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Discovery of 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones as potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors

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ABSTRACT

In recent years, dipeptidyl peptidase IV inhibitors have been noted as valuable agents for treatment of type 2 diabetes. Herein, we report the discovery of a novel potent DPP-4 inhibitor with 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one as skeleton. After efficient optimization of the lead compound **2a** at the 7- and 8-positions using a docking study, we found **28** as a novel DPP-4 inhibitor with excellent selectivity against various DPP-4 homologues. Compound **28** showed strong DPP-4 inhibitory activity compared to marketed DPP-4 inhibitors. We also found that a carboxyl group at the 7-position could interact with the residue of Lys554 to form a salt bridge. Additionally, introduction of a carboxyl group to 7-position led to both activity enhancement and reduced risk for hERG channel inhibition and induced phospholipidosis. In our synthesis of compounds with 7-carboxyl group, we achieved efficient regioselective synthesis using bulky ester in the intramolecular palladium coupling reaction.

1. Introduction

Type 2 diabetes (T2D) is a major metabolic disorder affecting approximately 194 million people worldwide. This number is estimated to reach 366 million by 2030.[1] Currently used antidiabetic agents, such as PPARγ agonists, sulphonylurea derivatives, and biguanide and α-glucosidase inhibitors, produce beneficial effects on T2D by effectively increasing insulin secretion or decreasing glucose absorption. However, these agents are known to be associated with a number of side effects, including hypoglycemia, weight gain, gastrointestinal disorders, and lactic acidosis, all of which are known to decrease quality of life for T2D patients. Even Pioglitazone, the widely used antidiabetic agent, has recently been reported to be associated with increased risk of bladder cancer after treatment for two years or more,[2,3] although no direct relationship was found between treatment with this drug and occurrence of cancer in diabetics. Under these circumstances, intensive efforts have been made to find better and safer oral drugs for T2D.

Glucagon-like peptide-1 (GLP-1) is secreted from the gut in response to glucose absorption following meal ingestion and stimulates insulin secretion from β-cells of the pancreas, thereby contributing to maintenance of postmeal glycemic control.[4] As GLP-1 in plasma is rapidly degraded by the serine protease dipeptidyl peptidase IV (DPP-4),[5,6] inhibition of DPP-4 is emerging as a promising approach for treatment of T2D with low risk of hypoglycemia.[7,8] Actually, clinical proof of concept has already been established with DPP-4 inhibitors, which proved to be more efficient and safer than conventional antidiabetic agents.[8,9] Based on these clinical findings, a number of DPP-4 inhibitors, including Sitagliptin,[10] Vildagliptin,[11] Saxagliptin,[12] Alogliptin[13] and Linagliptin[14] (Fig. 1) have already been approved as new valuable agents for treatment of T2D.

Considering that T2D requires chronic treatment, highly selective DPP-4 inhibitors with low affinity for DPP-4 homologues, including DPP-8,[15] DPP-9[16] and FAPα,[17] are desirable. The requirement for DPP-4 selectivity over DPP-8 and DPP-9 has become a hot debate over the years. While inhibition of DPP-8 and DPP-9 is reported to be associated with alopecia, thrombocytopenia, reticulocytopenia, enlarged spleen, multiorgan histopathological changes, and mortality in rats and GI toxicity in dogs,[18] there is a report indicating that an alternative mechanism, not DPP-8/DPP-9 inhibition, likely causes these toxicities.[19] In this way, it seems that the physiological roles of DPP-8, DPP-9 and FAPα in human have not yet been completely elucidated. However, we believe that characterizing the selectivity of DPP-4 inhibitors is important, because it is sensible, when considering T2D patients long term treatment, to confine inhibition to the target enzyme where we know the effect. Vildagliptin and Saxagliptin inhibit DPP-8 and DPP-9 with K_i and IC_{50} values of 810 and 244, and 95 and 104 nM, respectively.[20] Furthermore, it has been shown that Linagliptin inhibits FAPα, which is known to play a role in embryonic wound healing and tissue

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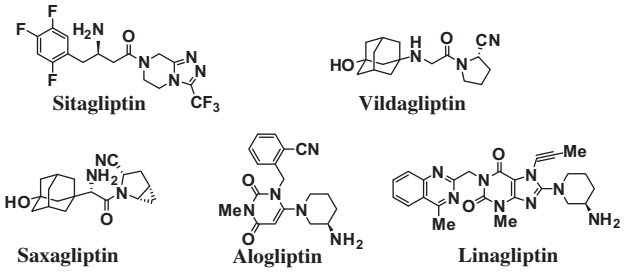


Figure 1. Marketed DPP-4 inhibitors.

remodeling,[21] with an IC_{50} value of 89 nM.[20] From a safety point of view, our search for DPP-4 inhibitors as drug candidates started with the aim of obtaining compounds with a selectivity for DPP-4 superior to that of Vildagliptin, Saxagliptin or Linagliptin. As Sitagliptin and Alogliptin already have excellent selectivity for DPP-4, we aimed at finding compounds with superior DPP-4 inhibitory activity and presumably better efficacy. As a result of our efforts,[22] 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **28** was found as potent and highly selective DPP-4 inhibitor. Herein, we report the discovery and evaluation of novel DPP-4 inhibitors with 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one scaffold. We also describe an efficient regioselective synthesis of selected compounds with substituents at the 7-position using intramolecular palladium coupling reaction.

By high-throughput screening of our chemical library, **1** was identified as a weak DPP-4 inhibitor (Fig. 2, bovine DPP-4 IC_{50} 676 nM). In our optimization of **1**, we focused on the piperazine ring, which is similar to the 3-amino piperidine moiety of reported DPP-4 inhibitors. Reports describing Alogliptin and other anti-diabetic agents[14] indicate that the (*R*)-3-amino piperidine group is essential for activity, as this group interacts with Glu205/Glu206 of DPP-4 protein. Thus, we decided to substitute the piperazine ring of **1** by an (*R*)-3-amino-piperidine ring. Furthermore, results of a docking study based on published DPP-4 enzyme-inhibitor crystal structures[23] indicated that the hydrophobic residue of Try547 could be located in a position that overlaps with the 2- and 3-positions in **1**. The π stacking interaction between **1** and DPP-4 protein could be formed by introduction of a fused aromatic ring at the 2- and 3-positions. Considering the above view, we decided to convert the Xanthine ring and designed a novel diverse 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one scaffold that has not been reported previously. Lead generation allowed us to obtain compound **2** with acceptable DPP-4 inhibitory activity (h-DPP-4 IC_{50} 418 nM). To further improve this inhibitory activity, the effect of a substitution at the 5-position of **2** was investigated (Table 1). Methylation (**2a**) improved DPP-4 inhibitory activity by 4-fold, while introduction of a sterically more bulky substituent, such as an ethyl (**2b**), propyl (**2c**) or benzyl group (**2d**), was not well tolerated. Thus, a methyl group at the 5-position was considered suitable, giving **2a** as lead compound with moderate DPP-4 inhibitory activity. Compounds DPP-4 inhibitory activity was measured using human plasma DPP-4.[24]

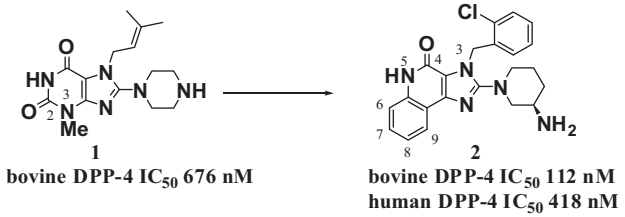
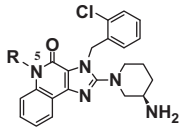


Figure 2. Synthesis of the DPP-4 inhibitor 2 from the HTS hit 1.

Table 1
DPP-4 inhibitory activity of **2** derivatives with different substituents at the 5-position



Compounds	R	h-DPP-4 IC_{50} (nM)
2	H	418
2a	Me	103
2b	Et	400
2c	nPr	3400
2d	Bn	>10000

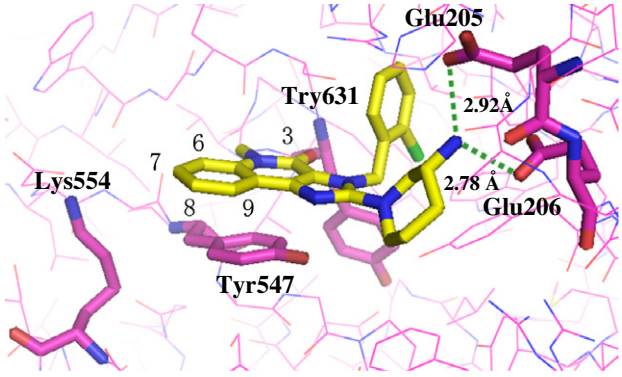
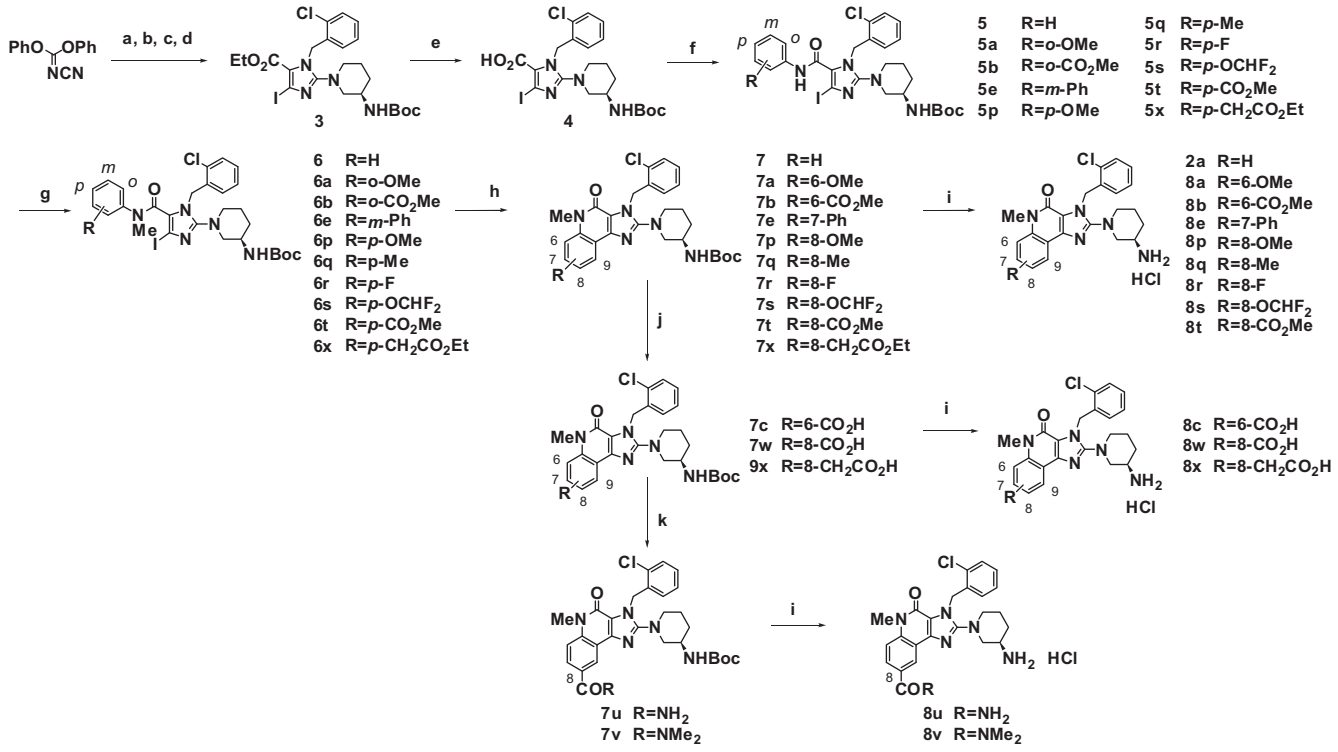


Figure 3. Docking structure of **2a** active site with 2RGU of DPP-4.

Next, we carried out a docking study to design a strategy for **2a** optimization (Fig. 3). As expected, a primary amino group at the piperidine moiety could form a salt bridge to Glu205/Glu206, since the distance between Glu205 and Glu206, and the amino group of **2a** was 2.92 and 2.78 Å, respectively. A chlorobenzyl group at the 3-position was expected to occupy the S1 pocket as previously reported. Similarly, a carbonyl group at the 4-position was anticipated to give an effective hydrogen bond to the main chain NH of Tyr631, while the 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one moiety was hoped to cover the phenyl moiety of Tyr547, affording the π-stack. Furthermore, we found that Lys554[25] residue was positioned near the benzene ring of the 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one scaffold and considered that interaction between this residue and a hydrophilic substituent on the benzene ring would significantly improve DPP-4 inhibitory activity. By this conformation, Lys554 would interact with the substituent at the 7-position. We hypothesized that an acidic substituent, such as a carboxyl group at the 7-position, would be especially effective in improving the affinity for DPP-4 due to formation of a salt bridge, especially. Based on the above information, we performed **2a** optimization, principally by introducing substituents at the 6–9 positions.

2. Chemistry

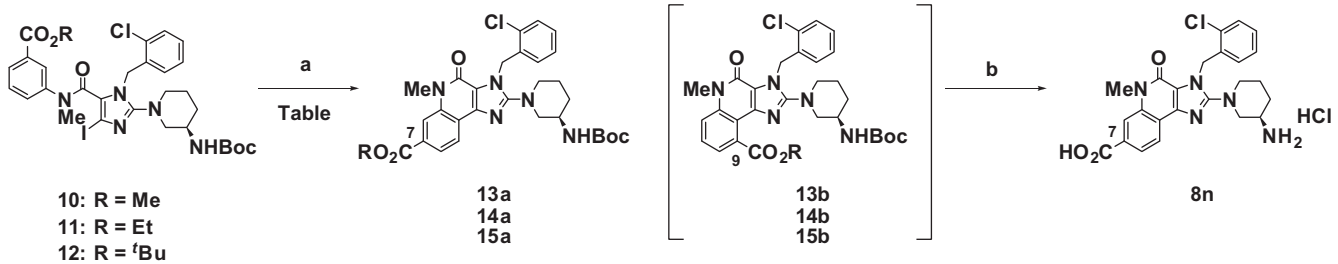
Compounds **2a**, **8a**, **8b**, **8e** and **8p**–**8t** were prepared according to the reported procedure[26] shown in Scheme 1. Intermediate **3** was obtained in four steps. Replacement of one phenoxy group in the commercially available diphenylcyanocarbonimidate with (*R*)-3-*tert*-butoxycarbonylaminopiperidine followed by treatment with excess amount of glycine ethyl ester in one pot, N-alkylation with 2-chlorobenzyl bromide, cyclization with sodium hydride and



Scheme 1. Reagents and conditions: (a) (*R*)-3-*tert*-butoxycarbonylaminopiperidine (1.0 equiv), ^{i}PrOH, rt then $EtO_2CCH_2NH_2$ (5.0 equiv), Et_3N (5.0 equiv), 80 °C, 92%; (b) 2-chlorobenzylbromide (1.5 equiv), K_2CO_3 (3.0 equiv), MeCN, 40 °C, 74%; (c) NaH (1.5 equiv), THF, 15 °C, quant.; (d) isoamylnitrite (5.0 equiv), CH_2I_2 (10 equiv), toluene, 80 °C, 53%; (e) 1 M NaOH (1.5 equiv), EtOH, 80 °C, quant.; (f) (1) $(COCl)_2$ (1.3 equiv), DMF (cat.), CH_2Cl_2, rt (2) DIPEA (3.0 equiv), R-substituted aniline (1.3 equiv), toluene, rt, 48–86%; (g) K_2CO_3 (4.0 equiv), MeI (4.0 equiv), DMF, rt, 81%-quant.; (h) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3 (2.0 equiv), DMF, 150 °C, 60–90%; (i) HCl, dioxane, rt, 59%-quant.; (j) 1 M NaOH/MeOH/THF (1/1/1), 80 °C, 58%-quant.; (k) WSC·HCl (1.5 equiv), HOBt (1.5 equiv), TEA (1.5–3.0 equiv), NH_4OH (1.5 equiv) or $NHMe_2$·HCl (2.0 equiv), DMF, rt, 73%-quant.

Sandmeiyer reaction gave the imidazole **3**. Alkaline hydrolysis of **3** afforded **4**, and amidation with the corresponding anilines, followed by N-methylation provided **6**, **6a**, **6b**, **6e**, **6p**–**6t**, and **6x**. Palladium coupling reaction of these compounds proceeded well, and removal of the Boc group afforded **2a**, **8a**, **8b**, **8e** and **8p**–**8t**. Alkaline hydrolysis of **7b**, **7t**, and **7x**, followed by removal of the Boc group gave **8c**, **8w**, and **8x**. The carboxylic acid **7w** was reacted with ammonia or dimethylamine to afford the amides **7u** and **7v**. **8u** and **8v** were obtained by removal of the Boc group.

In the synthesis of 7-substituted derivatives, especially with a carboxyl group (Scheme 2), intramolecular palladium cyclization of **10** possessing a methyl ester gave a mixture of **13a** and **13b** (**13a**/**13b** = 4/1, entry 1) inseparable by silica-gel column chromatography. It was therefore necessary to establish an efficient regioselective synthetic method to obtain **8n**. Considering the reaction mechanism, cyclization could proceed to form the cationic intermediates **16** and **17**[26] through oxidative addition of aryliodide to Pd(0) followed by abstraction of the iodide with Ag_2CO_3. As 7-substituted derivatives were afforded via intermediate **16**, it was necessary to increase the abundance of **16** for higher selectivity. To solve this problem, we attempted to use a sterically more bulky ester than the methyl ester to obtain the preferred intermediate **16**



Reagents and Conditions: (a) $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Ag_2CO_3 (2.0 equiv), DMF, 150 °C; (b) HCl, dioxane, 80 °C

Entry	Substrate R	Product ratio[a] (**a** / **b**)	Yield
1	**10** Me	**13** : 4 / 1	76% (**13a**+**13b**)
2	**11** Et	**14** : 14 / 1	none
3	**12** ^{t}Bu	**15** : 28 / 1	**15a** : 73%[b]

[a] The ratio was determined by HPLC. [b] Isolated yield.

Scheme 2. Regioselective synthesis of **8n** with carboxyl group at the 7-position. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3 (2.0 equiv), DMF, 150 °C; (b) HCl, dioxane, 80 °C.

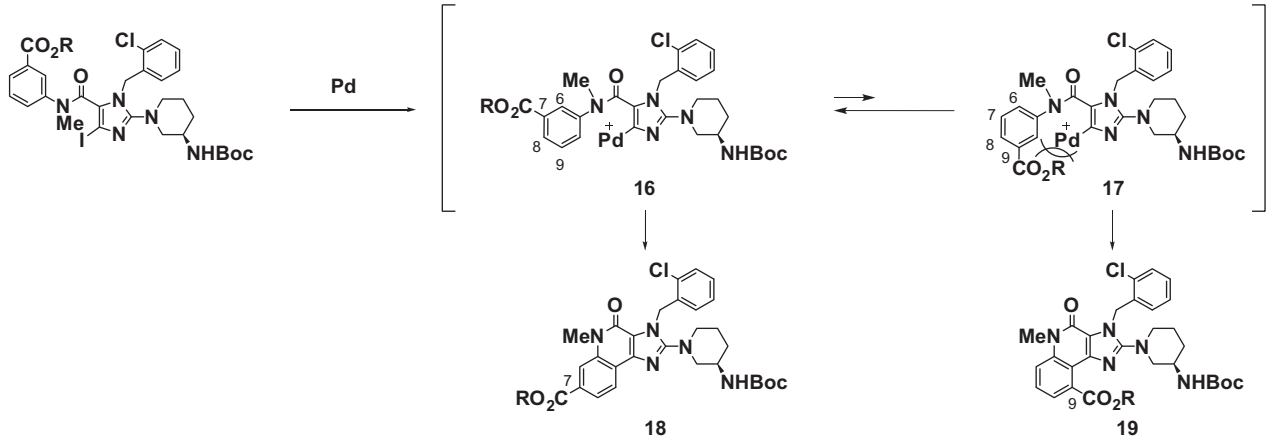
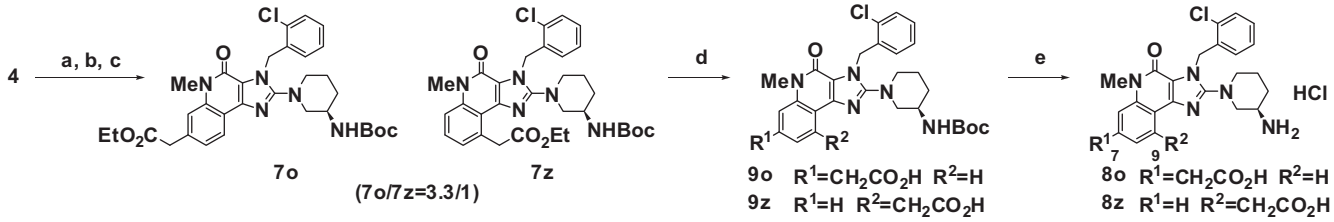


Figure 4. Proposed mechanism for predominantly producing 7-ester derivatives.

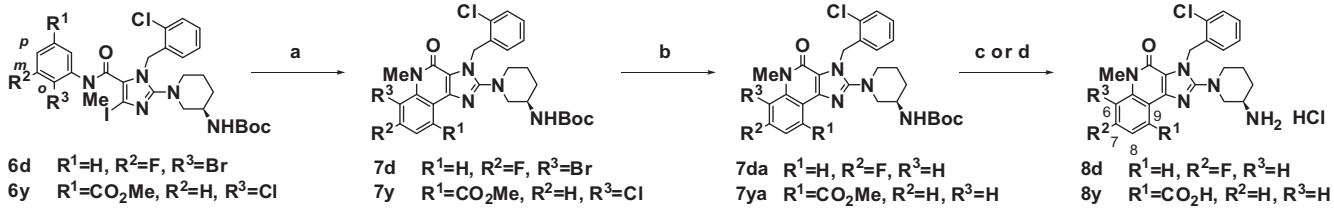


Scheme 3. Synthesis of **8o** and **8z**. Reagents and conditions: (a) (1) $(COCl)_2$ (1.3 equiv), DMF (cat.), CH_2Cl_2, rt (2) DIPEA (3.0 equiv), ethyl 2-(3-aminophenyl)acetate (1.3 equiv), toluene, rt, 62%; (b) K_2CO_3 (4.0 equiv), MeI (4.0 equiv), DMF, rt; (c) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3 (2.0 equiv), DMF, 150 °C, **7o** 43% for 2 steps, **7z** 13% for 2 steps; (d) 1 M NaOH/MeOH/THF (1/1/1), rt; (e) HCl, dioxane, rt, **8o** 88% for 2 steps, **8z** 53% for 2 steps.

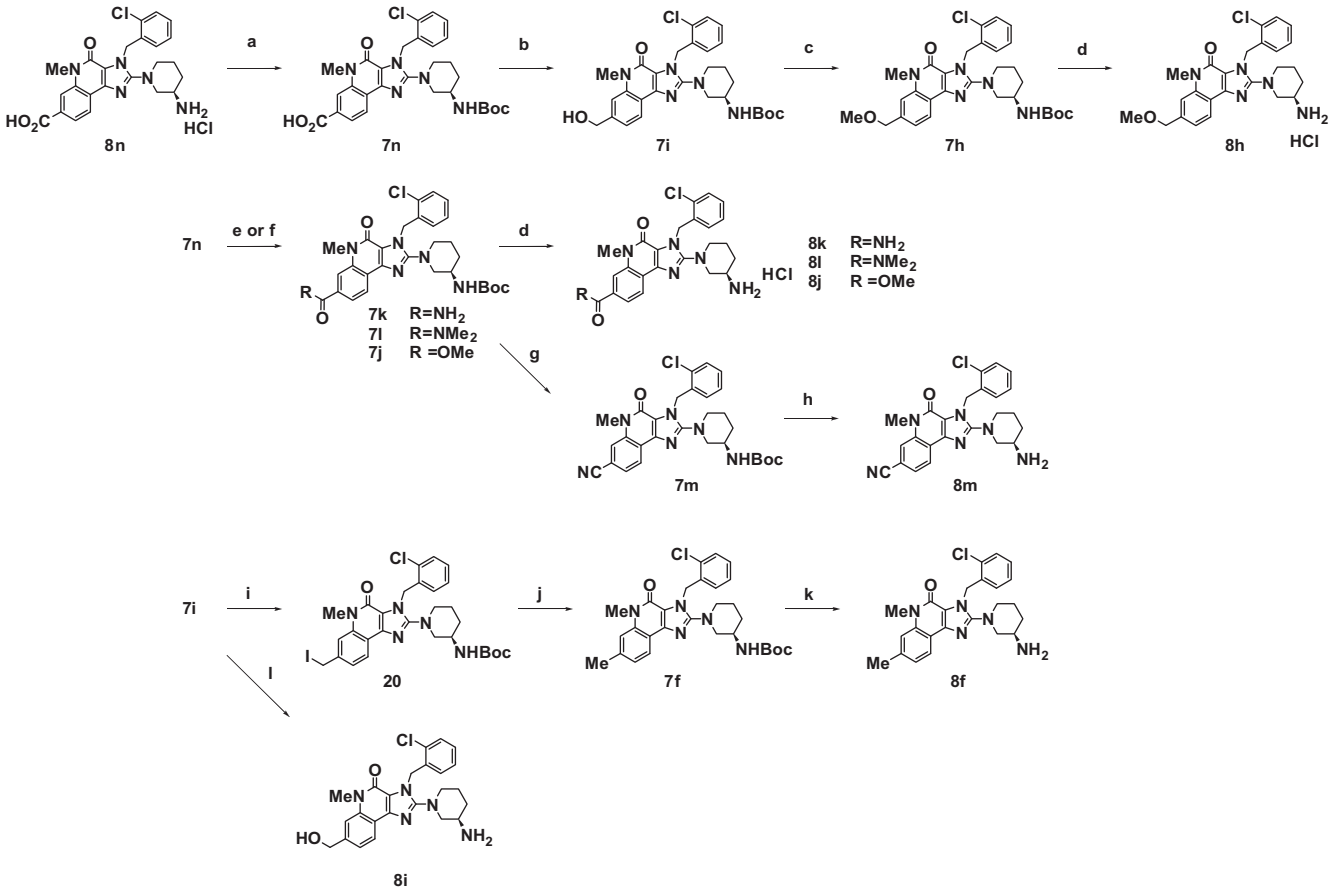
by steric hindrance between Pd and R group in the intermediate state (Fig. 4). By use of an ethyl ester (**11**), selectivity was certainly improved (**14a/14b** = 14/1, entry 2). This result encouraged us to use ^{t}Bu ester as a more bulky ester. As expected, intramolecular palladium coupling reaction of **12** possessing ^{t}Bu ester afforded **15a** with excellent selectivity (**15a/15b** = 28/1, entry 3). Fortunately, the mixture of **15a** and **15b** was separable by silica-gel column chromatography to give **15a** in good yield. Treatment of **15a** with hydrochloric acid at 80 °C afforded the desired compound **8n** after removal of the Boc group and *tert*-butyl ester.

As shown in Scheme 3, the carboxyl methyl derivatives **8o** and **8z** were synthesized by the same procedure described in Schemes 1 and 2. A palladium coupling reaction using ethyl ester was carried out to obtain a mixture of **7o** and **7z** as it was necessary to synthesize both **8o** and **8z**. The product ratio of **7o** to **7z** was approximately 3.3:1, and the mixture was separable by silica-gel column chromatography.

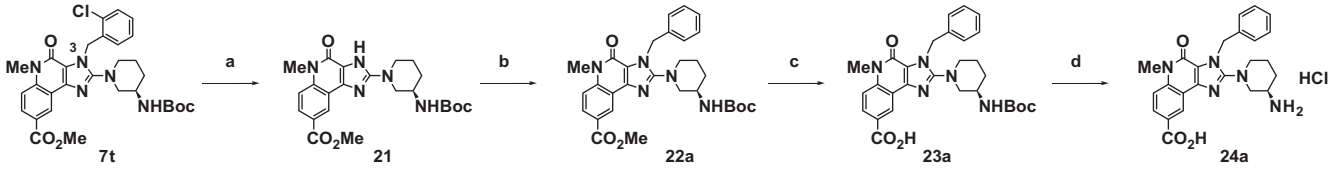
Compound **8d** with a fluorine atom at the 7-position could be synthesized from the precursor **6d** possessing a bromine atom as auxiliary at the *ortho*-position by palladium coupling reaction, followed by Pd/C-catalyzed debromination under hydrogen, and deprotection of the Boc group (Scheme 4). This allowed us to solve another problem, as regioselective synthesis of 9-substituted compounds could be achieved. Palladium coupling reaction of **6y** possessing a chlorine atom as auxiliary, followed by selective dechlorination gave **7ya**. **8y** was provided by alkaline hydrolysis of **7ya** followed by removal of the Boc group. Selective dehalogenation reaction could be used to eliminate the high steric hindrance between the chlorine or bromine atom at the 6-position and the N-methyl group. Synthesis of derivatives with various substituents at the 7-position was carried out as depicted in Scheme 5. The amino group of **8n** was protected by Boc group to give **7n**. Compound **7n** was treated with ethyl chloroformate followed by reduction with $NaBH_4$ to afford the hydroxymethyl **7i**, which was converted to the methylether **7h** by alkylation of the hydroxyl group. **7i** was deprotected with trifluoroacetic acid to give **8i**, and **7n** was converted to **7k** and **7l** by condensation with ammonia or dimethylamine and to **7j** by alkylation with iodomethane. Dehydration of **7k** with trifluoroacetic acid anhydride gave the nitrile **7m**. **7f** with a methyl group at the 7-position was prepared by iodination of **7i**, followed by reduction of the iodine atom with sodium borohydride. The desired compounds **8f**, **8h**, **8k**, **8l**, **8j** and **8m** were



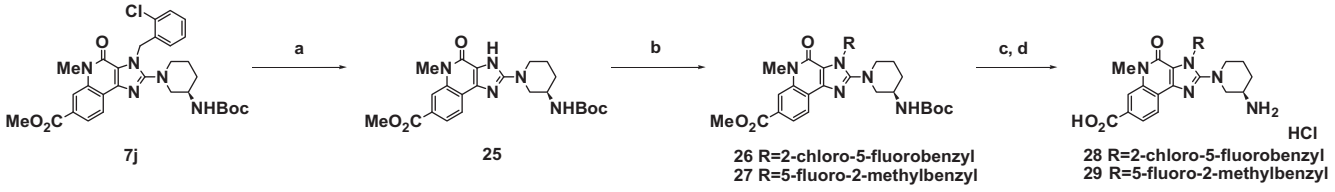
Scheme 4. Regioselective synthesis of **8d** and **8y**. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3 (2.0 equiv), DMF, 150 °C, **7d** 21%, **7y** 57%; (b) Pd/C, H_2, MeOH, rt, **7da** quant., **7ya** 97%; (c) HCl, dioxane, rt, quant.; (d) (1) 1 M NaOH, THF/MeOH (1/1), rt (2) HCl, dioxane, rt, quant.



Scheme 5. Synthesis of 7-substituted derivatives. Reagents and conditions: (a) $(Boc)_2O$ (1.3 equiv), sat. $NaHCO_3$/THF (1/1), rt, 60%; (b) $ClCO_2Et$ (1.5 equiv), TEA (2.0 equiv), THF, 0 °C then $NaBH_4$ (3.0 equiv), H2O, rt, 57%; (c) NaH (1.2 equiv), MeI (1.2 equiv), DMF, rt, 86%; (d) HCl, dioxane, rt, 95%-quant.; (e) WSC·HCl (1.5 equiv), HOBt (1.5 equiv), TEA (1.5 equiv), NH_4OH (1.5 equiv) or $NHMe_2$·HCl (2.0 equiv), DMF, rt, 7 k 80%, 7 l quant.; (f) MeI (2.0 equiv), K_2CO_3 (3.0 equiv), DMF, rt, quant.; (g) TFAA (4.5 equiv), THF, 65 °C then K_2CO_3 (4.0 equiv), MeOH, rt, 44%; (h) TFA, CHCl3, rt, then sat. $NaHCO_3$, 88%; (i) I_2 (2.0 equiv), imidazole (2.5 equiv), PPh_3 (1.5 equiv), THF, rt, 25%; (j) $NaBH_4$ (3.0 equiv), DMSO, 50 °C, 91%; (k) HCl, dioxane, rt then sat. $NaHCO_3$, quant.; (l) TFA, $CHCl_3$, rt (2) K_2CO_3 (3.0 equiv), MeOH, rt, 75%.



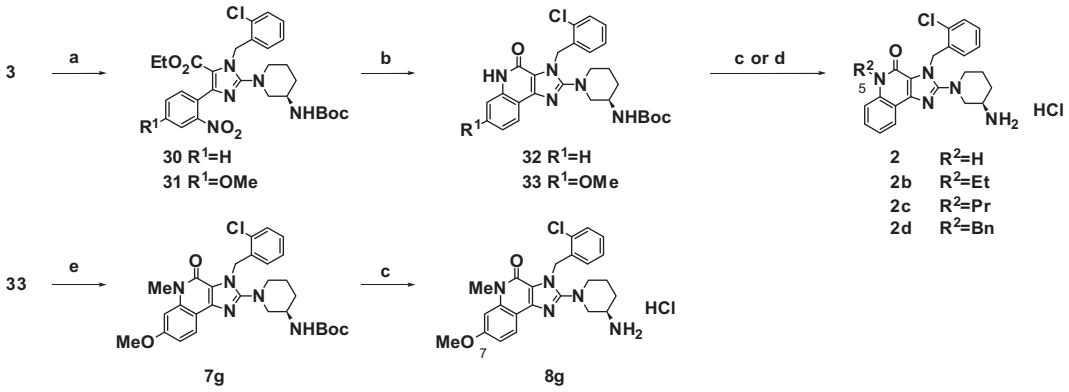
Scheme 6. Conversion of substituents in 8-carobxyl derivatives. Reagents and conditions: (a) Pd/C, HCO_2NH_4 (10 equiv), MeOH, reflux, 83%; (b) benzyl bromide (2.0 equiv), K_2CO_3 (3.0 equiv), DMF, 60 °C, 99%; (c) 1M NaOH/THF/MeOH (1/1/1), rt, 54%; (d) HCl, dioxane, rt, quant.



Scheme 7. Synthesis of **28** and **29.** Reagents and conditions: (a) Pd/C, HCO_2NH_4 (10 equiv), MeOH, reflux, 54%; (b) 2-chloro-5-fluorobenzyl bromide or 5-fluoro-2-methylbenzyl bromide (2.0 equiv), K_2CO_3 (3.0 equiv), DMF, 60 °C, **26** 71%, 27 66%; (c) 1 M NaOH/THF/MeOH (1/1/1), rt; (d) HCl, dioxane, rt, **28** 90%, **29** 84%.

readily obtained by removal of the Boc group of **7f**, **7h**, **7k**, **7l**, **7j** and **7m**, respectively.

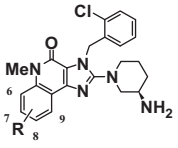
Conversion of the moiety at the 3-position is shown in Schemes 6 and 7. Pd/C catalytic hydrogenation of **7t** with HCO_2NH_4 in MeOH under reflux afforded **21** in high yield. N-benzylation at the 3-position using benzyl bromide, alkaline hydrolysis and removal of the Boc group gave **24a**. Compounds **24b**–**24n** were synthesized from **21** in the same manner described for compound **24a** using various halide. Compound **7j** was converted to **28** and **29** by the same procedure described in Scheme 6 (Scheme 7).



Scheme 8. Alternative synthetic route to **2**, **2b**-**2d** and **8g.** Reagents and Conditions: (a) $Pd(PPh_3)_4$ (10 mol %), Na_2CO_3 (2.0 equiv), 2-(2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane or 2-(4-methoxy-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 equiv), DME–H_2O (1/1), reflux, **30** 40%, **31** 89%, ; (b) Fe (6.0 equiv), AcOH, 80 °C, **32** 92%; (c) HCl, dioxane, rt, 2 83%, 8 g 89%; (d) (1) R^2-halide (3.0 equiv), K_2CO_3 (3.0 equiv), DMF, rt (2) HCl, dioxane, rt, 60–80% for 2 steps; (e) K_2CO_3 (2.0 equiv), MeI (2.0 equiv), DMF, 74% for 2 steps.

Another synthetic route[26] for introduction of various alkyl substituents at the 5-position or a methoxy group at the 7-position are shown in Scheme 8. Suzuki-Miyaura cross coupling reaction of **3** with the corresponding pinacol boronate yielded **30** and **31**, which were converted to 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **32** and **33** by reduction of the nitro group and subsequent intramolecular amidation. Removal of the Boc group in **32** resulted in compound **2**. **32** was alkylated with various alkyl halide, followed by N-Boc deprotection to afford **2b**–**2d**. After N-methylation of **33**, deprotection of the Boc group of the resulting **7g** provided **8g**. Using the above synthetic method, we could achieve efficient regioselective synthesis with substituent at the 7- or 9-position and produce 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones with various substituent at the 3, 5 and 6–9 positions.

Table 2
In vitro activity of the synthesized DPP-4 inhibitors



Compounds	R	h-DPP-4 IC_{50} (nM)
8a	6-OMe	660
8b	6-CO_2Me	271
8c	6-CO_2H	72
8d	7-F	66
8e	7-Ph	72
8f	7-Me	340
8g	7-OMe	66
8h	7-CH_2OMe	17
8i	7-CH_2OH	22
8j	7-CO_2Me	16
8k	7-$CONH_2$	12
8l	7-$CONMe_2$	10
8m	7-CN	6.3
8n	7-CO_2H	1.6
8o	7-CH_2CO_2H	3.8
8p	8-OMe	90
8q	8-Me	94
8r	8-F	56
8s	8-$OCHF_2$	60
8t	8-CO_2Me	21
8u	8-$CONH_2$	14
8v	8-$CONMe_2$	13
8w	8-CO_2H	5.8
8x	8-CH_2CO_2H	3.5
8y	9-CO_2H	54
8z	9-CH_2CO_2H	17

3. Results and discussion

In order to validate our hypothesis, **8a**–**8z** with substituents at the 6–9 positions were evaluated for their DPP-4 inhibitory activity. The results are shown in Table 2. Generally, a substituent at the 6-position had no beneficial effect on the inhibitory activity, although a carboxyl group (**8c**) slightly improved the activity. As for substitution at the 7-position, a hydrophobic fluoro or phenyl group (**8d**, **8e**) slightly improved the activity, while a methyl group (**8f**) decreased the activity by approximately 3-fold compared to that of **2a**. Hydrophobic substituents had no important contribution to the inhibitory activity. Meanwhile, **8g** with a methoxy group showed approximately 2-fold more potent inhibitory activity than **2a**, and **8h** with a methylene linked to **8g** and **8i** with a hydroxyl methyl group were more than 3-fold active than **8g**. A methyl ester (**8j**), carbamoyl (**8k**) or dimethylamide (**8l**) group resulted in good inhibitory activity with IC_{50} values of 16, 12 and 10 nM respectively. Additionally, introduction of a cyano group led to further improvement in DPP-4 inhibitory activity (**8m**, 6.3 nM). Especially, a carboxyl group produced a dramatic improvement in inhibitory activity (**8n**, 1.6 nM) with the resulting **8n** being 64-fold more active than **2a**. A carboxyl methyl group as alternative to the carboxyl substituent could also result in potent DPP-4 interaction (**8o**, 3.8 nM). As for substitution at the 8-position, a methoxy or methyl group (**8p**, **8q**) produced no improvement in DPP-4 inhibitory activity. A fluoro or difluoromethoxy group led to a slight improvement in the activity (**8r**, **8s**), while a methyl ester group (**8t**) and an amide group (**8u**, **8v**) led to acceptable DPP-4 inhibition. Interestingly, a carboxyl group significantly increased DPP-4 inhibitory activity as was the case with a substitution at the 7-position (**8w**). Surprisingly, **8x** with a methylene inserted into carboxyl group of **8w** showed further improvement of the activity. The effect of a carboxyl group at the 9-position (**8y**) was significantly less potent than that of a substituent at the 7- or 8-position, although the 9-carboxy methyl **8z** was good DPP-4 inhibitor. Introduction of hydrophilic substituent at the 7- or 8-position was found to be effective, especially, a carboxyl group or a carboxyl methyl group improved the activity dramatically.

To verify the interaction between the potent DPP-4 inhibitor **8n** with a 7-carboxyl group and DPP-4 protein, a docking study was attempted, and the results are shown in Fig. 5. Compound **8n** exhibited a binding mode similar to that shown by **2a** with a

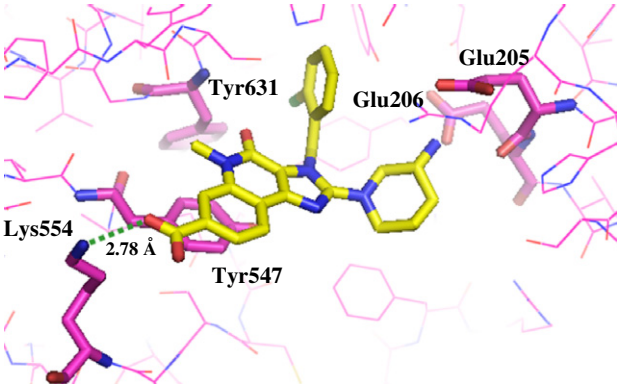


Figure 5. Docking structure of **8n** in the active site from 2RGU of DPP-4.

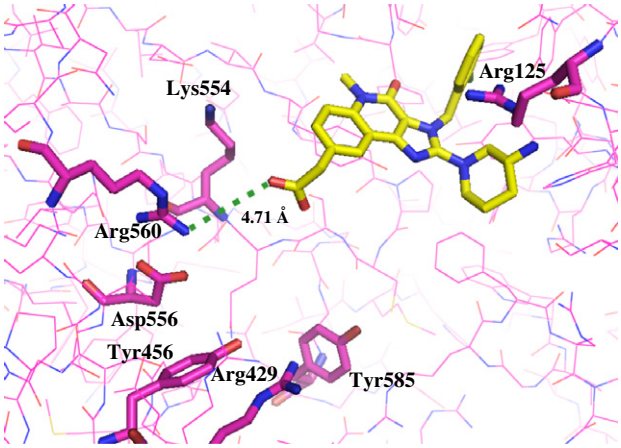
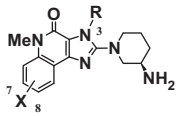


Figure 6. Docking structure of **8x** in the active site from 2RGU of DPP-4.

distance between the 7-carboxyl group and the residue of Lys554 of 2.78 Å. Accordingly, we could confirm that the 7-carboxyl group makes a salt bridge interaction with Lys554. This interaction serves to significantly enhance the inhibitory activity, giving the most potent inhibitor. Although **8o** with a carboxyl methyl group was also thought to interact with the residue of Lys554, DPP-4 inhibitory activity of **8o** was weaker than that of **8n** as the carboxyl methyl group was shifted from the most appropriate position for interaction with Lys554 compared to the carboxyl group of **8n**. A hydrogen bond between the oxygen atom of the methoxy methyl group (**8h**) or the hydroxy methyl group (**8i**) and the residue of Lys554 afforded acceptable activity. Although hydrophilic substituents were acceptable, the resulting inhibitory activity was weaker than that of the carboxyl group or the carboxyl methyl group, since interaction with the residue of Lys554 was weak compared to the electrovalent bond of the salt bridge. In order to understand the interaction between a carboxyl substituent at the 8-position and DPP-4 protein, a docking study using **8x** was performed (Fig. 6). Although no amino acid residue could directly interact with the carboxyl or carboxyl methyl group in the vicinity of the 8-position, there was a hydrophilic space surrounded by the residues of Lys554, Arg560, Asp556, Tyr456, Arg429 and Try585. Therefore, a hydrophilic substituent was considered to be acceptable. Especially, significant improvement of activity was achieved by introduction of a carboxyl methyl or carboxyl group. Although 8-carboxyl methyl group was positioned close to Arg560, the distance between the two was not appropriate for interaction (4.71 Å). Considering that a carboxyl methyl group led to more potent DPP-4 inhibitory activity than a carboxyl group, it is believed that

Table 3
In vitro activity of DPP-4 inhibitors with various moiety at 3-position



Compounds	X	R	h-DPP-4 IC_{50} (nM)
8w	8-CO_2H	2-Chlorobenzyl	5.8
24a	—	Benzyl	64
24b	—	2-Methylbenzyl	11
24c	—	2-Methoxybenzyl	38
24d	—	2-Fluorobenzyl	160
24e	—	3-Chlorobenzyl	110
24f	—	4-Chlorobenzyl	>10000
24g	—	3-Methoxybenzyl	150
24h	—	4-Methoxybenzyl	6900
24i	—	2-Chlorophenethyl	3500
24j	—	cyclohexylmethyl	8900
24k	—	methylbut-2-enyl	51
24l	—	But-2-ynyl	90
24m	—	2,5-Dichlorobenzyl	25
24n	—	2-chloro-5-fluorobenzyl	4.8
28	7-CO_2H	2-Chloro-5-fluorobenzyl	0.48
29	—	5-Fluoro-2-methylbenzyl	0.55

the carboxyl methyl group of **8x** might further interact with the residue of Arg560 by bridging of a water molecule and afford enhanced DPP-4 inhibitory activity. As mentioned above, it was found that introduction of a carboxyl substituent at the 7- or 8-position is important for enhanced inhibitory activity in this series of DPP-4 inhibitors.

Finally, to further improve DPP-4 inhibitory activity, optimization of the moiety at the 3-position, which occupies the S1 pocket, was attempted using **8n** and **8w** with a 7- or 8-carboxyl group (Table 3). First, we examined the effect of a substituent on the benzyl group. A chlorine atom at the *ortho* position of **8w** increased the inhibitory activity by 10-fold compared to the non-substituted **24a**. Next, an electron-donating or electron-withdrawing group was introduced to investigate the effect of a substitution at the *ortho* position (**24b**∼**24d**). Although a methyl group (**24b**) was acceptable, a methoxy (**24c**) or a fluoro group (**24d**) were not favorable for the inhibitory activity. It was subsequently found that the size of atom in the S1 pocket is important for DPP-4 inhibitory activity and that a chlorine atom or a methyl group are favorable. Additionally, the preferred position of the substituent was *ortho* (**8w**, **24c**) > *meta* (**24e**, **24g**) > *para* (**24f**, **24h**). However, a substituent at a site beside the benzyl group, such as at the 2-chlorophenethyl (**24i**) or cyclohexylmethyl group (**24j**), resulted in significant loss of activity. Substituents that were reported with other DPP-4 inhibitors such as those in **24k** and **24l** also resulted in remarkable loss of activity. Based on the above, we believed that compounds inhibitory activity would be further enhanced by introducing a new substituent into the 2-substituted benzyl group, such as a 2-chloro or a 2-methyl benzyl group. As our docking study showed that the S1 pocket is almost completely occupied by 2-substitued benzyl group, we realized that a substitution at the 5-position of the benzyl group would be possible due to the remaining slight space. Although the activity of the 2,5-dichloro substituted **24m** was slightly decreased, we considered that a chlorine atom was a little larger than the available space and that the smaller fluorine atom might be suitable. The inhibitory activity of **24n** with a 5-fluoro-2-chloro benzyl group was slightly improved (**24n**, 4.8 nM). Thus the most suitable moiety at the 3-position was found to be 5-fluoro-2-chlorobenzyl group. To further increase the activity, the 5-fluoro-2-chlorobenzyl group was attached a 7-carboxy compound, such as **8n**. This led to **28**, which showed the most potent

Table 4
DPP-4 inhibitory activity of **28** and other marketed drugs (IC_{50} nM)

Entry	DPP-4	FAPα	DPP-2	DPP-8	DPP-9	Fold selectivity		
						DPP-8	DPP-9	FAP
28	0.48	30,600	>10,000	>100,000	>100,000	>208,000	>208,000	63,750
Vildagliptin	K_i = 3	NA	>500,000	K_i = 810	K_i = 95	270	32	NA
Saxagliptin	3.37	NA	>30,000	244	104	72	31	NA
Linagliptin	1.0	89	>100,000	>40,000	>10,000	>40,000	>10,000	89
Alogliptin	4	>100,000	>100,000	>100,000	>100,000	>25,000	>25,000	>25,000
Sitagliptin	18	>100,000	>100,000	48,000	>10,000	>2667	>5550	>5550

Note: NA, Not available.

DPP-4 inhibitory activity in our series (0.48 nM). Compound **29** with a 5-fluoro-2-methyl benzyl group also showed potent inhibitory activity (0.55 nM). The effect of a fluorine atom in the docking study suggests interaction with the residue of Arg125 by forming a hydrogen bond and/or hydrophobic interaction by full occupation of the S1 pocket.

Compound **28** was evaluated for its inhibition of DPP-4 homologues, including DPP-2[27], DPP-8, DPP-9 and FAPα, and the results were compared to those of marketed DPP-4 inhibitors[20] (Table 4). Vildagliptin and Saxagliptin inhibited both DPP-8 and DPP-9 with a selectivity ratio for DPP-4 over DPP-9 of only about 30-fold. On the other hand, **28** showed no inhibition of DPP-8 or DPP-9. While Linagliptin inhibited FAPα with an IC_{50} value of 89 nM and a selectivity ratio for DPP-4 over FAPα of 89-fold, **28** hardly inhibited FAPα, and the selectivity ratio overwhelmingly surpassed that of Linagliptin. **28** showed excellent selectivity against all DPP-4 homologues and exhibited more than 8-fold and 37-fold potent DPP-4 inhibitory activity than Alogliptin and Sitagliptin, respectively. Based on these findings, it was assumed that **28** would have excellent pharmacological profile. Next, we evaluated compound **28** inhibition of hERG channel to assess its risk for cardiac disturbance. Although both **8h** and **8m** inhibited hERG channel with an IC_{50} values of 1.81 and 1.20 μM, respectively, compound **28** had no effect on hERG channel (IC_{50} >10 μM). Drug induced phospholipidosis is another specific toxicity associated with compounds lipophilicity.[28] Accordingly, we evaluated compounds **28**, **8h** and **8m** for their phospholipid index (PI) compared to the reference standard propranolol (PI = 1.00 at 30 μM) using isolated human hepatocytes.[29] The PIs of **8h** and **8m** were 0.33 and 0.37 at a concentration of 3 μM, respectively, whereas the PI of **28** was 0.014 and 0.008 at the concentration of 3 and 30 μM, respectively. These findings confirmed that **28** induced no phospholipidosis. Compound **28** also showed no concerns related to introduction of carboxyl group and formation of zwitter-ion.[30] Furthermore, compound **28** exhibited no CYP inhibition (IC_{50} >50 μM; 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 3A4) and no induced enzyme, making it a compound with clean safety profile.

4. Conclusion

In summary, we optimized the lead comound **2a** and obtained a series of novel DPP-4 inhibitors with 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one scaffold. In our synthesis of these derivatives, we could achieve efficient regioselective synthesis of 7- or 9-substituted compounds. Using *t*Bu ester, compounds, such as **8n** with a carboxyl group at the 7-position, could be obtained in good yield and regioselectivity. As a result of our effort, we could efficiently synthesize 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones with hydrophilic substituent at the 7- and 8-positions. We found that a carboxyl group at the 7-position enhances DPP-4 inhibitory activity by interacting with Lys554 residue. Further optimization led to **28** as the most potent DPP-4 inhibitor in our series. **28** has more than 8-fold potent DPP-4 inhibitory activity compared to Alogliptin. Furthermore, **28** showed excellent selectivity against various DPP-4 homologues superior to that of Vildagliptin, Saxagliptin or Linagliptin. It is therefore believed that **28** could be more valuable and safer drug for T2D than marketed DPP-4 inhibitors. Unfortunately, **28** showed poor oral absorption in rat PK test. Therefore, further studies, including improvement of **28** oral absorption, are underway and will be reported and discussed in due course.

5. Experimental section

Melting points were determined on an electrothermal apparatus without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300 spectrometer and a Brucker AVANCE 400 spectrometer in the stated solvents using tetramethylsilane as an internal standard. Chemical shift (d) are expressed in parts per million. IR spectra were recorded on a JEOL JIR-SPX60 spectrometer as ATR. High resolution MS spectra were recorded on a Thermo Fisher Scientific LTQ orbitrap Discovery MS equipment. Elemental analysis was conducted at Sumitomo Analytical Center Inc. Reactions were followed by TLC on silica gel 60 F254 using precoated TLC plates (E. Merck). Column chromatography was carried out on a Yamazen W-prep system using prepacked silica gel or amino silica gel or performed on silica gel 60 (230–400 or 70–230 mesh, Merck). Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All solvents were of the commercially available grade. Reactions requiring anhydrous conditions were performed under nitrogen atmosphere.

Compounds **3**, **4**, **5**, **6**, **7**, **7a**, **7b**, **7e**, **7p**, **7q**, **7r**, **2a**, **8a**, **8b**, **8e**, **8p**, **8q**, **8r**, **30** and **32** were synthesized as previously reported.[26]

5.1. Methyl 4-({[2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino] piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-*1H*-imidazol-5-yl] carbonyl}amino)benzoate (5t)

To a solution of **4** (56.08 g, 100 mmol) in CH_2Cl_2 (1.3 L) were added $(COCl)_2$ (16.5 g, 130 mmol) and DMF (5 ml) at 0 °C. The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was azeotroped with toluene and redissolved in toluene (1.3 L). To this solution was added DIPEA (38.8 g, 300 mmol) followed by methyl 4-aminobenzoate (19.7 g, 130 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **5t** (54.63 g, yield 79%) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.39–7.36 (m, 1H), 7.22–7.13 (m, 2H), 6.82–6.78 (m, 1H), 5.58 (d, J = 16.2 Hz, 1H), 5.50 (d, J = 16.2 Hz, 1H), 4.93–4.90 (m, 1H), 3.90 (s, 3H), 3.77 (br s, 1H),

3.31 (dd, J = 3.3, 12.0 Hz, 1H), 2.93–2.84 (m, 3H), 1.78–1.54 (m, 4H), 1.49 (s, 9H); HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{34}O_5N_5ClI$ 694.1288, found 694.1272; IR (ATR): 1714, 1675, 1591, 1513, 1434, 1405, 1311, 1280, 1243, 1222, 1172, 1110, 1060 cm^{-1}; Anal. calcd for $C_{29}H_{33}O_5N_5ClI$: C, 50.19; H, 4.79; N, 10.09, found: C, 50.52; H, 4.95; N, 9.92.

5.2. Methyl 4-[{[2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino] piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-*1H*-imidazol-5-yl] carbonyl}(methyl)amino]benzoate (6t)

A mixture of **5t** (109 mg, 0.157 mmol), K_2CO_3 (86.8 mg, 0.628 mmol), and MeI (39.1 μl, 0.63 mmol) in DMF (2 ml) was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **6t** (91.6 mg, yield 82%) as a pale yellow amorphous. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.46–7.43 (m, 1H), 7.34–7.18 (m, 3H), 6.79 (br s, 2H), 5.24 (br s, 2H), 4.99–4.97 (m, 1H), 3.90 (s, 3H), 3.82 (br s, 1H), 3.32 (br s, 1H), 3.23 (s, 3H), 3.00 (br s, 2H), 2.92–2.86 (m, 1H), 1.80–1.79 (m, 2H), 1.64 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 161.9, 155.9, 155.0, 147.0, 146.9, 134.2, 133.4, 131.4, 130.1, 130.0, 129.9, 129.9, 127.6, 126.9, 125.1, 79.2, 56.2, 52.2, 51.9, 46.4, 46.1, 38.1, 29.5, 28.3, 22.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{36}O_5N_5ClI$ 708.1444, found 708.1428; IR (ATR): 1716, 1704, 1699, 1652, 1646, 1635, 1506, 1488, 1473, 1456, 1436, 1363, 1276, 1241, 1170, 1105, 1049 cm^{-1}; Anal. Cacld for $C_{30}H_{35}O_5N_5ClI{\cdot}1.25H_2O$: C, 49.32; H, 5.17; N, 9.59, found: C, 49.17; H, 4.87; N, 9.33.

5.3. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-8-carboxylate (7t)

A mixture of **6t** (172 mg, 0.243 mmol), $Pd(OAc)_2$ (5.46 mg, 0.0234 mmol), PPh_3 (12.7 mg, 0.0484 mmol), and Ag_2CO_3 (133.9 mg, 0.486 mmol) in DMF (2 ml) was stirred at 150 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was washed with saturated NH_4Cl aqueous solution twice and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7t** (119.8 mg, yield 85%) as a pale yellow solids. Mp 186–188 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, J = 1.8 Hz, 1H), 8.18 (dd, J = 2.1, 9.0 Hz, 1H), 7.47 (d, J = 11.6 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.27–7.12 (m, 2H), 6.70 (d, J = 6.9 Hz, 1H), 5.78 (d, J = 17.4 Hz, 1H), 5.63 (d, J = 17.4 Hz, 1H), 5.40–5.37 (m, 1H), 3.98 (s, 3H), 3.84 (br s, 1H), 3.76 (s, 3H), 3.48–3.31 (m, 1H), 3.24–3.18 (m, 1H), 3.10 (m, 2H), 1.78 (m, 4H), 1.44 (s, 9H); HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{35}O_5N_5Cl$ 580.2321, found 580.2314; IR (ATR): 1718, 1689, 1652, 1569, 1500, 1446, 1429, 1388, 1353, 1313, 1274, 1234, 1174, 1124, 1110, 1066, 1039 cm^{-1}; Anal. calcd for $C_{30}H_{34}ClN_5O_5$: C, 62.12; H, 5.91; N, 12.09, found: C, 62.11; H, 5.88; N, 12.07.

5.4. Methyl 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-8-carboxylate hydrochloride (8t)

To a solution of **7t** (22.1 mg, 0.0381 mmol) in 1,4-dioxane (1 ml) was added 4 N HCl-1,4-dioxane (1 ml). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give **8t** (21.9 mg, quantitative yield) as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 2.1 Hz, 1H), 8.37 (br s, 3H), 8.09 (dd, J = 2.1, 8.9 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.51 (dd, J = 1.1, 7.9 Hz, 1H), 7.33–7.28 (m, 1H), 7.25–7.21 (m, 1H), 6.71 (d, J = 6.7 Hz, 1H), 5.62 (d, J = 17.2 Hz, 1H), 5.56 (d, J = 17.2 Hz, 1H), 3.73–3.69 (m, 1H), 3.64 (s, 3H), 3.38–3.36 (m, 1H), 3.28–3.23 (m, 1H), 3.11–3.08 (m, 1H), 2.88–2.83 (m, 1H), 1.99–1.97 (m, 1H), 1.78–1.75 (m, 1H), 1.63–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.0, 157.8, 154.2, 141.2, 140.4, 135.2, 131.1, 129.5, 129.1, 128.9, 127.8, 127.1, 123.5, 123.3, 119.3, 116.2, 116.1, 52.4, 52.3, 51.0, 46.4, 46.3, 29.2, 27.5, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{27}O_3N_5Cl$ 480.1797, found 480.1787; IR (ATR): 1710, 1670, 1652, 1646, 1594, 1558, 1521, 1506, 1473, 1288, 1261, 1112, 1004 cm^{-1}; Anal. Cacld for $C_{25}H_{26}O_3N_5Cl{\cdot}2.75HCl$: C, 51.75; H, 4.99; N, 12.07, found: C, 51.69; H, 5.36; N, 11.69.

5.5. 2-{(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-8-carboxylic acid (7w)

A mixture of **7t** (3.77 g, 6.49 mmol) and 1 M NaOH (16 ml) aqueous solution in THF (16 ml) and MeOH (16 ml) was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure. The residue was acidified with 10% $KHSO_4$ aqueous solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **7w** (2.13 g, yield 58%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.67 (d, J = 1.8 Hz, 1H), 8.05 (dd, J = 2.1, 8.7 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.48 (dd, J = 0.9, 7.8 Hz, 1H), 7.30–7.17 (m, 2H), 6.90 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.57 (d, J = 18.0 Hz, 1H), 5.51 (d, J = 18.0 Hz, 1H), 3.63 (s, 3H), 3.52–3.25 (m, 3H), 2.86–2.70 (m, 2H), 1.80–1.67 (m, 2H), 1.59–1.51 (m, 1H), 1.39–1.27 (m, 10H); HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{33}O_5N_5Cl$ 566.2165, found 566.2162; IR (ATR): 1700, 1685, 1654, 1508, 1457, 1388, 1309, 1238, 1168, 1116 cm^{-1}; Anal. calcd for $C_{29}H_{32}ClN_5O_5$: C, 61.53; H, 5.70; N, 12.37, found: C, 61.63; H, 5.73; N, 12.07.

5.6. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (8w)

To a solution of **7w** (39.9 mg, 0.0705 mmol) in 1,4-dioxane (1 ml) was added 4 N HCl-1,4-dioxane (1 ml). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give **8w** (40.2 mg, quantitative yield) as a white amorphous. ^1H NMR (300 MHz, CD_3OD) δ 8.96 (d, J = 2.0 Hz, 1H), 8.25 (dd, J = 2.0, 9.0 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.49 (dd, J = 1.1, 7.7 Hz, 1H), 7.35–7.23 (m, 2H), 6.98 (d, J = 8.2 Hz, 1H), 5.71 (s, 2H), 3.93 (brd, J = 11.3 Hz, 1H), 3.74–3.37 (m, 3H), 3.64 (s, 3H), 3.21–3.06 (m, 1H), 2.16 (m, 1H), 1.87–1.72 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 157.6, 154.0, 141.2, 140.0, 135.1, 130.9, 129.3, 128.9, 128.9, 127.7, 126.8, 124.3, 123.5, 119.1, 116.0, 115.9, 52.3, 50.9, 46.4, 46.1, 29.2, 27.5, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{25}O_3N_5Cl$ 466.1640, found 466.1636; IR(ATR): 2886, 1668, 1645, 1216, 1118 cm^{-1}; Anal. calcd for $C_{24}H_{24}O_3N_5Cl{\cdot}5HCl{\cdot}H_2O$: C, 43.27; H, 4.69; N, 10.51, found: C, 43.33; H, 4.59; N, 10.47.

5.7. *tert*-Butyl {(3*R*)-1-[8-carbamoyl-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinolin-2-yl]-piperidin-3-yl}carbamate (7u)

A mixture of **7w** (233.4 mg, 0.412 mmol), WSC·HCl (119 mg, 0.62 mmol), HOBt (94.7 mg, 0.62 mmol), TEA (86.2 μl, 0.62 mmol), and 28% NH_4OH (37.6 μl, 0.62 mmol) in DMF (2 ml) was stirred at room temperature for 3 h. The reaction mixture was quenched

with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7u** (170.6 mg, yield 73%) as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 2.0 Hz, 1H), 8.18 (br s, 1H), 8.04 (dd, J = 2.0, 9.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 1.0, 8.2 Hz, 1H), 7.40 (br s, 1H), 7.29–7.25 (m, 1H), 7.22–7.18 (m, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.59 (d, J = 17.2 Hz, 1H), 5.54 (d, J = 17.2 Hz, 1H), 3.63 (s, 3H), 3.49–3.38 (m, 2H), 3.26–3.23 (m, 1H), 2.84–2.71 (m, 2H), 1.78–1.68 (m, 2H), 1.57–1.54 (m, 1H), 1.38–1.22 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 158.1, 155.0, 154.3, 141.8, 139.1, 135.4, 131.2, 129.4, 128.9, 128.1, 127.7, 127.4, 126.9, 122.0, 119.1, 116.1, 115.5, 77.9, 55.2, 50.7, 46.7, 46.3, 29.8, 29.1, 28.4, 23.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{34}O_4N_6Cl$ 565.2330, found 565.2328; IR(ATR): 1677, 1662, 1618, 1527, 1508, 1457, 1434, 1388, 1349, 1309, 1238, 1170, 1114, 1051 cm^{-1}.

5.8. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-8-carboxamide hydrochloride (8u)

To a solution of **7u** (98.3 mg, 0.174 mmol) in 1,4-dioxane (2 ml) was added 4 N HCl-1,4-dioxane (2 ml). The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure to give **8u** (72.5 mg, yield 83%) as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6, free form) δ 8.66 (d, J = 2.1 Hz, 1H), 8.21 (br s, 1H), 8.05 (dd, J = 2.1, 8.9 Hz, 1H), 7.89–7.87 (m, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.50 (dd, J = 1.1, 7.9 Hz, 1H), 7.41 (br s, 1H), 7.31–7.27 (m, 1H), 7.23–7.19 (m, 1H), 6.64 (d, J = 6.7 Hz, 1H), 5.58 (s, 2H), 3.63 (s, 3H), 3.55–3.52 (m, 1H), 3.17–3.14 (m, 1H), 3.07–3.03 (m, 1H), 2.95–2.82 (m, 2H), 1.89–1.86 (m, 1H), 1.71–1.67 (m, 1H), 1.51–1.34 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, free form) δ 167.5, 158.1, 154.3, 141.8, 139.2, 135.4, 131.1, 129.5, 129.0, 128.0, 127.8, 127.4, 127.0, 122.1, 119.1, 116.1, 115.5, 55.8, 50.9, 46.9, 46.2, 30.7, 29.1, 22.9; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{26}O_2N_6Cl$ 465.1800, found 465.1795; IR (ATR): 1652, 1610, 1558, 1506, 1471, 1444, 1388, 1313, 1124 cm^{-1}.

5.9. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-8-(difluoromethoxy)-5-methyl-3,5-dihydro-*4H*-imidazo[4,5-*c*]-quinolin-4-one hydrochloride (8s)

Compound **8s** was prepared from **4** in a manner similar to that described for compound **8t** with total yield of 41% for 4 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (br s, 3H), 7.85 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.53–7.49 (m, 1H), 7.40 (d, J = 2.8 Hz, 1H), 7.34 (t, J (H, F) = 74 Hz, 1H), 7.31–7.27 (m, 1H), 7.23–7.19 (m, 1H), 6.66 (d, J = 6.8 Hz, 1H), 5.63 (s, 2H), 3.63–3.56 (m, 4H), 3.38–3.31 (m, 1H), 3.25–3.20 (m, 1H), 3.10–3.06 (m, 1H), 2.86–2.82 (m, 1H), 1.96–1.93 (m, 1H), 1.78–1.74 (m, 1H), 1.62–1.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.6, 154.0, 145.9, 140.5, 135.3, 134.8, 131.1, 129.5, 129.1, 127.8, 127.0, 120.3, 119.5, 117.8, 117.2, 117.1, 116.7 (t, J (C-F) = 257 Hz), 52.4, 51.1, 46.3, 34.3, 29.1, 27.4, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{25}O_2N_5ClF_2$ 488.1659, found 488.1643; IR(ATR): 1675, 1635, 1508, 1465, 1444, 1396, 1216, 1108, 1049, 1002 cm^{-1}.

5.10. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-6-carboxylic acid hydrochloride (8c)

Compound **8c** was prepared from **4** in a manner similar to that described for compound **8w** with total yield of 23% for 5 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 3H), 8.29 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.42–7.38 (m, 1H), 7.33–7.29 (m, 1H), 7.26–7.22 (m, 1H), 6.74 (d, J = 7.2 Hz, 1H), 5.58 (s, 2H), 3.73–3.56 (m, 1H), 3.48 (s, 3H), 3.38–3.16 (m, 2H), 3.07 (m, 1H), 2.88–2.84 (m, 1H), 1.96 (m, 1H), 1.77 (m, 1H), 1.62–1.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 157.8, 155.1, 141.5, 135.7, 135.2, 131.2, 129.5, 129.4, 129.1, 127.9, 127.2, 124.5, 124.1, 122.1, 118.9, 118.0, 52.3, 51.4, 46.4, 46.3, 34.9, 27.4, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{25}O_3N_5Cl$ 466.1640, found 466.1627; IR(ATR): 1704, 1664, 1557, 1490, 1471, 1367, 1220, 1199, 1124, 1095, 1066, 1049, 1018 cm^{-1}.

5.11. {2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinolin-8-yl}acetic acid hydrochloride (8x)

Compound **8x** was prepared from **4** in a manner similar to that described for compound **8w** with a yield of 48% for 5 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (br s, 3H), 8.06 (d, J = 2.0 Hz, 1H), 7.55–7.50 (m, 2H), 7.45 (dd, J = 2.0, 8.7 Hz, 1H), 7.32–7.28 (m, 1H), 7.24–7.20 (m, 1H), 6.64 (dd, J = 1.1, 6.6 Hz, 1H), 5.64 (s, 2H), 3.74 (s, 2H), 3.67–3.64 (m, 1H), 3.61 (s, 3H), 3.32 (m, 1H), 3.25–3.20 (m, 1H), 3.11–3.08 (m, 1H), 2.87–2.81 (m, 1H), 1.97–1.95 (m, 1H), 1.78–1.76 (m, 1H), 1.61–1.44 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.0, 157.4, 154.2, 141.0, 136.3, 135.4, 131.1, 130.1, 129.5, 129.4, 129.0, 127.8, 127.0, 122.7, 119.0, 116.1, 115.8, 52.4, 51.2, 46.3, 46.3, 28.9, 27.4, 27.4, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{27}O_3N_5Cl$ 480.1797, found 480.1785; IR(ATR): 2867, 1733, 1670, 1621, 1575, 1508, 1448, 1417, 1378, 1245, 1157, 1047 cm^{-1}; Anal. calcd for $C_{25}H_{26}O_3N_5Cl{\cdot}2.50HCl$: C, 52.58; H, 5.03; N, 12.26, found: C, 52.61; H, 5.11; N, 12.09.

5.12. *tert*-Butyl {(3*R*)-1-[3-(2-chlorobenzyl)-8-(dimethylcarbamoyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinolin-2-yl]piperidin-3-yl}carbamate (7v)

A mixture of **7w** (264.6 mg, 0.467 mmol), WSC·HCl (134 mg, 0.699 mmol), HOBt (107 mg, 0.699 mmol), TEA (195 μl, 1.40 mmol), and $NHMe_2$·HCl (76.2 mg, 0.934 mmol) in DMF (2 ml) was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7v** (303 mg, quantitative yield) as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.61 (dd, J = 1.5, 8.6 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 1.0, 8.8 Hz, 1H), 7.22–7.18 (m, 1H), 7.15–7.11 (m, 1H), 6.68 (d, J = 7.5 Hz, 1H), 5.77 (d, J = 16.8 Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 3.81 (br s, 1H), 3.75 (s, 3H), 3.43 (dd, J = 2.8, 12.5 Hz, 1H), 3.20–3.09 (m, 9H), 1.77–1.55 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 158.2, 155.1, 155.0, 141.8, 138.0, 135.0, 131.9, 130.1, 129.5, 128.5, 127.3, 127.1, 126.4, 121.6, 119.5, 116.6, 114.8, 79.0, 54.9, 51.4, 46.3, 45.8, 39.7, 35.4, 29.4, 29.0, 28.3, 21.7; HRMS (ESI) $[M+H]^+$ calcd for $C_{31}H_{38}O_4N_6Cl$ 593.2643, found 593.2642; IR(ATR): 1700, 1683, 1652, 1506, 1496, 1473, 1457, 1388, 1363, 1307, 1270, 1243, 1168, 1114, 1089, 1049 cm^{-1}.

5.13. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-N,N,5-trimethyl-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-*c*]quinoline-8-carboxamide hydrochloride (8v)

Compound **8v** was prepared from **7v** in a manner similar to that described for compound **8u** with a yield of 92% as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 3H), 8.20 (s, 1H), 7.65–7.60 (m, 2H), 7.51 (dd, J = 1.1, 7.9 Hz, 1H), 7.32–7.28 (m, 1H), 7.24–7.20 (m, 1H), 6.71 (d, J = 7.0 Hz, 1H), 5.64 (d, J = 17.2 Hz, 1H), 5.59 (d, J = 17.2 Hz, 1H), 3.70–3.66 (m, 1H), 3.63 (s, 3H), 3.37–3.35 (m, 1H), 3.29–3.23 (m, 1H), 3.10–3.08 (m, 1H), 3.01 (s, 6H), 2.90–2.85 (m, 1H), 1.97–1.94 (m, 1H), 1.77–1.74 (m, 1H), 1.63–1.58 (m, 1H), 1.53–1.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 156.6, 153.9, 139.3, 137.9, 135.0, 131.1, 130.4, 129.6, 129.2, 128.0, 127.8, 127.2, 121.5, 118.9, 115.9, 114.8, 59.4, 52.3, 50.9, 46.8, 46.2, 43.8, 29.2, 27.3, 22.1; HRMS (ESI) [M+H]$^+$ calcd for $C_{26}H_{30}O_2N_6Cl$ 493.2113, found 493.2114; IR(ATR): 1672, 1618, 1506, 1471, 1444, 1394, 1319, 1243, 1118, 1051 cm^{-1}.

5.14. Methyl 3-[{[2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino] piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-1*H*-imidazol-5-yl] carbonyl}(methyl)amino]benzoate (10)

Compound **10** was prepared from **4** in a manner similar to that described for compound **6t** with total yield of 57% for 2 steps as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 1.3 Hz, 1H), 7.97 (dd, J = 1.3, 8.1 Hz, 1H), 7.41 (dd, J = 1.5, 7.9 Hz, 1H), 7.36–7.25 (m, 2H), 7.20–7.18 (m, 1H), 6.93 (br s, 1H), 5.25–4.95 (m, 3H), 4.10 (s, 3H), 3.80 (br s, 1H), 3.32 (dd, J = 3.3, 11.9 Hz, 1H), 3.18 (s, 3H), 2.99–2.91 (m, 3H), 1.83–1.53 (m, 4H), 1.42 (s, 9H).

5.15. Ethyl 3-[{[2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino] piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-1*H*-imidazol-5-yl] carbonyl}(methyl)amino]benzoate (11)

Compound **11** was prepared from **4** in a manner similar to that described for compound **6t** with total yield of 17% for 2 steps as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.8 Hz, 1H), 7.70 (br s, 1H), 7.42 (dd, J = 1.1, 7.9 Hz, 1H), 7.34–7.28 (m, 3H), 7.18 (m, 1H), 6.95 (m, 1H), 5.25 (br s, 1H), 5.08 (br s, 1H), 4.89 (br s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.79 (br s, 1H), 3.32–3.29 (m, 1H), 3.16 (s, 3H), 2.98–2.87 (m, 3H), 1.77 (m, 2H), 1.64–1.63 (m, 1H), 1.56–1.49 (m, 1H), 1.42–1.25 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.0, 155.6, 155.0, 142.7, 134.0, 133.5, 131.4, 131.2, 130.3, 129.9, 129.8, 128.9, 127.8, 127.5, 127.0, 126.8, 83.9, 79.2, 61.2, 56.2, 51.9, 46.6, 46.1, 38.8, 31.6, 28.4, 22.6, 14.3; HRMS (ESI) [M+H]$^+$ calcd. for $C_{31}H_{38}O_5N_5ClI$ 722.1601, found 722.1591; IR(ATR): 1716, 1635, 1538, 1506, 1488, 1473, 1444, 1417, 1363, 1280, 1236, 1168, 1103, 1049, 1008 cm^{-1}.

5.16. *tert*-Butyl 3-[{[2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino] piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-1*H*-imidazol-5-yl] carbonyl}(methyl)amino]benzoate (12)

Compound **12** was prepared from **4** in a manner similar to that described for compound **6t** with total yield of 50% for 2 steps as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.42 (dd, J = 1.3, 7.6 Hz, 1H), 7.34–7.28 (m, 4H), 7.16 (br s, 1H), 5.26 (br s, 1H), 5.05 (br s, 1H), 4.85–4.59 (m, 1H), 3.79 (br s, 1H), 3.29 (d, J = 10.4 Hz, 1H), 3.16 (s, 3H), 2.96 (m, 3H), 1.76 (m, 2H), 1.59 (s, 9H), 1.54–1.50 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 161.9, 155.5, 154.9, 142.5, 133.7, 133.4, 132.8, 130.8, 129.8, 129.7, 129.7, 128.7, 127.6, 127.5, 126.9, 126.6, 83.9, 81.3, 79.0, 56.2, 51.8, 46.4, 46.0, 38.6, 29.4, 28.3, 28.1, 22.4; HRMS (ESI) [M+H]$^+$ calcd for $C_{33}H_{42}O_5N_5ClI$ 750.1914, found 750.1892; IR(ATR): 1700, 1652, 1646, 1635, 1506, 1488, 1363, 1303, 1243, 1160, 1128, 1079, 1049, 1008 cm^{-1}; Anal. Cacld for $C_{33}H_{41}O_5N_5ClI \cdot H_2O$: C, 51.60; H, 5.64; N, 9.12, found: C, 51.41; H, 5.40; N, 8.93.

5.17. *tert*-Butyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino] piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-*c*]quinoline-7-carboxylate (15a)

Compound **15a** was prepared from **12** in a manner similar to that described for compound **7t** with a yield of 73% as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 1.2 Hz, 1H), 7.91 (dd, J = 1.2, 8.4 Hz, 1H), 7.41 (dd, J = 1.5, 7.8 Hz, 1H), 7.27–7.11 (m, 2H), 6.70 (d, J = 6.0 Hz, 1H), 6.10–6.08 (m, 1H), 5.79 (d, J = 17.1 Hz, 1H), 5.65 (d, J = 17.1 Hz, 1H), 3.83 (br s, 1H), 3.80 (s, 3H), 3.45 (dd, J = 3.3, 12.6 Hz, 1H), 3.24 (dd, J = 5.4, 12.6 Hz, 1H), 3.10–3.08 (m, 2H), 1.73–1.54 (m, 13H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 158.4, 155.2, 155.1, 141.3, 137.1, 134.9, 132.0, 131.3, 129.6, 128.6, 127.2, 126.5, 122.9, 122.6, 120.5, 120.2, 116.2, 81.6, 79.1, 54.8, 51.5, 46.4, 45.7, 29.4, 29.1, 28.5, 28.2, 21.5; HRMS (ESI) [M+H]$^+$ calcd for $C_{33}H_{41}O_5N_5Cl$ 622.2791, found 622.2780; IR (ATR): 1706, 1652, 1506, 1473, 1390, 1365, 1307, 1240, 1224, 1160, 1108, 1039 cm^{-1}.

5.18. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-*c*]quinoline-7-carboxylic acid hydrochloride (8n)

To a solution of **15a** (337.5 mg, 0.542 mmol) in 1,4-dioxane (4 ml) was added 4 N HCl-1,4-dioxane (4 ml). The reaction mixture was stirred at 80 °C for 4 h and concentrated under reduced pressure to give **8n** (283 mg, quantitative yield) as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 3H), 8.22 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 1.5 Hz, 1H), 7.89 (dd, J = 1.5, 8.1 Hz, 1H), 7.50 (dd, J = 1.2, 7.8 Hz, 1H), 7.31–7.27 (m, 1H), 7.24–7.20 (m, 1H), 6.69 (dd, J = 1.4, 7.6 Hz, 1H), 5.65 (d, J = 17.1 Hz, 1H), 5.59 (d, J = 17.1 Hz, 1H), 3.66 (s, 3H), 3.66–3.64 (m, 1H), 3.30 (br s, 1H), 3.26–3.21 (m, 1H), 3.09–3.06 (m, 1H), 2.86–2.82 (m, 1H), 1.96 (m, 1H), 1.77–1.75 (m, 1H), 1.60–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.5, 154.0, 140.3, 136.8, 135.0, 130.9, 130.1, 129.3, 128.9, 127.6, 126.8, 122.8, 122.2, 120.1, 119.5, 116.5, 52.3, 51.1, 46.4, 46.3, 28.9, 27.4, 22.2; HRMS (ESI) [M+H]$^+$ calcd for $C_{24}H_{25}O_3N_5Cl$ 466.1640, found 466.1637; IR(ATR): 2869, 1716, 1679, 1652, 1623, 1508, 1473, 1457, 1444, 1419, 1394, 1326, 1245, 1222, 1178, 1130, 1052, 1041 cm^{-1}. Anal. Cacld for $C_{24}H_{24}O_3N_5Cl \cdot 2HCl \cdot 2H_2O$: C, 50.14; H, 5.26; N, 12.18, found: C, 50.15; H, 5.29; N, 12.06.

5.19. {2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3*H*-imidazo[4,5-*c*]quinolin-7-yl} acetic acid hydrochloride (8o)

Compound **8o** was prepared from **4** in a manner similar to that described for compound **8t** with total yield of 23% for 5 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (br s, 3H), 8.16 (d, J = 8.0 Hz, 1H), 7.54–7.50 (m, 2H), 7.33–7.27 (m, 2H), 7.24–7.20 (m, 1H), 6.71 (d, J = 7.6 Hz, 1H), 5.63 (s, 2H), 3.77 (s, 2H), 3.70–3.64 (m, 2H), 3.60 (s, 3H), 3.33–3.24 (m, 1H), 3.12–3.09 (m, 1H), 2.89–2.85 (m, 1H), 1.97–1.94 (m, 1H), 1.78–1.75 (m, 1H), 1.62–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 157.1, 154.2, 140.8, 137.4, 136.1, 135.3, 131.1, 129.5, 129.1, 127.8, 127.1, 124.0, 122.2, 118.6, 116.7, 114.5, 52.4, 51.1, 46.5, 46.3, 41.2, 29.0, 27.3, 22.1; HRMS (ESI) [M+H]$^+$ calcd for $C_{25}H_{27}O_3N_5Cl$ 480.1797, found 480.1786; IR(ATR): 1683, 1670,

1652, 1635, 1589, 1558, 1540, 1506, 1473 cm^{-1}; Anal. calcd for $C_{25}H_{26}O_3N_5Cl{\cdot}2.25HCl{\cdot}1.75H2O$: C, 50.59; H, 5.39; N, 11.80, found: C, 50.73; H, 45.47; N, 11.67.

5.20. {2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinolin-9-yl} acetic acid hydrochloride (8z)

Compound **8z** was prepared from **4** in a manner similar to that described for compound **8t** with total yield of 4.3% for 5 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 3H), 8.16 (d, J = 8.0 Hz, 1H), 7.52–7.50 (m, 2H), 7.32–7.27 (m, 2H), 7.24–7.21 (m, 1H), 6.71 (d, J = 7.5 Hz, 1H), 5.63 (s, 2H), 3.77 (s, 2H), 3.72–3.67 (m, 1H), 3.60 (s, 3H), 3.33–3.25 (m, 2H), 3.12–3.09 (m, 1H), 2.90–2.85 (m, 1H), 1.95 (m, 1H), 1.78–1.76 (m, 1H), 1.62–1.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 157.1, 154.2, 140.5, 137.5, 136.1, 135.3, 131.1, 129.5, 129.1, 127.8, 127.1, 124.0, 122.2, 118.6, 116.7, 114.5, 52.4, 51.1, 46.5, 46.2, 40.5, 28.9, 27.3, 22.1; HRMS (ESI) [M+H]$^+$ calcd for $C_{25}H_{27}O_3N_5Cl$ 480.1797, found 480.1783; IR(ATR): 2867, 1718, 1670, 1625, 1604, 1513, 1475, 1444, 1326, 1245, 1162, 1122, 1051, 1000 cm^{-1}.

5.21. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-9-carboxylate (7ya)

A mixture of compound **7y** (16.9 mg, 0.0275 mmol) which was prepared from **4** in a manner similar to that described for compound **7t** with total yield of 11% in 3 steps, and 10% Pd/C (50% wet, 40.0 mg) in MeOH (5 ml) was stirred at room temperature under H_2 atmosphere for 4 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7ya** (15.5 mg, yield 97%) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.32 (dd, J = 2.4, 5.9 Hz, 1H), 7.23–7.11 (m, 2H), 6.71 (d, J = 7.3 Hz, 1H), 5.80 (d, J = 17.0 Hz, 1H), 5.65 (d, J = 17.0 Hz, 1H), 4.69 (brd, J = 7.7 Hz, 1H), 4.03 (s, 3H), 3.81–3.79 (m, 1H), 3.76 (s, 3H), 3.39 (dd, J = 3.1, 12.1 Hz, 1H), 3.04–2.96 (m, 3H), 1.74–1.49 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 157.6, 154.9, 154.8, 140.6, 137.7, 134.9, 131.9, 129.9, 129.5, 128.6, 127.6, 127.2, 126.7, 120.7, 120.2, 116.2, 113.6, 79.4, 60.4, 55.5, 52.8, 51.5, 46.3, 29.3, 28.3, 22.3, 14.2; HRMS (ESI) [M+H]$^+$ calcd for $C_{30}H_{35}O_5N_5Cl$ 580.2321, found 580.2305; IR(ATR): 1733, 1716, 1652, 1506, 1496, 1471, 1457, 1311, 1278, 1213, 1168 cm^{-1}.

5.22. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-9-carboxylic acid hydrochloride (8y)

Compound **8y** was prepared from **7ya** in a manner similar to that described for compound **8w** with total yield of 99% for 2 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (br s, 3H), 7.69 (d, J = 8.3 Hz, 1H), 7.61–7.57 (m, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.35–7.28 (m, 1H), 7.24–7.21 (m, 1H), 6.66 (d, J = 7.4 Hz, 1H), 5.64 (s, 2H), 3.65 (s, 3H), 3.49–3.37 (m, 2H), 3.23–3.15 (m, 1H), 3.07–3.04 (m, 1H), 2.92–2.87 (m, 1H), 1.93 (br s, 1H), 1.72–1.62 (m, 2H), 1.48–1.46 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ169.8, 156.2, 153.7, 139.4, 137.5, 135.1, 130.9, 130.8, 129.3, 128.9, 127.9, 127.6, 126.7, 121.2, 119.3, 116.7, 112.1, 51.9, 50.6, 46.1, 45.6, 29.1, 27.1, 21.3; HRMS (ESI) [M+H]$^+$ calcd for $C_{24}H_{25}O_3N_5Cl$ 466.1640, found 466.1630; IR(ATR): 2915, 1652, 1575, 1558, 1540, 1508, 1456, 1444, 1419, 1375, 1319, 1245, 1095, 1039 cm^{-1}.

5.23. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-fluoro-5-methyl-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one hydrochloride (8d)

Compound **8d** was prepared from **4** in a manner similar to that described for compound **8y** with total yield of 14% for 5 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19–8.13 (m, 4H), 7.52–7.46 (m, 2H), 7.32–7.20 (m, 3H), 6.65 (d, J = 8.0 Hz, 1H), 5.60 (s, 2H), 3.58 (s, 3H), 3.49–3.46 (m, 1H), 3.37–3.33 (m, 1H), 3.23–3.18 (m, 1H), 3.08–3.05 (m, 1H), 2.86–2.82 (m, 1H), 1.98–1.93 (m, 1H), 1.75 (m, 1H), 1.58–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 156.5, 153.2, 138.9 (d, ^1J (C, F) = 238 Hz), 137.8, 134.2, 129.9, 128.2 (d, ^2J (C, F) = 44 Hz), 128.1 (d, ^2J (C, F) = 44 Hz), 126.7 (d, ^3J (C, F) = 8.8 Hz), 125.8, 122.9 (d, ^3J (C, F) = 8.8 Hz), 117.1 (d, ^4J (C, F) = 4.0 Hz), 112.1, 109.1, 108.9, 51.2, 50.0, 45.2, 42.7, 28.1, 26.3, 20.9; HRMS (ESI) [M+H]$^+$ calcd for $C_{23}H_{24}ON_5ClF$ 440.1648, found 440.1638; IR(ATR): 2921, 1673, 1652, 1577, 1523, 1508, 1473, 1415, 1394, 1353, 1309, 1243, 1224, 1149, 1128, 1106, 1051, cm^{-1}.

5.24. 2-{(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylic acid (7n)

A mixture of **8n** (1.53 g, 3.05 mmol), $(Boc)_2O$ (864 mg, 3.97 mmol) in THF (10 ml) and saturated $NaHCO_3$ aqueous solution (10 ml) was stirred at room temperature for 3 h. The reaction mixture was quenched with 5% $KHSO_4$ aqueous solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual solid was triturated with hexane to afford **7n** (1.04 g, yield 60%) as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 1.1 Hz, 1H), 7.88 (dd, J = 1.1, 8.1 Hz, 1H), 7.48 (dd, J = 1.0, 7.9 Hz, 1H), 7.29–7.25 (m, 1H), 7.22–7.17 (m, 1H), 6.93 (d, J = 7.7 Hz, 1H), 6.66 (m, 1H), 5.57 (d, J = 17.6 Hz, 1H), 5.53 (d, J = 17.6 Hz, 1H), 3.66 (s, 3H), 3.48–3.22 (m, 3H), 2.84–2.71 (m, 2H), 1.78–1.76 (m, 1H), 1.69–1.66 (m, 1H), 1.55–1.50 (m, 1H), 1.39–1.29 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.4, 158.1, 155.0, 154.2, 140.8, 136.9, 135.3, 131.2, 130.1, 129.4, 128.9, 127.7, 126.9, 122.8, 122.3, 120.0, 119.8, 116.5, 77.9, 55.1, 50.6, 46.6, 40.3, 29.8, 28.8, 28.4, 23.4; HRMS (ESI) [M+H]$^+$ calcd for $C_{29}H_{33}O_5N_5Cl$ 566.2165, found 566.2155; IR(ATR): 2935, 1685, 1646, 1621, 1585, 1558, 1508, 1473, 1446, 1409, 1365, 1349, 1307, 1241, 1222, 1168, 1122, 1070, 1049, 1039, 1024 cm^{-1}.

5.25. *tert*-Butyl {(3*R*)-1-[7-carbamoyl-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinolin-2-yl] piperidin-3-yl}carbamate (7k)

Compound **7k** was prepared from **7n** in a manner similar to that described for compound **7u** with a yield of 80% as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.1 Hz, 1H), 8.03 (s, 1H), 7.63 (dd, J = 1.0, 8.1 Hz, 1H), 7.40 (dd, J = 0.9, 7.9 Hz, 1H), 7.21–7.18 (m, 1H), 7.15–7.11 (m, 1H), 6.68 (d, J = 7.2 Hz, 1H), 6.02 (br s, 1H), 5.77 (d, J = 16.8 Hz, 1H), 5.64 (d, J = 16.8 Hz, 1H), 3.82 (br s, 1H), 3.77 (s, 3H), 3.44 (dd, J = 3.2, 12.7 Hz, 1H), 3.22 (dd, J = 4.9, 12.6 Hz, 1H), 3.08–3.06 (m, 2H), 1.83–1.65 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 158.4, 155.2, 155.1, 141.2, 137.5, 134.9, 132.5, 132.0, 129.6, 128.6, 127.2, 126.5, 122.9, 120.4, 120.1, 119.8, 115.0, 79.1, 54.9, 51.5, 46.4,

45.8, 29.2, 28.5, 28.2, 21.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{34}O_4N_6Cl$ 565.2325, found 565.2309; IR(ATR): 1716, 1699, 1683, 1652, 1646, 1635, 1558, 1540, 1521, 1506, 1473, 1457, 1386, 1363, 1319, 1224, 1164, 1039 cm^{-1}.

5.26. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxamide hydrochloride (8k)

Compound **8k** was prepared from **7k** in a manner similar to that described for compound **8u** with a quantitative yield as a white amorphous. ^1H NMR (400 MHz, DMSO-d6) δ 8.37 (br s, 3H), 8.28 (br s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.87 (dd, J = 1.0, 8.1 Hz, 1H), 7.58–7.49 (m, 2H), 7.32–7.29 (m, 1H), 7.25–7.16 (m, 1H), 6.71 (d, J = 7.2 Hz, 1H), 5.65 (d, J = 17.2 Hz, 1H), 5.59 (d, J = 17.2 Hz, 1H), 3.68 (s, 3H), 3.50–3.45 (m, 1H), 3.34 (br s, 1H), 3.28–3.25 (m, 1H), 3.09–3.06 (m, 1H), 2.87–2.82 (m, 1H), 1.95 (m, 1H), 1.78–1.75 (m, 1H), 1.61–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ167.6, 157.5, 154.3, 140.5, 137.1, 135.3, 134.0, 131.1, 129.5, 129.1, 127.9, 127.1, 122.0, 121.6, 119.8, 118.3, 115.1, 52.3, 51.1, 46.4, 43.8, 29.1, 27.4, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{26}O_2N_6Cl$ 465.1800, found 465.1790; IR(ATR): 1672, 1598, 1444, 1122, 1041 cm^{-1}.

5.27. *tert*-Butyl {(3*R*)-1-[3-(2-chlorobenzyl)-7-(dimethylcarbamoyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinolin-2-yl]piperidin-3-yl}carbamate (7l)

Compound **7l** was prepared from **7n** in a manner similar to that described for compound **7v** with a quantitative yield as a white amorphous. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 1.1 Hz, 1H), 7.40 (dd, J = 1.1, 7.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.22–7.18 (m, 1H), 7.15–7.11 (m, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.25 (br s, 1H), 5.77 (d, J = 16.8 Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 3.82 (br s, 1H), 3.74 (s, 3H), 3.43 (dd, J = 3.2, 12.9 Hz, 1H), 3.25 (dd, J = 4.3, 12.9 Hz, 1H), 3.17 (s, 3H), 3.09–3.07 (m, 2H), 3.03 (s, 3H), 1.73–1.50 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.3, 155.2, 155.1, 141.5, 137.5, 136.0, 135.0, 132.0, 129.6, 128.6, 127.2, 126.5, 122.7, 120.7, 119.9, 117.8, 114.0, 79.0, 54.7, 51.5, 46.4, 45.7, 39.7, 35.5, 29.4, 29.1, 28.4, 21.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{31}H_{38}O_4N_6Cl$ 593.2638, found 593.2621; IR(ATR): 1700, 1635, 1583, 1508, 1467, 1444, 1405, 1388, 1363, 1315, 1241, 1162, 1122, 1087, 1068, 1049, 1039 cm^{-1}.

5.28. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-N,N,5-trimethyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxamide hydrochloride (8l)

Compound **8l** was prepared from **7l** in a manner similar to that described for compound **8v** with a yield of 95% as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 3H), 8.22 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.51 (dd, J = 0.6, 7.9 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.32–7.29 (m, 1H), 7.24–7.21 (m, 1H), 6.71 (d, J = 7.4 Hz, 1H), 5.66 (d, J = 17.6 Hz, 1H), 5.61 (d, J = 17.6 Hz, 1H), 3.71–3.66 (m, 1H), 3.63 (s, 3H), 3.38–3.24 (m, 2H), 3.11–3.03 (m, 1H), 3.03 (s, 3H), 2.95 (s, 3H), 2.89–2.84 (m, 1H), 1.95 (m, 1H), 1.78–1.76 (m, 1H), 1.62–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ169.9, 157.5, 154.2, 140.5, 137.1, 136.6, 135.2, 131.1, 129.5, 129.1, 127.8, 127.1, 122.2, 121.0, 119.4, 116.7, 114.4, 52.3, 51.1, 46.4, 46.3, 43.8, 35.0, 29.0, 27.4, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{26}H_{30}O_2N_6Cl$ 493.2113, found 493.2101; IR(ATR): 1677, 1639, 1602, 1498, 1475, 1442, 1409, 1398, 1321, 1245, 1205, 1122, 1051, 1039 cm^{-1}.

5.29. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylate (7j)

A mixture of **7n** (1.02 g, 1.80 mmol), K_2CO_3 (746 mg, 5.40 mmol), and MeI (224 μl, 3.60 mmol) in DMF (5 ml) was stirred at 45 °C for 4 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7j** (1.12 g, quantitative yield) as a pale yellow amorphous. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 1.1 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 1.0, 7.9 Hz, 1H), 7.22–7.18 (m, 1H), 7.15–7.11 (m, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.16 (br s, 1H), 5.77 (d, J = 16.8 Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 3.99 (s, 3H), 3.81 (br s, 1H), 3.80 (s, 3H), 3.43 (dd, J = 3.3, 12.8 Hz, 1H), 3.24 (dd, J = 4.2, 12.5 Hz, 1H), 3.09–3.08 (m, 2H), 1.74–1.62 (m, 3H), 1.54–1.52 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 159.0, 155.9, 155.6, 141.7, 137.8, 135.6, 132.6, 130.2, 129.9, 129.2, 127.8, 127.1, 123.6, 123.4, 121.2, 121.1, 117.0, 79.7, 55.4, 53.0, 52.1, 47.0, 46.4, 30.0, 29.8, 29.1, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{35}O_5N_5Cl$ 580.2321, found 580.2314; IR (ATR): 1716, 1652, 1646, 1508, 1307, 1257, 1238, 1220, 1164, 1108, 1049, 1033 cm^{-1}.

5.30. Methyl 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylate hydrochloride (8j)

Compound **8j** was prepared from **7j** in a manner similar to that described for compound **8t** with a quantitative yield as a white amorphous. ^1H NMR (400 MHz, CD_3OD, free form) δ 8.18 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 1.2 Hz, 1H), 7.87 (dd, J = 1.2, 8.2 Hz, 1H), 7.46 (dd, J = 1.1, 8.0 Hz, 1H), 7.28–7.24 (m, 1H), 7.19–7.15 (m, 1H), 6.67 (dd, J = 1.1, 7.7 Hz, 1H), 5.62 (d, J = 16.8 Hz, 1H), 5.53 (d, J = 16.8 Hz, 1H), 3.97 (s, 3H), 3.64 (s, 3H), 3.52 (dd, J = 3.5, 11.6 Hz, 1H), 3.20–3.17 (m, 1H), 2.97–2.80 (m, 3H), 1.98–1.94 (m, 1H), 1.75–1.61 (m, 2H), 1.43–1.28 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 158.4, 154.1, 140.8, 136.8, 135.2, 131.0, 129.4, 129.0, 128.6, 127.8, 127.4, 127.0, 122.6, 122.4, 120.1, 116.2, 58.6, 52.6, 50.6, 47.4, 46.2, 33.3, 28.8, 23.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{27}O_3N_5Cl$ 480.1797, found 480.1792; IR(ATR): 1718, 1652, 1623, 1525, 1506, 1471, 1436, 1405, 1309, 1259, 1240, 1222, 1108, 1049, 1039, 1033, 1000 cm^{-1}.

5.31. *tert*-Butyl {(3R)-1-[3-(2-chlorobenzyl)-7-cyano-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate (7m)

To a solution of **7k** (255.8 mg, 0.410 mmol) in THF (3 ml) was added trifluoroacetic acid anhydride (256 μl, 1.84 mmol) at room temperature. The reaction mixture was stirred at 65 °C for 3 h. After cooling to room temperature, the reaction mixture was supplemented with K_2CO_3 (226 mg, 1.64 mmol) and MeOH (3 ml), and the whole was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7m** (99.6 mg, yield 44%) as a white amorphous. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 1.0 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.42 (dd, J = 1.2, 7.9 Hz, 1H), 7.23–7.19 (m, 1H), 7.16–7.12 (m, 1H), 6.67 (d, J = 7.4 Hz, 1H), 5.99 (br s, 1H), 5.76 (d, J = 16.8 Hz,

1H), 5.64 (d, J = 16.8 Hz, 1H), 3.82–3.78 (m, 1H), 3.74 (s, 3H), 3.45 (dd, J = 3.2, 12.7 Hz, 1H), 3.22 (dd, J = 4.7, 12.9 Hz, 1H), 3.08 (m, 2H), 1.78–1.70 (m, 3H), 1.61–1.51 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 155.1, 154.7, 140.8, 137.2, 134.6, 132.0, 129.6, 128.7, 127.2, 126.4, 124.9, 123.6, 120.8, 120.3, 119.0, 118.6, 111.1, 79.1, 54.8, 51.4, 46.5, 45.8, 31.5, 29.1, 28.4, 21.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{32}O_3N_6Cl$ 547.2219, found 547.2206; IR(ATR): 1700, 1652, 1581, 1508, 1471, 1444, 1409, 1390, 1365, 1315, 1240, 1162, 1124, 1070, 1049, 1041 cm^{-1}.

5.32. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinoline-7-carbonitrile (8m)

To a solution of **7m** (99.6 mg, 0.182 mmol) in $CHCl_3$ (2 ml) was added trifluoroacetic acid (0.5 ml, 6.49 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and concentrated under reduced pressure. To the residue was added saturated $NaHCO_3$ aqueous solution, and the whole was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **8m** (72.0 mg, yield 88%) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.55 (dd, J = 1.3, 8.1 Hz, 1H), 7.40 (dd, J = 1.3, 7.9 Hz, 1H), 7.23–7.10 (m, 2H), 6.70 (d, J = 7.5 Hz, 1H), 5.71 (d, J = 17.0 Hz, 1H), 5.64 (d, J = 17.0 Hz, 1H), 3.72 (s, 3H), 3.39–3.36 (m, 1H), 3.27–3.23 (m, 1H), 2.98–2.91 (m, 2H), 2.77–2.70 (m, 1H), 1.92–1.87 (m, 1H), 1.76–1.55 (m, 2H), 1.31–1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 155.4, 141.9, 137.9, 135.6, 132.5, 130.2, 129.3, 127.9, 127.3, 125.6, 124.3, 121.6, 121.2, 119.7, 119.3, 111.6, 59.5, 51.5, 48.0, 47.3, 33.4, 29.7, 24.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{24}ON_6Cl$ 447.1695, found 447.1694; IR(ATR): 1646, 1619, 1504, 1463, 1444, 1407, 1392, 1349, 1319, 1243, 1226, 1159, 1122, 1049 cm^{-1}.

5.33. *tert*-Butyl {(3*R*)-1-[3-(2-chlorobenzyl)-7-(hydroxymethyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinolin-2-yl]piperidin-3-yl}carbamate (7i)

To a solution of **7n** (471.5 mg, 0.833 mmol) and TEA (232 μl, 1.67 mmol) in THF (4 ml) was added ethyl chloroformate (119 μl, 1.25 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. To this reaction mixture was added sodium borohydride (94.5 mg, 2.50 mmol) in H_2O (1 ml) at 0 °C. The reaction mixture was stirred at room temperature for 5 h and then quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7i** (261 mg, yield 57%) as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.9 Hz, 1H), 7.44 (br s, 1H), 7.41 (dd, J = 1.0, 7.9 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.21–7.19 (m, 1H), 7.14–7.10 (m, 1H), 6.68 (d, J = 7.6 Hz, 1H), 5.76 (d, J = 17.2 Hz, 1H), 5.64 (d, J = 17.2 Hz, 1H), 4.85 (br s, 2H), 3.82 (br s, 1H), 3.72 (s, 3H), 3.43 (dd, J = 3.1, 12.9 Hz, 1H), 3.25 (dd, J = 4.1, 12.7 Hz, 1H), 3.08–3.07 (m, 2H), 1.73–1.51 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.3, 155.2, 141.9, 141.4, 137.7, 135.1, 131.9, 129.5, 128.5, 127.2, 126.5, 123.0, 120.9, 119.2, 116.3, 113.0, 79.0, 65.3, 54.7, 51.6, 46.3, 45.7, 29.5, 29.0, 28.5, 21.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}O_4N_5Cl$ 552.2372, found 552.2354; IR(ATR): 1685, 1637, 1581, 1508, 1473, 1444, 1413, 1388, 1363, 1317, 1241, 1160, 1122, 1068, 1049, 1039 cm^{-1}.

5.34. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-(hydroxymethyl)-5-methyl-3,5-dihydro-4H-imidazo[4,5-*c*]-quinolin-4-one (8i)

To a solution of **7i** (40.3 mg, 0.073 mmol) in $CHCl_3$ (2 ml) was added trifluoroacetic acid (112 μl, 1.45 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and concentrated under reduced pressure. The residue was azeotroped with toluene and dissolved in MeOH (3 ml). To this solution was added K_2CO_3 (30.3 mg, 0.219 mmol) and the reaction mixture was stirred at room temperature for 3 h, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **8i** (24.7 mg, yield 75%) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.36 (m, 2H), 7.24–7.14 (m, 3H), 6.72 (br s, 1H), 5.67 (br s, 2H), 4.78 (br s, 2H), 3.64 (s, 3H), 3.37–3.33 (m, 1H), 3.18 (m, 1H), 2.93 (m, 2H), 2.76–2.73 (m, 1H), 1.87–1.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 155.2, 142.3, 141.5, 137.5, 135.4, 131.8, 129.4, 128.5, 127.2, 126.7, 122.8, 120.8, 119.2, 116.2, 112.9, 65.0, 58.9, 51.0, 47.4, 46.3, 33.2, 29.0, 23.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}O_2N_5Cl$ 451641, found 452.1848; IR(ATR): 1641, 1581, 1508, 1471, 1444, 1413, 1392, 1353, 1319, 1214, 1159, 1120, 1049, 1039 cm^{-1}.

5.35. *tert*-butyl {(3*R*)-1-[3-(2-chlorobenzyl)-7-(methoxymethyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo-[4,5-*c*]quinolin-2-yl]piperidin-3-yl}carbamate (7h)

To a solution of **7i** (147.4 mg, 0.267 mmol) in THF (2 ml) was added sodium hydride (60% in oil, 12.8 mg, 0.32 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. To this reaction mixture was added MeI (19.9 μl, 0.32 mmol) at 0 °C, and the whole was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7h** (129.6 mg, yield 86%) as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 1.1 Hz, 1H), 7.40 (dd, J = 1.1, 8.0 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.21–7.17 (m, 1H), 7.14–7.10 (m ,1H), 6.67 (d, J = 7.5 Hz, 1H), 6.26 (br s, 1H), 5.77 (d, J = 16.8 Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 4.62 (s, 2H), 3.81 (m, 1H), 3.75 (s, 3H), 3.46 (s, 3H), 3.42 (dd, J = 3.2, 12.9 Hz, 1H), 3.28–3.23 (m, 1H), 3.08–3.07 (m, 2H), 1.73–1.62 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 155.9, 155.8, 142.5, 139.3, 138.3, 135.8, 132.5, 130.1, 129.1, 127.8, 127.2, 123.5, 122.2, 119.8, 117.0, 114.4, 79.6, 75.3, 58.9, 55.4, 52.2, 46.8, 46.4, 30.0, 29.6, 29.1, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{37}O_4N_5Cl$ 566.2529, found 566.2525; IR(ATR): 1700, 1652, 1646, 1583, 1508, 1473, 1457, 1444, 1417, 1388, 1363, 1315, 1241, 1159, 1101, 1070, 1049, 1039 cm^{-1}.

5.36. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-(methoxymethyl)-5-methyl-3,5-dihydro-4H-imidazo[4,5-*c*] quinolin-4-one hydrochloride (8h)

Compound **8h** was prepared from **7h** in a manner similar to that described for compound **8t** with a quantitative yield as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 3H), 8.20 (d, J = 8.0 Hz, 1H), 7.52–7.50 (m, 2H), 7.33–7.28 (m, 2H), 7.24–7.20 (m, 1H), 6.73 (d, J = 7.2 Hz, 1H), 5.62 (s, 2H), 4.57 (s, 2H), 3.70–3.66 (m, 1H), 3.61 (s, 3H), 3.34 (s, 3H), 3.30–3.25 (m, 2H), 3.11–3.08 (m, 1H), 2.89–2.87 (m, 1H), 1.96–1.94 (m, 1H), 1.76–1.74 (m, 1H), 1.62–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 154.1, 139.6, 139.6, 137.5, 135.1, 131.1, 129.5, 129.1,

127.8, 127.2, 122.6, 121.8, 118.5, 114.6, 114.5, 73.8, 57.9, 52.3, 51.0, 46.7, 46.3, 29.0, 27.3, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{29}O_2N_5Cl$ 466.2004, found 466.2003; IR(ATR): 1670, 1637, 1602, 1473, 1444, 1417, 1386, 1326, 1249, 1199, 1159, 1108, 1051, 1039, 1033 cm^{-1}.

5.37. *tert*-Butyl {(3*R*)-1-[3-(2-chlorobenzyl)-7-(iodomethyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinolin-2-yl]-piperidin-3-yl}carbamate (20)

A mixture of **7i** (274.3 mg, 0.497 mmol), I_2 (252 mg, 0.99 mmol), imidazole (84.6 mg, 1.25 mmol), and PPh_3 (196 mg, 0.75 mmol) in THF (2 ml) was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aqueous solution, extracted with EtOAc, washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **20** (81.5 mg, yield 25%) as a pale yellow amorphous. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 1.1 Hz, 1H), 7.40 (dd, J = 1.1, 7.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.21–7.17 (m, 1H), 7.13–7.09 (m, 1H), 6.64 (d, J = 7.6 Hz, 1H), 6.23 (br s, 1H), 5.75 (d, J = 17.3 Hz, 1H), 5.64 (d, J = 17.3 Hz, 1H), 4.63 (s, 2H), 3.82 (m, 1H), 3.74 (s, 3H), 3.42 (dd, J = 3.2, 12.9 Hz, 1H), 3.24 (dd, J = 4.4, 12.8 Hz, 1H), 3.08–3.07 (m, 2H), 1.73 (m, 2H), 1.62–1.58 (m, 1H), 1.53–1.47 (m, 1H), 1.47 (s, 9H); HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{34}O_3N_5ClI$ 662.1389, found 662.1375. IR(ATR): 1700, 1683, 1652, 1583, 1508, 1473, 1446, 1417, 1394, 1363, 1319, 1243, 1164, 1049 cm^{-1}.

5.38. *tert*-Butyl {(3*R*)-1-[3-(2-chlorobenzyl)-5,7-dimethyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinolin-2-yl]piperidin-3-yl}carbamate (7f)

A mixture of **20** (81.5 mg, 0.123 mmol) and $NaBH_4$ (14.0 mg, 0.369 mmol) in DMSO (2 ml) was stirred at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc, washed with saturated NH_4Cl aqueous solution twice and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **7f** (59.7 mg, yield 91%) as a pale yellow powder. Mp 207–209 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.40 (dd, J = 0.8, 7.8 Hz, 1H), 7.24 (br s, br s, 1H), 7.21–7.10 (m, 3H), 6.67 (d, J = 7.3 Hz, 1H), 5.76 (d, J = 16.8 Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 3.82–3.78 (m, 1H), 3.73 (s, 3H), 3.44–3.41 (m, 1H), 3.28–3.26 (m, 1H), 3.08 (m, 2H), 2.53 (s, 3H), 1.73–1.51 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 155.9, 155.9, 142.8, 139.2, 138.3, 135.9, 132.5, 130.1, 129.1, 127.8, 127.2, 124.1, 123.3, 119.3, 115.7, 115.3, 79.6, 55.3, 52.2, 46.8, 46.4, 30.1, 29.5, 29.1, 22.8, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}O_3N_5Cl$ 536.2423, found 536.2420; IR(ATR): 1700, 1646, 1583, 1508, 1473, 1411, 1390, 1363, 1317, 1243, 1164, 1049 cm^{-1}.

5.39. 2-[(3*R*)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5,7-dimethyl-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one (8f)

To a solution of **7f** (54.0 mg, 0.10 mmol) in 1,4-dioxane (2 ml) was added 4 N HCl-1,4-dioxane (2 ml). The reaction mixture was stirred at room temperature for 4 h, and concentrated under reduced pressure. To the residue was added saturated $NaHCO_3$ aqueous solution, and the whole was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **8f** (50.7 mg, quantitative yield) as a white amorphous. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.23–7.12 (m, 4H), 6.71 (d, J = 7.7 Hz, 1H), 5.72 (d, J = 16.8 Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 3.72 (s, 3H), 3.40–3.37 (m, 1H), 3.23–3.19 (m, 1H), 2.98–2.92 (m, 2H), 2.79 (dd, J = 8.4, 11.9 Hz, 1H), 2.53 (s, 3H), 1.72–1.60 (m, 2H), 1.30–1.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 155.9, 143.2, 139.1, 138.3, 136.2, 132.4, 130.0, 129.1, 127.9, 127.4, 124.2, 123.2, 119.4, 115.8, 115.5, 59.3, 51.7, 48.0, 46.9, 33.6, 29.6, 23.9, 22.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}ON_5Cl$ 436.1899, found 436.1897; IR(ATR): 1645, 1581, 1508, 1471, 1444, 1409, 1390, 1319, 1243, 1226, 1160, 1122, 1068, 1049, 1039 cm^{-1}.

5.40. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylate (21)

A mixture of **7t** (1.90 g, 3.28 mmol), 10% Pd/C (50% wet, 0.95 g), HCO_2NH_4 (2.07 g, 32.8 mmol) in MeOH (15 ml) was stirred under reflux for 2 h. After cooling to room temperature, the reaction mixture was filtered through a Celite pad. To the filtrate was added H_2O, and the whole was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **21** (1.23 g, yield 83%) as a white amorphous. ^1H NMR (300 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 8.55 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 4.12–4.02 (m, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.45 (br s, br s, 1H), 2.99–2.91 (m, 1H), 2.87–2.79 (m, 1H), 1.85–1.74 (m, 2H), 1.55–1.52 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.5, 156.0, 154.4, 152.9, 142.1, 139.6, 127.3, 122.9, 121.9, 117.9, 115.6, 115.1, 78.7, 51.6, 50.4, 45.7, 45.4, 29.7, 28.5, 27.8, 22.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{30}O_5N_5$ 456.2241, found 456.2229; IR(ATR): 1716, 1683, 1652, 1558, 1515, 1456, 1311, 1253, 1168, 1105, 1052 cm^{-1}. Anal. calcd for $C_{23}H_{29}O_5N_5 \cdot 0.75H_2O$: C, 58.90; H, 6.55; N, 14.93, found: C, 58.93; H, 6.32; N, 14.69.

5.41. Methyl 3-benzyl-2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylate (22a)

A mixture of **21** (82.4 mg, 0.181 mmol), K_2CO_3 (75.0 mg, 0.543 mmol), and BnBr (43.1 μl, 0.362 mmol) in DMF (2 ml) was stirred at 65 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **22a** (97.8 mg, yield 99%) as a white powder. Mp 205–207 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, J = 2.0 Hz, 1H), 8.16 (dd, J = 2.0, 9.0 Hz, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.33–7.21 (m, 2H), 7.19–7.17 (m, 2H), 5.77 (d, J = 15.4 Hz, 1H), 5.55 (d, J = 15.4 Hz, 1H), 5.21–5.19 (m, 1H), 3.99 (s, 3H), 3.87–3.80 (m, 1H), 3.79 (s, 3H), 3.46 (dd, J = 2.9, 12.2 Hz, 1H), 3.16–3.11 (m, 3H), 1.86–1.71 (m, 2H), 1.65–1.58 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.4, 155.2, 155.0, 142.2, 140.3, 137.2, 128.9, 128.7, 127.5, 126.5, 124.7, 123.8, 119.3, 116.7, 114.6, 79.2, 55.5, 52.0, 51.3, 48.3, 46.2, 29.6, 29.2, 28.3, 22.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{36}O_5N_5$ 546.2711, found 546.2699; IR (ATR): 1714, 1652, 1569, 1496, 1465, 1456, 1436, 1427, 1390, 1365, 1309, 1276, 1240, 1166, 1126, 1112, 1064 cm^{-1}; Anal. calcd for $C_{30}H_{35}O_5N_5$: C, 66.04; H, 6.47; N, 12.84, found: C, 65.84; H, 6.53; N, 12.77.

5.42. 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid (23a)

A mixture of **22a** (85.8 mg, 0.157 mmol) and 1 M NaOH aqueous solution (1 ml) in THF (1 ml) and MeOH (1 ml) was stirred at room

temperature for 6 h. The mixture was concentrated under reduced pressure. The residue was supplemented with 10% $KHSO_4$ aqueous solution until the pH reached at 2∼3. the resulting solids were filtered, washed sequentially with water, Et_2O and hexane, and dried in vacuo to give **23a** (44.8 mg, yield 54%) as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.31–7.24 (m, 2H), 7.24–7.17 (m, 3H), 6.93 (d, J = 7.5 Hz, 1H), 5.57 (s, 2H), 3.68 (s, 3H), 3.53 (br s, 1H), 3.42–3.39 (m, 1H), 3.30–3.27 (m, 1H), 2.88–2.74 (m, 2H), 1.79–1.71 (m, 2H), 1.61–1.58 (m, 1H), 1.37 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 157.6, 154.4, 153.9, 141.2, 138.7, 137.2, 128.4, 128.0, 126.7, 126.1, 122.8, 122.8, 118.2, 115.5, 114.8, 77.3, 54.6, 50.1, 47.3, 46.1, 29.1, 28.4, 27.7, 22.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{34}O_5N_5$ 532.2554, found 532.2537; IR(ATR): 1700, 1652, 1506, 1496, 1456, 1386, 1307, 1240, 1166, 1116 cm^{-1}.

5.43. 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-benzyl-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24a)

Compound **24a** was prepared from **23a** in a manner similar to that described for compound **8t** with a quantitative yield as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 2.0 Hz, 1H), 8.43 (br s, 3H), 8.05 (dd, J = 2.0, 8.9 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.32–7.28 (m, 2H), 7.25–7.22 (m, 1H), 7.17 (d, J = 7.2 Hz, 2H), 5.68 (d, J = 16.0 Hz, 1H), 5.62 (d, J = 16.0 Hz, 1H), 3.74–3.70 (m, 1H), 3.68 (s, 3H), 3.37–3.35 (m, 1H), 3.22–3.15 (m, 2H), 2.87–2.82 (m, 1H), 1.99–1.97 (m, 1H), 1.82–1.79 (m, 1H), 1.62–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 157.7, 154.5, 141.1, 140.2, 137.8, 129.1, 128.8, 127.6, 126.7, 124.5, 123.7, 119.1, 116.0, 115.9, 52.5, 51.1, 48.1, 46.4, 29.3, 27.5, 21.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{26}O_3N_5$ 432.2030, found 432.2015; IR (ATR): 1700, 1670, 1652, 1594, 1506, 1496, 1456, 1375, 1305, 1216, 1114, 1049 cm^{-1}.

5.44. 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-methyl-3-(2-methylbenzyl)-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24b)

Compound **24b** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 70% for 3 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J = 2.0 Hz, 1H), 8.35 (br s, 3H), 8.06 (dd, J = 2.0, 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.23–7.21 (m, 1H), 7.15–7.11 (m, 1H), 7.06–7.02 (m, 1H), 6.47 (d, J = 7.6 Hz, 1H), 5.58 (d, J = 17.2 Hz, 1H), 5.51 (d, J = 17.2 Hz, 1H), 3.74–3.66 (m, 1H), 3.66 (s, 3H), 3.40–3.38 (m, 1H), 3.28–3.23 (m, 1H), 3.13–3.10 (m, 1H), 2.90–2.85 (m, 1H), 2.38 (s, 3H), 1.94 (m, 1H), 1.76–1.75 (m, 1H), 1.61–1.57 (m, 1H), 1.51–1.46 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 157.8, 154.2, 141.1, 140.2, 136.1, 134.6, 130.2, 129.0, 127.0, 126.3, 124.5, 124.4, 123.7, 119.3, 116.0, 116.0, 52.3, 50.9, 46.4, 46.2, 29.1, 27.4, 22.0, 18.9; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{28}O_3N_5$ 446.2187, found 446.2173; IR (ATR): 1700, 1670, 1623, 1596, 1506, 1457, 1386, 1317, 1245, 1220, 1106, 1051 cm^{-1}.

5.45. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24c)

Compound **24c** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 11% for 3 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 2.0 Hz, 1H), 8.28 (br s, 3H), 8.05 (dd, J = 2.0, 8.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.25–7.21 (m, 1H), 7.03 (d, J = 8.7 Hz, 1H), 6.82–6.78 (m, 1H), 6.53 (d, J = 7.0 Hz, 1H), 5.52 (s, 2H), 3.85 (s, 3H), 3.74–3.69 (m, 1H), 3.64 (s, 3H), 3.43–3.38 (m, 1H), 3.22–3.19 (m, 1H), 3.15–3.12 (m, 1H), 2.87–2.82 (m, 1H), 1.98–1.96 (m, 1H), 1.72–1.69 (m, 1H), 1.59–1.45 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 157.9, 156.1, 154.3, 141.3, 140.2, 129.0, 128.5, 125.9, 125.7, 124.4, 123.7, 120.7, 119.4, 116.1, 116.0, 110.8, 55.7, 52.3, 50.7, 46.2, 43.9, 29.1, 27.6, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{28}O_4N_5$ 462.2136, found 462.2136; IR (ATR): 1714, 1652, 1569, 1506, 1463, 1436, 1386, 1309, 1245, 1108, 1051, 1024 cm^{-1}.

5.46. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-fluorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24d)

Compound **24d** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 55% for 3 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 2.0 Hz, 1H), 8.43 (br s, 3H), 8.05 (dd, J = 2.0, 9.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.34–7.29 (m, 1H), 7.25–7.20 (m, 1H), 7.10–7.07 (m, 1H), 6.89–6.86 (m, 1H), 5.68 (d, J = 16.8 Hz, 1H), 5.62 (d, J = 16.8 Hz, 1H), 3.73–3.68 (m, 1H), 3.64 (s, 3H), 3.38–3.36 (m, 1H), 3.25–3.15 (m, 2H), 2.94–2.89 (m, 1H), 1.98 (m, 1H), 1.82–1.79 (m, 1H), 1.66–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 159.6 (d, ^1J (C, F) = 243 Hz), 157.8, 154.3, 141.1, 140.2, 129.5 (d, ^3J (C, F) = 7.9 Hz), 129.1, 128.0 (d, ^4J (C, F) = 3.9 Hz), 124.8 (d, ^2J (C, F) = 25 Hz), 124.8 (d, ^3J (C, F) = 8.0 Hz), 124.5, 123.7, 119.1, 116.0, 115.8, 115.4 (d, ^2J (C, F) = 21 Hz), 52.4, 51.0, 46.3, 43.8, 29.2, 27.4, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{25}O_3N_5F$ 450.1936, found 450.1925; IR (ATR): 1716, 1673, 1596, 1508, 1456, 1375, 1317, 1218, 1126 cm^{-1}.

5.47. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(3-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24e)

Compound **24e** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 54% for 3 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 2.0 Hz, 1H), 8.42 (br s, 3H), 8.06 (dd, J = 2.0, 8.8 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.37–7.32 (m, 3H), 7.17–7.10 (m, 1H), 5.69 (d, J = 16.4 Hz, 1H), 5.61 (d, J = 16.4 Hz, 1H), 3.72–3.66 (m, 4H), 3.38 (m, 1H), 3.24–3.13 (m, 2H), 2.88–2.84 (m, 1H), 1.98 (m, 1H), 1.85–1.82 (m, 1H), 1.64–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.8, 154.5, 142.2, 140.3, 140.2, 133.4, 130.8, 129.1, 127.6, 126.7, 125.4, 124.5, 123.7, 119.0, 116.1, 116.0, 52.4, 51.2, 47.5, 46.3, 29.3, 27.4, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{25}O_3N_5Cl$ 466.1640, found 466.1627; IR (ATR): 1700, 1670, 1594, 1508, 1473, 1457, 1419, 1375, 1313, 1216, 1110 cm^{-1}.

5.48. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(4-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24f)

Compound **24f** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 86% for 3 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 1.9 Hz, 1H), 8.42 (br s, 3H), 8.04 (dd, J = 1.9, 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.66 (d, J = 16.0 Hz, 1H), 5.60 (d, J = 16.0 Hz, 1H), 3.71–3.65 (m, 4H), 3.37 (m, 1H), 3.23–3.14 (m, 2H), 2.89–2.84 (m, 1H), 1.97 (m, 1H), 1.85–1.82 (m, 1H), 1.63–1.52 (m, 2H); ^{13}C NMR (100 MHz,

DMSO-d_6) δ 167.0, 157.7, 154.5, 141.1, 140.1, 136.8, 132.1, 129.1, 128.8, 128.7, 124.5, 123.7, 119.0, 116.0, 115.9, 52.4, 51.2, 47.5, 46.3, 29.3, 27.4, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{25}O_3N_5Cl$ 466.1640, found 466.1624; IR (ATR): 1700, 1670, 1596, 1506, 1490, 1471, 1317, 1218 cm^{-1}.

5.49. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(3-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24g)

Compound **24g** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 78% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 2.0 Hz, 1H), 8.40 (br s, 3H), 8.05 (dd, J = 2.0, 8.9 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.23–7.19 (m, 1H), 6.82–6.78 (m, 2H), 6.70 (d, J = 7.7 Hz, 1H), 5.64 (d, J = 16.4 Hz, 1H), 5.57 (d, J = 16.4 Hz, 1H), 3.74–3.64 (m, 7H), 3.37–3.36 (m, 1H), 3.22–3.17 (m, 2H), 2.88–2.83 (m, 1H), 2.00–1.97 (m, 1H), 1.83–1.80 (m, 1H), 1.62–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 159.5, 157.7, 154.5, 141.0, 140.1, 139.4, 130.0, 129.1, 124.5, 123.7, 119.1, 118.7, 116.0, 116.0, 115.9, 112.7, 55.2, 52.4, 51.0, 48.0, 46.4, 29.3, 27.5, 22.2; HRMS (ESI) $[M+H]^+$ calcd calcd for $C_{25}H_{28}O_4N_5$ 462.2136, found 462.2120; IR (ATR): 1700, 1670, 1652, 1594, 1558, 1506, 1456, 1375, 1218, 1049 cm^{-1}.

5.50. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(4-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24h)

Compound **24h** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 54% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 1.9 Hz, 1H), 8.47 (br s, 3H), 8.04 (dd, J = 1.9, 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.60 (d, J = 15.2 Hz, 1H), 5.53 (d, J = 15.2 Hz, 1H), 3.72–3.65 (m, 7H), 3.39–3.38 (m, 1H), 3.23–3.18 (m, 2H), 2.91–2.85 (m, 1H), 2.01 (m, 1H), 1.84–1.83 (m, 1H), 1.64–1.55 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 158.7, 157.5, 154.5, 140.8, 140.1, 129.6, 129.1, 128.3, 124.4, 123.7, 118.9, 116.0, 115.7, 114.1, 55.2, 52.5, 51.1, 47.6, 46.4, 29.3, 27.5, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{28}O_4N_5$ 462.2136, found 462.2119; IR (ATR): 1700, 1670, 1596, 1511, 1457, 1378, 1309, 1243, 1176, 1110, 1025 cm^{-1}; Anal. calcd calcd for $C_{25}H_{27}O_4N_5{\cdot}3HCl{\cdot}2.25H2O$: C, 49.11; H, 5.69; N, 11.45, found: C, 49.31; H, 5.63; N, 11.23.

5.51. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-[2-(2-chlorophenyl) ethyl]-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*] quinoline-8-carboxylic acid hydrochloride (24i)

Compound **24i** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 25% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 1.6 Hz, 1H), 8.31 (br s, 3H), 8.05 (dd, J = 1.6, 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.24–7.21 (m, 1H), 7.16–7.12 (m, 1H), 6.99 (d, J = 6.9 Hz, 1H), 4.53 (t, J = 6.0 Hz, 2H), 3.75 (s, 3H), 3.69–3.65 (m, 1H), 3.39–3.36 (m, 1H), 3.21 (t, J = 6.0 Hz, 2H), 3.10–3.06 (m, 1H), 2.94–2.91 (m, 1H), 2.83–2.78 (m, 1H), 2.06–2.03 (m, 1H), 1.77 (m, 1H), 1.57–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.7, 154.6, 141.3, 140.2, 135.4, 133.4, 131.4, 129.3, 129.0, 129.0, 128.9, 127.4, 124.4, 123.7, 118.9, 116.0, 52.8, 51.0, 46.6, 44.6, 34.4, 29.4, 27.9, 22.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{27}O_3N_5Cl$ 480.1797, found 480.1782; IR (ATR): 1699, 1646, 1569, 1498, 1437, 1386, 1303, 1255, 1238, 1114, 1049, 1033 cm^{-1}.

5.52. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(cyclohexylmethyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24j)

Compound **24j** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 60% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (br s, 1H), 8.44 (br s, 3H), 8.04 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 4.19 (br s, 2H), 3.71 (s, 3H), 3.48–3.38 (m, 3H), 3.12–3.07 (m, 1H), 2.96 (m, 1H), 2.11 (br s, 1H), 1.88–1.61 (m, 7H), 1.33–0.84 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.8, 154.5, 140.7, 140.2, 129.0, 124.4, 123.8, 118.9, 116.0, 115.7, 52.8, 51.0, 50.9, 46.7, 43.8, 29.8, 29.3, 27.8, 26.0, 25.3, 22.8; HRMS (ESI) $[M+H]^+$ calcd calcd for $C_{24}H_{32}O_3N_5$ 438.2500, found 438.2484; IR (ATR): 1699, 1670, 1592, 1521, 1508, 1465, 1457, 1419, 1375, 1305, 1253, 1230, 1112, 1043 cm^{-1}.

5.53. 2-[(3*R*)-3-aminopiperidin-1-yl]-5-methyl-3-(3-methylbut-2-en-1-yl)-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24k)

Compound **24k** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 17% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 1.3 Hz, 1H), 8.47 (br s, 3H), 8.03 (d, J = 8.8 Hz, 1H), 7.66 (dd, J = 1.3, 8.8 Hz, 1H), 5.39 (m, 1H), 5.00–4.95 (m, 1H), 4.90–4.83 (m, 1H), 3.75 (m, 1H), 3.70 (s, 3H), 3.48–3.38 (m, 2H), 3.32–3.20 (m, 1H), 3.09–3.02 (m, 1H), 2.08–1.99 (m, 1H), 1.93 (br s, 2H), 1.78–1.66 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 156.7, 154.2, 140.1, 136.4, 129.0, 124.4, 123.7, 123.7, 120.8, 118.9, 115.9, 115.5, 52.8, 51.0, 46.5, 43.5, 29.4, 29.4, 29.3, 27.6, 22.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{28}O_3N_5$ 410.2187, found 410.2176; IR (ATR): 1716, 1683, 1635, 1508, 1473, 1456, 1375, 1311, 1216 cm^{-1}.

5.54. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(but-2-yn-1-yl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24l)

Compound **24l** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 41% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 2.0 Hz, 1H), 8.25 (br s, 3H), 8.05 (dd, J = 2.0, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 5.18 (d, J = 19.2 Hz, 1H), 5.12 (d, J = 19.2 Hz, 1H), 3.75 (s, 3H), 3.60–3.48 (m, 3H), 3.31–3.19 (m, 2H), 2.04–2.01 (m, 1H), 1.94–1.90 (m, 1H), 1.79 (s, 3H), 1.76–1.67 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 157.2, 154.3, 141.1, 140.2, 129.0, 124.4, 123.6, 118.6, 116.0, 116.0, 81.0, 74.6, 52.1, 50.8, 46.2, 35.3, 27.5, 25.0, 22.0, 3.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{24}O_3N_5$ 394.1874, found 394.1874; IR (ATR): 1699, 1652, 1569, 1538, 1506, 1457, 1375, 1309, 1241, 1110 cm^{-1}.

5.55. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2,5-dichlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24m)

Compound **24m** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 40% for 3 steps as a white amorphous. ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 2.0 Hz, 1H), 8.42 (br s, 3H), 8.06 (dd, J = 2.0, 8.9 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.40 (dd, J = 2.2, 8.5 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 5.58 (d, J = 17.6 Hz, 1H), 5.52 (d, J = 17.6 Hz, 1H), 3.72–3.69 (m, 1H), 3.63 (s, 3H), 3.37 (m, 1H), 3.30–3.24 (m, 1H), 3.15–3.10 (m, 1H), 2.93–2.88 (m, 1H),

1.98–1.97 (m, 1H), 1.78 (m, 1H), 1.64–1.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 157.7, 154.2, 141.1, 140.2, 137.4, 132.4, 131.3, 130.0, 129.2, 129.1, 127.1, 124.5, 123.8, 119.1, 116.1, 115.8, 52.2, 50.9, 46.5, 46.2, 29.2, 27.4, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{24}O_3N_5Cl_2$ 500.1251, found 500.1240; IR (ATR): 1652, 1646, 1623, 1558, 1506, 1457, 1419, 1386, 1313, 1216, 1101, 1049 cm^{-1}.

5.56. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-8-carboxylic acid hydrochloride (24n)

Compound **24n** was prepared from **21** in a manner similar to that described for compound **24a** with total yield of 75% for 3 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J = 2.0 Hz, 1H), 8.40 (br s, 3H), 8.06 (dd, J = 2.0, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.59–7.56 (m, 1H), 7.22–7.17 (m, 1H), 6.64 (dd, J = 2.8, 9.4 Hz, 1H), 5.57 (d, J = 17.6 Hz, 1H), 5.52 (d, J = 17.6 Hz, 1H), 3.72–3.67 (m, 1H), 3.64 (s, 3H), 3.41–3.37 (m, 1H), 3.29–3.24 (m, 1H), 3.12–3.09 (m, 1H), 2.93–2.88 (m, 1H), 1.97 (m, 1H), 1.80–1.77 (m, 1H), 1.63–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 161.3 (d, ^1J (C, F) = 243 Hz), 157.5, 154.2, 140.9, 140.2, 137.8 (d, ^3J (C, F) = 7.4 Hz), 131.4 (d, ^3J (C, F) = 8.4 Hz), 129.2, 126.4 (d, ^4J (C, F) = 2.6 Hz), 124.5, 123.8, 119.1, 116.1 (d, ^2J (C, F) = 24 Hz), 116.0, 115.7, 114.5 (d, ^2J (C, F) = 25 Hz), 52.2, 51.0, 46.7, 46.1, 46.1, 29.2, 27.4, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{24}O_3N_5ClF$ 484.1546, found 484.1533; IR (ATR): 1714, 1670, 1627, 1594, 1471, 1425, 1251, 1224, 1112 cm^{-1}.

5.57. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylate (25)

Compound **25** was prepared from **7j** in a manner similar to that described for compound **21** with a yield of 54% as a white amorphous. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (br s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 8.04 (d, J = 1.1 Hz, 1H), 7.83 (dd, J = 1.1, 8.2 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 4.18–4.14 (m, 1H), 4.05–4.01 (m, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.43 (br s, 1H), 2.97–2.90 (m, 1H), 2.83–2.76 (m, 1H), 1.85–1.74 (m, 2H), 1.55–1.51 (m, 1H), 1.40–1.32 (m, 10H); HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{30}O_5N_5$ 456.2241, found 456.2241; IR(ATR): 1716, 1683, 1646, 1618, 1594, 1515, 1307, 1267, 1224, 1168, 1108 cm^{-1}.

5.58. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chloro-5-fluorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylate (26)

Compound **26** was prepared from **25** in a manner similar to that described for compound **22a** with a yield of 71% as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 1.0 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.40–7.36 (m, 1H), 6.94–6.89 (m, 1H), 6.44–6.41 (m, 1H), 6.09 (br s, 1H), 5.70 (d, J = 16.8 Hz, 1H), 5.61 (d, J = 16.8 Hz, 1H), 3.99 (s, 3H), 3.82 (m, 1H), 3.80 (s, 3H), 3.45 (dd, J = 3.2, 12.8 Hz, 1H), 3.24–3.09 (m, 3H), 1.77–1.46 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 161.5 (d, ^1J (C, F) = 245 Hz), 158.0, 155.1, 154.7, 141.0, 137.2 (d, ^3J (C, F) = 7.3 Hz), 137.0, 130.7 (d, ^3J (C, F) = 8.2 Hz), 129.2, 126.6 (d, ^4J (C, F) = 2.9 Hz), 122.8, 122.6, 120.2, 120.1, 116.3, 115.6 (d, ^2J (C, F) = 23 Hz), 113.7 (d, ^2J (C, F) = 25 Hz), 78.9, 54.8 52.3, 51.4, 46.1, 45.7, 29.3, 29.0, 28.3, 21.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{34}O_5N_5ClF$ 598.2227, found 598.2227; IR(ATR): 1716, 1652, 1506, 1471, 1309, 1240, 1220, 1168, 1110 cm^{-1}.

5.59. Methyl 2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-3-(5-fluoro-2-methylbenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylate (27)

Compound **27** was prepared from **25** in a manner similar to that described for compound **22a** with a yield of 66% as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 1.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.16–7.12 (m, 1H), 6.85–6.80 (m, 1H), 6.24 (dd, J = 2.3, 9.8 Hz, 1H), 6.03 (br s, 1H), 5.62 (d, J = 16.8 Hz, 1H), 5.48 (d, J = 16.8 Hz, 1H), 3.99 (s, 3H), 3.84–3.82 (m, 1H), 3.79 (s, 3H), 3.44 (dd, J = 3.3, 12.8 Hz, 1H), 3.19–3.10 (m, 3H), 1.80–1.67 (m, 3H), 1.56–1.46 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 161.5 (d, ^1J (C, F) = 242 Hz), 158.0, 155.1, 154.9, 141.0, 137.6 (d, ^3J (C, F) = 6.8 Hz), 137.1, 131.6 (d, ^3J (C, F) = 7.8 Hz), 129.9 (d, ^4J (C, F) = 2.9 Hz), 129.2, 122.8, 122.7, 120.4, 120.3, 116.3, 113.7 (d, ^2J (C, F) = 21 Hz), 111.4 (d, ^2J (C, F) = 23 Hz), 79.0, 55.0, 52.3, 51.2, 46.2, 45.9, 29.5, 29.0, 28.3, 21.7, 18.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{31}H_{37}O_5N_5F$ 578.2773, found 578.2766; IR(ATR): 1716, 1652, 1506, 1307, 1259, 1220, 1164, 1108 cm^{-1}.

5.60. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chloro-5-fluorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]-quinoline-7-carboxylic acid hydrochloride (28)

Compound **28** was prepared from **26** in a manner similar to that described for compound **24a** with total yield of 90% for 2 steps as a white powder. All of the following equipment data is methane sulfonic acid salt of **28**. Mp 208–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 7.98 (br s, 3H), 7.90 (dd, J = 1.3, 8.2 Hz, 1H), 7.60–7.57 (m, 1H), 7.22–7.17 (m, 1H), 6.60 (dd, J = 3.0, 9.4 Hz, 1H), 5.57 (s, 2H), 3.67 (s, 3H), 3.62 (dd, J = 2.8, 12.4 Hz, 1H), 3.38 (br s, 1H), 3.23–3.18 (m, 1H), 3.11–3.08 (m, 1H), 2.89–2.88 (m, 1H), 2.34 (s, 3H), 1.95 (m, 1H), 1.78 (m, 1H), 1.57–1.55 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 161.3 (d, ^1J (C, F) = 243 Hz), 157.8, 154.3, 140.7, 137.9 (d, ^3J (C, F) = 7.5 Hz), 137.1, 131.4 (d, ^3J (C, F) = 8.7 Hz), 130.4, 126.4 (d, ^4J (C, F) = 2.7 Hz), 123.0, 122.4, 120.2, 119.7, 116.7, 116.2 (d, ^2J (C, F) = 22.7 Hz), 114.4 (d, ^2J (C, F) = 24.6 Hz), 52.3, 51.2, 46.6, 46.3, 29.0, 27.5, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{24}O_3N_5ClF$ 484.1546, found 484.1547; IR(ATR): 1673, 1639, 1467, 1151, 1124, 1041 cm^{-1}.

5.61. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(5-fluoro-2-methylbenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-*c*]quinoline-7-carboxylic acid hydrochloric acid (29)

Compound **29** was prepared from **27** in a manner similar to that described for compound **24a** with total yield of 84% for 2 steps as a white powder. Mp 231–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6, Me-SO_3H salt) δ 8.20 (d, J = 8.2 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 7.98 (br s, 3H), 7.90 (dd, J = 1.2, 8.2 Hz, 1H), 7.28–7.24 (m, 1H), 7.01–6.96 (m, 1H), 6.28 (dd, J = 2.8, 10.0 Hz, 1H), 5.51 (s, 2H), 3.67 (s, 3H), 3.63–3.62 (m, 1H), 3.39–3.38 (br s, 1H), 3.24–3.19 (m, 1H), 3.12–3.09 (m, 1H), 2.89–2.85 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 1.94–1.90 (m, 1H), 1.76–1.75 (m, 1H), 1.56–1.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, HCl salt) δ 167.4, 161.1 (d, ^1J (C, F) = 239 Hz), 157.8, 154.2, 140.6, 138.7 (d, ^3J (C, F) = 7.9 Hz), 137.1, 132.0 (d, ^3J (C, F) = 8.0 Hz), 130.7 (d, ^4J (C, F) = 2.9 Hz), 130.3, 123.0, 122.3, 120.3, 119.7, 116.7, 113.7 (d, ^2J (C, F) = 23.0 Hz), 111.7 (d, ^2J (C, F) = 22.8 Hz), 52.3, 51.7, 46.4, 46.3, 28.9, 27.5, 22.0, 18.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{27}O_3N_5F$ 464.2092, found 464.2076; IR (ATR): 1716, 1683, 1635, 1506, 1473, 1456, 1230 cm^{-1}; Anal. calcd for $C_{25}H_{26}O_3N_5F{\cdot}2.25MeSO_3H{\cdot}2.5H_2O$: C, 45.16; H, 5.56; N, 9.66, found: C, 45.06; H, 5.63; N, 9.76.

5.62. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one (2)

Compound **2** was prepared from **32** in a manner similar to that described for compound **8t** with a yield of 83% as a white amorphous. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.28 (br s, 3H), 7.50–7.26 (m, 7H), 6.69 (m, 1H), 5.63 (s, 2H), 3.65–3.62 (m, 1H), 3.24–3.07 (m, 2H), 2.94 (m, 1H), 2.81 (m, 1H), 1.93 (m, 1H), 1.74 (m, 1H), 1.52 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.1, 154.8, 142.2, 136.6, 135.3, 131.1, 129.5, 129.1, 128.3, 127.8, 127.1, 122.2, 121.7, 119.4, 116.1, 115.5, 52.4, 51.1, 46.4, 46.2, 27.5, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{23}ON_5Cl$ 408.1586, found 408.1576; IR (ATR): 1652, 1616, 1506, 1473, 1444, 1419, 1386, 1214, 1049 cm^{-1}.

5.63. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-ethyl-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one hydrochloride (2b)

To a solution of **32** (61.3 mg, 0.121 mmol) and K_2CO_3 (50.0 mg, 0.363 mmol) in DMF (2 ml) was added EtI (29.0 μl, 0.363 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give *tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5-ethyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate* (58.9 mg, yield 91%). To a solution of the *tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5-ethyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate* (58.9 mg, 0.11 mmol) in 1,4-dioxane (0.5 ml) was added 4 N HCl-1,4-dioxane (2 ml). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give **34a** (41.8 mg, yield 80%) as a white powder. Mp 207–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (br s, 3H), 8.19 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.59–7.55 (m, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.36–7.28 (m, 2H), 7.24–7.20 (m, 1H), 6.68 (d, J = 7.4 Hz, 1H), 5.64 (s, 2H), 3.70–3.58 (m, 2H), 3.49–3.45 (m, 1H), 3.31 (br s, 1H), 3.24–3.19 (m, 1H), 3.11–3.08 (m, 1H), 2.87–2.82 (m, 1H), 1.98–1.94 (m, 1H), 1.75 (br s, 1H), 1.59–1.51 (m, 2H), 1.16 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.7, 153.2, 140.4, 135.5, 134.7, 130.4, 128.8, 128.4, 128.2, 127.1, 126.3, 121.8, 121.6, 118.1, 115.8, 114.9, 51.7, 50.4, 45.6, 43.1, 35.5, 26.7, 21.4, 12.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}ON_5Cl$ 436.1899, found 436.1887; IR (ATR): 1670, 1637, 1592, 1477, 1442, 1240, 1199, 1160, 1122, 1085, 1051, 1041, 1027 cm^{-1}.

5.64. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-propyl-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one hydrochloride (2c)

Compound **2c** was prepared from **32** in a manner similar to that described for compound **2b** with total yield of 60% for 2 steps as a white powder. Mp 197–200 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (br s, 3H), 8.19 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.58–7.54 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.36–7.28 (m, 2H), 7.23–7.19 (m, 1H), 6.68 (d, J = 7.6 Hz, 1H), 5.63 (s, 2H), 4.22–4.18 (m, 2H), 3.71–3.64 (m, 1H), 3.26–3.21 (m, 2H), 3.11–3.08 (m, 1H), 2.88–2.83 (m, 1H), 1.97–1.95 (m, 1H), 1.75 (br s, 1H), 1.61–1.48 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.7, 153.4, 140.3, 135.8, 134.6, 130.4, 128.8, 128.4, 128.2, 127.1, 126.3, 121.8, 121.6, 118.0, 115.7, 115.1, 51.7, 50.4, 45.7, 45.6, 41.8, 26.7, 21.4, 20.3, 10.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{29}ON_5Cl$ 450.2055, found 450.2044; IR (ATR): 1670, 1637, 1592, 1473, 1442, 1355, 1128, 1051, 1039 cm^{-1}.

5.65. 2-[(3*R*)-3-aminopiperidin-1-yl]-5-benzyl-3-(2-chlorobenzyl)-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one hydrochloride (2d)

Compound **2d** was prepared from **32** in a manner similar to that described for compound **2b** with total yield of 69% for 2 steps as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (br s, 3H), 8.21 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 3.6 Hz, 1H), 7.32–7.16 (m, 6H), 7.10 (d, J = 7.3 Hz, 2H), 6.76 (d, J = 7.4 Hz, 1H), 5.67 (s, 2H), 5.52 (br s, 2H), 3.69–3.64 (m, 1H), 3.37–3.25 (m, 2H), 3.16–3.13 (m, 1H), 2.92–2.87 (m, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.63–1.52 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 153.8, 140.7, 136.6, 135.9, 134.6, 130.5, 128.8, 128.4, 128.1, 128.0, 127.1, 126.5, 126.4, 125.9, 121.9, 121.8, 118.0, 115.8, 115.6, 51.7, 50.5, 45.9, 45.6, 43.5, 26.7, 21.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{29}ON_5Cl$ 498.2055, found 498.2042; IR (ATR): 1670, 1646, 1637, 1610, 1575, 1540, 1515, 1508, 1442, 1396, 1353, 1326, 1176, 1153 cm^{-1}; Anal. calcd for $C_{29}H_{28}ON_5$·Cl·2HCl··1.75H2O: C, 57.81; H, 5.60; N, 11.62, found: C, 58.15; H, 5.51; N, 11.28.

5.66. {2-[2-{(3*R*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-5-(ethoxycarbonyl)-1H-imidazol-4-yl]-5-methoxyphenyl}(hydroxy)oxoammonium (31)

A mixture of **3** (353 mg, 0.599 mmol), 2-(4-methoxy-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (251 mg, 0.90 mmol), $Pd(PPh_3)_4$ (69.2 mg, 0.060 mmol) and Na_2CO_3 (127 mg, 1.20 mmol) was stirred under reflux for 10 h. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was washed with saturated $NaHCO_3$ aqueous solution, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **31** (329.0 mg, yield 89%) as a pale yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.41–7.38 (m, 1H), 7.25–7.20 (m, 2H), 7.17 (dd, J = 2.6, 8.4 Hz, 1H), 6.68 (d, J =6.8 Hz, 1H), 5.50 (s, 2H), 5.16–5.13 (m, 1H), 3.93 (q, J = 7.0 Hz, 2H), 3.91 (s, 3H), 3.77 (br s, 1H), 3.34 (dd, J = 3.3, 12.1 Hz, 1H), 2.98–2.94 (m, 3H), 1.74 (m, 2H), 1.63–1.55 (m, 2H), 1.42 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 159.5, 155.6, 155.0, 149.8, 143.3, 135.1, 133.3, 131.7, 129.3, 128.4, 127.4, 126.2, 122.7, 118.7, 116.8, 109.0, 79.2, 60.3, 55.9, 55.7, 51.9, 46.9, 46.0, 29.5, 28.3, 24.8, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{37}O_7N_5Cl$ 614.2376, found 614.2360; IR (ATR): 1699, 1527, 1506, 1490, 1456, 1444, 1363, 1353, 1330, 1297, 1276, 1232, 1170, 1072, 1049, 1039 cm^{-1}.

5.67. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-methoxy-5-methyl-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one (7g)

A mixture of Fe (253 mg, 4.53 mmol) in acetic acid (5 ml) was stirred at 80 °C for 30 min. To this suspension was added **31** (278.3 mg, 0.453 mmol) in acetic acid (3 ml) dropwise, and the mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was washed with water, saturated $NaHCO_3$ aqueous solution twice and brine, dried over Na_2SO_4, and concentrated in vacuo. To a mixture of the residue and K_2CO_3 (125 mg, 0.906 mmol) in DMF (3 ml) was added MeI (56.4 μl, 0.906 mmol). The reaction mixture was stirred at 65 °C for 7 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution twice and brine, dried over Na_2SO_4, and concentrated under

reduced pressure. The residue was purified by silica-gel column chromatography to give **7g** (184.2 mg, yield 74% for 2 steps) as a pale yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.20–7.09 (m, 2H), 6.93–6.88 (m, 2H), 6.68 (d, J = 7.1 Hz, 1H), 6.34 (br s, 1H), 5.73 (d, J = 17.0 Hz, 1H), 5.61 (d, J = 17.0 Hz, 1H), 3.93 (s, 3H), 3.81 (br s, 1H), 3.69 (s, 3H), 3.41 (dd, J = 3.1, 13.0 Hz, 1H), 3.25 (dd, J = 4.6, 12.5 Hz, 1H), 3.06 (br s, 2H), 1.79–1.72 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 158.8, 156.1, 143.1, 139.8, 136.0, 132.6, 130.2, 129.1, 127.8, 127.2, 127.2, 124.7, 118.2, 111.6, 110.0, 100.5, 79.6, 56.2, 55.4, 52.3, 46.9, 46.4, 30.2, 29.7, 29.1, 22.0; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}O_4N_5Cl$ 552.2372, found 552.2371; IR (ATR): 1700, 1646, 1577, 1508, 1473, 1417, 1388, 1363, 1315, 1236, 1164, 1066, 1039 cm^{-1}.

5.68. 2-[(3*R*)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-7-methoxy-5-methyl-3,5-dihydro-4H-imidazo[4,5-*c*]quinolin-4-one (8g)

Compound **8g** was prepared from **7g** in a manner similar to that described for compound **8t** with a yield of 89% as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.41 (br s, 3H), 8.21 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.32–7.28 (m, 1H), 7.25–7.21 (m, 1H), 7.02–7.00 (m, 2H), 6.77 (d, J = 7.4 Hz, 1H), 5.59 (s, 2H), 3.89 (s, 3H), 3.70 (d, J = 10.2 Hz, 1H), 3.58 (s, 3H), 3.37–3.27 (m, 2H), 3.12–3.09 (m, 1H), 2.92–2.87 (m, 1H), 1.97–1.94 (m, 1H), 1.75 (m, 1H), 1.62–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 156.4, 154.2, 139.1, 135.2, 131.0, 129.5, 129.1, 128.4, 127.8, 127.1, 123.9, 116.9, 110.2, 109.0, 100.4, 55.8, 52.3, 51.0, 46.6, 46.3, 29.0, 27.2, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}O_2N_5Cl$ 452.1848, found 452.1838; IR (ATR): 1675, 1652, 1635, 1604, 1558, 1508, 1473, 1457, 1436, 1419, 1251, 1047 cm^{-1}.

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