Tetrahedron 67 (2011) 9509–9517

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Preparation of 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones by palladium-assisted internal biaryl coupling reaction

Yohei Ikuma *, Hiroyuki Nakahira

Drug Research Division, Dainippon Sumitomo Pharma Co., Ltd., Kasugade Naka 3-1-98, Konohana-ku, Osaka 554-0022, Japan

ARTICLE INFO

Article history:
Received 26 July 2011
Received in revised form 3 October 2011
Accepted 5 October 2011
Available online 10 October 2011

Keywords:
2-Aminosubstituted-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones
Palladium-assisted internal biaryl coupling reaction
Silver carbonate
High reaction temperature

ABSTRACT

Representatives of the 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones have shown interesting biological activity. We have found 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one as a potent dipeptidyl peptidase 4 inhibitor. However effective synthesis of this nucleus with various substituents at the 6–9-positions has not been reported. We report herein the development of a novel and efficient synthesis of 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones by palladium-assisted internal biaryl coupling reaction. Our optimization of the reaction conditions revealed that the most important factors for this reaction are use of silver carbonate as a base and high reaction temperature.

1. Introduction

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.[1] As GLP-1 in plasma is rapidly degraded by the serine protease dipeptidyl peptidase 4 (DPP-4),[2,3] inhibition of DPP-4 is emerging as a promising approach for the treatment of type 2 diabetes with low risk of hypoglycemia.[4,5] A number of xanthine-based DPP-4 inhibitors, such as **1**[6] and **2**[7] (Fig. 1), have been reported.[8] Using the core structure of these compounds, we have found 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **3** as lead compound with moderate DPP-4 inhibitory activity.[9] To optimize this lead compound, we synthesized the 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one, which possesses various substituents at the 6–9-positions and evaluated its structure–activity relationship. The 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **4** is known as bronchodilator and its synthetic route is disclosed in the literature.[10] However, information on the synthesis of **4** includes a limited number of examples, and is not suitable for producing compounds that possess various substituents at the 6–9-positions. Furthermore, no synthetic route has been disclosed on compounds that have an amino group at the 2-position. Therefore, it was necessary for us to develop an efficient synthetic method for the 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one.

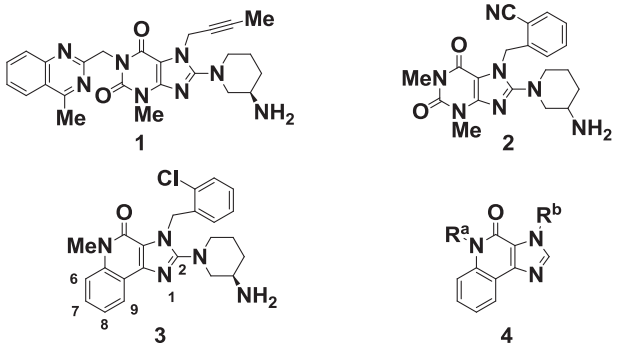


Fig. 1. Structure of small molecule DPP-4 inhibitors and new DPP-4 inhibitor **3** as lead compound.

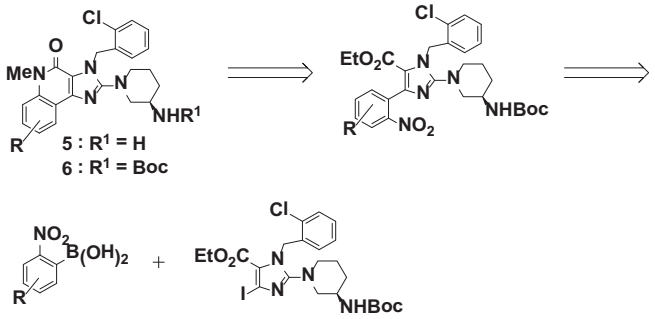
In this report, we present a convenient and efficient method for construction of a series of 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones, such as **5** and **6** using palladium-assisted internal biaryl coupling reaction.

2. Results and discussion

Initially, we considered path A (Scheme 1) for synthesis of the 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one

* Corresponding author. Tel.: +81 6 6466 5193; fax: +81 6 6466 5491; e-mail address: yohei-ikuma@ds-pharma.co.jp (Y. Ikuma).

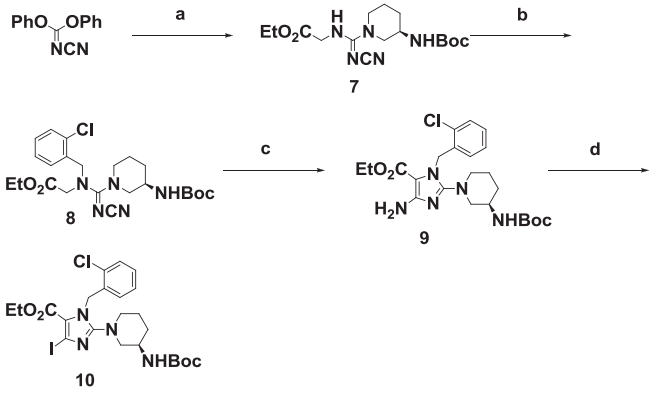
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.015



Scheme 1. Path A.

framework using Suzuki–Miyaura cross coupling,[11] followed by intramolecular amidation. As the predicted number of reaction steps was acceptable (eight steps), and the substituent R could be derived from the corresponding boronate, we decided to undertake this synthetic path.

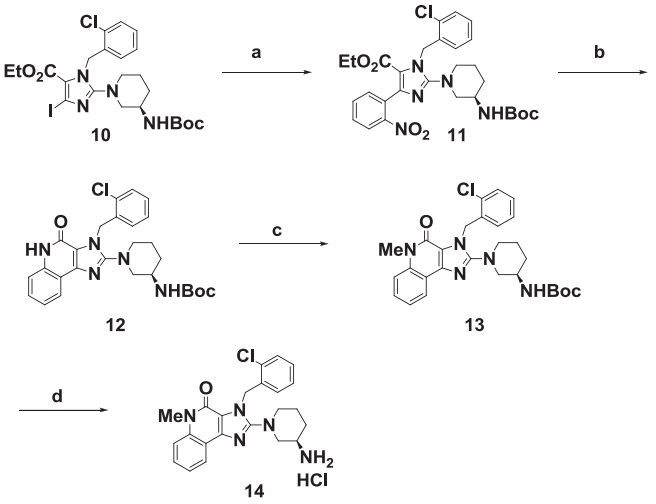
Synthesis of the intermediate **10** is shown in Scheme 2. Replacement of one phenoxy group in the diphenyl cyanocarbonimidate with (*R*)-3-*tert*-butoxycarbonylaminopiperidine, followed by treatment with excess amount of glycine ethyl ester at 80 °C provided **7** in high yield.[12] N-Alkylation of **7** with 2-chlorobenzylbromide, followed by cyclization with sodium hydride in tetrahydrofuran gave the 2-aminosubstituted imidazole **9**. The target **10** was obtained by Sandmeyer reaction of **9**, i.e., treatment with isoamylnitrite and CH_2I_2 in toluene.[13]



Scheme 2. Reagents and conditions: (a) (*R*)-3-*tert*-butoxycarbonylaminopiperidine (1.0 equiv), ^{i}PrOH 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%.

Next, Suzuki–Miyaura cross coupling reaction of **10** with 2-nitrophenylboronic acid yielded the desired biaryl compound **11** in low yield (24%, Scheme 3). The use of pinacol boronate, a stable boronic acid, gave **11** with slightly improved yield (40%). Reduction of the nitro group in **11** with iron in acetic acid at 80 °C, followed by intramolecular amidation gave the desired 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **12** in high yield. Compound **12** was quantitatively converted to **13** by N-methylation. Deprotection of the *tert*-butoxycarbonyl group by treatment with hydrochloric acid afforded the desired compound **14**.

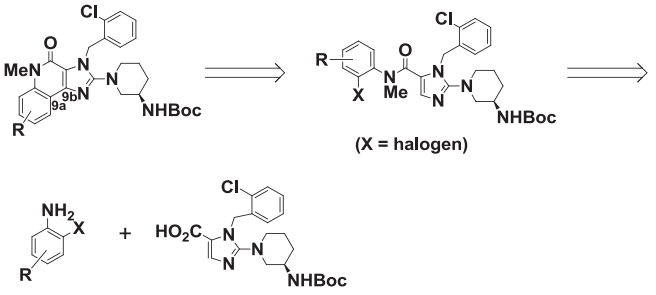
In path A, the concern was improvement of the low yield in Suzuki–Miyaura cross coupling reaction. For that, we considered that the intermolecular reaction between **10** and the corresponding boron reagent might have been prevented by both steric hindrance of the ethyl ester adjacent to the iodine atom in **10** and the nitro group adjacent to the boron in boronic acid. Furthermore, we realized that it would be difficult to obtain multisubstituted boronic



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$ (10 mol %), Na_2CO_3 (2.0 equiv), 2-nitrophenylboronic acid or 2-nitrophenylboronic acid pinacol ester (1.1 equiv), DME/H_2O (1/1), reflux, 24% or 40%; (b) Fe (6.0 equiv), AcOH, 80 °C, 92%; (c) K_2CO_3 (2.0 equiv), MeI (1.5 equiv), DMF, quant.; (d) HCl, dioxane, quant.

acid or boronic acid pinacol ester and that this synthetic route might have limitations.

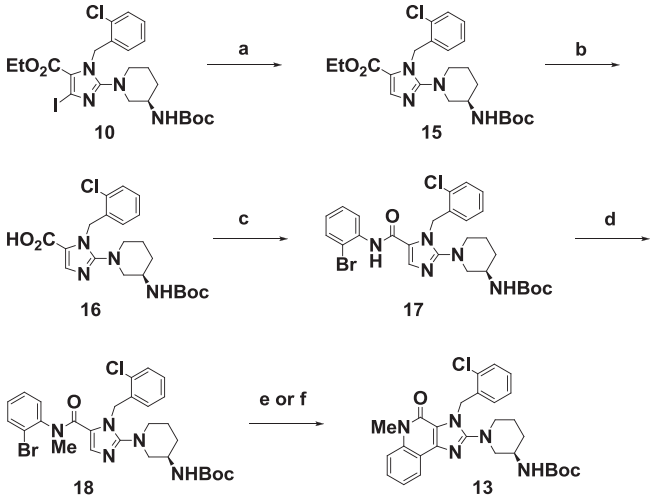
Based on the findings above, we designed an alternative synthetic route, path B, for better diversity of the product and improvement of the chemical yield. In path B, we considered that formation of the C–C bond between 9a- and 9b-positions would be enhanced by intramolecular reaction rather than intermolecular reaction of substrates with adjacent bulky substituents and that it would be easier to obtain substituted 2-haloaniline as substrate. Therefore, amidation was carried out first, followed by either intramolecular radical cyclization or palladium coupling reaction in path B (Scheme 4).



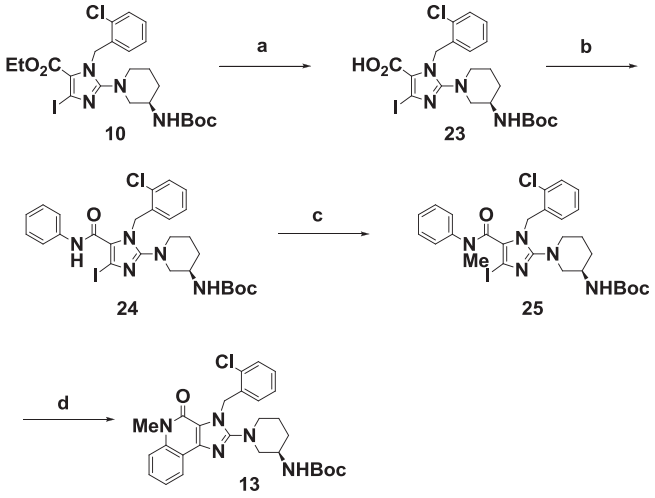
Scheme 4. Proposed path B using intramolecular key reaction.

Pd/C-catalyzed hydrogenation of **10** followed by alkaline hydrolysis provided **16** in high yield (Scheme 5). Coupling of **16** with 2-bromoaniline gave **17**, and treatment of **17** with iodomethane and K_2CO_3 gave **18** in moderate yield. Treatment of **18** with tributyltin hydride in toluene under reflux[14] gave no cyclized product, whereas palladium-catalyzed cyclization[15] fortunately proceeded. However, this reaction was complicated, leaving a small amount of substrate **18** and giving the target compound **13** in poor yield (13%).

Obtaining the desired cyclized compound **13** encouraged us to perform further modifications of this synthetic route. First, we considered the cause of poor yield in the formation of product **13** from substrate **18**. As shown in Fig. 2, it seems that after oxidative addition of Pd(0) to **18**, the six-membered intermediate **19** was formed by chelating with the neighboring carbonyl group to stabilize and remove both reactive sites (**A**). Moreover, intermediate **20** might have been unstable for cleavage of the amide bond. This led to a poor chemical yield. To prevent occurrence of these events,



Scheme 5. Reagents and conditions: (a) Pd/C, H_2, MeOH, quant.; (b) 1 M NaOH, THF/EtOH (1/1), 92%; (c) (1) $(COCl)_2$ (1.5 equiv), DMF (cat.), CH_2Cl_2 (2) DIPEA (3.0 equiv), 2-bromoaniline (1.0 equiv), toluene, 100 °C, 43%; (d) K_2CO_3 (1.5 equiv), MeI (1.5 equiv), DMF, 66%; (e) Bu_3SnH (1.3 equiv), AIBN (0.05 equiv), toluene, reflux, gave no product; (f) $Pd(OAc)_2$ (10 mol %), $NaHCO_3$ (2.5 equiv), DMA, 170 °C, 13%.



Scheme 6. Reagents and conditions: (a) 1 M NaOH (1.5 equiv), EtOH, 80 °C, quant.; (b) (1) $(COCl)_2$ (1.3 equiv), DMF (cat.), CH_2Cl_2 (2) DIPEA (3.0 equiv), aniline (1.3 equiv), toluene, 86%; (c) K_2CO_3 (4.0 equiv), MeI (4.0 equiv), DMF, 86%; (d) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2.0 equiv), THF, 39% or DMF, 31%.

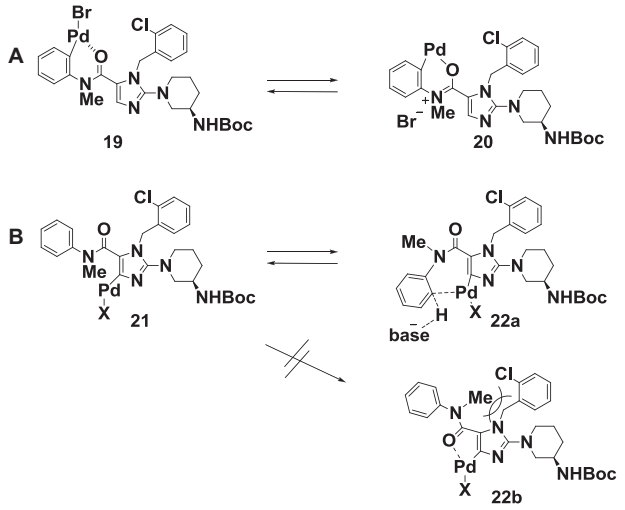


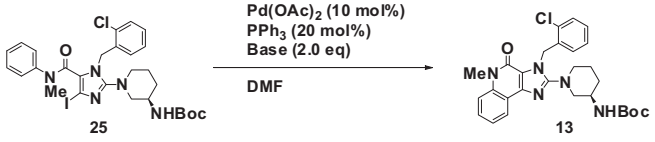
Fig. 2. Alternative palladium coupling reaction.

a synthetic route via **21** was designed (**B**). In this case, the transition state **22a** could be formed, and the reaction proceeded to metalation of the deprotonative C–H bond, followed by reductive elimination,[16] whereas formation of the five-membered intermediate **22b** could be prevented due to steric hindrance from the adjacent group.

Based on the assumptions above, we attempted intramolecular palladium coupling reaction with **25**[17,18] (Scheme 6). Alkaline hydrolysis of **10** and amidation with aniline, followed by N-methylation provided the precursor **25** in good yield. Pd catalyzed cyclization was carried out with $Pd(OAc)_2$, PPh_3, K_2CO_3, and THF or DMF at 60 °C, and the desired **13** was obtained in 39% or 31% yield, respectively. However, unlike intramolecular palladium coupling reaction with **18**, a substantial amount of substrate **25** remained and further improvement of the chemical yield in this reaction was considered feasible.

Next, we examined whether reaction rate can be accelerated by changing the base. This was done by monitoring **13** production rate and **25** survival rate at 60 °C after 0.5 h and 4 h (Table 1). With K_2CO_3, about 25% of **25** was converted to **13** after 0.5 h with no further consumption of **25** observed thereafter. A similar result was obtained when Na_2CO_3 was used instead of K_2CO_3. In the case of

Table 1
Time course consumption of **25** and production of **13** with various base at 60 °C and 100 °C in palladium coupling reaction (**25**/**13**) (%)



Entry	Base	60 °C (**25**/**13**)		100 °C (**25**/**13**)	
		0.5 h	4 h	0.5 h	4 h
1	K_2CO_3	76.8/23.2	76.1/23.9	69.9/30.1	34.6/58.9
2	Na_2CO_3	82.1/17.9	72.5/27.6	70.8/27.7	39.8/59.0
3	Ag_2CO_3	82.2/3.5	81.2/10.3	47.2/51.3	28.8/70.6

The reaction was monitored by HPLC at 203 nm.

Ag_2CO_3, the consumption of **25** was less than that in the case of K_2CO_3 or Na_2CO_3. To further accelerate the reaction, reaction temperature was raised to 100 °C. With K_2CO_3 and Na_2CO_3, the amount of remaining **25** decreased to about 35% after 4 h with no further change thereafter. Interestingly, in the case of Ag_2CO_3, substrate **25**, unlike at 60 °C, was consumed more than in the case of K_2CO_3 or Na_2CO_3, and the amount of **13** increased remarkably. The use of Ag_2CO_3 as a base seemed to produce good result at high reaction temperature. The positive effect of Ag_2CO_3 at high reaction temperature is presumably caused by abstraction of iodine from the arylpalladium complex to generate palladium cationic species that are more reactive.[19]

To explain the influence of reaction temperature on reaction with Ag_2CO_3 and its completion, we examined the effect of reaction temperature on consumption of **25** (Fig. 3). Consumption of **25** was hardly observed at 25 °C and its rate was very slow at 60 °C. Though **25** survival rate remained at about 30% after 2 h at 100 °C, no further consumption was observed. The amount of remaining **25** decreased to about 25% after 0.5 h at 125 °C with no further change thereafter. In contrast, **25** was immediately and completely consumed at 150 °C. It was therefore concluded that the use of Ag_2CO_3 and high reaction temperature play a very important role in this reaction, especially, a temperature of 150 °C is required to complete the reaction. In addition, we found that when the reaction is allowed to proceed longer with increasing temperature, the amount of **13** decreased gradually and production of by-products

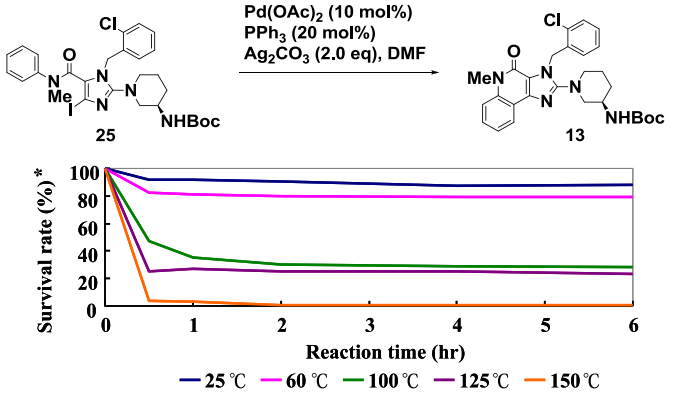


Fig. 3. Survival rate of **25** in the palladium coupling reaction. *The reaction was monitored by HPLC at 203 nm.

increased (Fig. 4). It is therefore necessary to consider conditions that would not compromise stability of the desired product.

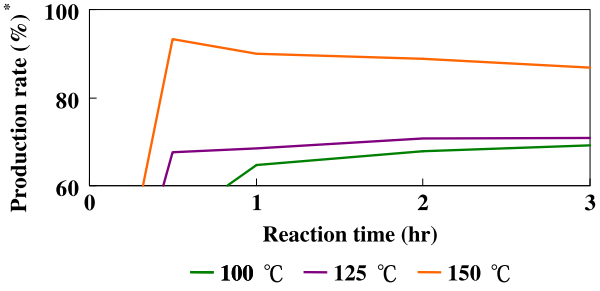


Fig. 4. Production rate of **13** in palladium coupling reaction. *The reaction was monitored by HPLC at 203 nm.

Next, we considered the mechanism of this palladium coupling reaction. As shown in Fig. 5, cyclization proceeded through oxidative addition of aryliodide to Pd(0) followed by abstraction of the iodide with Ag_2CO_3, leading to a cationic intermediate that gave **26A** and **26B**. The transition state **27** was immediately afforded from the cationic intermediate **26A**. Concerted deprotonative C–H bond metalation of **27** proceeded to give **28**, which underwent reductive elimination to give the desired product **13**. Based on these findings, we considered that oxidative addition of aryliodide to Pd(0) might be the rate-limiting step, since no by-products, including dehalogenation products, were obtained in this reaction. In addition, insertion of Pd(0) into the iodide is unlikely to occur because the 4-position is sterically hindered by a bulky substituent at the 5-position and the imidazole is electron-rich to have an amino group at the 2-positon. Finally, we examined whether the reaction oxidative addition can be accelerated by changing the ligand under mild conditions (Table 2). The use of P(*o*-tol)$_3$ or P^{n}Bu$_3$ resulted in no significant difference in **25** survival rate compared to PPh_3. We therefore concluded that the ligand does not affect the oxidative addition step. The only factor that positively affects Pd(0) oxidative addition in the reaction is thus high reaction temperature. Furthermore, it seemed that **26B** is significantly occupied for less steric hindrance than **26A** and that palladium coupling reaction proceeded not from **26B** but from **26A**. High reaction temperature is also necessary for transition from **26B** to **26A**. Indeed, at low reaction temperature, oxidative addition of Pd(0) is delayed, and transition rate from **26B** to **26A** is slow. This leads to very low chemical yield. On the other hand, at high reaction temperature, oxidative addition of Pd(0) proceeds smoothly and abundance of **26A** reduces steric hindrance, affording the transition state **27**. Therefore, high temperature plays an important role in two of the reaction steps, oxidative addition of Pd(0) and transition rate between **26A** and **26B**. Adopting these optimal conditions, allowed improvement of the conversion yield of **13** to 90% (Table 2, entry 4).

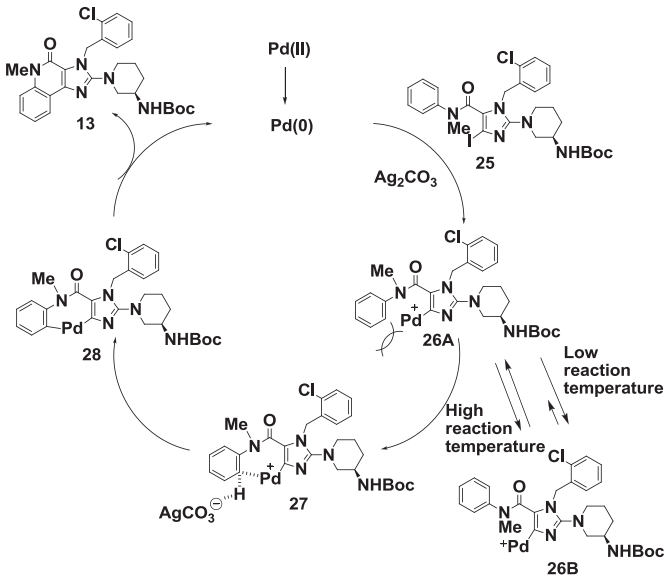
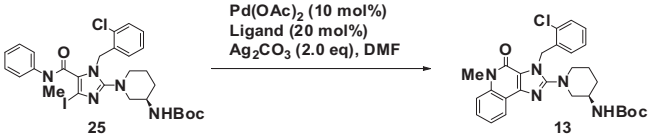


Fig. 5. Mechanism of the palladium coupling reaction.

Table 2
Ligand effect in the optimization of palladium coupling reaction of **25**

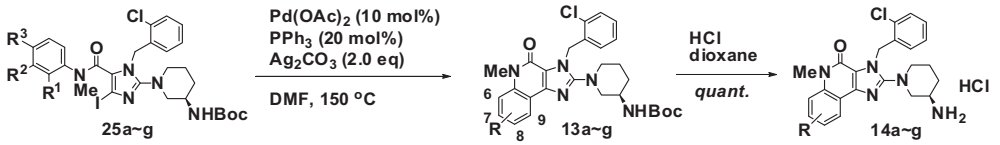


Entry	Temp (°C)	Ligand	Time (h)	**25**/**13** (%)	Yield[a] (%)
1	60	PPh_3	10	78.3/14.8	
2	60	P(*o*-tol)$_3$	10	82.8/9.1	
3	60	P^{n}Bu$_3$	10	77.1/15.7	
4	150	PPh_3	0.5		90

The reaction was monitored by HPLC at 203 nm.
[a] Isolated yield.

Based on the findings of this study, we conducted palladium-assisted internal biaryl coupling reaction of **25a**–**g** possessing a substituent at R^1–R^3 positions (Table 3). Coupling reaction of **25a**–**g** with either an electron-withdrawing group or an electron donating group afforded **13a**–**g** in good yield. With a substituent at R^2 position, a mixture of products with substituent at the 7- and 9-positions was obtained. Generation rate of a product with substituent at the 7-position was superior to that of a product with substituent at the 9-position. We therefore considered that product with substituent at the 7-position was dominantly obtained due to influence of steric hindrance between Pd and R^2 in the intermediate (Fig. 6). When R^2 was a phenyl group, a mixture of products separated by silica-gel column chromatography afforded **13$_1$c** in good yield (entry 3). When R^2 was CO_2Me, the mixture was inseparable by silica-gel column chromatography and a combination of products was obtained (entry 4). Though problems, such as development of regioselective synthesis at the 7- and 9-positions, remained to be solved, we have achieved the synthesis of various 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones in this reaction. Deprotection of the *tert*-butoxycarbonyl group by treatment with hydrochloric acid afforded the desired compound **14a**–**g**.

Table 3
Palladium coupling reaction of **25a**–**g** with different substituents



Entry	S.M.	R^1	R^2	R^3	**13**	Time (min)	Yield (%) of **13**	Product
1	**25a**	OMe	H	H	**13a**: 6-OMe	50	70	**14a**
2	**25b**	CO_2Me	H	H	**13b**: 6-CO_2Me	60	64	**14b**
3	**25c**	H	Ph	H	**13_1c**: 7-Ph/**13_2c**: 9-Ph (**13_1c**/**13_2c**, 11.8/1[a])	80	**13_1c** 72[b]	**14_1c**
4	**25d**	H	CO_2Me	H	**13_1d**: 7-CO_2Me/**13_2d**: 9-CO_2Me (**13_1d**/**13_2d**, 4/1[a])	80	76[c]	—[d]
5	**25e**	H	H	F	**13e**: 8-F	60	76	**14e**
6	**25f**	H	H	OMe	**13f**: 8-OMe	60	60	**14f**
7	**25g**	H	H	Me	**13g**: 8-Me	60	78	**14g**

[a] The rate was determined by HPLC.
[b] Isolated yield.
[c] Combined yield.
[d] The reaction of **13d** was not conducted due to the inseparable mixture of **13_1d** and **13_2d**.

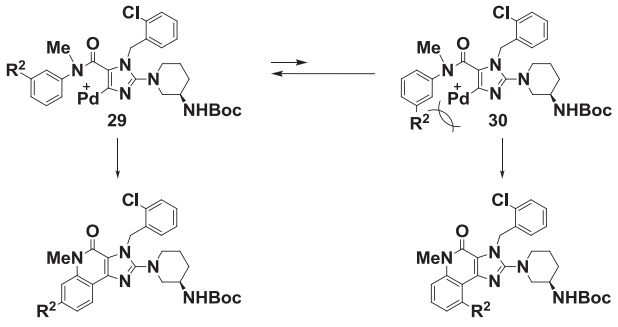


Fig. 6. Regioselectivity of the palladium coupling reaction.

3. Conclusion

In summary, we have developed an efficient synthesis of 2-aminosubstituted 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives by palladium-assisted internal biaryl coupling reaction. We have also shown that the most important factors of this reaction are use of silver carbonate as a base and high reaction temperature (150 °C). It is believed that the development of this synthetic route will facilitate construction of derivatives that can be excellent DPP-4 inhibitors and that this synthetic route can also afford new 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives that are difficult to produce by conventional methods.

4. Experimental section

4.1. General

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 (δ) 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 F_{254} 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). HPLC was performed on a Shimadzu Corporation system. Samples were applied onto a YMC-Pack Ph column (250 mm×4.6 mm, 5 μm) and eluted at 1 mL/min with a 40 min isocratic flow (42.5% B), where solvent A is water (0.1% TFA solution) and solvent B is acetonitrile (0.1% TFA solution). 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.

4.2. Procedures and analytical date

*4.2.1. Preparation of the intermediates **10**. 4.2.1.1. Ethyl N-[(E)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino) methyl]glycinate (**7**).* To solution of (*R*)-3-*tert*-butoxycarbonylaminopipiridine (154.0 g, 0.769 mol) in ^{i}PrOH (3.0 L) was added diphenyl cyanocarbonimidate (183.2 g, 0.769 mol). The mixture was stirred at room temperature for 2.5 h. To the reaction mixture was added glycine ethyl ester·hydrochloride (536.7 g, 3.85 mol) at 0 °C, and the mixture was stirred at 80 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt (1.4 L) and the precipitate was removed by filtration through a Celite pad. The filtrate was concentrated in vacuo, and the residue was diluted with 5% sodium carbonate solution and extracted with $CHCl_3$ three times. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to give **7** (249.2 g, yield 92%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 4.66 (br s, 1H), 4.28–4.19 (m, 4H), 3.81–3.34 (m, 5H), 2.05–1.51 (m, 4H), 1.45 (s, 9H), 1.30 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 160.0, 155.5, 117.1, 80.1, 61.8, 51.2, 47.3, 45.4, 44.6, 29.8, 28.3, 22.8, 14.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{28}N_5O_4$ 354.2136, found 354.2128; IR (ATR): 1743, 1685, 1575, 1531, 1440, 1390, 1365, 1309, 1243, 1197, 1162, 1051, 1031, 1018 cm^{-1}.

*4.2.1.2. Ethyl N-[(Z)-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}(cyanoimino)methyl]-N-(2-chlorobenzyl) glycinate (**8**).* A

mixture of **7** (249.2 g, 0.705 mol), 2-chlorobenzylbromide (225 g, 1.09 mol), and potassium carbonate (292 g, 2.11 mol) in MeCN (1.5 L) was stirred at 40 °C for 3 days. After cooling to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **8** (249.5 g, yield 74%) as a pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.38 (m, 1H), 7.31–7.16 (m, 3H), 4.87 (br s, 1H), 4.62 (d, J=15.0 Hz, 1H), 4.55 (d, J=15.0 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 3.98–3.89 (m, 2H), 3.77–3.69 (m, 2H), 3.54–3.25 (m, 3H), 1.94–1.83 (m, 2H), 1.72–1.63 (m, 2H), 1.44 (s, 9H), 1.29 (q, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.2, 155.0, 134.2, 132.5, 130.3, 130.2, 129.8, 127.3, 116.3, 79.6, 61.6, 60.4, 53.4, 52.6, 49.0, 46.7, 29.8, 28.3, 23.0, 14.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{33}ClN_5O_4$ 478.2216, found 478.2209; IR (ATR): 1741, 1700, 1535, 1496, 1442, 1390, 1365, 1164 cm^{-1}.

*4.2.1.3. Ethyl 4-amino-2-{(3R)-3-[(tert-butoxycarbonyl)amino] piperidin-1-yl}-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylate (**9**).* To a solution of sodium hydride (60% in oil, 15.94 g, 0.399 mol) in THF (1.8 L) was added **8** in THF (1.2 L) dropwise at 0 °C, and the mixture was stirred for 2.5 h at 15 °C. The reaction mixture was quenched with saturated NH_4Cl solution and water. The mixture was concentrated under reduced pressure. The residue was extracted with AcOEt, washed with 10% sodium carbonate solution and brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to give **9** (132.57 g, quant.) as a pale brown amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.35 (m, 1H), 7.27–7.14 (m, 2H), 6.78–6.75 (m, 1H), 5.25 (br s, 2H), 5.01–4.78 (m, 3H), 4.11–4.07 (m, 2H), 3.73–3.71 (m, 1H), 3.31–3.25 (m, 1H), 2.96–2.85 (m, 3H), 1.75–1.51 (m, 4H), 1.42 (s, 9H), 1.34 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 154.4, 135.7, 131.6, 129.6, 129.1, 128.0, 126.9, 126.5, 99.3, 79.1, 59.1, 55.3, 51.4, 46.8, 45.9, 29.5, 28.2, 22.3, 13.9; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{33}ClN_5O_4$ 478.2216, found 478.2210; IR (ATR): 2360, 1710, 1645, 1606, 1515, 1436, 1392, 1369, 1342, 1311, 1166, 1120, 1051 cm^{-1}.

*4.2.1.4. Ethyl 2-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-1H-imidazole-5-carboxylate (**10**).* A mixture of **9** (261.7 g, 0.548 mol), isoamylnitrite (368 ml, 2.74 mol), and CH_2I_2 (440 ml, 5.46 mol) in toluene (2.6 L) was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **10** (170.8 g, yield 53%) as a pale yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.38 (m, 1H), 7.37–7.13 (m, 2H), 6.60–6.57 (dd, J=1.8, 6.6 Hz, 1H), 5.49 (d, J=17.1 Hz, 1H), 5.42 (d, J=17.1 Hz, 1H), 4.92 (br d, J=7.5 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 3.75 (br s, 1H), 3.29 (dd, J=3.6, 12.3 Hz, 1H), 2.94–2.82 (m, 3H), 1.81–1.65 (m, 2H), 1.60–1.46 (m, 2H), 1.42 (s, 9H), 1.19 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 157.2, 154.9, 134.8, 131.8, 129.5, 128.5, 127.1, 126.2, 122.7, 92.3, 79.3, 60.7, 55.9, 51.8, 47.4, 46.1, 29.5, 28.3, 22.4, 13.8; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{31}ClIN_4O_4$ 589.1073, found 589.1078; IR (ATR): 1697, 1673, 1521, 1517, 1488, 1475, 1438, 1313, 1297, 1238, 1224, 1176, 1149, 1066, 1056, 1049, 1033, 1016 cm^{-1}.

*4.2.2. General procedure for the synthesis of **13** via Suzuki coupling reaction. 4.2.2.1. Ethyl 2-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-(2-nitrophenyl)-1H-imidazole-5-carboxylate (**11**).* A mixture of **10** (589.0 mg, 1.00 mmol), 2-nitrophenylboronic acid pinacol ester (274 mg, 1.10 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), and Na_2CO_3 (212 mg, 2.00 mmol) was stirred under reflux for 10 h. After cooling to room temperature, the mixture was diluted with AcOEt and filtered through a Celite pad. The filtrate was washed with saturated $NaHCO_3$ solution. 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 **11** (235.8 mg, yield 40%) as a pale yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J=0.9, 8.1 Hz, 1H), 7.63–7.61 (m, 2H), 7.55–7.49 (m, 1H), 7.42–7.39 (m, 1H), 7.26–7.22 (m, 2H), 6.70–6.68 (m, 1H), 5.55 (d, J=16.8 Hz, 1H), 5.49 (d, J=16.8 Hz, 1H), 5.11–5.09 (m, 1H), 3.92 (q, J=6.9 Hz, 2H), 3.79 (br s, 1H), 3.34 (dd, J=3.3, 12.0 Hz, 1H), 2.99–2.93 (m, 3H), 1.77–1.74 (m, 2H), 1.60–1.55 (m, 2H), 1.42 (s, 9H), 0.96 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 155.8, 155.0, 154.8, 149.2, 143.3, 135.0, 132.5, 131.7, 130.6, 129.3, 128.9, 128.4, 127.4, 126.2, 124.0, 117.9, 79.2, 60.4, 55.8, 51.9, 46.9, 46.0, 31.5, 29.5, 28.4, 22.2, 13.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}ClN_5O_6$ 584.2270, found 584.2273; IR (ATR): 1700, 1525, 1477, 1442, 1349, 1240, 1170, 1081, 1064, 1039, 1024 cm^{-1}. Anal. Calcd for $C_{29}H_{34}ClN_5O_6$: C, 59.64; H, 5.87; N, 11.99, found: C, 59.69; H, 5.93, N, 11.69.

*4.2.2.2. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}-carbamate (**12**).* A mixture of Fe (87.8 mg, 1.57 mmol) in acetic acid (4 ml) was stirred at 80 °C for 30 min. To this suspension was added **11** (91.8 mg, 0.157 mmol) in acetic acid (2 ml) dropwise, and the mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the mixture was diluted with AcOEt and filtered through a Celite pad. The filtrate was washed with water, saturated $NaHCO_3$ solution twice and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to give **12** (71.5 mg, yield 90%) as a white powder. Mp 241–243 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.87 (br s, 1H), 8.21 (dd, J=1.2, 7.8 Hz, 1H), 7.44 (dd, J=1.5, 7.8 Hz, 1H), 7.40–7.34 (m, 1H), 7.30–7.18 (m, 2H), 7.14–7.09 (m, 2H), 6.73 (d, J=7.2 Hz, 1H), 6.31 (br s, 1H), 5.80 (d, J=16.8 Hz, 1H), 5.68 (d, J=16.8 Hz, 1H), 3.83 (br s, 1H), 3.45 (dd, J=3.6, 12.9 Hz, 1H), 3.32–3.27 (m, 1H), 3.12–3.11 (m, 2H), 1.75 (m, 2H), 1.63–1.50 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 154.9, 154.8, 142.7, 136.4, 135.3, 131.1, 129.3, 128.9, 127.9, 127.7, 127.0, 122.0, 121.6, 119.2, 116.0, 115.8, 77.8, 55.0, 50.6, 46.5, 46.0, 29.8, 28.4, 23.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{27}H_{31}ClN_5O_3$ 508.2110, found 508.2096; IR (ATR): 1679, 1658, 1533, 1498, 1444, 1419, 1386, 1365, 1340, 1311, 1243, 1170, 1051, 1033, 1014 cm^{-1}.

*4.2.2.3. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate (**13**).* To a solution of **12** (50.3 mg, 99.9 μmol) and K_2CO_3 (27.3 mg, 0.198 mmol) in DMF (2 ml) was added MeI (9.2 μl, 0.148 mmol). The reaction mixture was stirred at room temperature for 12 h and quenched with saturated NH_4Cl solution, extracted with AcOEt. The organic layer was washed with saturated NH_4Cl 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 **13** (55.0 mg, quant.) as a yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (dd, J=1.5, 7.8 Hz, 1H), 7.56–7.51 (m, 1H), 7.45–7.40 (m, 2H), 7.36–7.29 (m, 1H), 7.22–7.10 (m, 2H), 6.67 (d, J=6.8 Hz, 1H), 6.37–6.35 (m, 1H), 5.78 (d, J=16.8 Hz, 1H), 5.65 (d, J=16.8 Hz, 1H), 3.82–3.79 (m, 1H), 3.75 (s, 3H), 3.43 (dd, J=3.0, 12.9 Hz, 1H), 3.27 (dd, J=3.6, 13.5 Hz, 1H), 3.08 (br s, 2H), 1.74–1.51 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 155.2, 155.0, 141.8, 137.4, 135.1, 131.8, 129.4, 128.4, 128.2, 127.1, 126.4, 122.7, 122.1, 119.1, 116.9, 114.7, 78.8, 54.6, 51.4, 46.1, 45.6, 29.3, 28.8, 28.4, 21.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{28}H_{33}ClN_5O_3$ 522.2266, found 522.2260; IR (ATR): 1707, 1645, 1521, 1502, 1465, 1444, 1388, 1362, 1319, 1240, 1224, 1166, 1114, 1049, 1039 cm^{-1}.

*4.2.2.4. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-3,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one (**14**).* To a solution of **13** (240.5 mg, 0.461 mmol) in 1,4-dioxane (5 ml) was added 4 N HCl-1,4-dioxane (5 ml). The reaction mixture was stirred at room temperature for 5 h and concentrated under reduced

pressure to give **14** (215.2 mg, quant.) as a white amorphous. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 3H), 8.21 (d, J=7.6 Hz, 1H), 7.62–7.56 (m, 2H), 7.52 (dd, J=1.1, 7.9 Hz, 1H), 7.39–7.35 (m, 1H), 7.33–7.29 (m, 1H), 7.25–7.21 (m, 1H), 6.71 (d, J=7.2 Hz, 1H), 5.66 (d, J=17.6 Hz, 1H), 5.61 (d, J=17.6 Hz, 1H), 3.69–3.66 (m, 1H), 3.62 (s, 3H), 3.38–3.24 (m, 2H), 3.11–3.08 (m, 1H), 2.89–2.84 (m, 1H), 1.96 (m, 1H), 1.79–1.76 (m, 1H), 1.62–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 154.1, 140.3, 137.5, 135.3, 131.1, 129.5, 129.1, 129.0, 127.9, 127.1, 122.6, 122.4, 118.7, 115.9, 115.8, 52.4, 51.1, 46.6, 46.3, 29.0, 27.3, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{25}ClN_5O$ 422.1742, found 422.1734; IR (ATR): 2657, 1672, 1591, 1477, 1444, 1330, 1249, 1114, 1052, 1033, 1016 cm^{-1}.

*4.2.3. General procedure for the synthesis of **13** from **18**. 4.2.3.1. Ethyl 2-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylate (**15**).* A mixture of **10** (1.66 g, 2.82 mmol) and 10% Pd/C (50% wet, 2.22 g) in MeOH (15 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 to give **15** (1.66 g, quant.) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.41 (d, J=1.8, 7.8H, 1H), 7.25–7.18 (m, 2H), 6.68 (m, 1H), 5.53 (d, J=16.8 Hz, 1H), 5.46 (d, J=16.8 Hz, 1H), 4.76 (br d, J=7.5 Hz, 1H), 4.21 (q, J=7.2 Hz, 2H), 3.74–3.72 (m, 2H), 3.49–3.46 (m, 1H), 3.19–2.97 (m, 2H), 1.87–1.77 (m, 2H), 1.67–1.44 (m, 2H), 1.40 (s, 9H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 155.6, 155.1, 134.6, 133.6, 131.9, 129.5, 128.6, 127.2, 126.4, 121.2, 79.5, 60.6, 55.7, 51.7, 46.7, 46.1, 29.5, 28.4, 22.6, 14.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{32}ClN_4O_4$ 463.2107, found 463.2104; IR (ATR): 1702, 1685, 1506, 1444, 1392, 1365, 1307, 1238, 1168, 1066, 1049, 1039, 1024 cm^{-1}.

*4.2.3.2. 2-{(3R)-3-[(tert-Butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-1H-imidazole-5-carboxylic acid (**16**).* A mixture of **15** (1.31 g, 2.82 mmol) and 1 M NaOH (5.54 ml) in EtOH (10 ml) was stirred at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was acidified with 10% $KHSO_4$ solution and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **16** (1.20 g, yield 92%) as a pale brown amorphous. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.49 (br s, 1H), 7.53 (s, 1H), 7.47–7.44 (m, 1H), 7.26–7.23 (m, 2H), 6.78 (m, 1H), 6.48–6.45 (m, 1H), 5.36 (s, 2H), 3.43–3.30 (m, 1H), 3.21–3.08 (m, 1H), 2.96–2.92 (m, 1H), 2.65–2.50 (m, 2H), 1.74–1.45 (m, 3H), 1.37–1.11 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD) δ 162.5, 157.5, 157.1, 136.4, 134.1, 133.2, 130.6, 129.8, 128.3, 127.8, 123.1, 80.1, 56.8, 52.4, 48.1, 47.4, 30.8, 28.7, 24.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{28}ClN_4O_4$ 435.1794, found 435.1789; IR (ATR): 1691, 1502, 1444, 1411, 1365, 1305, 1243, 1168 cm^{-1}.

*4.2.3.3. tert-Butyl [(3R)-1-{5-[(2-bromophenyl)carbamoyl]-1-(2-chlorobenzyl)-1H-imidazol-2-yl}piperidin-3-yl]carbamate (**17**).* To a solution of **16** (783.1 mg, 1.80 mmol) in CH_2Cl_2 (6 ml) were added $(COCl)_2$ (240 μl, 2.75 mmol) and DMF (5 μl). The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure. The residue was azeotroped with toluene and redissolved in toluene (6 ml). To this solution was added DIPEA (943 μl, 5.4 mmol) followed by 2-bromoaniline (237 μl, 2.16 mmol). The reaction mixture was stirred at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution. The mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **17** (454.4 mg, yield 43%) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, J=1.2, 8.1 Hz, 1H), 8.11 (br s, 1H), 7.58 (s, 1H), 7.54 (dd, J=1.5, 6.6 Hz, 1H), 7.40–7.37 (m, 1H), 7.29–7.13 (m, 3H), 6.96 (m, 1H), 6.70–6.67 (m, 1H), 5.62 (d, J=16.5 Hz, 1H), 5.53 (d, J=16.5 Hz, 1H), 4.98–4.95 (m, 1H), 3.79 (br s, 1H), 3.28 (dd, J=3.6, 12.0 Hz, 1H), 2.91–2.85 (m, 3H), 1.72–1.56 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.7, 155.0, 135.4, 135.0, 132.2, 132.1, 130.3, 129.5, 128.5, 128.4, 127.1, 126.8, 125.1, 124.2, 121.7, 113.4, 79.2, 55.8, 51.9, 46.1, 45.9, 29.4, 28.4, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{27}H_{32}ClBrN_5O_3$ 588.1372, found 588.1365; IR (ATR): 1679, 1577, 1506, 1430, 1388, 1368, 1309, 1280, 1236, 1168 cm^{-1}.

*4.2.3.4. tert-Butyl [(3R)-1-{5-[(2-bromophenyl)(methyl) carbamoyl]-1-(2-chlorobenzyl)-1H-imidazol-2-yl}piperidin-3-yl]carbamate (**18**).* A mixture of **17** (418.5 mg, 0.711 mmol), K_2CO_3 (147.0 mg, 1.06 mmol), and MeI (66.4 μl, 1.07 mmol) in DMF (2 ml) was stirred at 40 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with AcOEt. The organic layer was washed with saturated NH_4Cl 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 **18** (284.0 mg, yield 66%) as a white amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J=8.1 Hz, 1H), 7.39 (dd, J=1.5, 7.5 Hz, 1H), 7.29–7.16 (m, 4H), 6.96–6.90 (m, 1H), 6.81–6.76 (m, 1H), 6.15 (br s, 1H), 5.55–5.42 (m, 2H), 4.93–4.82 (m, 1H), 3.74 (br s, 1H), 3.22–3.16 (m, 4H), 2.84–2.74 (m, 3H), 1.63–1.50 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 155.3, 155.0, 143.1, 135.5, 134.0, 132.7, 132.3, 130.0, 129.7, 129.4, 128.8, 128.7, 128.6, 126.7, 123.5, 123.2, 79.2, 55.9, 51.9, 46.6, 45.9, 31.6, 29.4, 28.4, 22.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{28}H_{34}ClBrN_5O_3$ 602.1528, found 602.1528; IR (ATR): 1700, 1635, 1477, 1440, 1363, 1309, 1241, 1168, 1051, 1033, 1016 cm^{-1}.

*4.2.3.5. Palladium coupling reaction of **18** to give **13**.* A mixture of **18** (85.5 mg, 0.142 mmol), $Pd(OAc)_2$ (3.5 mg, 15.6 μmol), and $NaHCO_3$ (29.8 mg, 0.355 mmol) in DMA (2 ml) was stirred at 170 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The filtrate was washed with saturated NH_4Cl solution twice, saturated $NaHCO_3$, 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 **13** (9.3 mg, yield 13%) as a pale yellow amorphous.

*4.2.4. General procedure for the synthesis of **13** from **25**. 4.2.4.1. 2-{(3R)-3-[(tert-Butoxycarbonyl)amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-iodo-1H-imidazole-5-carboxylic acid (**23**).* A mixture of **10** (170.8 g, 0.29 mol) and 1 M NaOH (435 ml, 0.435 mol) in EtOH (2.3 L) was stirred at 80 °C for 6 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was acidified with 5% $KHSO_4$ solution and extracted with AcOEt. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to give **19** (168.1 g, quant.) as a pale yellow amorphous. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.46–7.43 (m, 1H), 7.27–7.24 (m, 2H), 6.82 (d, J=7.8 Hz, 1H), 6.56–6.53 (m, 1H), 5.37 (s, 2H), 3.38–3.33 (m, 2H), 3.15–3.08 (m, 1H), 2.96–2.92 (m, 1H), 2.66–2.54 (m, 1H), 1.90–1.60 (m, 2H), 1.54–1.45 (m, 1H), 1.33 (s, 9H), 1.22–0.95 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.9, 158.6, 157.6, 136.4, 133.2, 130.6, 129.8, 128.3, 127.9, 124.9, 92.0, 80.1, 66.9, 56.9, 52.5, 30.8, 28.8, 24.6, 15.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{21}H_{27}ClIN_4O_4$ 561.0760, found 561.0754; IR (ATR): 1683, 1496, 1490, 1473, 1442, 1409, 1392, 1365, 1349, 1240, 1222, 1162, 1066, 1051, 1033, 1020 cm^{-1}.

*4.2.4.2. tert-Butyl {(3R)-1-[1-(2-chlorobenzyl)-4-iodo-5-(phenylcarbamoyl)-1H-imidazol-2-yl]piperidin-3-yl}carbamate (**24**).* To a solution of **23** (1.96 g, 3.49 mmol) in CH_2Cl_2 (11 ml) were added

$(COCl)_2$ (396 μl, 4.54 mmol) and DMF (5 μl) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure. The residue was azeotroped with toluene and redissolved in toluene (11 ml). To this solution was added DIPEA (1.83 ml, 10.5 mmol) followed by aniline (414 μl, 4.53 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **24** (1.91 g, yield 86%) as a white solid. Mp 161–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.54–7.51 (m, 2H), 7.38–7.30 (m, 3H), 7.22–7.10 (m, 3H), 6.83–6.79 (m, 1H), 5.58 (d, J=16.2 Hz, 1H), 5.51 (d, J=16.2 Hz, 1H), 4.94–4.91 (m, 1H), 3.77 (br s, 1H), 3.29 (dd, J=3.3, 12.0 Hz, 1H), 2.92–2.83 (m, 3H), 1.76–1.64 (m, 2H), 1.58–1.49 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 157.0, 154.9, 137.1, 134.6, 132.4, 129.5, 129.0, 128.7, 127.7, 127.0, 126.5, 125.1, 124.7, 120.0, 85.3, 55.8, 51.9, 47.1, 45.9, 29.4, 28.4, 22.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{27}H_{32}ClIN_5O_3$ 636.1233, found 636.1230; IR (ATR): 1679, 1643, 1529, 1510, 1479, 1442, 1434, 1315, 1307, 1236, 1220, 1176, 1066, 1041 cm^{-1}.

*4.2.4.3. tert-Butyl [(3R)-1-{1-(2-chlorobenzyl)-4-iodo-5-[methyl(phenyl)carbamoyl]-1H-imidazol-2-yl}piperidin-3-yl]-carbamate (**25**).* A mixture of **24** (213.0 mg, 0.335 mmol), K_2CO_3 (185.0 mg, 1.34 mmol), and MeI (83.4 μl, 1.34 mmol) in DMF (2 ml) was stirred at room temperature for 15 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with AcOEt. The organic layer was washed with saturated NH_4Cl 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 **25** (187.6 mg, yield 86%) as a pale yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, J=1.8, 7.8 Hz, 1H), 7.33–7.11 (m, 7H), 6.85 (br d, J=6.9 Hz, 2H), 5.16 (br s, 2H), 3.78 (br s, 1H), 3.28–3.24 (m, 1H), 3.21 (s, 3H), 2.94–2.81 (m, 3H), 1.79–1.75 (m, 2H), 1.65–1.51 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 155.5, 155.0, 142.7, 133.9, 133.6, 130.8, 129.8, 129.7, 128.9, 128.0, 127.0, 126.7, 125.8, 125.1, 84.0, 56.2, 51.9, 46.4, 46.1, 38.6, 29.5, 28.4, 22.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{28}H_{34}ClIN_5O_3$ 650.1389, found 650.1385; IR (ATR): 1700, 1635, 1506, 1492, 1473, 1442, 1417, 1363, 1307, 1238, 1209, 1166, 1106, 1049, 1041, 1025, 1006 cm^{-1}.

*4.2.4.4. Palladium coupling reaction of **25** to give **13** (Table 3, entry 5).* A mixture of **25** (72.4 mg, 0.111 mmol), $Pd(OAc)_2$ (2.50 mg, 11.1 μmol), PPh_3 (5.84 mg, 22.3 μmol), and Ag_2CO_3 (61.4 mg, 0.223 mmol) in DMF (2 ml) was stirred at 150 °C for 30 min. After cooling to room temperature, the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The filtrate was washed with saturated NH_4Cl 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 **13** (52.6 mg, yield 90%) as a pale yellow amorphous.

*4.2.4.5. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-6-methoxy-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate (**13a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J=8.0 Hz, 1H), 7.32 (d, J=7.9 Hz, 1H), 7.19–7.01 (m, 3H), 6.96 (d, J=7.9 Hz, 1H), 6.60 (d, J=7.5 Hz, 1H), 6.38 (br s, 1H), 5.71 (d, J=16.9 Hz, 1H), 5.57 (d, J=16.9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.75 (br s, 1H), 3.34 (dd, J=3.1, 13.2 Hz, 1H), 3.21 (dd, J=4.1, 12.8 Hz, 1H), 3.00 (br s, 2H), 1.66–1.56 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.2, 155.2, 149.1, 141.8, 135.1, 131.8, 129.4, 128.9, 128.4, 127.0, 126.5, 123.0, 119.3, 119.2, 115.5, 111.8, 78.8, 56.4, 54.5, 51.4, 46.1, 45.6, 31.5, 29.3, 28.4, 21.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}ClN_5O_4$ 552.2372, found 552.2372; IR (ATR): 1706, 1648, 1492, 1469, 1442, 1386, 1363, 1309, 1241, 1168, 1074, 1049, 1039 cm^{-1}.

*4.2.4.6. Methyl 2-{(3R)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinoline-6-carboxylate (**13b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (dd, J=0.9, 7.7 Hz, 1H), 7.66 (dd, J=0.9, 7.5 Hz, 1H), 7.38 (d, J=7.7 Hz, 1H), 7.32–7.27 (m, 1H), 7.21–7.12 (m, 2H), 6.69 (d, J=7.1 Hz, 1H), 6.24 (br s, 1H), 5.74 (d, J=16.9 Hz, 1H), 5.61 (d, J=16.9 Hz, 1H), 3.95 (s, 3H), 3.80 (br s, 1H), 3.55 (s, 3H), 3.41 (dd, J=3.3, 13.0 Hz, 1H), 3.25 (dd, J=3.8, 12.6 Hz, 1H), 3.06 (m, 2H), 1.71–1.50 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 158.3, 155.9, 155.2, 142.0, 136.4, 134.8, 131.9, 129.8, 129.5, 128.6, 127.2, 126.6, 125.6, 122.0, 121.6, 119.3, 118.6, 78.9, 54.6, 52.7, 51.5, 46.3, 45.7, 31.5, 29.4, 28.4, 21.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{30}H_{35}ClN_5O_5$ 580.2321, found 580.2316; IR (ATR): 1716, 1683, 1654, 1490, 1386, 1263, 1201, 1166, 1130, 1066 cm^{-1}.

*4.2.4.7. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5-methyl-4-oxo-7-phenyl-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate (**13$_1$c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J=8.1 Hz, 1H), 7.70–7.68 (m, 2H), 7.61 (d, J=1.2 Hz, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.52–7.48 (m, 2H), 7.42–7.39 (m, 2H), 7.21–7.18 (m, 1H), 7.15–7.11 (m, 1H), 6.69 (d, J=7.6 Hz, 1H), 6.29 (br s, 1H), 5.79 (d, J=16.8 Hz, 1H), 5.67 (d, J=16.8 Hz, 1H), 3.81 (s, 3H), 3.81 (br s, 1H), 3.44 (dd, J=3.1, 9.6 Hz, 1H), 3.30–3.26 (m, 1H), 3.09 (br s, 2H), 1.74–1.68 (m, 3H), 1.53–1.51 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.2, 155.1, 141.8, 141.4, 140.9, 137.9, 135.2, 131.9, 129.4, 128.9, 128.4, 127.7, 127.4, 127.1, 126.5, 123.2, 121.4, 119.2, 116.0, 113.3, 78.9, 54.7, 51.5, 46.2, 45.7, 29.4, 29.0, 28.4, 21.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{34}H_{37}ClN_5O_3$ 598.2579, found 598.2583; IR (ATR): 1706, 1646, 1581, 1508, 1363, 1315, 1224, 1164, 1049, 981 cm^{-1}.

*4.2.4.8. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-8-fluoro-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-l}carbamate (**13e**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.95 (m, 1H), 7.42–7.37 (m, 2H), 7.25–7.10 (m, 3H), 6.68 (d, J=7.5 Hz, 1H), 6.36–6.35 (m, 1H), 5.77 (d, J=16.9 Hz, 1H), 5.64 (d, J=16.9 Hz, 1H), 3.82 (br s, 1H), 3.73 (s, 3H), 3.42 (dd, J=3.3, 13.0 Hz, 1H), 3.27 (dd, J=4.0, 12.6 Hz, 1H), 3.09–3.08 (m, 2H), 1.74–1.64 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (^1J (C,F)=240 Hz), 158.2, 155.3, 154.8, 141.3, 135.1, 134.1, 132.0, 129.6, 128.6, 127.2, 126.5, 119.8, 118.2 (^3J (C,F)=8.8 Hz), 116.4 (^3J (C,F)=8.8 Hz), 115.8 (^2J (C,F)=24 Hz), 108.3 (^2J (C,F)=24 Hz), 79.1, 54.7, 51.5, 46.4, 45.7, 29.4, 29.3, 28.5, 21.3; HRMS (ESI) $[M+H]^+$ calcd for $C_{28}H_{32}ClFN_5O_3$ 540.2172, found 540.2156; IR (ATR): 1706, 1652, 1506, 1434, 1363, 1307, 1241, 1166, 1106, 1049, 995 cm^{-1}.

*4.2.4.9. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-8-methoxy-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate (**13f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J=2.9 Hz, 1H), 7.42–7.35 (m, 2H), 7.19–7.11 (m, 3H), 6.67 (d, J=7.3 Hz, 1H), 5.83 (d, J=17.0 Hz, 1H), 5.67 (d, J=17.0 Hz, 1H), 5.34–5.31 (m, 1H), 3.96 (s, 3H), 3.83 (br s, 1H), 3.73 (s, 3H), 3.43 (dd, J=2.7, 12.3 Hz, 1H), 3.17 (dd, J=5.3, 11.9 Hz, 1H), 3.06–3.05 (m, 2H), 1.73–1.59 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.1, 155.1, 154.8, 141.9, 135.2, 132.0, 131.9, 129.5, 128.5, 127.2, 126.6, 119.7, 117.9, 117.0, 116.2, 104.6, 79.2, 55.9, 55.2, 51.6, 46.2, 45.9, 29.5, 29.1, 28.4, 21.9; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}ClN_5O_4$ 552.2372, found 552.2355; IR (ATR): 1706, 1648, 1506, 1423, 1363, 1307, 1214, 1166, 1116, 1039 cm^{-1}.

*4.2.4.10. tert-Butyl {(3R)-1-[3-(2-chlorobenzyl)-5,8-dimethyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinolin-2-yl]piperidin-3-yl}carbamate (**13g**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.40 (dd, J=1.1, 7.7 Hz, 1H), 7.33 (s, 2H), 7.22–7.09 (m, 2H), 6.67 (d, J=7.1 Hz, 1H), 5.81 (br s, 1H), 5.80 (d, J=16.8 Hz, 1H), 5.65 (d, J=16.8 Hz, 1H), 3.83 (br s, 1H), 3.73 (s, 3H), 3.42 (dd, J=2.9, 12.5 Hz, 1H), 3.23 (dd, J=4.6, 13.2 Hz, 1H), 3.07–3.05 (m, 2H), 2.49 (s, 3H), 1.72–1.49 (m,

4H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.2, 155.1, 142.0, 135.6, 135.3, 131.9, 131.9, 129.5, 128.5, 127.2, 126.6, 122.5, 119.4, 117.0, 114.7, 114.7, 79.1, 54.9, 51.6, 46.2, 45.8, 29.4, 29.0, 28.5, 28.0, 21.6; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{35}ClN_5O_3$ 536.2423, found 536.2410; IR (ATR): 1689, 1646, 1521, 1498, 1388, 1353, 1309, 1234, 1176, 1116, 1068, 1039 cm^{-1}.

*4.2.4.11. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-6-methoxy-5-methyl-3,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one hydrochloride (**14a**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (br s, 3H), 7.85 (d, J=7.6 Hz, 1H), 7.50 (d, J=7.8 Hz, 1H), 7.32–7.28 (m, 2H), 7.22–7.19 (m, 2H), 6.74 (d, J=7.5 Hz, 1H), 5.63 (d, J=18.0 Hz, 1H), 5.58 (d, J=18.0 Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.69–3.67 (m, 1H), 3.32–3.24 (m, 2H), 3.10–3.07 (m, 1H), 2.89–2.84 (m, 1H), 1.95 (br s, 1H), 1.75 (br s, 1H), 1.62–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 155.2, 149.1, 140.4, 135.2, 131.1, 129.5, 129.1, 128.6, 127.8, 127.2, 123.7, 118.7, 118.0, 115.1, 113.0, 56.9, 52.4, 51.1, 46.5, 46.3, 34.8, 27.3, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}ClN_5O_2$ 452.1848, found 452.1835; IR (ATR): 1673, 1594, 1483, 1444, 1247, 1074, 1051, 1041, 977 cm^{-1}. Anal. Calcd for $C_{24}H_{26}ClN_5O_2\cdot 2.75HCl$: C, 52.20; H, 5.25; N, 12.68, found: C, 52.25; H, 5.56, N, 12.30.

*4.2.4.12. Methyl 2-[(3R)-3-aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-4-oxo-4,5-dihydro-3H-imidazo[4,5-c]quinoline-6-carboxylate hydrochloride (**14b**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (br s, 3H), 8.30 (d, J=7.0 Hz, 1H), 7.70 (d, J=6.7 Hz, 1H), 7.51 (d, J=7.7 Hz, 1H), 7.43–7.39 (m, 1H), 7.32–7.29 (m, 1H), 7.25–7.21 (m, 1H), 6.73 (d, J=7.7 Hz, 1H), 5.63 (d, J=17.2 Hz, 1H), 5.58 (d, J=17.2 Hz, 1H), 3.90 (s, 3H), 3.72–3.58 (m, 2H), 3.37 (s, 3H), 3.27–3.22 (m, 1H), 3.09–3.06 (m, 1H), 2.87–2.82 (m, 1H), 1.95 (br s, 1H), 1.76 (br s, 1H), 1.61–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 157.9, 155.1, 141.6, 135.8, 135.2, 131.2, 129.8, 129.5, 129.1, 127.9, 127.2, 125.1, 122.2, 122.2, 119.0, 118.2, 53.1, 52.3, 51.1, 46.4, 46.3, 34.8, 27.4, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{27}ClN_5O_3$ 480.1797, found 480.1783; IR (ATR): 1722, 1658, 1577, 1527, 1496, 1471, 1267 cm^{-1}.

*4.2.4.13. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5-methyl-7-phenyl-3,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one hydrochloride (**14$_1$c**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (br s, 3H), 8.33–8.31 (m, 1H), 7.82 (d, J=7.5 Hz, 2H), 7.76 (s, 1H), 7.67 (d, J=8.1 Hz, 1H), 7.53–7.49 (m, 3H), 7.43–7.39 (m, 1H), 7.32–7.28 (m, 1H), 7.25–7.21 (m, 1H), 6.75 (d, J=7.5 Hz, 1H), 5.63 (d, J=17.2 Hz, 1H), 5.58 (d, J=17.2 Hz, 1H), 3.69–3.64 (m, 1H), 3.66 (s, 3H), 3.38–3.29 (m, 2H), 3.12–3.09 (m, 1H), 2.91–2.86 (m, 1H), 1.97 (br s, 1H), 1.76 (br s, 1H), 1.64–1.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 154.2, 140.7, 140.0, 139.8, 138.0, 135.2, 131.1, 129.5, 129.2, 129.1, 128.1, 127.8, 127.4, 127.1, 123.1, 121.3, 118.7, 114.8, 113.9, 52.4, 51.1, 46.7, 46.3, 29.0, 27.3, 21.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{29}ClN_5O$ 498.2055, found 498.2040; IR (ATR): 1668, 1596, 1444, 1419, 1324, 1051, 1033, 1016 cm^{-1}.

*4.2.4.14. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-8-fluoro-5-methyl-3,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one hydrochloride (**14e**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (br s, 3H), 7.80 (dd, J=3.0, 8.7 Hz, 1H), 7.65 (dd, J=4.5, 9.3 Hz, 1H), 7.52 (dd, J=1.1, 7.9 Hz, 1H), 7.47–7.42 (m, 1H), 7.33–7.29 (m, 1H), 7.25–7.21 (m, 1H), 6.66 (d, J=6.4 Hz, 1H), 5.63 (s, 2H), 3.62 (s, 3H), 3.61–3.56 (m, 1H), 3.38–3.36 (m, 1H), 3.23–3.18 (m, 1H), 3.09–3.06 (m, 1H), 2.85–2.82 (m, 1H), 1.98–1.90 (m, 1H), 1.77–1.75 (m, 1H), 1.58–1.49 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 157.7 (^1J (C,F)=240 Hz), 154.0, 140.9 (^4J (C,F)=3.1 Hz), 135.4, 134.0, 131.0, 129.4, 128.9, 127.7, 126.9, 119.4, 117.8 (^3J (C,F)=8.7 Hz), 117.8 (^3J (C,F)=8.7 Hz), 115.7 (^2J (C,F)=31 Hz), 107.1 (^2J (C,F)=31 Hz), 58.6, 50.7, 47.4, 46.1, 33.2, 29.1, 23.5; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{24}ClFN_5O$ 440.1648, found 440.1639; IR (ATR): 1672, 1604, 1525, 1463, 1313, 1245, 1213, 1110, 1051, 1000 cm^{-1}.

*4.2.4.15. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-8-methoxy-5-methyl-3,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one hydrochloride (**14f**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (br s, 3H), 7.63 (d, J=2.9 Hz, 1H), 7.56–7.51 (m, 2H), 7.33–7.29 (m, 1H), 7.23 (dd, J=1.1, 7.7 Hz, 1H), 7.21–7.18 (m, 1H), 6.67 (d, J=7.2 Hz, 1H), 5.64 (s, 2H), 3.88 (s, 3H), 3.72–3.63 (m, 1H), 3.60 (s, 3H), 3.50–3.46 (m, 1H), 3.28–3.25 (m, 1H), 3.11–3.07 (m, 1H), 2.88–2.83 (m, 1H), 1.99–1.94 (m, 1H), 1.79–1.76 (m, 1H), 1.60–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 154.9, 153.7, 140.1, 135.3, 131.9, 130.3, 129.5, 129.1, 127.8, 127.0, 119.1, 117.4, 117.3, 116.4, 104.1, 55.8, 52.4, 51.2, 46.4, 46.3, 29.0, 27.3, 22.1; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}ClN_5O_2$ 452.1848, found 452.1834; IR (ATR): 1670, 1508, 1471, 1423, 1230, 1051, 1033 cm^{-1}.

*4.2.4.16. 2-[(3R)-3-Aminopiperidin-1-yl]-3-(2-chlorobenzyl)-5,8-dimethyl-3,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one hydrochloride (**14g**).* ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (br s, 3H), 7.99 (s, 1H), 7.52–7.48 (m, 2H), 7.40–7.38 (m, 1H), 7.34–7.02 (m, 2H), 6.67 (d, J=7.6 Hz, 1H), 5.58 (s, 2H), 3.59 (s, 3H), 3.48–3.44 (m, 1H), 3.37–3.33 (m, 1H), 3.25–3.22 (m, 1H), 3.10–3.06 (m, 1H), 2.87–2.85 (m, 1H), 1.97 (m, 1H), 1.74 (m, 1H), 1.57–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 155.1, 142.3, 135.6, 135.5, 131.9, 131.8, 129.4, 129.3, 128.4, 127.2, 126.7, 122.5, 119.4, 117.0, 114.7, 59.1, 51.1, 47.4, 46.2, 33.3, 28.9, 23.3, 20.7; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{27}ClN_5O$ 436.1899, found 436.1890; IR (ATR): 1666, 1575, 1506, 1471, 1444, 1052, 1033 cm^{-1}.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.10.015. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Arulmozhi, D. K.; Portha, B. *Eur. J. Pharm. Sci.* **2006**, *28*, 96; (b) Knudsen, L. B. *J. Med. Chem.* **2004**, *47*, 4128.
2. (a) Kieffer, T. J.; Mclntosh, C. H. S.; Pederson, R. A. *Endocrinology* **1995**, *136*, 3585; (b) Deacon, C. F.; Nauck, M. A.; Toft-Nielson, M.; Pridal, L.; Willms, B.; Holst, J. J. *Diabetes* **1995**, *44*, 1126.
3. For recent reviews see (a) Havale, S. H.; Pal, M. *Bioorg. Med. Chem.* **2009**, *17*, 1783; (b) Mest, H. J.; Mentlein, R. *Diabetologia* **2005**, *48*, 616; (c) Weber, A. E. *J. Med. Chem.* **2004**, *47*, 4135; (d) Augustyns, K.; Van der Veken, P.; Senten, K.; Haemers, A. *Expert Opin. Ther. Pat.* **2003**, *13*, 499.
4. Drucker, D. J.; Nauck, M. A. *Lancet* **2006**, *368*, 1696.
5. Ahren, B. *Expert Opin. Emerging Drugs* **2008**, *13*, 593.
6. (a) Eckhardt, M.; Langkopf, E.; Mark, M.; Tadayyon, M.; Thomas, L.; Nar, H.; Pfrengle, W.; Guth, B.; Lotz, R.; Sieger, P.; Fuchs, H.; Himmelsbach, F. *J. Med. Chem.* **2007**, *50*, 6450; (b) Thomas, L.; Tadayyon, M.; Mark, M. *J. Pharmacol. Exp. Ther.* **2009**, *328*, 556.
7. Rasmussen, K. G.; Jensen, A. F.; Nygaard, L. World Patent WO2004033455A2; *Chem. Abstr.* **2004**, *140*, 357368.
8. Bruce, G. S.; Ravi, K. *Curr. Topp. Med. Chem.* **2007**, *7*, 569.
9. Nakahira, H.; Kimura, H.; Kobayashi, T.; Hochigai, H. World Patent WO2005051949A1; *Chem. Abstr.* **2005**, *143*, 26614.
10. Suzuki, F.; Kuroda, T.; Hayashi, H.; Nakasato, Y.; Manabe, H.; Ohmori, K. *Chem. Pharm. Bull.* **1992**, *40*, 3245.
11. Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047.
12. Richard, B.; Peter, J. G.; Christopher, J. H.; Helen, M. R.; Mannan, S. *Tetrahedron* **1990**, *46*, 7803; (b) Peter, J. G.; Simon, N. T.; Roger, W. *Tetrahedron Lett.* **1991**, *32*, 691.
13. (a) Minakawa, N.; Takeda, T.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1991**, *34*, 778; (b) Minakawa, N.; Sasabuchi, Y.; Kiyosue, A.; Kojima, N.; Matsuda, A. *Chem. Pharm. Bull.* **1996**, *44*, 288.
14. Suzuki, F.; Kuroda, T. *J. Heterocycl. Chem.* **1993**, *30*, 811.
15. Kuroda, T.; Suzuki, F. *Tetrahedron Lett.* **1991**, *32*, 6915.
16. (a) Domingo, G. C.; Paula, M.; Ataualpa, A. C. B.; Feliu, M.; Antonio, M. E. *J. Am. Chem. Soc.* **2007**, *129*, 6880; (b) Lutz, A. *Chem. Rev.* **2011**, *111*, 1315.
17. Beccalli, E. M.; Broggini, G.; Marchesini, A.; Rossi, E. *Tetrahedron* **2002**, *58*, 6673.
18. (a) Harayama, T.; Akiyama, T.; Akamatsu, H.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, *3*, 444; (b) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, *2*, 237.
19. (a) Rozhkov, R. V.; Larock, R. C. *Org. Lett.* **2003**, *5*, 797; (b) Kotora, M.; Matsumuia, H.; Gao, G.; Takahashi, T. *Org. Lett.* **2001**, *3*, 3467.