PI3Kγ. Furthermore, Duvelisib, which demonstrated simultaneously inhibitory ability toward PI3Kδ and PI3Kγ, was introduced as a highly promising drug for the treatment of blood cancer and autoimmune diseases, but its drug development scenario was similar to that of **1** for almost similar reasons. The selectivity of this drug for PI3Kδ

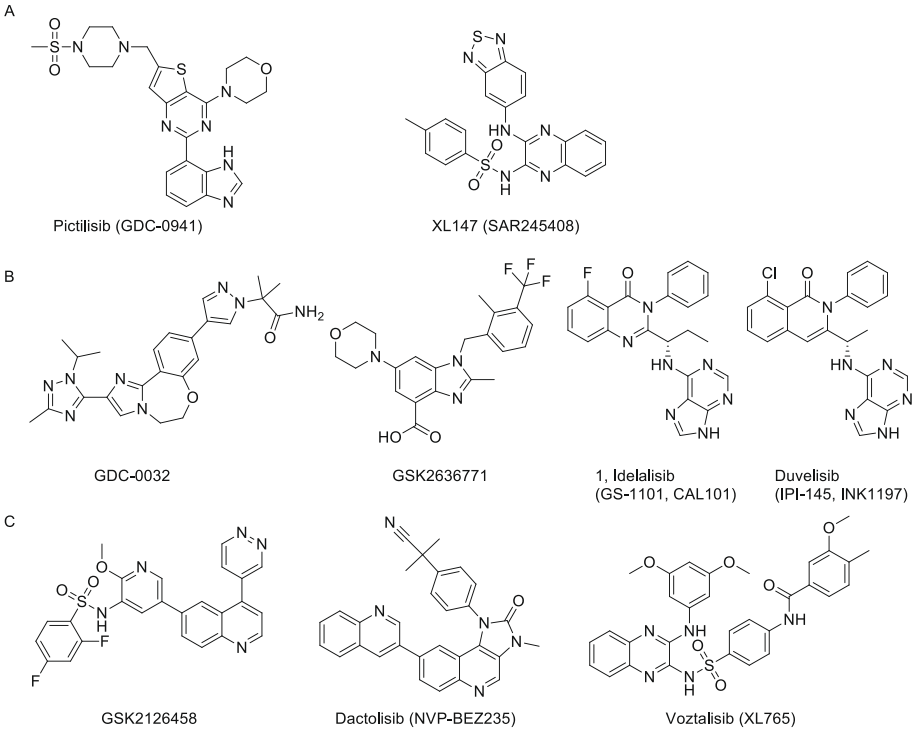



**Fig. 1.** Representative structures of PI3K inhibitors. (A) pan-PI3K inhibitors. (B) Isoform-selective PI3K inhibitors. (C) Dual PI3K/mTOR inhibitors.

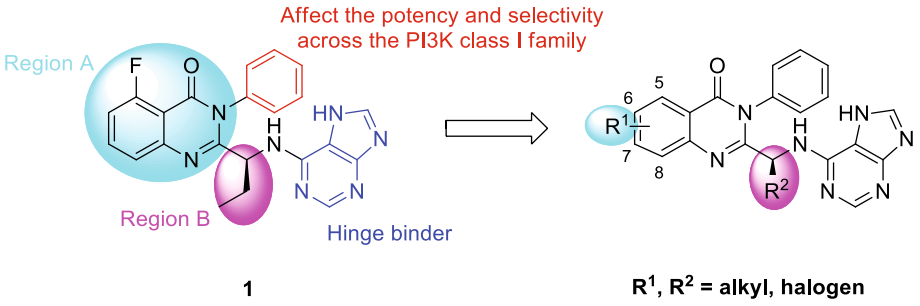
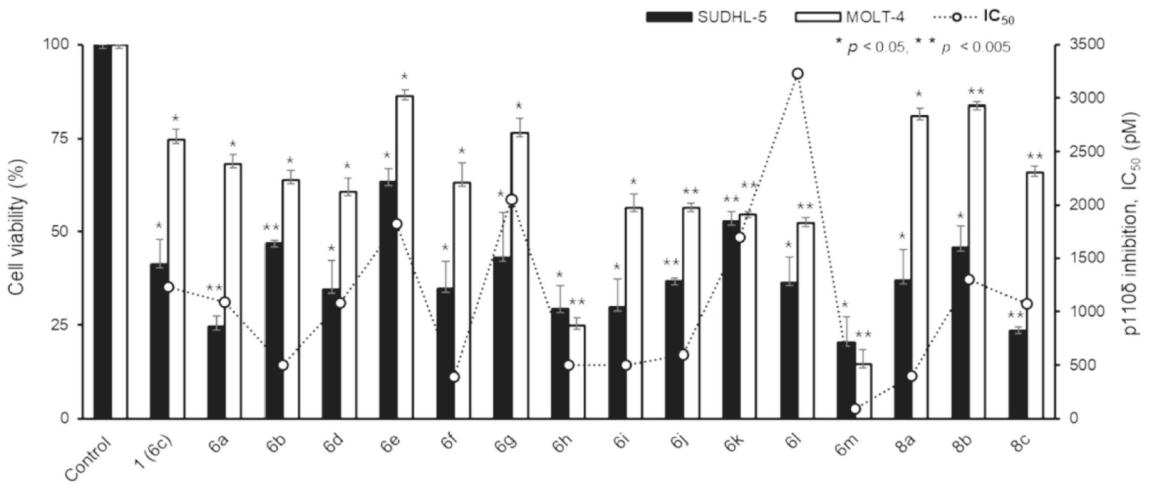



**Fig. 2.** Design of quinazolinone derivatives as PI3Kδ inhibitors based on **1**.




| | Control | 1(6c) | 6a | 6b | 6d | 6e | 6f | 6g | 6h | 6i | 6j | 6k | 6l | 6m | 8a | 8b | 8c |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SUDHL-5 | 100.00 | 41.34 ±6.61 | 24.45 ±2.92 | 46.09 ±0.71 | 34.42 ±7.85 | 63.35 ±3.50 | 34.79 ±7.17 | 43.00 ±12.21 | 29.31 ±6.21 | 29.74 ±7.54 | 36.67 ±0.88 | 52.84 ±2.63 | 36.40 ±6.75 | 20.24 ±6.93 | 36.91 ±8.23 | 45.81 ±5.78 | 23.52 ±0.82 |
| MOLT-4 | 100.00 | 74.57 ±2.93 | 68.11 ±2.64 | 63.72 ±2.69 | 60.68 ±3.75 | 86.19 ±1.66 | 63.15 ±5.35 | 76.49 ±4.01 | 24.73 ±2.23 | 56.42 ±3.75 | 56.46 ±1.20 | 54.69 ±0.69 | 52.23 ±1.55 | 14.59 ±3.71 | 80.94 ±2.26 | 83.63 ±1.08 | 65.81 ±1.83 |
| $IC_{50}$ (nM) | - | 1.08 | 1.09 | 0.5 | 1.08 | 1.82 | 0.39 | 2.05 | 0.5 | 0.5 | 0.6 | 1.7 | 3.23 | 0.09 | 0.4 | 1.3 | 1.07 |

**Fig. 3.** Anticancer activity of quinazolinone derivatives against two hematological malignant cell lines (SUDHL-5 and MOLT-4). The anti-proliferative activity of SUDHL-5 and MOLT-4 was measured by CellTiter-Glo Luminescent Cell Viability Assay, and a p110δ enzymatic inhibitory activity assay was conducted using the SelectScreen™ Biochemical Kinase Profiling Service. SUDHL-5 cell was treated with 10 μM of each compound and MOLT-4 cell was treated with 20 μM of each compound. Each $IC_{50}$ value is representative data.

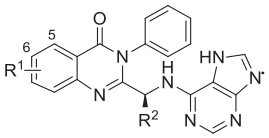
and PI3Kγ is poor compared with the inhibitory efficacy for PI3Kβ. Therefore, it is necessary to develop new drugs that can selectively inhibit PI3Kδ, at least, rather than **1**.

Table 1 shows the SAR of quinazolinone derivatives intended for the development of novel PI3Kδ-specific inhibitors with improved selectivity for PI3Kδ over **1**. As the size of the $R^1$ and $R^2$ groups increased, the activity and selectivity tended to improve (Table 1 and Fig. 4). Thus, due to the structure of their binding pocket, lipophilic $R^1$ and cyclic group $R^2$ were functionally better than hydrophilic and linear groups, respectively. Similarly, the longer the side chain $R^2$, the better the activity. However, its activity decreased sharply if the length of the side chain of $R^2$ exceeded four carbons, such as a butyl group. Therefore, it was appropriate for the side chain length of $R^2$ to remain within the butyl group. **6e** was the best in p110 γ/δ selectivity but was excluded because its affinity to p110δ was lower than **1** ($IC_{50}$ = 1.82 nM, γ/δ ratio = 171.97). Although poor in isomeric selectivity, generally **6m** showed remarkable inhibitory potency with an $IC_{50}$ value of 0.09 nM and selectivity to p110δ, and **6f** appeared to exhibit the second-highest potency with an $IC_{50}$ of 0.39 nM. Subsequently, when these two compounds, **6m,** and **6f**, were selected and the activity for various kinases was evaluated, it was confirmed that they have excellent PI3K selectivity, which means that the off-target effect on other kinases will be very low. Therefore, based on the inhibition results, **6f** and **6m** were ultimately selected and used for the following experiments including various kinases inhibitory activity (Supporting Table 1).

### 2.1.2. *Docking model*

The strong affinity of **6f** and **6m** for PI3Kδ was once again explained by the docking results, in which the purinyl group established hydrogen bonding with Glu826 and Val828 at a distance of 2.9 Å as the hinge binder, which was critical for the activity and stability of the PI3Kδ inhibitor (Fig. 4). In addition, docking analysis showed that the quinazolinone moiety forms a hydrophobic interaction with Ile777, Trp760, and Met752, and a water-mediated hydrogen bonding bridge with Asp911. The cyclopropyl and phenyl groups showed hydrophobic interaction with Met752, Met900, and Thr833 and electrostatic interaction with Asp832, Met900, and Thr833 in the hydrophobic pocket. These findings suggest that the activity and selectivity of PI3Kδ are increased by positioning a substituent of an appropriate size in the hydrophobic pocket due to competitive binding in the ATP-binding pocket for interaction

**Table 1**
PI3K isoform inhibitory activity for purinyl-quinazolinone derivatives **6a-6m**, **8a-8c**



| Comp. No. | $R_1$ | $R_2$ | $IC_{50}$ (nM)[a] | | | | Ratio (γ/δ) |
|---|---|---|---|---|---|---|---|
| | | | p110α | p110β | p110γ | p110δ | |
| **1 (6c)** | 5-F | Et | 409 | 613 | 27.4 | 1.08 | 25.37 |
| **6a** | 6-F | *c*Pr | 295 | 200 | 29.2 | 1.09 | 26.78 |
| **6b** | 5-F | Me | 152 | 145 | 15.3 | 0.50 | 30.60 |
| **6d** | 5-F | *n*Pr | 385 | 440 | 72.2 | 1.08 | 66.85 |
| **6e** | 5-F | *i*Pr | 878 | 1670 | 313.0 | 1.82 | 171.97 |
| **6f** | 5-F | *c*Pr | 222 | 199 | 19.1 | 0.39 | 48.97 |
| **6g** | 5-F | *c*Bu | 879 | 854 | 155 | 2.05 | 75.60 |
| **6h** | 5-Cl | *n*Pr | 301 | 129 | 18.3 | 0.50 | 36.60 |
| **6i** | 5-Cl | *i*Pr | 356 | 1040 | 62.5 | 0.50 | 125.00 |
| **6j** | 5-Cl | *c*Pr | 205 | 87.6 | 10.4 | 0.60 | 17.33 |
| **6k** | 5-Cl | *c*Bu | 490 | 470 | 63.8 | 1.70 | 37.52 |
| **6l** | 5-$CF_3$ | *n*Pr | 326 | >1000 | 56.3 | 3.23 | 17.43 |
| **6m** | 5-$CH_3$ | *c*Pr | 134 | 162 | 8.6 | 0.09 | 95.55 |
| **8a** | 5-$NH_2$ | Me | 127 | 250 | 7.5 | 0.40 | 18.75 |
| **8b** | 5-$NH_2$ | Et | 475 | 287 | 24.7 | 1.30 | 19.00 |
| **8c** | 5-$NH_2$ | *c*Pr | 369 | 562 | 24.7 | 1.07 | 23.08 |

[a] $IC_{50}$ values of enzyme activity have been taken as a mean from three independent experiments.

with amino acid residues outside the ATP-binding pocket (Fig. 5).

### 2.1.3. Cell-based in vitro study and tumor growth inhibition: A xenograft model

PI3K catalyzes the conversion of $PIP_2$ to $PIP_3$, which induces phosphorylation at Ser473 and Thr308 of AKT, leading to signaling cascades of downstream effectors. Activated AKT controls diverse cellular events such as cell proliferation, protein synthesis, and survival via mTORC1, which is upstream of 4EBP and S6. To investigate the effects of the primary screened compounds **6f** and **6m** on the signal transduction of PI3K, changes in the expression of key downstream factors were analyzed by western blot in SUDHL-5 and MOLT-4 after treatment with the compounds (Fig. 6A). Consistent with the inhibitory potency to PI3Kδ, treatment with **6f** and **6m** demonstrated dramatic inhibition of the expression of phospho-AKT at S473 and T308 compared to **1** in both cell lines. Also, the activation of its downstream targets, S6 and 4EBP1, was remarkably inhibited by treatment with **6f** and **6m**. Next, we evaluated the ability of **6f** and **6m** to induce apoptotic cell death.

As shown in Fig. 6B, the rate of cell death increased with the treatment using **6f** and **6m** in both early and late stages of apoptosis. Compared to **1**, the compounds **6f** and **6m** were substantially more powerful in inducing apoptosis of MOLT-4, while only **6m** was excellent in SUDHL-10. These results indicate that **6f** and **6m** are potent inhibitors of PI3Kδ and remarkably suppress signal transduction during cancer cell proliferation and survival. Subsequently, the antitumor activity of compounds **6f** and **6m** was evaluated *in vivo* using a xenograft model. To evaluate the antitumor effects of **6f** and **6m** in nude mice transplanted with MOLT-4, **6f** and **6m** including **1** were administered once a day and the variation in tumor mass was measured for 57 days. Oral administration to mice of 10 mg/kg of **6f** and **6m** led to a tumor growth inhibition rate (IR) of 55.1% for **6f** and 56.7% for **6m**, similar to reference substance **1**. It was also found that the three compounds do not induce body weight loss. In conclusion, **6f** and **6m** are effective in suppressing tumor growth in MOLT-4, although no significant improvement compared to **1** was detected in the xenograft model (Fig. 6C).

### 2.1.4. In vivo PK study

The pharmacokinetic profile was further evaluated to determine the pharmacological potential of **6f** and **6m** (Fig. 7). Treatment with an oral dose of 3 mg/kg of **6f** yielded an area under the curve ($AUC_{last}$) and $C_{max}$ of 255.00 h*ng/mL and 41.89 ng/mL, respectively. The median $T_{max}$ and $t_{1/2}$ were 1 h and 7.7 h, respectively. These values were improved overall compared to **1** under the same dose ($AUC_{last}$ = 201.88 h*ng/mL,

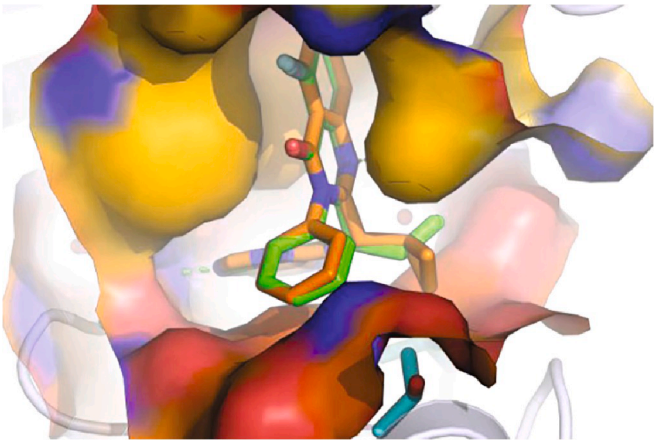


**Fig. 5.** Space-filling representation and structure overlay of **1** (green) and **6f** (orange) bound to PI3Kδ active site.

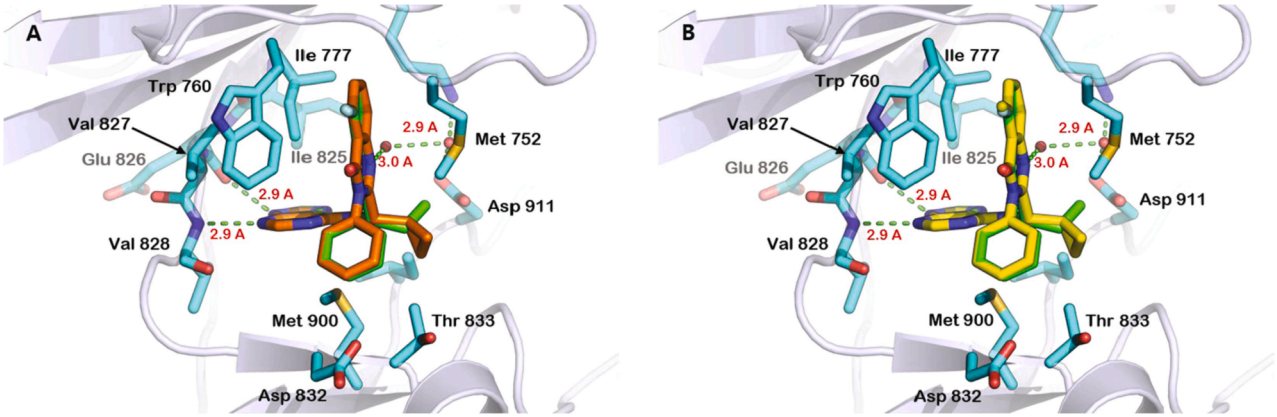



**Fig. 4.** Predicted binding modes of compounds **6f** (orange, Fig. 4A) and **6m** (yellow, Fig. 4B) with PI3Kδ [PDB code: 4XE0]. Compound **1** is shown in green. Hydrogen bonds are shown as green dashed lines. Key residues, as well as water molecules with the compounds, are indicated.

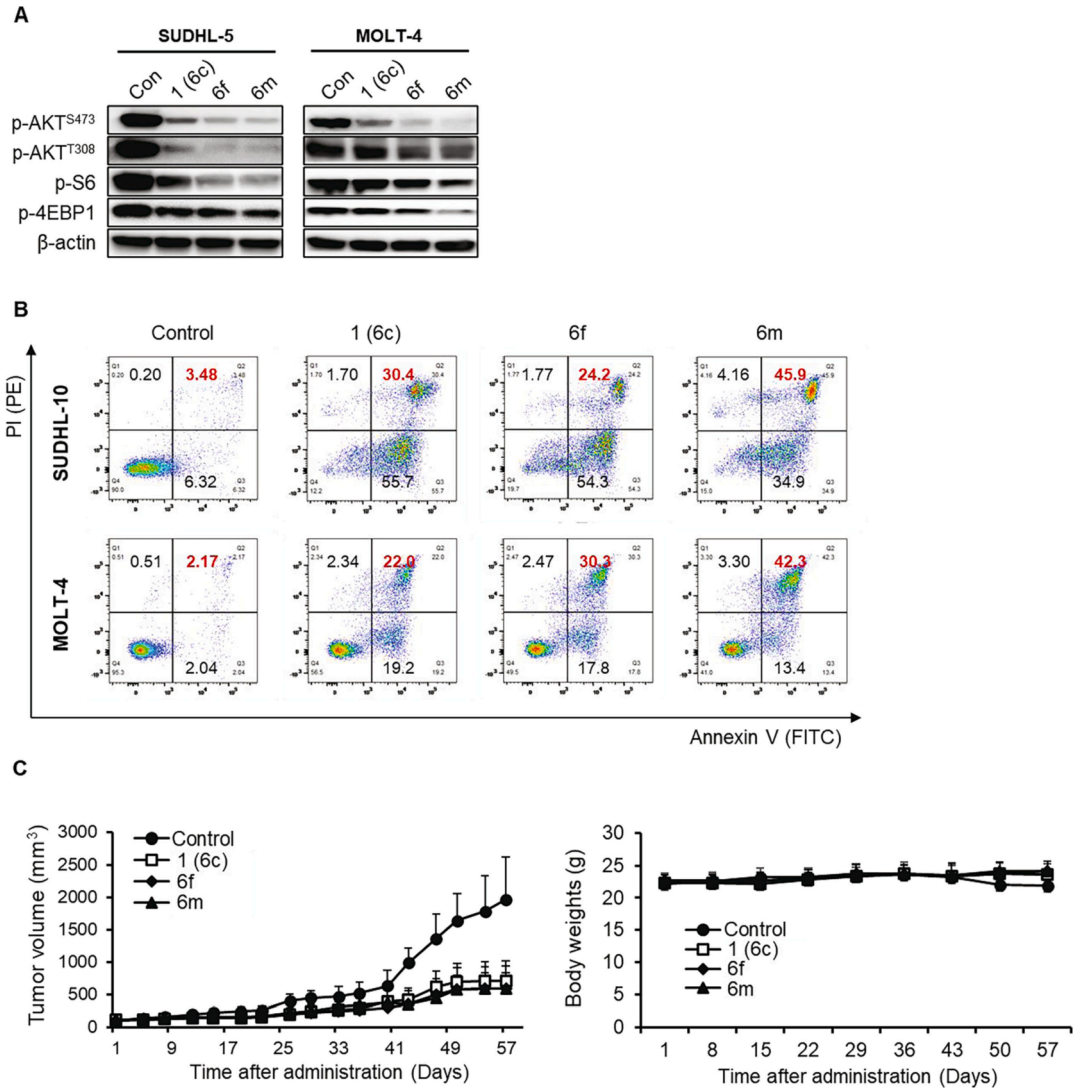



**Fig. 6.** Compounds **6f** and **6m** induce apoptosis-mediated cell death via inhibition of p-AKT activation and block tumor growth in the xenograft model. (**A**) SUDHL-5 and MOLT-4 cells were treated with 1 μM and 5 μM of each compound for 3 h, respectively. Western blot was performed to detect the phosphorylation levels of AKT S473/T308, S6, and 4EBP1. β-actin was used as a loading control. (**B**) Flow cytometry was performed to measure apoptosis with annexin-V/propidium iodide (PI) double staining. Cells were treated with 20 μM of each compound for 24 h, and then apoptotic cell death was measured. (**C**) In vivo antitumor efficacy in the MOLT-4 xenograft model. Tumor volume (TV) and changes in average body weight were measured after treatment with each compound at an oral dose of 10 mg/kg for 57 days.

$C_{max}$ = 53.02 ng/mL, $T_{max}$ = 0.5 h, $t_{1/2}$ = 2.7 h). In contrast to **6f**, and contrary to our expectations, the pharmacokinetic parameters of **6m** were very poor ($AUC_{last}$ = 37.24 h*ng/mL, $C_{max}$ = 11.06 ng/mL, $T_{max}$ = 0.5 h, $t_{1/2}$ = 8.3 h). Accordingly, the results indicate poor metabolic stability of **6m** compared with **6f**.

### 2.1.5. *Cytotoxicity*

Investigation of toxicity against normal cells is an important aspect to determine the safety profile of the drug molecule. Hence the potent compounds **6f** and **6m** including standard compound **1(6c)** were examined for their toxicity. To determine the potential cytotoxicity of these compounds (**6f** and **6m**), we carried out an MTT assay with an MRC-5 cell line. As shown in Table 2, none of the compounds showed a high level of cytotoxicity. These results implied that **6f** was an effective and safe drug candidate for the treatment of hematologic malignancies.

## 2.2. *Chemistry*

Quinazolinone derivatives **6a-m** (Table 1) were synthesized starting from commercially available anthranilic acids **2a-e** and amino acids **3a-f**, as shown in Scheme 1. Quinazolinone intermediate compounds **4a-m** were synthesized in one pot by reacting appropriate anthranilic acid **2** and the corresponding Boc-amino acid **3** with diphenyl phosphite and pyridine, followed by the addition of aniline. Boc-deprotection of **4** with trifluoroacetic acid (TFA) in dichloromethane yielded the primary amines **5**. Finally, the targeted derivatives **6a-m** were synthesized by reacting 6-chloropurine with amine **5** in the presence of trimethylamine (TEA) and *tert*-butanol (*t*-BuOH).[41,42]

Quinazolinone derivatives **8a-c** (Table 1) containing amine group on 5th position was synthesized starting from the appropriate fluoro compounds (Scheme 2). Nucleophilic attack of 4-methoxybenzylamine on the appropriate fluoro compound (**6b, 6c,** and **6f)** in the presence of TEA in ethanol (EtOH) yielded intermediate compound **7**. Deprotection of **7** with TFA in dichloromethane furnished the amino-quinazolinone **8**.[27]

## 3. Conclusion

In summary, we have discovered a series of potent and selective

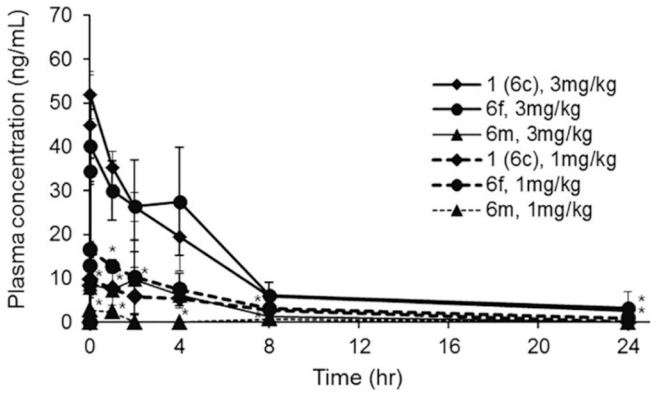
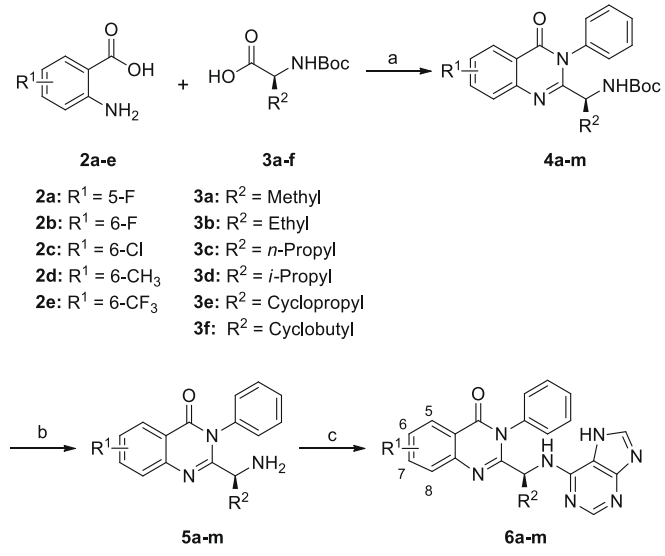



**Fig. 7.** Plasma concentration and pharmacokinetic parameters of compounds **6f** and **6m**. Plasma concentration versus time profile and pharmacokinetic parameters following treatment with 1 and 3 mg/kg **6f** and **6m** administered P. O. to Sprague-Dawley rats. Pharmacokinetic parameters include maximum concentration ($C_{max}$), an area under the concentration versus time curve ($AUC_{last}$), time of maximum concentration ($T_{max}$), and half-life ($t_{1/2}$). *$P < 0.05$ vs. control.*

**Table 2**
Cytotoxicity of **6f** and **6m** against MRC-5 cell line.

| Comp. No. | % of Inhibition 20 μM | $IC_{50}$ (μM) |
|---|---|---|
| **1 (6c)** | 18.41 ± 1.15 | >100 |
| **6f** | 3.93 ± 2.13 | >100 |
| **6m** | 23.12 ± 5.23 | 49.11 ± 3.23 |




**Scheme 1.** Reagents and conditions: (a) (i) diphenyl phosphite, pyridine, 50 °C; (ii) aniline, 55 °C; 1 N HCl, pH = 7 (2 steps); (b) $CF_3COOH$, $CH_2Cl_2$, rt; ammonia, pH = 8–12; (c) 6-chloropurine, TEA, *t*-BuOH, 80 °C.

quinazolinone PI3Kδ inhibitors. SAR studies revealed that fluoro or methyl substitution in the quinazolinone ring and hydrophobic cyclopropyl groups contributes to the potency and selectivity of PI3Kδ inhibition. Further studies were conducted with **6f** and **6m**, and both exhibited nanomolar enzymatic potencies against PI3Kδ. In addition, **6f** and **6m** exhibited target modulation in cancer cells in the western blotting analysis of SUDHL-5 and MOLT-4 cell lines and therefore increased cell apoptosis. In particular, **6m** displayed high selectivity for the enzyme PI3Kδ and enhanced efficacy for cell viability; however, the PK results were poor compared to **1**. Compound **6f** demonstrated antitumor efficacies in xenograft models, in which PI3K pathways were adequately inhibited as indicated by the reduction of p-AKT, p-S6, and p-4EBP1 in tumor tissues. Hence, compound **6f** was selected as a preclinical candidate, and future communications will detail additional evaluation of this compound.

## 4. Material and methods

### 4.1. Biological method

#### 4.1.1. Cell viability assay

Cell viability was analyzed according to the manufacturer's instructions using CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison MI, USA). Cells were seeded into 96-well plates at a density of $5x10^4$ cells in a 100 μL culture medium. CellTiter-Glo reagent was added at a 1:1 vol ratio. After mixing the contents for 2 min on a shaker to induce cell lysis, the plates were incubated for 10 min at room temperature, and then the luminescence signal was read on a plate reader (BioTek Instruments, Inc., Winooski, VT, USA). Luminescence readings were background-subtracted and normalized to control wells.

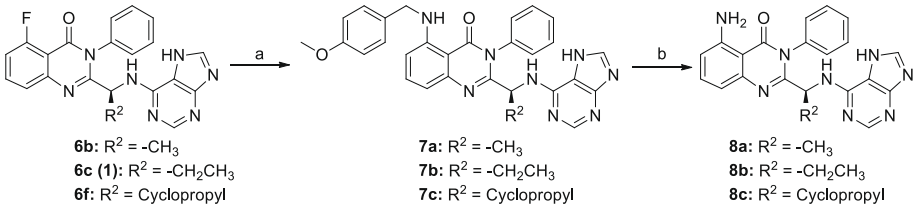
#### 4.1.2. Biochemical kinase assay

The enzymatic inhibitor activity assay was performed by SelectScreen™ Biochemical Kinase Profiling Service (SSBK; Thermo Fisher Scientific) according to the manufacturer's instructions. The $IC_{50}$ value of the compound was determined by 10-point titration with 1 μM final concentration of the compound in an ATP-competitive binding experimental manner. For the kinase reaction, the kinase reaction buffer (30 mM HEPES, 4X ATP solution, 2x substrate/kinase mixture) was added to the wells and then incubated for 60 min. A detection solution consisting of europium labeled anti-ADP antibody, Alexa Fluor™ 647 labeled ADP tracer and EDTA (to stop the kinase reaction) was added to the assay well. $IC_{50}$ values were determined by calculating the release rate of ADP formation from the analytical well. The emission ratio was calculated by dividing the intensity of the tracer (receptor) emission by the intensity of the Eu (donor) emission at 615 nm, as shown in the equation below.

Emission Ratio = AlexaFluor647 Emission (665 nm)/Europium Emission (615 nm)

#### 4.1.3. Western blot assay

Cells were collected and washed twice with cold PBS, and then proteins were obtained with cell lysis buffer (CST, Danvers, MA, USA). The proteins were separated by 10–12% SDS-polyacrylamide gel




**Scheme 2.** Reagents and conditions: (a) 4-methoxybenzylamine, TEA, EtOH, 180 °C; (b) $CF_3COOH$, $CH_2Cl_2$, rt; ammonia, pH = 7.

electrophoresis and then transferred onto PVDF membranes (Millipore, Burlington, MA, USA). The antibodies used for Western blot were as follows: p-AKT S473 (CST; 9271), p-AKT T308 (CST; 9275), p-S6 (CST; 5364), p-4E-BP1 (CST; 9451), and β-actin (CST; 3700). The analysis was performed with Peroxidase-AffiniPure Goat Anti-Rabbit (Jackson ImmunoResearch; 111-035-003) or Horse Anti-Mouse (CST; 7076) IgG antibodies, using the ECL western blotting detection system from GE Healthcare Amersham™ (GE Healthcare, Chalfont St. Giles, UK).

#### 4.1.4. Cell apoptosis analysis by flow cytometry

Apoptosis analysis was performed according to the manufacturer's recommended procedures using the Annexin V-FITC/PI apoptosis detection kit (BD Biosciences, Franklin Lakes, NJ, USA). Cells were seeded into 6-well plates and incubated with the compounds for 24 h. The cells were then washed with cold PBS and stained with Annexin V-FITC and PI for 15 min at room temperature. Apoptotic cells were analyzed using a flow cytometer (BD FACSCalibur, Franklin Lakes, NJ, USA).

#### 4.1.5. Animal tumor experiments (Xenograft model and survival rate)

All animal experiments were performed by Biotoxtech (Biotoxtech co. ltd, Cheongju, South Korea) according to relevant ethical regulations. For xenograft studies, MOLT-4 cells were harvested and $2 \times 10^6$ cells in 0.1 mL of D-PBS were implanted subcutaneously on the back of BALB/c-nude mice. After tumor growth, mice were treated daily with Idelalisib **1**, **6f,** and **6m** at 10 mg/kg by oral gavage for 57 consecutive days. Tumor growth was monitored by a caliper (CD-15CX, Mitutoyo, Japan), and tumor volume was calculated according to the formula of ½ × length × width. To evaluate survival results, BALB/c hematological malignancies mice were administered intravenously with Daudi cells. The test group was divided into 3 groups with 15 animals each, with negative control (0 mg/kg), a test substance group (8 mg/kg), and a comparative group. The compounds were administered orally in a dose of 8 mg/kg for 56 days in the test substance groups. During the observation period, clinical signs were observed once daily. The body weight was measured once a week.

#### 4.1.6. PK study

The pharmacokinetics were performed by ChemOn Inc. (ChemOn Inc., Suwon, South Korea) according to relevant ethical regulations. Sprague-Dawley rats were used in PK studies of Idelalisib **1**, **6f,** and **6m**, and these compounds were administered once a day to three mice per group at 1 and 3 mg/kg. The time points for blood samples collected were 0.25, 0.5, 1, 2, 4, 8, and 24 h after oral administration. After centrifugation, plasma samples were extracted and analyzed by LC-MS/MS. The PK parameters were calculated with PhoenixTM WinNonlin® software Ver. 6.2. (Pharsight Corporation, Mountain View, USA).

#### 4.1.7. MTT assay

Cytotoxicity was determined using an MTT assay. MRC-5 cells were purchased from Korea Cell Line Bank. The cells were plated in 96-well culture plates and seeded with $2 \times 10^6$ cells/mL (cells/well density). Next, the cells were treated with 100 μL/well of the compound and 1% FBS EMEM and incubated for 48 h at 37 °C in a $CO_2$ incubator. Further, at respective time points, 150 μL/well of culture media contained 10 times MTT solution (10:1 vol ratio) was added into each well, and cells were incubated in a $CO_2$ incubator for 3 h at 37 °C. The medium was removed and Formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved using 100 μL of DMSO followed by transfer in new 96 well plate. The absorbance was read at 540 nm using 630 nm as a reference wavelength on an ELISA reader.

### 4.2. Chemistry

Commercially available reagents were used without additional purification unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen. Nuclear magnetic resonance spectra ($^1$H and $^{13}$C NMR) were recorded on a Bruker Unit 400 (400 MHz for $^1$H and 100 MHz for $^{13}$C) and Unity Inova (500 MHz for $^1$H and 125 MHz for $^{13}$C) instrument with $CDCl_3$, $CD_3OD$, and DMSO-$d_6$ as a solvent and residual $CHCl_3$ ($\delta$ 7.26 ppm), $CH_3OH$ ($\delta$ 3.31 ppm), and DMSO ($\delta$ 2.50 ppm) as an internal standard for $^1$H and $CDCl_3$ ($\delta$ 77.0 ppm), $CD_3OD$ ($\delta$ 49.0 ppm), and DMSO-$d_6$ ($\delta$ 39.5 ppm) as an internal standard for $^{13}$C. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation brs is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a JASCO FT/IR-4600 and reported as cm-1. Optical rotations were measured with a JASCO P1020 polarimetry or JASCO P2000 polarimetry and are reported as $[\alpha]_D^t$ (concentration g/100 mL, solvent). The melting point was recorded on an Electrothermal IA9300 or Mettler Toledo MP90 and reported as °C. Thin-layer chromatography was carried out using plates coated with Kieselgel 60F254 (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. Low-resolution mass spectra (LRMS) were recorded on an SQ Detector 2 mass spectrometer. XBridge®-C18 column (250 × 4.6 mm) was used as the stationary phase. High-Performance Liquid Chromatography (HPLC) was recorded on a waters 2695 separations module/2996 PDA detector with acetonitrile and water as eluent and a detection wavelength of 254 nm.

#### 4.2.1. General procedure a for the preparation of compounds 4a-m.

Diphenyl phosphite (1.65 eq. or 5 eq) was added to a stirred solution of the corresponding anthranilic acid **2** (1 eq.) and appropriate Boc-amino acid **3** (1.2 eq.) in pyridine (6 vol) at room temperature under $N_2$ gas. The reaction mixture was heated to 40–45 °C and stirred for 4–18 h (in case of using 1.65 eq diphenyl phosphite) or 2–5 h (in using 5 eq diphenyl phosphite). And then, aniline (1.4 eq.) was added to the reaction mixture and the resulting reaction mixture was heated to 55 °C for 5–16 h (in case of using 1.65 eq diphenyl phosphite) or 2–4 h (in case of using 5 eq diphenyl phosphite). The completion of the reaction was monitored by TLC on silica (Hexane-EtOAc = 4:1). The mixture was cooled to room temperature, quenched with water, and then extracted with EtOAc (2x times). The combined organic extracts were washed with 1 N HCl solution (to remove pyridine and aniline) and brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was subjected to flash silica gel (230–400 mesh) column chromatography (Hexane-EtOAc gradient) to afford the title compounds.

*4.2.1.1. (S)-tert-Butyl (cyclopropyl(6-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)methyl)carbamate **(4a)**.*. Synthesized from general procedure A using compound **2a** and **3e** under diphenyl phosphite (1.65 eq). 22% yield of the product as light ivory solid; mp 75.6–78 °C; $[\alpha]_D^{20}$ −35.2886(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.90 (dd, $J$ = 8.4 Hz, 2.8 Hz, 1H), 7.74–7.71 (m, 1H), 7.60–7.46 (m, 4H), 7.39 (d, $J$ = 7.6 Hz, 1H), 7.32 (d, $J$ = 7.6 Hz, 1H), 5.54 (d, $J$ = 7.6 Hz, 1H), 4.24–4.20 (m, 1H), 1.41 (s, 9H), 1.12–1.10 (m, 1H), 0.41–0.38 (m, 2H), 0.28–0.22 (m, 1H), 0.07–0.02 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.55 (d, $J_{C\text{-}F}$ = 3.1 Hz), 161.00 (d, $J_{C\text{-}F}$ = 247 Hz), 156.28, 155.00, 143.91 (d, $J_{C\text{-}F}$ = 1.9 Hz), 135.93, 130.22, 129.60, 129.53 (d, $J_{C\text{-}F}$ = 28.9 Hz), 129.33, 128.50, 123.06 (d, $J_{C\text{-}F}$ = 23.9 Hz), 122.28 (d, $J_{C\text{-}F}$ = 8.4 Hz), 111.96 (d, $J_{C\text{-}F}$ = 23.5 Hz), 79.68, 53.60, 28.31, 15.23, 3.49, 2.46; IR (neat) 3343, 2977, 1681, 1604, 1590, 1482, 1364, 1336, 1273, 1228, 1159, 1067, 1021, 948, 886, 833, 748, 697 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{25}FN_3O_3$ $[M + H]^+$ 410.18, found 409.93.

*4.2.1.2. (S)-tert-Butyl (1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)carbamate **(4b)**.* Synthesized from general procedure A using compound **2b** and **3a** under diphenyl phosphite (1.65 eq). 20% yield of the product as feather-like white solid; mp 158.6–163.9 °C; $[\alpha]_D^{21.8}$ −39.9600(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.72–7.66

(m, 1H), 7.62–7.50 (m, 4H), 7.39–7.37 (m, 1H), 7.29–7.28 (m, 1H), 7.14–7.09 (m, 1H), 5.60 (d, $J = 7.6$ Hz, 1H), 4.54–4.50 (m, 1H), 1.40 (s, 9H), 1.25 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.49 (d, $J_{C\text{-}F} = 265.1$ Hz), 159.15 (d, $J_{C\text{-}F} = 4.3$ Hz), 154.82, 149.19, 135.51, 134.92 (d, $J_{C\text{-}F} = 10.3$ Hz), 130.39, 129.69, 129.60, 128.95, 128.90, 128.58, 123.07 (d, $J_{C\text{-}F} = 4.2$ Hz), 113.55 (d, $J_{C\text{-}F} = 20.6$ Hz), 110.79 (d, $J_{C\text{-}F} = 5.7$ Hz), 79.77, 47.85, 28.37, 20.68; IR (neat) 3315, 2977, 1705, 1681, 1610, 1590, 1524, 1473, 1364, 1294, 1238, 1170, 1071, 1018, 864, 820, 765, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{21}H_{22}FN_3O_3$ $[M + H]^+$ 384.16, found 383.88.

*4.2.1.3. (S)-tert-Butyl (1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)butyl)carbamate (**4d**).* Synthesized from general procedure A using compound **2b** and **3c** under diphenyl phosphite (1.65 eq). 38% yield of the product as a white solid; mp 113.8–117 °C; $[\alpha]_D^{20}$ −47.6933 (c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.71–7.66 (m, 1H), 7.62–7.48 (m, 4H), 7.40 (d, $J = 7.2$ Hz, 1H), 7.29 (s, 1H), 7.13–7.08 (m, 1H), 5.42 (d, $J = 8.8$ Hz, 1H), 4.51–4.47 (m, 1H), 1.60–1.58 (m, 1H), 1.52–1.46 (m, 1H), 1.42 (s, 9H), 1.27–1.25 (m, 1H), 1.15–1.08 (m, 1H), 0.62 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.45 (d, $J_{C\text{-}F} = 265.5$ Hz), 159.15 (d, $J_{C\text{-}F} = 4.2$ Hz), 158.69, 155.33, 149.18, 135.43, 134.82 (d, $J_{C\text{-}F} = 10.6$ Hz), 130.32, 129.59, 129.41, 129.01, 128.57, 123.04 (d, $J_{C\text{-}F} = 2.8$ Hz), 113.42 (d, $J_{C\text{-}F} = 20.9$ Hz), 110.74 (d, $J_{C\text{-}F} = 5.3$ Hz), 79.63, 51.19, 36.77, 28.32, 18.55, 13.11; IR (neat) 3394, 3052, 2977, 2963, 2876, 1768, 1694, 1608, 1589, 1473, 1294, 1244, 1163, 1037, 817, 736, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{26}FN_3O_3$ $[M + H]^+$ 412.20, found 412.22.

*4.2.1.4. (S)-tert-Butyl (1-(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-2-methylpropyl)carbamate (**4e**).* Synthesized from general procedure A using compound **2b** and **3d** under diphenyl phosphite (1.65 eq). 32% yield of the product as a white solid; mp 78–80.2 °C; $[\alpha]_D^{20}$ −55.2933 (c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.70 (m, 1H), 7.60–7.48 (m, 4H), 7.34–7.28 (m, 2H), 7.09 (t, $J = 9.2$ Hz, 1H), 5.43 (d, $J = 9.6$ Hz, 1H), 4.41–4.38 (m, 1H), 2.05–1.98 (m, 1H), 1.43 (s, 9H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.71 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.25 (d, $J_{C\text{-}F} = 265.2$ Hz), 158.98 (d, $J_{C\text{-}F} = 4.2$ Hz), 157.64, 155.15, 148.84, 135.37, 134.71 (d, $J_{C\text{-}F} = 10.3$ Hz), 130.08, 129.39, 129.18, 128.42, 123.00 (d, $J_{C\text{-}F} = 3.6$ Hz), 113.32 (d, $J_{C\text{-}F} = 20.5$ Hz), 110.56 (d, $J_{C\text{-}F} = 5.7$ Hz), 79.39, 56.05, 32.11, 28.16, 19.89, 16.28; IR (neat) 3771, 3525, 2979, 2964, 2874, 1698, 1590, 1474, 1391, 1294, 1244, 1168, 1038, 818, 776, 735, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{26}FN_3O_3$ $[M + H]^+$ 412.20, found 412.35.

*4.2.1.5. (S)-tert-Butyl (cyclopropyl(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)methyl)carbamate (**4f**).* Synthesized from general procedure A using compound **2b** and **3e** under diphenyl phosphite (1.65 eq). 31% yield of the product as a white solid; mp 76.3–78.8 °C; $[\alpha]_D^{16.8}$ −36.7400 (c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.72–7.76 (m, 1H), 7.59–7.50 (m, 4H), 7.39–7.37 (m, 1H), 7.33–7.32 (m, 1H), 7.11 (t, $J = 9.2$ Hz, 1H), 5.54 (d, $J = 8$ Hz, 1H), 4.22–4.18 (m, 1H), 1.41 (s, 9H), 1.11–1.10 (m, 1H), 0.42–0.38 (m, 2H), 0.29–0.24 (m, 1H), 0.07–0.03 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.48 (d, $J_{C\text{-}F} = 265.3$ Hz), 159.17 (d, $J_{C\text{-}F} = 4.5$ Hz), 157.97, 154.97, 149.23, 135.59, 134.82 (d, $J_{C\text{-}F} = 10$ Hz), 130.15, 129.62, 129.60, 129.22, 128.61, 123.11 (d, $J_{C\text{-}F} = 3.4$ Hz), 113.46 (d, $J_{C\text{-}F} = 20.9$ Hz), 110.79 (d, $J_{C\text{-}F} = 5.7$ Hz), 79.70, 53.66, 28.30, 15.13, 3.52, 2.43; IR (neat) 3389, 2975, 1690, 1618, 1605, 1587, 1491, 1472, 1390, 1364, 1320, 1230, 1159, 1037, 882, 816, 763, 696 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{24}FN_3O_3$ $[M + H]^+$ 410.18, found 409.99.

*4.2.1.6. (S)-tert-Butyl (cyclobutyl(5-fluoro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)methyl)carbamate (**4g**).* Synthesized from general procedure A using compound **2b** and **3f** under diphenyl phosphite (5 eq). 80% yield of the product as a colorless liquid; $[\alpha]_D^{20}$ −64.9000(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.67 (td, $J = 8$ Hz, 5.2 Hz, 1H), 7.59–7.47 (m, 4H) 7.34–7.29 (m, 2H), 7.12–7.07 (m, 1H), 5.46 (d, $J = 8.8$ Hz, 1H), 4.53–4.49 (m, 1H), 2.71–2.62 (m, 1H), 1.88–1.64 (m, 6H), 1.42 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.43 (d, $J_{C\text{-}F} = 265.2$ Hz), 159.15 (d, $J_{C\text{-}F} = 4.4$ Hz), 157.21, 155.16, 149.09, 135.45, 134.80 (d, $J_{C\text{-}F} = 9.9$ Hz), 130.23, 129.60, 129.34, 129.15, 128.61, 123.13 (d, $J_{C\text{-}F} = 3.6$ Hz), 113.44 (d, $J_{C\text{-}F} = 20.6$ Hz), 110.72 (d, $J_{C\text{-}F} = 5.6$ Hz), 79.65, 54.03, 39.01, 28.29, 24.60, 23.41, 17.80; IR (neat) 3416, 3061, 2974, 2867, 1693, 1618, 1589, 1491, 1473, 1365, 1320, 1294, 1232, 1163, 1038, 869, 818, 736, 698 cm$^{-1}$; LCMS (ESI) *m/z* calculated for $C_{24}H_{26}FN_3O_3$ $[M + H]^+$ 424.20, found 424.20.

*4.2.1.7. (S)-tert-Butyl (1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)butyl)carbamate (**4h**).* Synthesized from general procedure A using compound **2c** and **3c** under diphenyl phosphite (1.65 eq). 45% yield of the product as pale yellow solid; mp 187.6–188.8 °C; $[\alpha]_D^{20}$ −45.7533(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.61–7.51 (m, 5H), 7.46 (t, $J = 4.8$ Hz, 1H), 7.40 (d, $J = 7.2$ Hz, 1H), 7.28 (d, $J = 7.2$ Hz, 1H), 5.41 (d, $J = 8.8$ Hz, 1H), 4.50–4.45 (m, 1H), 1.61–1.56 (m, 1H), 1.52–1.45 (m, 1H), 1.29–1.25 (m, 1H), 1.14–1.09 (m, 1H), 0.63 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.28, 158.33, 155.32, 149.61, 135.67, 134.58, 133.84, 130.32, 129.59, 129.55, 129.42, 129.01, 128.55, 126.47, 118.18, 79.62, 51.23, 36.69, 28.32, 18.53, 13.11; IR (neat) 3383, 3053, 2982, 2877, 1693, 1613, 1588, 1552, 1493, 1455, 1392, 1266, 1174, 951, 813, 743, 703 cm$^{-1}$; LCMS (ESI) *m/z* calculated for $C_{23}H_{26}ClN_3O_3$ $[M + H]^+$ 428.17, found 428.35.

*4.2.1.8. (S)-tert-Butyl (1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-2-methylpropyl)carbamate (**4i**).* Synthesized from general procedure A using compound **2c** and **3d** under diphenyl phosphite (1.65 eq). 37% yield of the product as light yellow solid; mp 55.7 °C; $[\alpha]_D^{20}$ −12.9000(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, $J = 8$ Hz, 1H), 7.88 (d, $J = 7.5$ Hz, 1H), 7.60–7.50 (m, 3H), 7.36–7.23 (m, 3H), 5.36 (d, $J = 9.5$ Hz, 1H), 4.43–4.40 (m, 1H), 2.03–1.98 (m, 1H), 1.42 (s, 9H), 0.84 (d, $J = 6.5$ Hz, 3H), 0.72 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 160.32, 157.48, 155.29, 149.43, 135.71, 134.58, 133.84, 130.26, 129.67, 129.52, 129.31, 129.27, 128.54, 126.58, 118.20, 79.60, 56.19, 32.23, 28.30, 20.02, 16.38; IR (neat) 3429, 3312, 2965, 2926, 1690, 1587, 1490, 1455, 1365, 1276, 1161, 947, 814, 697 cm$^{-1}$; LCMS (ESI) *m/z* calculated for $C_{23}H_{26}ClN_3O_3$ $[M + H]^+$ 428.17, found 428.28.

*4.2.1.9. (S)-tert-Butyl ((5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate (**4j**).* Synthesized from general procedure A using compound **2c** and **3e** under diphenyl phosphite (5 eq). 77% yield of the product as a white solid; mp 168.5 °C; $[\alpha]_D^{20}$ −248.6667(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.63–7.60 (m, 2H), 7.59–7.48 (m, 3H), 7.46 (dd, $J = 6.5$ Hz, 3 Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 7$ Hz, 1H), 5.53 (d, $J = 7.5$ Hz, 1H), 4.20–4.17 (m, 1H), 1.41 (s, 9H), 1.10–1.19 (m, 1H), 0.41–0.38 (m, 2H), 0.28–0.24 (m, 1H), 0.07–0.04 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 160.31, 157.61, 154.96, 149.63, 135.78, 134.59, 133.85, 130.15, 129.63, 129.57, 129.23, 128.57, 126.51, 118.19, 79.70, 53.66, 28.29, 15.05, 3.52, 2.41; IR (neat) 3728, 3704, 3622, 3595, 3385, 3055, 2975, 2931, 1693, 1610, 1587, 1491, 1455, 1365, 1165, 960, 813, 780, 737, 701 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{24}ClN_3O_3$ $[M + H]^+$ 426.16, found 426.22.

*4.2.1.10. (S)-tert-Butyl ((5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)(cyclobutyl)methyl)carbamate (**4k**).* Synthesized from general procedure A using compound **2c** and **3f** under diphenyl phosphite (5 eq). 95% yield of the product as a white solid; mp 61.5 °C; $[\alpha]_D^{20}$ −630.1333(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.62–7.50 (m, 5H), 7.46 (t, $J$

= 4.5 Hz, 1H), 7.34–7.30 (m, 2H), 5.45 (d, $J$ = 9 Hz, 1H), 4.51–4.48 (m, 1H), 2.69–2.64 (m, 1H), 1.87–1.64 (m, 6H), 1.42 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 160.30, 156.86, 155.15, 149.51, 135.67, 134.55, 133.83, 130.25, 129.62, 129.58, 129.36, 129.13, 128.58, 126.56, 118.16, 79.65, 54.04, 38.94, 28.29, 24.59, 23.38, 17.81; IR (neat) 3733, 3692, 3623, 3596, 3423, 3062, 2974, 1693, 1587, 1491, 1455, 1365, 1249, 1164, 1057, 951, 814, 776, 738, 696 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{26}ClN_3O_3$ $[M + H]^+$ 440.17, found 439.96.

*4.2.1.11. (S)-tert-Butyl (1-(4-oxo-3-phenyl-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)butyl)carbamate (**4l**).* Synthesized from general procedure A using compound **2e** and **3c** under diphenyl phosphite (5 eq). 80% yield of the product as light yellow solid; mp 71.2 °C; $[\alpha]_D^{20}$ −35.9667(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, $J$ = 8 Hz, 1H), 7.87 (d, $J$ = 7.5 Hz, 1H), 7.80 (t, $J$ = 8 Hz, 1H), 7.62–7.50 (m, 3H), 7.42 (d, $J$ = 7 Hz, 1H), 7.29 (d, $J$ = 7.5 Hz, 1H), 5.40 (d, $J$ = 9 Hz, 1H), 4.52–4.49 (m, 1H), 1.62–1.60 (m, 1H), 1.53–1.47 (m, 1H), 1.42 (s, 9H), 1.29–1.27 (m, 1H), 1.16–1.10 (m, 1H), 0.63 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 159.12, 159.07, 155.36, 149.64, 135.56, 133.31, 132.27, 130.43, 129.65, 129.57, 129.29 (q, $J_{C\text{-}F}$ = 33 Hz), 128.89, 128.50, 126.17 (q, $J_{C\text{-}F}$ = 7.2 Hz), 123.17 (q, $J_{C\text{-}F}$ = 271.6 Hz), 118.36, 79.71, 51.23, 36.65, 28.32, 18.57, 13.08; IR (neat) 3735, 3595, 3054, 2964, 2932, 1698, 1590, 1490, 1367, 1307, 1156, 952, 830, 737, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{26}F_3N_3O_3$ $[M + H]^+$ 462.20, found 462.09.

*4.2.1.12. (S)-tert-Butyl (cyclopropyl(5-methyl-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)methyl)carbamate (**4m**).* Synthesized from general procedure A using compound **2d** and **3e** under diphenyl phosphite (1.65 eq). 32% yield of the product as yellow solid; mp 155.3–165.8 °C; $[\alpha]_D^{20}$ −33.0320(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.48 (m, 5H), 7.38–7.32 (m, 2H), 7.23 (t, $J$ = 6.8 Hz, 1H), 5.62 (d, $J$ = 8 Hz, 1H), 4.23–4.19 (m, 1H), 2.82 (s, 3H), 1.41 (s, 9H), 1.12–1.10 (m, 1H), 0.40–0.37 (m, 2H), 0.30–0.25 (m, 1H), 0.08–0.04 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 162.81, 156.33, 155.02, 148.76, 141.63, 136.29, 133.64, 130.20, 129.62, 129.57, 129.40, 129.25, 128.62, 125.43, 119.46, 79.53, 53.36, 28.29, 23.06, 15.15, 3.46, 2.32; IR (neat) 3376, 1980, 1669, 1590, 1499, 1472, 1364, 1226, 1161, 1045, 881, 810, 761, 691 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{27}N_3O_3$ $[M + H]^+$ 406.21, found 405.98.

*4.2.2. General procedure B for the preparation of compound 5a-m*

To a stirred solution of the corresponding compound **4** (1 eq.) in $CH_2Cl_2$ (0.085 M) was added trifluoroacetic acid (0.34 M) slowly at 0 °C under $N_2$ gas and stirred at room temperature for 1 h. The completion of the reaction was monitored by TLC on silica ($CH_2Cl_2$-MeOH = 15:1) and the reaction mixture was quenched with aq. ammonia (pH 8–12) solution at 0 °C. The reaction mixture was extracted with $CH_2Cl_2$. The combined extracts were washed with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was subjected to flash column chromatography ($CH_2Cl_2$-MeOH gradient or EtOAc-MeOH gradient) on silica gel to afford title compounds.

*4.2.2.1. (S)-2-(Amino(cyclopropyl)methyl)-6-fluoro-3-phenylquinazolin-4(3H)-one (**5a**).* Synthesized from general procedure B using compound **4a**. 87% yield of the product as yellow syrup; $[\alpha]_D^{20}$ −9.0157(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, $J$ = 8.4 Hz, 2.8 Hz, 1H), 7.73 (dd, $J$ = 9.2 Hz, 4.8 Hz, 1H), 7.57–7.46 (m, 4H), 7.31–7.26 (m, 2H), 2.99 (d, $J$ = 8 Hz, 1H), 1.82 (brs, 2H), 1.30–1.25 (m, 1H), 0.52–0.40 (m, 2H), 0.12–0.01 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.58 (d, $J_{C\text{-}F}$ = 3.3 Hz), 160.79 (d, $J_{C\text{-}F}$ = 246.6 Hz), 158.62, 144.12 (d, $J_{C\text{-}F}$ = 1.6 Hz), 136.47, 129.88, 129.67, 129.59, 129.50, 129.24 (d, $J_{C\text{-}F}$ = 34.9 Hz), 128.01, 122.92 (d, $J_{C\text{-}F}$ = 23.9 Hz), 122.03 (d, $J_{C\text{-}F}$ = 8.5 Hz), 111.71 (d, $J_{C\text{-}F}$ = 23.5 Hz), 56.04, 17.95, 3.43, 3.06; IR (neat) 3370, 3066, 3005, 1676, 1588, 1482, 1344, 1271, 1226, 1161, 1019, 948, 833, 749, 697 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{16}FN_3O$ $[M + H]^+$ 310.13, found 309.97.

*4.2.2.2. (S)-2-(1-Aminoethyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**5b**).* Synthesized from general procedure B using compound **4b**. 91% yield of the product as a white solid; mp 164.2–168.3 °C; $[\alpha]_D^{22.3}$ −8.8000(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.68 (td, $J$ = 8 Hz, 5.6 Hz, 1H), 7.57–7.50 (m, 4H), 7.28–7.26 (m, 2H), 7.09 (dd, $J$ = 10.4 Hz, 8 Hz, 1H), 3.68 (q, $J$ = 6.4 Hz, 1H), 1.87 (brs, 2H), 1.27 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.38 (d, $J_{C\text{-}F}$ = 264.9 Hz), 161.96, 159.32 (d, $J_{C\text{-}F}$ = 4.4 Hz), 149.42, 136.01, 134.80 (d, $J_{C\text{-}F}$ = 10.3 Hz), 129.98, 129.77, 129.46, 128.78, 128.25, 123.05 (d, $J_{C\text{-}F}$ = 4.2 Hz), 113.25 (d, $J_{C\text{-}F}$ = 20.5 Hz), 110.57 (d, $J_{C\text{-}F}$ = 5.6 Hz), 48.51, 23.29; IR (neat) 3361, 3299, 2971, 1677, 1589, 1474, 1454, 1324, 1229, 1066, 904, 819, 758, 697 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{16}H_{14}FN_3O$ $[M + H]^+$ 284.11, found 284.20.

*4.2.2.3. (S)-2-(1-Aminobutyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**5d**).* Synthesized from general procedure B using compound **4d**. 87% yield of the product as colorless oil; $[\alpha]_D^{20}$ −5.4867(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.67 (td, $J$ = 8.4 Hz, 5.2 Hz, 1H), 7.57–7.48 (m, 4H), 7.28–7.25 (m, 2H), 7.08 (ddd, $J$ = 10.4 Hz, 8.4 Hz, 0.8 Hz, 1H), 3.51 (dd, $J$ = 8.4 Hz, 4.8 Hz, 1H), 1.73–1.65 (m, 3H), 1.50–1.42 (m, 1H), 1.38–1.28 (m, 1H), 1.18–1.09 (m, 1H), 0.69 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.51, 161.43 (d, $J_{C\text{-}F}$ = 265.1 Hz), 159.34 (d, $J_{C\text{-}F}$ = 4.3 Hz), 149.49, 136.10, 134.73 (d, $J_{C\text{-}F}$ = 10.4 Hz), 129.95, 129.65, 129.38, 129.05, 128.23, 123.08 (d, $J_{C\text{-}F}$ = 4.2 Hz), 113.17 (d, $J_{C\text{-}F}$ = 20.7 Hz), 110.60 (d, $J_{C\text{-}F}$ = 5.8 Hz), 52.39, 39.15, 19.05, 13.39; IR (neat) 3372, 3051, 2962, 2873, 1689, 1586, 1472, 1394, 1295, 1274, 1180, 1036, 817, 749, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{18}FN_3O$ $[M + H]^+$ 312.15, found 312.29.

*4.2.2.4. (S)-2-(1-Amino-2-methylpropyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**5e**).* Synthesized from general procedure B using compound **4e**. 77% yield of the product as a white solid; mp 159.6–160.4 °C; $[\alpha]_D^{20}$ + 33.0067(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.64 (td, $J$ = 8 Hz, 5.6 Hz, 1H), 7.56–7.47 (m, 4H), 7.28–7.26 (m, 2H), 7.06 (dd, $J$ = 10 Hz, 8.4 Hz, 1H), 3.23 (d, $J$ = 6.4 Hz, 1H), 2.05–1.97 (m, 1H), 1.63 (brs, 2H), 0.87 (d, $J$ = 6.8 Hz, 3H), 0.73 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.17 (d, $J_{C\text{-}F}$ = 264.8 Hz), 160.66, 159.17 (d, $J_{C\text{-}F}$ = 4.3 Hz), 149.21, 136.11, 134.55 (d, $J_{C\text{-}F}$ = 10.5 Hz), 129.77, 129.37, 129.15, 129.10, 127.99, 122.96 (d, $J_{C\text{-}F}$ = 4.1 Hz), 112.94 (d, $J_{C\text{-}F}$ = 20.6 Hz), 110.36 (d, $J_{C\text{-}F}$ = 5.8 Hz), 58.03, 32.79, 20.23, 16.50; IR (neat) 3525, 3384, 3050, 2962, 2869, 1690, 1619, 1586, 1473, 1395, 1295, 1181, 1037, 818, 777, 733, 702 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{18}FN_3O$ $[M + H]^+$ 312.15, found 312.29.

*4.2.2.5. (S)-2-(Amino(cyclopropyl)methyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**5f**).* Synthesized from general procedure B using compound **4f**. 99% yield of the product as pale yellow solid; mp 124.1–126.5 °C; $[\alpha]_D^{16.1}$ + 9.24667(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.68 (td, $J$ = 8 Hz, 5.6 Hz, 1H), 7.56–7.49 (m, 4H), 7.30–7.26 (m, 2H), 7.09 (dd, $J$ = 10 Hz, 8.4 Hz, 1H), 2.97 (d, $J$ = 8.4 Hz, 1H), 1.79 (brs, 2H), 1.29–1.23 (m,1H), 0.53–0.38 (m, 2H), 0.14–0.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.56 (d, $J_{C\text{-}F}$ = 230.4 Hz), 160.07, 159.29 (d, $J_{C\text{-}F}$ = 4.3 Hz), 149.53, 136.19, 134.73 (d, $J_{C\text{-}F}$ = 10.4 Hz), 129.87, 129.46, 129.39, 129.30, 128.16, 123.15 (d, $J_{C\text{-}F}$ = 4.2 Hz), 113.19 (d, $J_{C\text{-}F}$ = 20.5 Hz), 110.62 (d, $J_{C\text{-}F}$ = 5.7 Hz), 56.17, 17.92, 3.45, 3.07; IR (neat) 3357, 3056, 3006, 1714, 1678, 1621, 1583, 1473, 1319, 1226, 1038, 940, 897, 813, 762, 707 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{16}FN_3O$ $[M + H]^+$ 310.13, found 309.97.

*4.2.2.6. (S)-2-(Amino(cyclobutyl)methyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**5g**).* Synthesized from general procedure B using compound

**4g**. 99% yield of the product as a colorless liquid; $[\alpha]_D^{20}$ + 3.7666(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.66 (td, $J$ = 8 Hz, 5.6 Hz, 1H), 7.60–7.47 (m, 4H), 7.30–7.26 (m, 2H), 7.08 (dd, $J$ = 9.6 Hz, 8.8 Hz, 1H), 3.43 (d, $J$ = 7.6 Hz, 1H), 2.81–2.71 (m, 1H), 1.99–1.94 (m, 1H), 1.86–1.58 (m, 7H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.38 (d, $J_{C\text{-}F}$ = 264.8 Hz), 159.96, 159.34 (d, $J_{C\text{-}F}$ = 4.3 Hz), 149.50, 136.26, 134.69 (d, $J_{C\text{-}F}$ = 10.5 Hz), 129.98, 129.66, 129.38, 129.09, 128.26, 123.16 (d, $J_{C\text{-}F}$ = 4.2 Hz), 113.17 (d, $J_{C\text{-}F}$ = 20.5 Hz), 110.61 (d, $J_{C\text{-}F}$ = 5.7 Hz), 56.80, 40.50, 24.90, 24.43, 17.71; IR (neat) 3370, 3061, 2968, 1857, 1688, 1618, 1586, 1472, 1365, 1295, 1232, 1066, 1037, 818, 735, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{19}H_{18}FN_3O$ [M + H]$^+$ 324.15, found 324.18.

*4.2.2.7. (S)-2-(1-Aminobutyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**5h**).* Synthesized from general procedure B using compound **4h**. 54% yield of the product as a white solid; mp 114.2–114.8 °C; $[\alpha]_D^{20}$ −14.9933(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.60 (m, 2H), 7.58–7.48 (m, 3H), 7.45 (dd, $J$ = 6.4 Hz, 2.8 Hz, 1H), 7.28–7.25 (m, 2H), 3.50 (dd, $J$ = 8 Hz, 4.4 Hz, 1H), 1.73–1.65 (m, 3H), 1.50–1.41 (m, 1H), 1.38–1.29 (m, 1H), 1.19–1.09 (m, 1H), 0.69 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.15, 160.51, 149.91, 136.31, 134.47, 133.82, 129.97, 129.69, 129.42, 129.38, 129.05, 128.21, 126.54, 118.04, 52.43, 39.12, 19.05, 13.41; IR (neat) 3752, 3015, 2968, 2954, 2868, 1737, 1716, 1674, 1586, 1456, 1365, 1284, 1216, 1044, 810, 700 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{18}ClN_3O$ [M + H]$^+$ 328.12, found 328.20.

*4.2.2.8. (S)-2-(1-Amino-2-methylpropyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**5i**).* Synthesized from general procedure B using compound **4i**. 36% yield of the product as a white solid; mp 94.5 °C in decomposition; $[\alpha]_D^{20}$ + 15.5400(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.64–7.48 (m, 5H), 7.45 (dd, $J$ = 6.4 Hz, 2.4 Hz, 1H), 7.29–7.25 (m, 2H), 3.24 (d, $J$ = 6.4 Hz, 1H), 2.06–1.98 (m, 1H), 1.71 (brs, 2H), 0.87 (d, $J$ = 6.8 Hz, 3H), 0.74 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.54, 160.35, 149.77, 136.46, 134.43, 133.79, 129.97, 129.59, 129.41, 129.30, 129.28, 128.11, 126.59, 118.03, 58.22, 32.93, 20.40, 16.61; IR (neat) 3525, 3384, 3050, 2962, 2869, 1690, 1619, 1586, 1473, 1295, 1250, 1181, 1037, 818, 777, 702 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{18}ClN_3O$ [M + H]$^+$ 428.12, found 328.20.

*4.2.2.9. (S)-2-(Amino(cyclopropyl)methyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**5j**).* Synthesized from general procedure B using compound **4j**. 98% yield of the product as a white solid; mp 147.2–148.7 °C; $[\alpha]_D^{20}$ −43.3333(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.65–7.60 (m, 2H), 7.56–7.46 (m, 4H), 7.31–7.26 (m, 2H), 2.97 (d, $J$ = 8.5 Hz, 1H), 1.76 (brs, 2H), 1.29–1.23 (m, 1H), 0.52–0.40 (m, 2H), 0.13–0.03 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 160.51, 160.09, 149.98, 136.44, 134.51, 133.85, 129.94, 129.54, 129.50, 129.43, 129.35, 128.18, 126.64, 118.11, 56.26, 17.95, 3.52, 3.12; IR (neat) 3727, 3706, 3623, 3598, 3366, 3066, 2943, 1685, 1585, 1550, 1490, 1455, 1285, 1240, 957, 813, 777, 735, 699 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{18}H_{16}ClN_3O$ [M + H]$^+$ 326.11, found 326.07.

*4.2.2.10. (S)-2-(Amino(cyclobutyl)methyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**5k**).* Synthesized from general procedure B using compound **4k**. 99% yield of the product as a white solid; mp 80–82 °C; $[\alpha]_D^{20}$ −39.6667(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.59–7.50 (m, 5H), 7.43 (dd, $J$ = 6 Hz, 2.5 Hz, 1H), 7.29 (d, $J$ = 7.5 Hz, 2H), 3.41 (d, $J$ = 8 Hz, 1H), 2.78–2.73 (m, 1H), 1.95–1.94 (m, 1H), 1.81–1.59 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 160.43, 159.61, 149.87, 136.44, 134.31, 133.71, 129.94, 129.64, 129.33, 129.29, 129.01, 128.18, 126.56, 117.97, 56.81, 40.40, 24.86, 24.36, 17.67; IR (neat) 3726, 3705, 3623, 3597, 3376, 3059, 2973, 2939, 1687, 1585, 1550, 1489, 1455, 1330, 1268, 1211, 951, 814, 774, 694, 671 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{19}H_{18}ClN_3O$ [M + H]$^+$ 340.12, found 340.19.

*4.2.2.11. (S)-2-(1-Aminobutyl)-3-phenyl-5-(trifluoromethyl)quinazolin-4(3H)-one (**5l**).* Synthesized from general procedure B using compound **4l**. 99.6% yield of the product as a white solid; mp 136.2–136.8 °C; $[\alpha]_D^{20}$ −156.1333(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, $J$ = 8 Hz, 1H), 7.85 (d, $J$ = 7.5 Hz, 1H), 7.79 (t, $J$ = 8 Hz, 1H), 7.56–7.48 (m, 3H), 7.27 (d, $J$ = 7.5 Hz, 2H), 3.53 (dd, $J$ = 8.5 Hz, 5 Hz, 1H), 1.81 (brs, 2H), 1.74–1.67 (m, 1H), 1.50–1.43 (m, 1H), 1.37–1.30 (m, 1H), 1.18–1.11 (m, 1H), 0.69 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 161.71, 159.31, 149.88, 136.14, 133.24, 132.33, 130.06, 129.81, 129.44, 129.13 (q, $J_{C\text{-}F}$ = 32.7 Hz), 128.89, 128.08, 125.98 (q, $J_{C\text{-}F}$ = 7.2 Hz), 123.18 (q, $J_{C\text{-}F}$ = 271.8 Hz), 118.12, 52.32, 39.07, 19.02, 13.36; IR (neat) 3803, 3688, 3380, 3065, 2960, 2872, 1698, 1590, 1443, 1308, 1148, 956, 830, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{19}H_{18}F_3N_3O$ [M + H]$^+$ 362.15, found 362.03.

*4.2.2.12. (S)-2-(Amino(cyclopropyl)methyl)-5-methyl-3-phenylquinazolin-4(3H)-one (**5m**).* Synthesized from general procedure B using compound **4m**. 77% yield of the product as pale yellow solid; mp 123.4–126.4 °C; $[\alpha]_D^{20}$ −4.2880(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.48 (m, 5H), 7.31–7.26 (m, 2H), 7.22–7.21 (m, 1H), 2.96 (d, $J$ = 8.4 Hz, 1H), 2.82 (s, 3H), 1.89 (brs, 2H), 1.29–1.25 (m, 1H), 0.49–0.39 (m, 2H), 0.13–0.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 162.95, 158.82, 149.06, 141.47, 136.93, 133.58, 129.91, 129.47, 129.37, 129.17, 128.22, 125.47, 119.34, 56.08, 23.04, 17.97, 3.46, 3.10; IR (neat) 3371, 3009, 2968, 2923, 1715, 1677, 1565, 1472, 1375, 1285, 1134, 1041, 830, 765, 104 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{19}H_{19}N_3O$ [M + H]$^+$ 306.15, found 305.96.

*4.2.3. General procedure C for the preparation of compound 6a-m*

To a stirred solution of the corresponding amine **5** (1 eq.) in *tert*-butanol (0.15 M) were added TEA (2 eq.) and 6-chloropurine (2 eq.) at room temperature and the reaction mixture was refluxed for 10–27 h under $N_2$ gas. The completion of the reaction was monitored by TLC on silica ($CH_2Cl_2$-MeOH = 20:1). After cooling to room temperature, the reaction mixture was diluted with $CH_2Cl_2$ and washed with water until 6-chloropurine disappeared. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was subjected to flash column chromatography ($CH_2Cl_2$-MeOH gradient) on silica gel to afford the title compound.

*4.2.3.1. (S)-2-(((7H-Purin-6-yl)amino)(cyclopropyl)methyl)-6-fluoro-3-phenylquinazolin-4(3H)-one (**6a**).* Synthesized from general procedure C for 24 h using compound **5a**. 62% yield of the product as light ivory solid; mp 168.3 °C; $[\alpha]_D^{16.4}$ + 111.833(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 13.67 (brs, 1H), 8.30 (s, 1H), 7.98 (s, 1H), 7.89 (dd, $J$ = 8 Hz, 2.4 Hz, 1H), 7.74–7.71 (m, 1H), 7.64–7.40 (m, 6H), 6.84–6.82 (m, 1H), 4.96 (m, 1H), 1.41–1.37 (m, 1H), 0.51–0.49 (m, 2H), 0.40–0.38 (m, 1H), 0.24–0.21 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.73 (d, $J_{C\text{-}F}$ = 3.3 Hz), 160.99 (d, $J_{C\text{-}F}$ = 247 Hz), 156.05, 153.60, 151.90, 149.78, 143.90 (d, $J_{C\text{-}F}$ = 1.7 Hz), 138,45, 136.07, 129.85, 129.64, 129.60 (d, $J_{C\text{-}F}$ = 35.4 Hz), 129.41, 128.81, 123.08 (d, $J_{C\text{-}F}$ = 23.8 Hz), 122.21 (d, $J_{C\text{-}F}$ = 8.7 Hz), 119.35, 111.87 (d, $J_{C\text{-}F}$ = 23.5 Hz), 53.55, 15.32, 3.63, 3.10; IR (neat) 3724, 3623, 3008, 1679, 1588, 1482, 1357, 1226, 946, 834, 747 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{18}FN_7O$ [M + H]$^+$ 428.16, found 427.97; HPLC purity 100% ee.

*4.2.3.2. (S)-2-(1-((7H-Purin-6-yl)amino)ethyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**6b**).* Synthesized from general procedure C for 36 h using compound **5b**. 51% yield of the product as a white solid; mp 282.4–284 °C; $[\alpha]_D^{20}$ + 189.8638(c 0.5, $CH_2Cl_2$). $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 12.93 (brs, 1H), 8.17 (m, 2H), 7.93 (d, $J$ = 4.8 Hz, 1H), 7.79 (td, $J$ = 8 Hz, 5.6 Hz, 1H), 7.67–7.66 (m, 1H), 7.58 (m, 2H), 7.49–7.47

(m, 2H), 7.30–7.26 (m, 1H), 4.82 (m, 1H), 1.46 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 160.54 (d, $J_{C\text{-}F} = 262$ Hz), 159.83, 158.44 (d, $J_{C\text{-}F} = 3.9$ Hz), 151.91, 149.14, 136.10, 135.29 (d, $J_{C\text{-}F} = 10.6$ Hz), 129.33, 129.23, 129.10, 129.06, 128.88, 123.06 (d, $J_{C\text{-}F} = 2.7$ Hz), 113.09 (d, $J_{C\text{-}F} = 20.5$ Hz), 111.31 (d, $J_{C\text{-}F} = 5.4$ Hz), 47.87, 18.89; IR (neat) 3370, 3136, 2989, 2934, 1687, 1606, 1513, 1476, 1230, 1080, 1021, 830, 813, 753, 699 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{21}H_{16}FN_7O$ [M + H]$^+$ 402.14, found 402.18; HPLC purity 95.67% ee.

*4.2.3.3. (S)-2-(1-((7H-Purin-6-yl)amino)butyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**6d**).* Synthesized from general procedure C for 15 h using compound **5d**. 68% yield of the product as pale yellow solid; mp 160.3 °C in decomposition; $[\alpha]_D^{20}$ + 156.7200(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 7.97 (s, 1H), 7.65–7.55 (m, 5H), 7.45 (d, $J = 8.5$ Hz, 1H), 7.34 (d, $J = 8$ Hz, 1H), 7.06 (t, $J = 9.5$ Hz, 1H), 6.82 (d, $J = 7.5$ Hz, 1H), 5.27 (m, 1H), 1.81–1.79 (m, 2H), 1.40–1.32 (m, 1H), 1.22–1.18 (m, 1H), 0.65 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 161.37 (d, $J_{C\text{-}F} = 265.2$ Hz), 159.39 (d, $J_{C\text{-}F} = 4.2$ Hz), 158.69, 154.15, 152.02, 149.75, 149.21, 138.51, 135.63, 134.84 (d, $J_{C\text{-}F} = 10.2$ Hz), 129.88, 129.61, 129.51, 128.96, 123.23 (d, $J_{C\text{-}F} = 4$ Hz), 119.51, 113.42 (d, $J_{C\text{-}F} = 20.5$ Hz), 110.71 (d, $J_{C\text{-}F} = 5.7$ Hz), 50.80, 36.41, 18.74, 13.16; IR (neat) 3414, 3050, 2978, 2963, 2879, 1768, 1696, 1611, 1590, 1474, 1396, 1324, 1266, 1244, 1180, 819, 737, 700 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{20}FN_7O$ [M + H]$^+$ 430.18, found 430.02; HPLC purity 100% ee.

*4.2.3.4. (S)-2-(1-((7H-Purin-6-yl)amino)-2-methylpropyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**6e**).* Synthesized from general procedure C for 24 h using compound **5e**. 46% yield of the product as a white solid; mp 217.2 °C; $[\alpha]_D^{20}$ + 94.0267(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 13.65 (brs, 1H), 8.30 (s, 1H), 7.98 (s, 1H), 7.67 (td, $J = 8.4$ Hz, 5.6 Hz, 1H), 7.62–7.51 (m, 4H), 7.38–7.33 (m, 2H), 7.12–7.07 (m, 1H), 6.64 (d, $J = 8.8$ Hz, 1H), 5.31–5.29 (m, 1H), 2.32–2.23 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.39 (d, $J_{C\text{-}F} = 265$ Hz), 159.38 (d, $J_{C\text{-}F} = 4.3$ Hz), 157.73, 154.32, 151.93, 149.06, 138.48, 135.65, 134.91 (d, $J_{C\text{-}F} = 10.1$ Hz), 129.87, 129.55, 129.42, 129.36, 128.99, 123.37 (d, $J_{C\text{-}F} = 4.3$ Hz), 113.56 (d, $J_{C\text{-}F} = 20.6$ Hz), 110.71 (d, $J_{C\text{-}F} = 5.5$ Hz), 55.42, 32.88, 20.06, 17.03; IR (neat) 3734, 3649, 3418, 3065, 2965, 1691, 1608, 1473, 1294, 1232, 1038, 932, 818, 735, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{20}FN_7O$ [M + H]$^+$ 430.18, found 430.32; HPLC purity 100% ee.

*4.2.3.5. (S)-2-(((7H-Purin-6-yl)amino)(cyclopropyl)methyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**6f**).* Synthesized from general procedure C for 10 h using compound **5f**. 46% yield of the product as a white solid; mp 183 °C; $[\alpha]_D^{18.3}$ + 153.953(c 0.5, $CH_3OH$); $^1$H NMR (400 MHz, $CD_3OD$) δ: 8.16 (s, 1H), 8.13 (s, 1H), 7.79–7.73 (m, 1H), 7.61–7.47 (m, 6H), 7.20–7.15 (m, 1H), 4.79–4.78 (m, 1H), 3.33–3.32 (m, 1H), 1.49–1.46 (m, 1H), 0.59–0.56 (m, 2H), 0.42 (m, 1H), 0.26–0.22 (m, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ: 162.55 (d, $J_{C\text{-}F} = 263.2$ Hz), 161.16 (d, $J_{C\text{-}F} = 4.3$ Hz), 159.44, 153.50, 150.77, 141.06, 137.33, 136.56 (d, $J_{C\text{-}F} = 10.5$ Hz), 130.89, 130.61, 130.48, 130.45, 124.41 (d, $J_{C\text{-}F} = 4$ Hz), 114.50 (d, $J_{C\text{-}F} = 20.9$ Hz), 111.54 (d, $J_{C\text{-}F} = 5.9$ Hz), 55.74, 15.62, 4.18, 3.77; IR (neat) 3412, 3005, 2806, 1714, 1610, 1589, 1473, 1362, 1228, 1037, 818, 697 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{18}FN_7O$ [M + H]$^+$ 428.16, found 427.95; HPLC purity 100% ee.

*4.2.3.6. (S)-2-(((7H-Purin-6-yl)amino)(cyclobutyl)methyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (**6g**).* Synthesized from general procedure C for 33 h using compound **5 g**. 35% yield of the product as light ivory solid; mp 154.8 °C; $[\alpha]_D^{20}$ + 73.1266(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 13.92 (brs, 1H), 8.28 (s, 1H), 7.98 (s, 1H), 7.69–7.63 (m, 1H), 7.59 (t, $J = 7.6$ Hz, 1H), 7.52–7.50 (m, 2H), 7.47–7.4 (m, 1H), 7.38 (d, $J = 8$ Hz, 1H), 7.35 (m, 1H), 7.08 (t, $J = 9.2$ Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 5.43 (m, 1H), 2.98–2.93 (m, 1H), 2.04–2.01 (m, 1H), 1.91–1.68 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.33 (d, $J_{C\text{-}F} = 265$ Hz), 159.35 (d, $J_{C\text{-}F} = 4.2$ Hz), 157.01, 154.09, 151.87, 149.81, 149.09, 138.50, 135.60, 134.85 (d, $J_{C\text{-}F} = 10.3$ Hz), 129.67, 129.45, 129.18, 129.02, 123.33 (d, $J_{C\text{-}F} = 3.9$ Hz), 119.39, 113.50 (d, $J_{C\text{-}F} = 20.5$ Hz), 110.67 (d, $J_{C\text{-}F} = 5.7$ Hz), 53.64, 39.25, 24.94, 24.04, 17.94; IR (neat) 3217, 3060, 2970, 2861, 1690, 1608, 1588, 1473, 1321, 1295, 1242, 1037, 1024, 933, 893, 818, 735, 698 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{20}FN_7O$ [M + H]$^+$ 442.18, found 442.04; HPLC purity 96.92% ee.

*4.2.3.7. (S)-2-(1-((7H-Purin-6-yl)amino)butyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**6h**).* Synthesized from general procedure C for 16 h using compound **5h**. 63% yield of the product as pale yellow solid; mp 171.8–173.0 °C; $[\alpha]_D^{20}$ + 187.3333(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 13.82 (brs, 1H), 8.35 (s, 1H), 7.98 (s, 1H), 7.61–7.53 (m, 6H), 7.42 (dd, $J = 6.4$ Hz, 2.8 Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 5.25 (m, 1H), 1.83–1.78 (m, 2H), 1.40–1.33 (m, 1H), 1.27–1.20 (m, 1H), 0.66 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.49, 158.31, 154.19, 152.02, 149.65, 138.47, 135.86, 134.47, 133.85, 129.87, 129.61, 129.57, 129.52, 128.95, 126.64, 118.16, 50.83, 36.35, 18.73, 13.16; IR (neat) 3545, 3399, 3255, 3051, 2962, 2873, 2824, 1686, 1611, 1585, 1551, 1265, 1175, 947, 814, 735, 699 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{20}ClN_7O$ [M + H]$^+$ 446.15, found 446.24; HPLC purity 100% ee.

*4.2.3.8. (S)-2-(1-((7H-Purin-6-yl)amino)-2-methylpropyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**6i**).* Synthesized from general procedure C for 36 h using compound **5i**. 73% yield of the product as an ivory solid; mp 159.3 °C; $[\alpha]_D^{20}$ + 139.5933(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 13.87 (brs, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.62–7.53 (m, 5H), 7.45 (dd, $J = 7.6$ Hz, 0.8 Hz, 1H), 7.38–7.36 (m, 1H), 7.33–7.32 (m, 1H), 6.62 (d, $J = 9.2$ Hz, 1H), 5.29 (m, 1H), 2.32–3.24 (m, 1H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.48, 157.39, 154.36, 151.91, 149.50, 138.48, 135.89, 134.49, 133.91, 129.85, 129.73, 129.49, 129.42, 129.35, 128.98, 126.78, 119.49, 118.16, 55.46, 32.79, 20.06, 16.99; IR (neat) 3650, 3409, 3061, 2964, 2928, 1714, 1689, 1610, 1586, 1455, 1362, 1298, 1221, 951, 814, 737, 700 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{20}ClN_7O$ [M + H]$^+$ 446.15, found 446.24; HPLC purity 98.49% ee.

*4.2.3.9. (S)-2-(((7H-Purin-6-yl)amino)(cyclopropyl)methyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**6j**).* Synthesized from general procedure C for 19 h using compound **5j**. 72% yield of the product as pale yellow solid; mp 169.7 °C; $[\alpha]_D^{20}$ + 800.1333(c 0.5, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) δ: 13.90 (brs, 1H), 8.30 (s, 1H), 7.97 (s, 1H), 7.58–7.51 (m, 6H), 7.43–7.39 (m, 2H), 6.93 (d, $J = 7$ Hz, 1H), 4.87 (m, 1H), 1.38–1.37 (m, 1H), 0.51–0.49 (m, 2H), 0.38 (m, 1H), 0.23–0.22 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 160.52, 157.43, 153.54, 151.86, 149.62, 138.52, 135.96, 134.44, 133.87, 129.67, 129.57, 129.33, 128.92, 126.69, 119.38, 118.12, 53.76, 15.08, 3.70, 3.11; IR (neat) 3728, 3706, 3623, 3600, 2919, 2850, 1691, 1614, 1588, 1456, 1286, 1269, 1247, 962, 777, 756, 735, 671 cm$^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{18}ClN_7O$ [M + H]$^+$ 444.13, found 444.12; HPLC purity 98.61% ee.

*4.2.3.10. (S)-2-(((7H-Purin-6-yl)amino)(cyclobutyl)methyl)-5-chloro-3-phenylquinazolin-4(3H)-one (**6k**).* Synthesized from general procedure C for 36 h using compound **5k**. 50% yield of the product as pale yellow solid; mp 155.0–157.0 °C; $[\alpha]_D^{20}$ + 640.0000(c 0.5, $CH_2Cl_2$); 13.37 (brs, 1H), 8.29 (s, 1H), 8.00 (s, 1H), 7.65–7.58 (m, 3H), 7.55–7.44 (m, 3H), 7.39–7.34 (m, 2H), 6.68 (d, $J = 9.2$ Hz, 1H), 5.40 (m, 1H), 2.97–2.91 (m, 1H), 2.05–2.01 (m, 1H), 1.90–1.67 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.45, 156.66, 154.08, 151.82, 149.77, 149.53, 138.49, 135.84, 134.44, 133.87, 129.70, 129.68, 129.46, 129.43, 129.19, 129.01, 126.75, 119.27, 118.13, 53.73, 39.17, 24.94, 24.05, 17.95; IR (neat)

3725, 3703, 3623, 3600, 3414, 3057, 2969, 1714, 1612, 1587, 1455, 1363, 1222, 1092, 953, 815, 736, 701 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{20}ClN_7O$ $[M + H]^+$ 458.15, found 458.33; HPLC purity 96.17% ee.

*4.2.3.11. (S)-2-(1-((7H-Purin-6-yl)amino)butyl)-3-phenyl-5-(trifluoromethyl)quinazolin-4(3H)-one (**6l**).* Synthesized from general procedure C for 27 h using compound **5l**. 76% yield of the product as a white solid; mp 159.9 °C; $[\alpha]_D^{20}$ + 193.5867(c 0.5, $CH_2Cl_2$); $^1H$ NMR (500 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 7.99 (s, 1H), 7.86 (d, $J = 8$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.74 (t, $J = 8$ Hz, 1H), 7.60–7.53 (m, 4H), 7.36 (d, $J = 8$ Hz, 1H), 6.87 (d, $J = 7$ Hz, 1H), 5.28–5.27 (m, 1H), 1.82–1.81 (m, 2H), 1.42–1.35 (m, 1H), 1.24–1.19 (m, 1H), 0.65 (t, $J = 7.5$ Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 159.32, 159.02, 154.17, 151.99, 149.68, 138.55, 135.74, 133.29, 132.43, 129.95, 129.65, 129.14 (q, $J_{C\text{-}F} = 32.6$ Hz), 128.87, 128.81, 126.18 (q, $J_{C\text{-}F} = 7.1$ Hz), 123.17 (q, $J_{C\text{-}F} = 271.6$ Hz), 119.51, 118.30, 50.84, 36.29, 18.76, 13.11; IR (neat) 3735, 3596, 3421, 3051, 2962, 2933, 2872, 1697, 1613, 1590, 1474, 1456, 1307, 1153, 951, 830, 737, 698 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{20}F_3N_7O$ $[M + H]^+$ 480.18, found 480.16; HPLC purity 100% ee.

*4.2.3.12. (S)-2-(((7H-Purin-6-yl)amino)(cyclopropyl)methyl)-5-methyl-3-phenylquinazolin-4(3H)-one (**6m**).* Synthesized from general procedure C for 15 h using compound **5m**. 62% yield of the product as a white solid; mp 183–185 °C; $[\alpha]_D^{20}$ + 93.3759(c 0.5, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ: 13.90 (brs, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.61–7.51 (m, 5H), 7.41 (d, $J = 8$ Hz, 1H), 7.21–7.19 (m, 1H), 7.00 (d, $J = 8$ Hz, 1H), 4.94 (m, 1H), 2.81 (s, 3H), 1.42–1.37 (m, 1H), 0.49–0.40 (m, 3H), 0.25–0.23 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 162.97, 156.13, 153.67, 151.93, 149.68, 148.77, 141.52, 138.42, 136.48, 133.65, 129.75, 129.63, 129.61, 129.36, 128.98, 125.61, 119.43, 53.38, 23.05, 15.23, 3.58, 2.98; IR (neat) 3380, 3198, 3008, 2812, 1738, 1680, 1588, 1470, 1288, 1228, 1131, 1043, 810, 749, 697 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{24}H_{21}N_7O$ $[M + H]^+$ 424.18, found 423.94; HPLC purity 100% ee.

*4.2.4. General procedure d for the preparation of compound 7a-c*

In a sealed tube, 4-methoxy benzylamine (1 eq.) was added to a stirred solution of the appropriate compound (**6b, 6c,** and **6f)** (1 eq.) and TEA (1.44 M) dissolved in ethanol (0.1 M). The reaction mixture was heated to 160–180 °C for 3–4 days. The completion of the reaction was monitored by TLC on silica ($CH_2Cl_2$-MeOH = 10:1). After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The crude residue was subjected to flash silica gel column chromatography ($CH_2Cl_2$-MeOH gradient) to afford title compounds.

*4.2.4.1. (S)-2-(1-((7H-purin-6-yl)amino)ethyl)-5-((4-methoxybenzyl)amino)-3-phenylquinazolin-4(3H)-one (**7a**).* Synthesized from general procedure D using the compound **6b**. 43% yield of the product as pale yellow solid; mp 130 °C in decomposition; $[\alpha]_D^{20}$ + 204.8238(c 0.5, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.81–8.87 (m, 1H), 8.32 (s, 1H), 7.95 (s, 1H), 7.59–7.49 (m, 5H), 7.36–7.34 (m, 1H), 7.25–7.23 (m, 2H), 7.13 (m, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.47 (d, $J = 8.4$ Hz, 1H), 5.17 (m, 1H), 4.32–4.30 (m, 2H), 3.75 (s, 3H), 1.48 (d, $J = 6.8$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 164.68, 158.78, 156.75, 153.44, 152.06, 150.48, 148.91, 138.38, 136.05, 135.82, 130.22, 130.00, 129.96, 129.51, 129.00, 128.91, 128.61, 114.02, 112.94, 106.87, 105.06, 55.25, 46.73, 29.72, 20.31; IR (neat) 3318, 3010, 2950, 2882, 1780, 1655, 1566, 1509, 1410, 1328, 1247, 1143, 1033, 908, 813, 698 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{29}H_{26}N_8O_2$ $[M + H]^+$ 519.22, found 519.29.

*4.2.4.2. (S)-2-(1-((7H-purin-6-yl)amino)propyl)-5-((4-methoxybenzyl)amino)-3-phenylquinazolin-4(3H)-one (**7b**).* Synthesized from general procedure D using compound **6c**. 29% yield of the product as pale yellow solid; mp 145.8 °C; $[\alpha]_D^{20}$ + 64.8079(c 0.5, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.81–8.79 (m, 1H), 8.31 (s, 1H), 7.96 (s, 1H), 7.60–7.54 (m, 3H), 7.46–7.42 (m, 2H), 7.36–7.34 (m, 1H), 7.25–7.23 (m, 2H), 6.86 (d, $J = 8$ Hz, 1H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.47 (d, $J = 8.4$ Hz, 1H), 5.13 (m, 1H), 4.32–4.30 (m, 2H), 3.76 (s, 3H), 1.98–1.93 (m, 1H), 1.81–1.78 (m, 1H), 0.86 (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 164.72, 158.78, 152.06, 150.46, 148.92, 136.05, 135.79, 130.24, 129.99, 129.57, 129.01, 128.63, 114.02, 113.07, 106.81, 105.07, 55.27, 53.43, 46.75, 27.62, 10.00; IR (neat) 3321, 3040, 2932, 2884, 2830, 1703, 1655, 1564, 1510, 1445, 1327, 1247, 1132, 1031, 814, 698 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{30}H_{28}N_8O_2$ $[M + H]^+$ 533.23, found 533.37.

*4.2.4.3. (S)-2-(((7H-purin-6-yl)amino)(cyclopropyl)methyl)-5-((4-methoxybenzyl)amino)-3-phenylquinazolin-4(3H)-one (**7c**).* Synthesized from general procedure D using compound **6f**. 31% yield of the product as yellow solid; mp 153.8 °C; $[\alpha]_D^{16.3}$ + 256.727(c 0.5, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ: 14.03 (brs, 1H), 8.83–8.81 (m, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.58–7.39 (m, 6H), 7.24–7.22 (m, 2H), 7.03 (d, $J = 8.4$ Hz, 1H), 6.86 (d, $J = 7.6$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 2H), 6.46 (d, $J = 8$ Hz, 1H), 4.90 (m, 1H), 4.31–4.30 (m, 2H), 3.74 (s, 3H), 1.39–1.38 (m, 1H), 0.48–0.39 (m, 3H), 0.23 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 164.69, 158.70, 155.56, 151.87, 150.39, 148.93, 138.43, 136.08, 135.73, 130.17, 129.74, 129.61, 129.42, 129.31, 129.03, 128.56, 113.94, 112.96, 106.74, 105.01, 55.19, 53.23, 46.67, 15.13, 3.56, 2.97; IR (neat) 3328, 3005, 2831,1714, 1655, 1590, 1567, 1472, 1363, 1223, 1026, 813, 698 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{31}H_{28}N_8O_2$ $[M + H]^+$ 545.23, found 544.99.

*4.2.5. General procedure E for the preparation of compound 8a-c*

Trifluoroacetic acid (0.15 M) was added to a stirred solution of the corresponding compound (**7**–**9**, 1 eq.) in $CH_2Cl_2$ (0.3 M) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The completion of the reaction was monitored by TLC on silica ($CH_2Cl_2$-MeOH = 10:1). The reaction mixture was quenched with 1 M NaOH (pH ~ 7) at 0 °C, and then the aqueous layer was extracted with $CH_2Cl_2$. The combined extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was subjected to flash silica gel column chromatography ($CH_2Cl_2$-MeOH gradient or EtOAc-MeOH gradient) to afford title compounds.

*4.2.5.1. (S)-2-(1-((7H-Purin-6-yl)amino)ethyl)-5-amino-3-phenylquinazolin-4(3H)-one (**8a**).* Synthesized from general procedure E using compound **7a**. 77% yield of the product as an ivory solid; mp 161 °C; $[\alpha]_D^{20}$ + 138.8879(c 0.5, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CD_3OD$) δ: 8.19 (s, 1H), 8.11 (s, 1H), 7.61–7.56 (m, 2H), 7.49–7.44 (m, 3H), 7.40 (t, $J = 8$ Hz, 1H), 6.80 (dd, $J = 8$ Hz, 0.8 Hz, 1H), 6.63 (dd, $J = 8$ Hz, 0.8 Hz, 1H), 6.16 (s, 2H), 5.00–4.98 (m, 1H), 1.51 (d, $J = 6.8$ Hz, 3H); $^{13}C$ NMR (100 MHz, MeOD) δ: 164.51, 157.01, 152.18, 151.12, 148.50, 139.63, 136.26, 135.02, 129.28, 129.27, 128.97, 128.90, 112.61, 111.46, 104.66, 18.35; IR (neat) 3344, 2922, 2851, 1663, 1604, 1576, 1463, 1245, 1137, 1017, 816, 755, 699 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{21}H_{18}N_8O$ $[M + H]^+$ 399.16, found 399.17; HPLC purity 91.83% ee.

*4.2.5.2. (S)-2-(1-((7H-Purin-6-yl)amino)propyl)-5-amino-3-phenylquinazolin-4(3H)-one (**8b**).* Synthesized from general procedure E using compound **7b**. 73% yield of the product as yellow solid; mp 174 °C; $[\alpha]_D^{20}$ + 185.7359(c 0.5, $CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ: 13.79 (brs, 1H), 8.31 (s, 1H), 7.96 (s, 1H), 7.61–7.34 (m, 6H), 7.03 (d, $J = 8$ Hz, 1H), 6.88 (d, $J = 8$ Hz, 1H), 6.51 (d, $J = 8$ Hz, 1H), 6.18 (s, 2H), 5.13 (m, 1H), 2.04–1.93 (m, 1H), 1.83–1.75 (m, 1H), 0.85 (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 164.47, 155.91, 154.10, 152.03, 150.18, 148.52, 138.35, 136.05, 135.29, 129.94, 129.54, 129.44, 129.03, 114.31, 111.82, 52.24, 27.57, 10.06; IR (neat) 3343, 3040, 2818, 1714, 1660, 1574, 1470, 1293, 1131, 1013, 816, 751, 698 $cm^{-1}$; LRMS (ESI)

*m/z* calculated for $C_{22}H_{20}N_8O$ $[M + H]^+$ 413.18, found 413.33; HPLC purity 98.42% ee.

*4.2.5.3. (S)-2-(((7H-Purin-6-yl)amino)(cyclopropyl)methyl)-5-amino-3-phenylquinazolin-4(3H)-one (**8c**).* Synthesized from general procedure E using compound **7c**. 60% yield of the product as a white solid; mp 173.5 °C; $[\alpha]_D^{16.5}$ + 184.378(c 0.5, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ: 13.80 (brs, 1H), 8.30 (s, 1H), 7.97 (s, 1H), 7.61–7.38 (m, 6H), 6.95–6.90 (m, 2H), 6.53 (d, $J = 8$ Hz, 1H), 6.16 (s, 2H), 4.91 (m, 1H), 1.40–1.35 (m, 1H), 0.49–0.39 (m, 3H), 0.24–0.21 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 164.44, 155.60, 153.56, 151.88, 150.16, 148.54, 138.44, 136.08, 135.23, 129.70, 129.62, 129.38, 129.29, 129.05, 114.18, 111.76, 105.46, 53.23, 15.14, 3.56, 2.95; IR (neat) 3439, 3340, 3002, 1659, 1601, 1673, 1470, 1292, 1234, 1133, 1071, 1023, 935, 816, 749, 698 $cm^{-1}$; LRMS (ESI) *m/z* calculated for $C_{23}H_{20}N_8O$ $[M + H]^+$ 425.18, found 425.15; HPLC purity 100% ee.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

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