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Synthesis and biological evaluation of substituted imidazoquinoline derivatives as mPGES-1 inhibitors

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ABSTRACT

We have previously reported 7-bromo-2-(2-chrolophenyl)-imidazoquinolin-4(5*H*)-one (**1**) as a novel potent mPGES-1 inhibitor. To clarify the essential functional groups of **1** for inhibition of mPGES-1, we investigated this compound structure–activity relationship following substitution at the *C*(4)-position and N-alkylation at the *N*(1)-, the *N*(3)-, and the *N*(5)-positions of **1**. To prepare the target compounds, we established a good methodology for selective N-alkylation of the imidazoquinolin-4-one, that is, selective alkylation of **1** at the *N*(3)- and *N*(5)-positions was achieved by use of an appropriate base and introduction of a protecting group at the nitrogen atom in the imidazole part, respectively. Replacement of the *C*(4)-oxo group with nitrogen- or sulfur- linked substituents gave decreased inhibitory activity for mPGES-1, and introduction of alkyl groups on the nitrogen atom at the *N*(1)-, the *N*(3)-, and the *N*(5)-positions resulted in even larger loss of inhibitory activity. These results revealed that the *C*(4)-oxo group, and the hydrogen atoms at the *N*(5)-position and the imidazole part were the best substituents.

1. Introduction

Arachidonic acid is transformed by cyclooxygenase 1 and 2 (COX-1 and COX-2) to prostaglandin H_2 (PGH_2), which is subsequently metabolized through terminal synthases to biologically active prostanoids, such as thromboxane A_2 (TXA_2), PGI_2, PGD_2, PGF_2, PGE_2.[1] Among these prostanoids, PGE_2 is well known as an important lipid mediator with broad range of biological activities in various cells and tissues.[2] Isomerization of PGH_2 to PGE_2 is catalyzed by PGE_2 synthases (PGES), which are classified into three isoforms: microsomal PGES-1 (mPGES-1), -2 (mPGES-2), and cytosolic PGES (cPGES).[3] mPGES-1, which is functionally coupled with COX-2 and up-regulated by proinflammatory stimuli, such as IL-1, TNF-, and LPS, is responsible for the release of PGE_2.[4] It is reported that the symptoms of various diseases, such as collagen induced arthritis, pain hypersensitivity, and neuropathic pain, can be significantly relieved by suppression of PGE_2 production in mPGES-1 knockout mice.[5] Therefore, it is expected that inhibition of mPGES-1 can lead to improvement of mPGES-1-related disorders.[6] mPGES-1 inhibitors have recently been receiving a great deal of attention as potential drug candidates. Although a number of selective mPGES-1 inhibitors have been reported,[7] information on the essential functional groups, including a scaffold, for potent mPGES-1 inhibitory activity has not been satisfactory. One reason for this shortcomings is that no report of X-ray crystallography of complexes with the inhibitor and mPGES-1 in the open active conformation has made it difficult to perform rational drug design to identify interaction sites between the amino acid residues of mPGES-1 and the substituents of the inhibitors.[8] Therefore, it is necessary shed light on the essential functional groups involved in mPGES-1 inhibition. We have previously reported the imidazoquinolin-4(5*H*)-one derivative **1** as a novel structural mPGES-1 inhibitor (Fig. 1).[9] Preliminary examination of the chemical structure of this compound revealed that hydrophilic groups may be preferable as *C*(4)-substituents, and that more information is required to clarify the roles of the hydrogen atoms at the *N*(5)-position and the imidazole part. In this study, we set to clarify these preliminary information by conducting the following chemical modifications of **1**; (1) replacement of the *C*(4)-oxo group with nitrogen or sulfur atom linked substituents. (2) Introduction of an alkyl group at the *N*(5)-position. (3) Introduction of an alkyl group at the nitrogen atom in the imidazole part.

2. Results and discussion

2.1. Chemistry

The general synthetic methods of *N*-alkyl-imidazoquinolin-4-one derivatives are shown in Scheme 1. *N*(1)- or *N*(3)-alkyl derivatives can be synthesized from a common precursor, that is,

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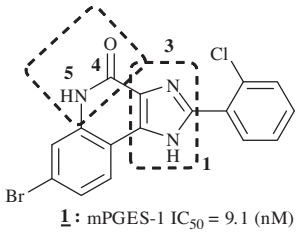


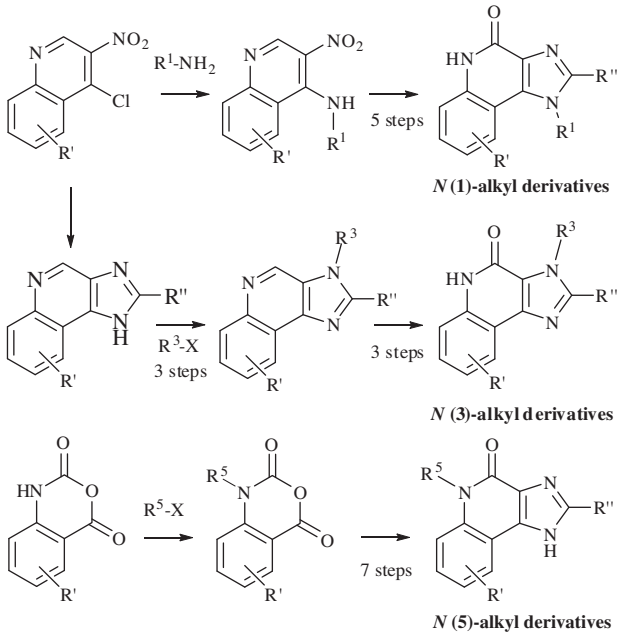
Figure 1. Structure of **1**.

substituted 4-chrolo-3-nitro-quinoline derivative, in 6 or 7 reaction steps, respectively.[10] Synthesis of the *N*(5)-alkyl derivatives can be achieved by N-alkylation of the substituted isatoic anhydride followed by seven reaction steps.[11] However, these conventional methods are not suitable for medicinal chemistry work, since our aim was to optimize the substituents at the *N*(1)-, the *N*(3)-, and the *N*(5)-positions, and to synthesize the desired analogues in a minimum number of reaction steps. It was therefore necessary to establish alternative convenient methods for the synthesis of *N*-alkyl-imidazoquinolin-4-one derivatives. As there has been no report on N-alkylation of the imidazoquinolin-4(*5H*)-one derivatives, we initially conducted a direct N-alkylation of **1** (Scheme 2). Compound **1** was reacted with 1.5 equiv of methyl iodide (MeI) and sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) at room temperature for 2 h. Although four types of compounds could be considered as possible mono-methylated compounds **2**–**5** (Fig. 2), the reaction afforded only two products. MS analysis indicated that one was mono-methylated, while the other was di-methylated. To specify the position of the methyl group in the mono-methylated compound, we carried out NOESY experiment. A clear NOE correlation between the *N*(5)-proton and the *C*(6)-proton indicated that the methyl group was introduced into either the *N*(1)- or *N*(3)-position.

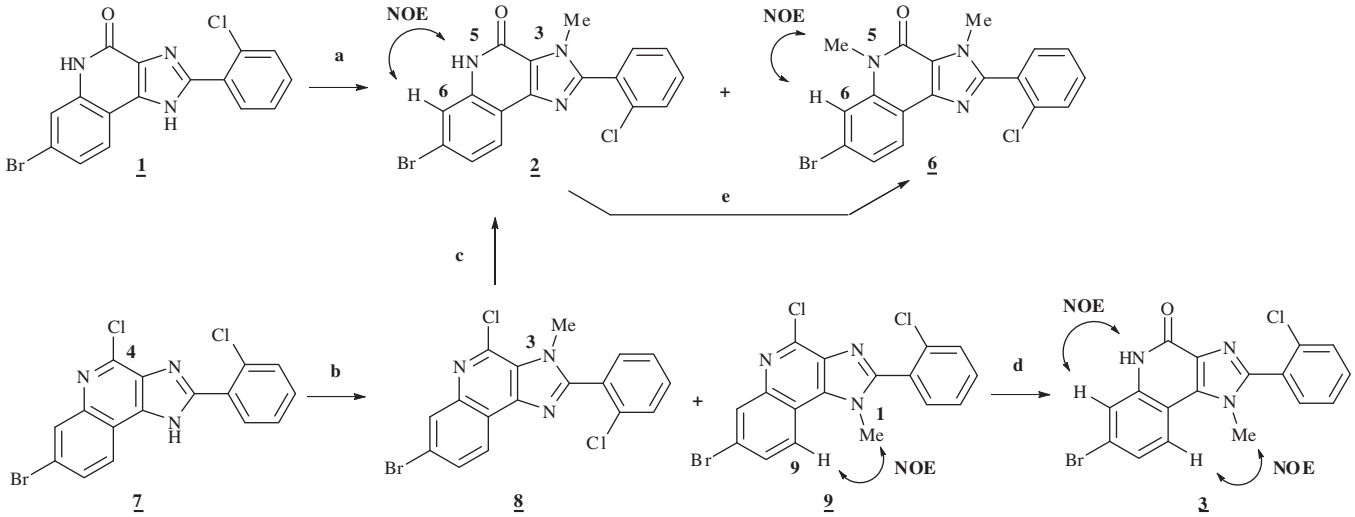
Next, to determine the position of the methyl group in the imidazole part, we performed methylation of the 4-chrolo-imidazoquinoline derivative **7**. Like in the case of **1**, **7** was reacted with MeI and NaH in DMF. This reaction provided two types of mono-methylated compounds, which were subsequently purified by column chromatography. NOE correlation between the proton in the methyl group and the *C*(9)-proton was observed in the minor product, but not in the major product, indicating that the major product was the N(3)-methylated compound **8** and the minor product was the N(1)-methylated compound **9**. The major product **8** was next hydrolyzed by refluxing in 5 M HCl and subjected to ^{1}H NMR and HPLC analyses. Analysis data perfectly agree with that of the product prepared by direct methylation of **1**, allowing identification of the structure of **2**. Hydrolysis of **9** gave the *N*(1)-methylimidazoquinolin-4(*5H*)-one derivative **3**. The isolated yields of the major and minor products in methylation of **7** were 76% and 21%, respectively. The reason why methylation of **7** proceeded at both the *N*(1)- and the *N*(3)-positions might be steric hindrance by the chloro atom around the *N*(3)-position. Meanwhile, the steric hindrance by the *C*(9)-hydrogen atom would interrupt the methylation to the *N*(1)-position in the case of **1**. Methylation of **2** afforded the dimethylated derivative **6**, whose NMR spectrum was consistent with that of the dimethylated compound synthesized by direct methylation of **1**, and whose NOE revealed a correlation between the proton in the methyl group and the *C*(6)-proton. Therefore, direct methylation of **1** initially proceeded at the *N*(3)-position and then the *N*(5)-position was methylated. As the chemical yield of **2** was poor (22%), we next tried to optimize the reaction conditions. First, we investigated the effect of a base on the selectivity (Table 1). Although the yield of **2** was improved by use of Cs_2CO_3, the dimethylated compound **6** was also generated (entry 2). The reaction with K_2CO_3, which is a milder base than Cs_2CO_3, increased the yield of **2** and decreased that of **3** (entry 3). Finally, reaction with the very mild base $NaHCO_3$ afforded only **2** in spite of 8% conversion (entry 4). These results indicated that selectivity of the *N*(3)-methylation can be improved by use of mild bases.

Next, we investigated the effects of organic bases on regioselectivity. Reaction of **1** with 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave results similar to those obtained with NaH or Cs_2CO_3 (entries 5 and 6), both of which are strong organic bases. These findings led us to use weak organic bases, such as *N*,*N*-diisopropylethylamine (*i*-Pr_2EtN), triethylamine (Et_3N), and pyridine. Although the reaction with *i*-Pr_2EtN at room temperature for 5 h gave only **2** without generating **6**, it reached saturation at 20% conversion, and extension of the reaction time had no beneficial effect on the conversion (entry 7). The reaction was accelerated by use of higher temperatures, that is, 40% conversion at 40 °C for 5 h, 62% at 60 °C for 3 h, and 100% at 60 °C for 5 h (entries 8–10). The reaction was further accelerated at 80 °C, that is, 42% conversion for 1 h and 100% for 3 h (entries 11 and 12). On the other hand, increase of the concentration of **1** from 0.1 M (entries 7–12) to 1.0 M (entries 13–15) shortened the reaction time, that is, 74% conversion at 40 °C for 3 h, 85% at 60 °C for 3 h, and 100% at 80 °C for 1 h. The isolated yields of **2** at 80 °C were 95% and 96% in 0.1 M and 1.0 M, respectively (entries 12 and 15). The reaction with Et_3N instead of *i*-Pr_2EtN at 80 °C gave only **2** in 18%, but did not proceed at 40 °C (entries 16 and 17). On the other hand, the reaction with pyridine did not proceed even at 80 °C (entry 18). These results indicated that selection of a suitable organic base for the imidazole ring allows selective mono-methylation at the *N*(3)-position. In all, we found that use of *i*-Pr_2EtN in DMF at 80 °C for 1 h provided the best conditions for selective *N*(3)-methylation of **1**.

Next, we investigated alkylation of **1** with various alkyl halides using the established optimum conditions (Table 2). Conversion to the target compound was clearly lower with ethyl iodide (EtI) than with MeI, that is, 10% conversion for 1 h and 18% for 5 h (entries 1 and 2). When the equivalent of EtI and *i*-Pr_2EtN was increased



Scheme 1. Conventional synthetic methods of *N*-alkyl derivatives.



Scheme 2. Reagents and conditions. (a) MeI, NaH, DMF, rt, 3 h, **2** (22%) and **6** (63%); MeI, NaH, DMF, rt, 2 h, **8** (76%) and **9** (21%); (c) 5 M HCL aq, EtOH, reflux, 4 h, **2** (90%); (d) 5 M HCL aq, EtOH, reflux, 4 h, **3** (89%); (e) MeI, NaH, DMF, rt, 0.5 h, **6** (90%).

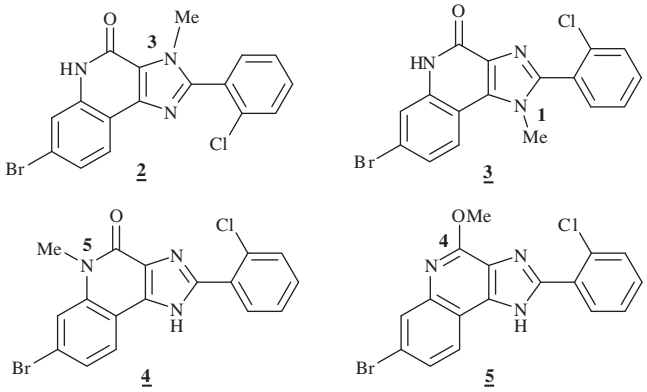


Figure 2. Structure of mono-methylated compounds.

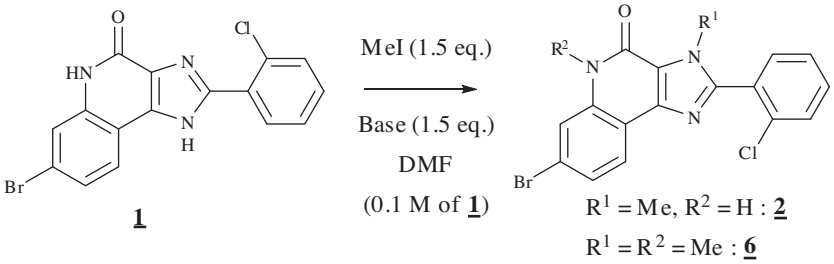
(3.0 equiv), the reaction promptly proceeded, reaching 79% conversion after 1 h (entry 3). The reaction was completed in 2 h and afforded **10** in 96% isolated yield without generating the di-ethylated compound (entry 4). Reaction of **1** with 3.0 equiv of *normal*-propyl iodide (*n*-PrI)/benzyl bromide (BnBr) and *i*-Pr_2EtN gave **11** and **12** in 95% and 98% isolated yields, respectively (entries 5 and 6). On the other hand, reaction with 2-(bromomethyl)-pyridine hydrobromide with 6.0 equiv of *i*-Pr_2EtN for 3 h gave **13** in 94% isolated yield (entry 7). Reaction with 2-bromoethanol, having a low reactivity compared to EtI, took 5 h to reach 95% conversion and gave **14** in 88% isolated yield (entry 8). NOESY experiments of **10**–**14** showed a similar NOE-correlation to **2**. These results indicated that various alkyl halides can be used for selective *N*(3)-alkylation of **1** using *i*-Pr_2EtN. This methodology seems to be suitable for medicinal chemistry work.

From the findings above, it became clear that acidity of the *N*(3)-proton was higher than that of the *N*(5)-proton and that direct and selective *N*(5)-alkylation of **1** would be extremely difficult. We therefore needed to develop an alternative route to prepare the *N*(5)-alkyl derivatives. Our first attempt was to introduce an appropriate protecting group at the imidazole nitrogen atom, since reactivity at the *N*(3)-position was higher than that at the *N*(5) (Table 3). 2-(Trimethylsilyl)ethoxymethyl (SEM), *tert*-butoxycarbonyl (Boc), tetrahydropyranyl (THP), and tosyl (Ts) groups are well known as protecting groups that can be easily removed.[12] Reaction of **1** with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) in the presence of *i*-Pr_2EtN gave the SEM protected derivative **15** in 74% yield without producing the di-SEM protected derivative (entry 1). On the other hand, reaction with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of *N*,*N*-dimethyl-4-aminopyridine (DMAP) afforded the Boc protected derivative **16** in 72% yield (entry 2). Reaction with dihydropyrane (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTS) as a catalyst or with tosyl chloride (TsCl) in the presence of *i*-Pr_2EtN did not give the target compound (entries 3 and 4). As expected, a good NOE correlation between **15** and **16** indicated that SEM and Boc groups can be introduced at the *N*(3)-position.

As shown in Scheme 3, reaction of **15** and **16** with MeI in the presence of K_2CO_3 promptly proceeded and gave the *N*(5)-methyl derivatives **17** and **18** in good yields. NOESY experiments of **17** and **18** showed a good NOE correlation between the *N*(5)-methyl group and the *C*(6)-proton. We therefore succeeded in achieving selective *N*(5)-mono-methylation via selective introduction of protecting group (SEM and Boc groups) into the *N*(3)-position of **1**. As imidazoquinoline derivatives having an SEM or Boc group on the imidazole ring have not previously been reported, we investigated the stability of the protecting groups in **17** and **18** (Table 4). The SEM group of **17** was easily removed with trifluoroacetic acid (TFA) at room temperature ($T_{comp.}$ = <15 min, entry 1), and was stable in the presence of the strong base NaOH (Entry 2). The SEM group showed resistance to tetrabutylammonium fluoride (TBAF) in tetrahydrofurane (THF) at room temperature, with deprotection proceeding up to 15% after 3 h (data not shown). On the other hand, under reflux condition, this group was completely removed after 5 h (Entry 3). The Boc group of **18** was also easily removed with TFA at room temperature ($T_{comp.}$ = <15 min, entry 4), while in the presence of HCl complete deprotection took up to 8 h (Entry 5). Interestingly, the Boc group of **18** was easily removed with 1 M NaOH and MeOH, leading to complete deprotection after 0.5 h (entry 6). This finding indicated that the Boc group could be removed under not only general acidic conditions, but also under basic conditions. All deprotection reactions afforded only **4** without byproducts.

The finding that the Boc group of **18** could be easily removed by use of 1 M NaOH and MeOH encouraged us to investigate one-pot synthesis of *N*(5)-alkyl derivatives from **16** (Scheme 3). After complete conversion of **16** was indicated by LC/MS, 1 M NaOH and MeOH were added to the reaction mixture, and the whole was vigorously stirred for 0.5 h to give the *N*(5)-methyl derivative **4** in 92% yield. NOESY experiment of **4** showed NOE correlation

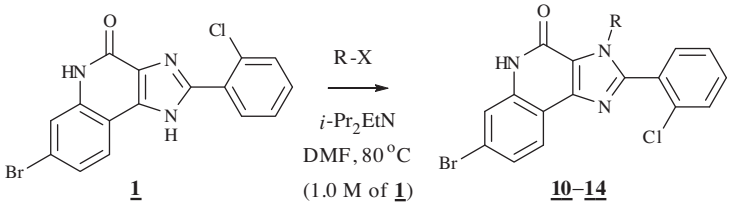
Table 1
Optimization of the N-methylation of **1**

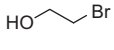
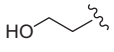


Entry	Base	Temp. (°C)	Time (h)	Conversion[b] (%)	Isolated yield (%)	
					2	**6**
1[a]	NaH	rt	3	100	22	63
2	Cs_2CO_3	rt	3	100	51	35
3	K_2CO_3	rt	3	100	56	27
4	$NaHCO_3$	rt	5	8		
5	BEMP	rt	3	100	21	59
6	DBU	rt	3	100	49	26
7	*i*-Pr_2EtN	rt	5	20		
8	*i*-Pr_2EtN	40	5	40		
9	*i*-Pr_2EtN	60	3	62		
10	*i*-Pr_2EtN	60	5	100		
11	*i*-Pr_2EtN	80	1	42		
12	*i*-Pr_2EtN	80	3	100	95	0
13[c]	*i*-Pr_2EtN	40	3	74		
14[c]	*i*-Pr_2EtN	60	3	85		
15[c]	*i*-Pr_2EtN	80	1	100	96	0
16	Et_3N	40	5	0		
17	Et_3N	80	5	20	18	0
18	pyridine	80	5	0		

[a] Result of reaction (a) in Scheme 2.
[b] Conversion yields were detected by LC/MS at 254 nM.
[c] 1.0 mmol/ml (M) concentration of **1** in DMF.

Table 2
Introduction of alkyl groups to **1**



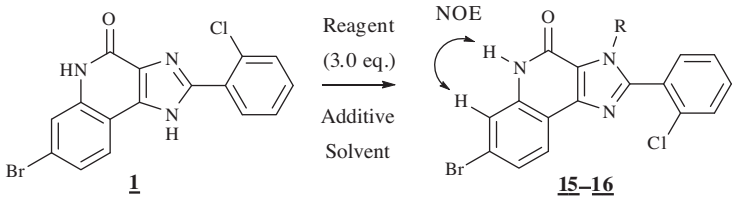
Entry	R–X (equiv)	*i*-Pr_2EtN (equiv)	Time (h)	R	Conversion[a]/isolated yield (%)
1	EtI (1.5)	1.5	1	Et	10 (10/—)
2	EtI (1.5)	1.5	5	Et	10 (18/—)
3	EtI (3.0)	3.0	1	Et	10 (79/—)
4	EtI (3.0)	3.0	2	Et	10 (100/96)
5	*n*-PrI (3.0)	3.0	2	*n*-Pr	11 (100/95)
6	BnBr (3.0)	3.0	1	Bn	12 (100/98)
7		6.0	3		13 (100/94)
8		3.0	5		14 (95/88)

[a] Conversion yields were detected by LC/MS at 254 nM.

between the *N*(5)-methyl group and the *C*(6)-proton. Moreover, ^{1}H NMR spectrum of **4** was not consistent with that of the *C*(4)-methyl ether derivative **5** synthesized from **7**,[9] which strictly proved that methylation of **15** and **16** selectively proceeded at the *N*(5)-position, not at the *C*(4)-oxygen atom. The *N*(5)-ethyl and the *N*(5)-benzyl derivatives **19** and **20** were also synthesized in good yields using the same method. Hence, we could establish a more convenient synthetic method of the *N*(5)-alkyl-imidazoquinolin-4-one derivatives from **1** than the conventional method that requires many reaction steps.[11]

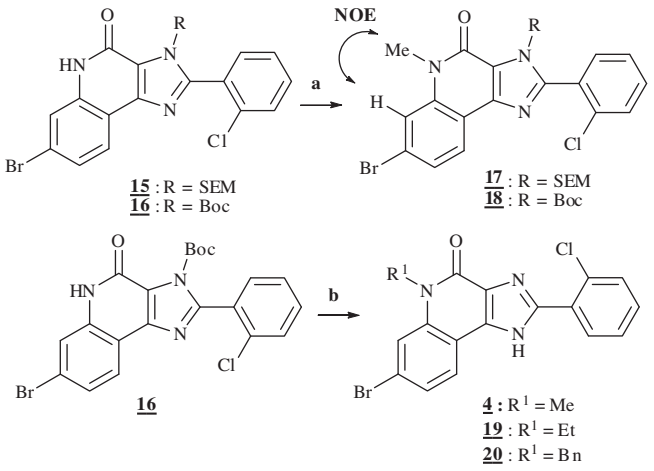
The synthetic methods for the *C*(4)-substituted derivatives **21**–**26** are shown in Scheme 4. Replacement of the chlorine atom of **7** with corresponding amines or sodium sulfide reagents under microwave irradiation (m.w.) provided **21**–**26**. The

Table 3
Introduction of protective groups to **1**



Entry	Reagent	Additive (equiv)	Solvent	Temp. (°C)	Time (h)	R	Yield[a] (%)
1	SEMC1	*i*-Pr_2EtN (3.0)	DMF	80	1	SEM	15 (74)
2	Boc_2O	DMAP (0.5)	THF	50	1	Boc	16 (72)
3	DHP	PPTS (0.5)	THF	Reflux	8	THP	No reaction
4	TsCl	*i*-Pr_2EtN (3.0)	DMF	80	8	Ts	No reaction

[a] isolated yield.



Scheme 3. Reagents and conditions. (a) MeI, K_2CO_3, DMF, rt, 2 h, **17** (94%), **18** (92%), respectively; (b) MeI, EtI, or BnBr, K_2CO_3, DMF, rt, 2 h and then 1 M NaOH, MeOH, rt, 0.5 h, **4**, **19**, and **20** (90–92%) in two steps, respectively.

quinoline-4(5*H*)-thione structure of **26** was identified by characteristic NOE correlation between the *N*(5)-proton and the *C*(6)-proton, and FT-IR spectrum.

2.2. Biological evaluation

We initially investigated the effects of the substituents at the *C*(4)-position. The results are summarized in Table 5. The amino derivative **21**, the monomethylamino **22**, and the dimethylamino **23** exhibited remarkably lower inhibitory activity for mPGES-1 than **1** (IC_{50} values of 1068, 631, and 387 nM, respectively), indicating that basic substituents were not preferable for mPGES-1 inhibitory activity. The IC_{50} value of the thione derivative **26** for inhibition of mPGES-1 was 83 nM, ninefold weaker than that of **1**. No improvement in activity was seen with the methylthio derivative **24** and the ethylthio **25** compared to **1**. As previously reported, the IC_{50} values of the *C*(4)-methoxy derivative **5** and the *C*(4)-unsubstituted derivative **27** for mPGES-1 inhibition were 62 and 251 nM, respectively.[9] These results suggested that sterically small and non-basic substituent should be placed onto the *C*(4)-position for potent inhibitory activity.

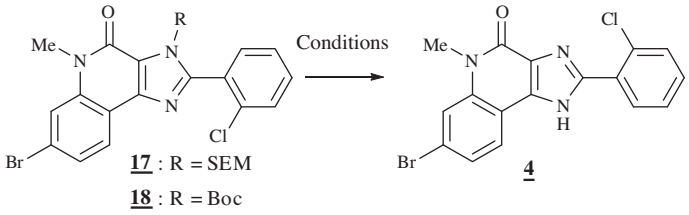
Next, in order to investigate the effects of the proton source at the *N*(5)-position and the imidazole part of **1**, the *N*-alkyl-imidazoquinolin-4-one derivatives were evaluated. As shown in Table 6, the *N*(5)-methyl derivative **4** resulted in ninefold loss of inhibitory activity compared to **1**. mPGES-1 inhibitory activity was also decreased by introduction of sterically large substituents, that is, the ethyl group (**19**) and the benzyl group (**20**). We guessed that the proton at the *N*(5)-position may have interacted with mPGES-1, leading to decreased inhibitory activity following *N*(5)-alkylation.

With regard to the *N*(1)- or the *N*(3)-methyl derivatives, the inhibitory activity was completely diminished in the *N*(1)-methyl derivative **3**, and over 1000-fold loss in activity was seen in the *N*(3)-methyl derivative **2**. The *N*(3)-*N*(5)-dimethyl derivative **6** also showed no inhibition for mPGES-1 even at 10 μM. Finally, the proton in the imidazole part was found to be essential for tight binding with the active site of mPGES-1.[13]

3. Conclusion

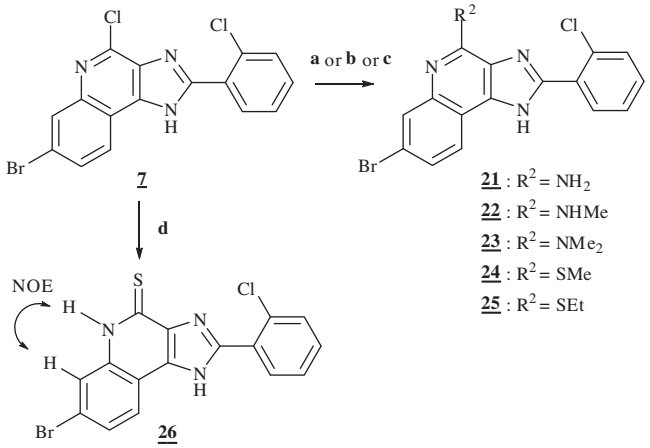
In this study, we succeeded in establishing a novel convenient synthetic route for medicinal chemistry work. We found that direct alkylation of the imidazoquinolin-4(5*H*)-one derivative **1** in the presence of *i*-Pr_2EtN proceeds selectively at the *N*(3)-position, and that *N*(5)-alkyl derivatives can be prepared by first protecting the imidazole nitrogen atom with a Boc group and then removing the protecting group. This methodology can significantly reduce reaction steps for synthesis of the *N*(3)- or *N*(5)-alkyl imidazoquinolin-4-one derivatives compared to conventional methods, thereby allowing an efficient SAR study. These novel synthetic findings can contribute to the development of an efficient synthetic route for the *N*-alkyl imidazoquinoline derivatives. To identify the essential functional groups of the imidazoquinolin-4(5*H*)-one derivative **1** for potent mPGES-1 inhibitory activity, we carried out optimization work, particularly of the substituents at the *N*(1), *N*(3), *N*(5), *C*(4)-positions. As for the *C*(4)-substituent, amino groups gave >400-fold loss of inhibitory activity. A thione or methylthio gave decreased inhibitory activity compared to **1**, suggesting that non-basic small substituent could be considered best. The *N*(5)-alkyl derivatives also showed weaker activity, indicating that the *C*(4)-oxo group and the *N*(5)-proton were essential substituents for strong inhibitory activity. Introduction of alkyl groups at the *N*(1)- or *N*(3)-position of **1** resulted in large loss of inhibitory activity. These results indicate that the oxo group at the *C*(4)-position and the protons at the *N*(1), *N*(3), and *N*(5)-positions were essential for potent the inhibitory activity. On the basis of these findings, we reconfirmed that the imidazoquinolin-4(5*H*)-one derivative **1** is promising lead compound for further optimization. At present, further SAR studies focused on substitution of the *C*(7)-bromine group of **1** are in progress to find orally active mPGES-1 inhibitors with good pharmacokinetic properties.

Table 4
Stability study of **17** and **18**



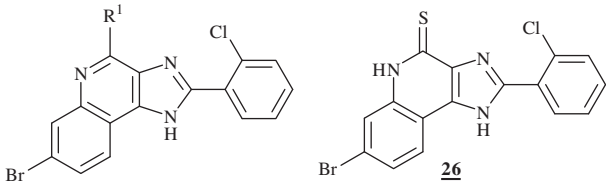
Entry	R	Condition	Deprotection rate[a]	
			$T_{1/2}$[b]	$T_{comp.}$[c]
1	SEM	TFA (100 equiv), rt	<5 min	<15 min
2	SEM	1 M NaOH (10 equiv), THF, rt	No reaction for 12 h	
3	SEM	1 M TBAF (3 equiv), THF, reflux	0.5 h	5 h
4	Boc	TFA (100 equiv), rt	<5 min	<15 min
5	Boc	4 M HCl (10 equiv), THF, rt	0.5 h	8 h
6	Boc	1 M NaOH (10 equiv), THF/MeOH, rt	15 min	30 min

[a] Deprotection rate was monitored by LC/MS at 254 nm.
[b] $T_{1/2}$ = half-life time of **17** or **18**.
[c] $T_{comp.}$ = the time which the deprotection completed.



Scheme 4. Reagents and conditions: (a) NH_4C1, *i*-Pr_2EtN, NMP, 150 °C under m.w., 1 h, **21** (48%); (b) 2 M Me_2NH or 2 M $MeNH_2$ in THF, NMP, 140 °C under m.w., 0.5 h, **22** (78%) or **23** (99%); (c) NaSMe or NaSEt, NMP, 80 °C under m.w., 1 h, **24** (80%) or **25** (94%);(d) NaSH/nH_2O, NMP, 100 °C under m.w., 0.5 h, **26** (42%).

Table 5
Effects of substituents on the *c*(4)-position



Compound	R^1	mPGES-1 IC_{50} (nM)
21	NH_2	1068
22	NHMe	631
23	NMe_2	387
26	—	83
24	SMe	31
25	SEt	59
27[a]	H	251
5[a]	OMe	62
1[a]	—	9.1

[a] See Ref. 9.

4. Experimental

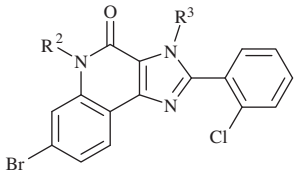
4.1. General

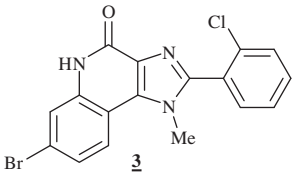
Nuclear magnetic resonance spectra (NMR) were recorded on a JEOL JMN-LA300 spectrometer or on a Bruker AVANCE 400 spectrometer. Chemical shifts (δ) are given in parts per million, and tetramethylsilane was used as internal standard for spectra obtained in DMSO-d_6 and $CDCl_3$. All *J* values are given in Hz. Splitting pattern designed as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet; dd, double of doublets; dt, doublet of triplets. Melting points were determined on an electrothermal apparatus without correction. IR spectra were recorded on a JEOL JNM-LA300 spectrometer as ATR. Low-resolution mass spectra were recorded on a Waters ACQUITY® LCMS system under electron spray ionization (ESI) conditions. High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific LTQ orbitrap Discovery MS equipment. Elemental analysis was performed on a CE Instrument EA1110 and a Yokokawa analytical system IC7000. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was carried out using a Yamazen W-prep system and performed using prepacked silica-gel columns. Reaction progress was determined by TLC analysis on a silica-gel coated glass plate. Visualization was done with UV light (254 nm) or iodine. HPLC was performed using a Waters ACQUITY UPLC® equipment.

4.1.1. 7-Bromo-2-(2-chlorophenyl)-3-methyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (2) and 7-bromo-2-(2-chlorophenyl)-3,5-dimethyl-3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one (6)

To a solution of **1** (30.0 mg, 0.0801 mmol) in DMF (1.0 mL) was added NaH (60% in oil, 4.8 mg, 0.200 mmol) and MeI (0.008 mL, 0.120 mmol) at 0 °C and then the mixture was stirred for 3 h at room temperature. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with ethyl acetate (AcOEt) twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column

Table 6
Effects of substituents on the *N*(1)-, *N*(3)-, and *N*(5)-position





3

Compound	R^2	R^3	mPGES-1 IC_{50} (nM)
4	Me	H	85
19	Et	H	106
20	Bn	H	226
3	—	—	>10,000
2	H	Me	9810
12	H	Bn	>10,000
6	Me	Me	>10,000
1[a]	H	H	9.1

[a] See Ref. 9.

chromatography ($CHCl_3$/MeOH = 10/1). The obtained solids were triturated with diisopropylether (IPE), respectively, to afford **2** (6.8 mg, 22%) and **6** (19.8 mg, 63%) as a white solid.

Compound **2**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.87 (1H, s), 7.98 (1H, d, J = 8.4 Hz), 7.65–7.73 (3H, m), 7.61 (1H, d, J = 1.5 Hz), 7.54–7.58 (1H, m), 7.42 (1H, dd, J = 1.5, 8.4 Hz), 3.86 (3H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.4, 151.4, 143.1, 137.4, 133.1, 132.6, 132.3, 129.7, 128.5, 127.6, 125.0, 123.4, 121.2, 120.6, 118.1, 115.1, 32.6; mp 313–315 °C; IR (ATR) ν 1672, 1543, 1460, 1414, 1392, 1375, 1313, 1217, 1159, 1072, 1039 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{12}BrClN_3O$ (M+H)$^+$: 387.9847, found: 387.9859; Anal. Calcd for $C_{17}H_{11}BrClN_3O\cdot0.50H_2O$; C, 51.35; H, 3.04; N, 10.57. Found: C, 51.43; H, 2.92; N, 10.43. Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (1H, d, J = 8.4 Hz), 7.55 (1H, d, J = 1.7 Hz), 7.47–7.52 (2H, m), 7.42–7.45 (1H, m), 7.35–7.41 (2H, m), 3.92 (3H, s), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 152.1, 143.0, 138.5, 134.4, 132.3, 131.8, 129.9, 128.8, 127.2, 125.7, 124.1, 122.4, 121.3, 117.9, 116.3, 33.2, 29.2; mp 250–251 °C; IR (ATR) ν 1651, 1568, 1554, 1464, 1443, 1419, 1400, 1365, 1306, 1257, 1225, 1159, 1122, 1082, 1039, 1001 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{14}BrClN_3O$ (M+H)$^+$: 402.0003, found: 402.0009; Anal. Calcd for $C_{18}H_{13}BrClN_3O$; C, 53.69; H, 3.25; N, 10.44. Found: C, 53.51; H, 3.32; N, 10.29.

4.1.2. Preparation of compound 6 from 2

To a solution of **2** (30.0 mg, 0.0772 mmol) in DMF (0.5 mL) was added NaH (60% in oil, 4.3 mg, 0.180 mmol) and MeI (0.007 mL, 0.116 mmol) at room temperature and then the mixture was stirred for 0.5 h. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30/1) and triturated with IPE to afford **6** (27.9 mg, 90%) as a white solid. ^{1}H NMR spectra of **6** were consistent with that of **6** synthesized from **1**.

4.1.3. 7-Bromo-4-chloro-2-(2-chlorophenyl)-3-methyl-*3H*-imidazo[4,5-*c*]quinoline (8) and 7-bromo-4-chloro-2-(2-chlorophenyl)-1-methyl-*1H*-imidazo[4,5-*c*]quinoline (9)

To a solution of **7** (30.0 mg, 0.0763 mmol) in DMF (1.0 mL) was added NaH (60% in oil, 4.6 mg, 0.191 mmol) and MeI (0.007 mL, 0.114 mmol) at 0 °C and then the mixture was stirred for 2 h at room temperature. The reaction mixture was cooled with ice bath, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) 2 times. The separated fractions were triturated with hexane/IPE, respectively, to afford **8** (23.3 mg, 76%) and **9** (6.7 mg, 21%) as a white solid, respectively.

Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (1H, d, J = 8.8 Hz), 8.22 (1H, d, J = 2.0 Hz), 7.68 (1H, dd, J = 2.0, 8.8 Hz), 7.49–7.57 (3H, m), 7.40–7.47 (1H, m), 3.99 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.0, 146.4, 144.2, 136.3, 134.4, 132.4, 132.2, 130.9, 130.5, 130.0, 128.7, 127.4, 125.5, 123.4, 122.1, 120.7, 33.9; mp 255–256 °C; IR (ATR) ν 1558, 1498, 1460, 1443, 1381, 1356, 1286, 1176, 1107, 1043, 1014 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{11}BrCl_2N_3$ (M+H)$^+$: 405.9508, found: 405.9521; Anal. Calcd for $C_{17}H_{10}BrCl_2N_3$; C, 50.16; H, 2.48; N, 10.32. Found: C, 50.03; H, 2.58; N, 10.19. Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (1H, d, J = 2.0 Hz), 8.19 (1H, d, J = 9.0 Hz), 7.72 (1H, dd, J = 2.0, 8.8 Hz), 7.64–7.67 (1H, m), 7.53–7.57 (2H, m), 7.44–7.50 (1H, m), 4.08 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.3, 145.3, 144.8, 135.5, 134.5, 134.2, 133.0, 132.5, 132.1, 130.0, 129.8, 128.4, 127.4, 121.8, 121.3, 116.7, 34.7; mp 219–221 °C; IR (ATR) ν 1560, 1491, 1450, 1369, 1350, 1313, 1288, 1153, 1111, 1039 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{11}BrCl_2N_3$ (M+H)$^+$: 405.9508, found: 405.9520; Anal. Calcd for $C_{17}H_{10}BrCl_2N_3$; C, 50.16; H, 2.48; N, 10.32. Found: C, 50.09; H, 2.51; N, 10.27.

4.1.4. Preparation of compound 2 from 8

A solution of **8** (25.0 mg, 0.061 mmol) in EtOH/H_2O (2.0:0.1 mL) and 5 M HCl (0.260 mL, 1.30 mmol) was stirred at reflux for 3 h. After cooling to room temperature, the solvent was removed in vacuo. The obtained solid was triturated with $CHCl_3$/MeOH (50:1) to afford **2** (21.0 mg, 90%) as a white solid. ^{1}H NMR spectra of **2** were consistent with that of **2** synthesized from **1**.

4.1.5. 7-Bromo-2-(2-chlorophenyl)-1-methyl-*1H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (3)

The title compound **3** was synthesized from **9** in 89% yield according to the procedure to prepare **2** from **8**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.78 (1H, s), 8.14 (1H, d, J = 8.6 Hz), 7.71-7.73 (1H, m), 7.69 (1H, d, J = 2.0 Hz), 7.64–7.68 (2H, m), 7.54–7.59 (1H, m), 7.43 (1H, dd, J = 2.0, 8.6 Hz), 3.91 (3H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.7, 150.3, 138.5, 134.7, 134.0, 133.5, 132.7, 131.5, 130.2, 129.3, 128.2, 125.0, 123.9, 121.5, 118.9, 111.7, 34.8; mp 313–315 °C; IR (ATR) ν 1672, 1543, 1460, 1414, 1392, 1375, 1313, 1217, 1159, 1072, 1039 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{12}BrClN_3O$ (M+H)$^+$: 387.9847, found: 387.9858; Anal. Calcd for $C_{17}H_{11}BrClN_3O\cdot0.25H_2O$; C, 51.93; H, 2.95; N, 10.69. Found: C, 51.89; H, 2.91; N, 10.62.

4.1.6. Preparation of compound 2 from 1 (in Table 1, entry 15)

To a solution of **1** (30.0 mg, 0.0801 mmol) in DMF (0.08 mL) was added *i*-Pr_2EtN (0.021 mL, 0.120 mmol) and MeI (0.008 mL, 0.120 mmol) at room temperature and then the mixture was stirred for 1 h at 80 °C. After cooling to room temperature, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) and triturated with IPE to afford **2** (30.7 mg, 96%) as a white solid. ^{1}H NMR spectra of **2** were consistent with that of **2** synthesized from **1** using NaH.

4.1.7. 7-Bromo-2-(2-chlorophenyl)-3-ethyl-*3H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (10)

To a solution of **1** (30.0 mg, 0.0801 mmol) in DMF (0.08 mL) was added *i*-Pr_2EtN (0.041 mL, 0.240 mmol) and EtI (0.019 mL,

0.240 mmol) at room temperature and then the mixture was stirred for 5 h at 80 °C. After cooling to room temperature, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) and triturated with IPE to afford **10** (31.0 mg, 96%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.89 (1H, s), 7.98 (1H, d, J = 8.4 Hz), 7.64–7.74 (3H, m), 7.64 (1H, d, J = 1.9 Hz), 7.55–7.59 (1H, m), 7.42 (1H, dd, J = 1.9, 8.4 Hz), 4.24 (2H, q, J = 7.1 Hz), 1.23 (3H, t, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.0, 150.6, 143.5, 137.5, 133.2, 132.4, 132.3, 129.7, 128.8, 127.6, 125.0, 123.4, 120.7, 120.4, 118.1, 115.0, 40.8, 16.3; mp 312–314 °C; IR (ATR) ν 2816, 1660, 1587, 1541, 1427, 1392, 1379, 1333, 1321, 1205, 1153, 1068, 1041 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{14}BrClN_3O$ (M+H)$^+$: 402.0003, found: 402.0005; Anal. Calcd for $C_{18}H_{13}BrClN_3O\cdot 0.25H_2O$; C, 53.10; H, 3.34; N, 10.32. Found: C, 53.10; H, 3.25; N, 10.23.

4.1.8. 7-Bromo-2-(2-chlorophenyl)-3-(1-propyl)-*3H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (11)

The title compound **11** was synthesized from **1** in 95% yield using *n*-PrI according to the procedure to prepare **10**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.94 (1H, s), 7.99 (1H, d, J = 8.4 Hz), 7.66–7.73 (3H, m), 7.64 (1H, d, J = 1.8 Hz), 7.55–7.59 (1H, m), 7.43 (1H, dd, J = 1.8, 8.4 Hz), 4.22 (2H, t, J = 7.0 Hz), 1.61–1.67 (2H, m), 0.66 (3H, t, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.1, 151.5, 143.9, 138.0, 133.7, 133.1, 132.8, 130.3, 129.4, 128.1, 125.5, 124.4, 124.0, 121.3, 118.6, 115.5, 47.4, 24.3, 11.0; mp 288–290 °C; IR (ATR) ν 2877, 1662, 1597, 1578, 1543, 1543, 1458, 1389, 1336, 1138, 1047 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{16}BrClN_3O$ (M+H)$^+$: 416.0160, found: 416.0162; Anal. Calcd for $C_{19}H_{15}BrClN_3O$; C, 54.76; H, 3.63; N, 10.08. Found: C, 54.70; H, 3.63; N, 10.09.

4.1.9. 3-Benzyl-7-bromo-2-(2-chlorophenyl)-*3H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (12)

The title compound **12** was synthesized from **1** in 98% yield using BnBr according to the procedure to prepare **10**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.94 (1H, s), 8.01 (1H, d, J = 8.4 Hz), 7.65–7.66 (2H, m), 7.59–7.63 (1H, m), 7.44–7.50 (3H, m), 7.18–7.19 (3H, m), 6.83–6.86 (2H, m), 5.62 (2H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.2, 151.3, 143.4, 137.4, 136.6, 133.2, 132.3, 132.2, 129.7, 128.5, 128.4, 127.5, 127.4, 126.7, 125.1, 123.4, 120.8, 120.6, 118.2, 115.0, 48.2; mp 314–316 °C; IR (ATR) ν 2845, 1662, 1589, 1540, 1456, 1421, 1390, 1373, 1334, 1319, 1192, 1155, 1105, 1072, 1049, 1034 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{16}BrClN_3O$ (M+H)$^+$: 464.0160, found: 464.0160; Anal. Calcd for $C_{23}H_{15}BrClN_3O\cdot 0.25H_2O$; C, 58.87; H, 3.33; N, 8.95. Found: C, 59.08; H, 3.30; N, 8.91.

4.1.10. 7-Bromo-2-(2-chlorophenyl)-3-(pyridin-2-ylmethyl)-3*H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (13)

The title compound **13** was synthesized from **1** in 94% yield using 3.0 equiv of 2-(bromomethyl)pyridine hydrobromide and 6.0 equiv of *i*-Pr_2EtN according to the procedure to prepare **10**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.85 (1H, s), 8.32 (1H, d, J = 4.0 Hz), 8.02 (1H, d, J = 8.4 Hz), 7.59–7.67 (3H, m), 7.54 (1H, dt, J = 3.8, 10.8 Hz), 7.36–7.47 (3H, m), 7.17–7.21 (1H, m), 7.01 (1H, d, J = 7.9 Hz), 5.68 (2H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.4, 155.2, 151.8, 149.0, 143.3, 137.5, 136.8, 133.1, 132.4, 132.1, 129.6, 128.5, 127.3, 125.2, 123.5, 122.6, 121.2, 121.0, 120.8, 118.2, 115.1, 49.6; mp 283–285 °C; IR (ATR) ν 2848, 1664, 1591, 1545, 1441, 1416, 1392, 1371, 1335, 1323, 1192, 1157, 1109, 1072, 1051 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{15}BrClN_4O$ (M+H)$^+$: 465.0112, found: 465.0112; Anal. Calcd for $C_{22}H_{14}BrClN_4O\cdot 0.25H_2O$; C, 56.19; H, 3.11; N, 11.91. Found: C, 55.96; H, 3.05; N, 11.89.

4.1.11. 7-Bromo-2-(2-chlorophenyl)-3-(2-hydroxyethyl)-3*H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (14)

The title compound **14** was synthesized from **1** in 88% yield using 2-bromoethanol according to the procedure to prepare **10**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.88 (1H, s), 7.99 (1H, d, J = 8.4 Hz), 7.52-7.70 (5H, m), 7.42 (1H, dd, J = 1.8, 8.4 Hz), 4.80 (1H, t, J = 5.6 Hz), 4.25 (2H, br s), 3.62 (1H, q, J = 5.6 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.2, 151.8, 143.6, 137.5, 133.2, 133.1, 132.0, 129.5, 129.0, 127.4, 125.1, 123.4, 120.7, 118.1, 115.1, 60.3, 48.1; mp 271–275 °C; IR (ATR) ν 2852, 1660, 1591, 1545, 1450, 1425, 1390, 1373, 1346, 1333, 1317, 1188, 1111, 1080, 1070, 1043 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{14}BrClN_3O_2$ (M+H)$^+$: 417.9952, found: 417.9954; Anal. Calcd for $C_{18}H_{13}BrClN_3O_2\cdot 1.00H_2O$; C, 49.51; H, 3.46; N, 9.62. Found: C, 49.47; H, 3.34; N, 9.54.

4.1.12. 7-Bromo-2-(2-chlorophenyl)-3-((2-(trimethylsilyl)ethoxy)methyl)-*3H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (15)

To a solution of **1** (300.0 mg, 0.801 mmol) in DMF (5.0 mL) was added *i*-Pr_2EtN (0.419 mL, 2.40 mmol) and SEMCl (0.24 mL, 0.240 mmol) at room temperature and then the mixture was stirred for 1 h at 80 °C. After cooling to room temperature, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30/1) and triturated with IPE to afford **15** (299.0 mg, 74%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.17 (0.9H, br s), 8.17 (1H, d, J = 8.4 Hz), 7.77–7.87 (4H, m), 7.68–7.73 (1H, m), 7.60 (1H, dd, J = 2.0, 8.4 Hz), 5.86 (2H, s), 3.54 (2H, t, J = 8.3 Hz), 0.85 (2H, t, J = 8.3 Hz), −0.01 (9H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.1, 151.7, 143.3, 137.5, 133.3, 132.5, 132.2, 129.8, 128.6, 127.4, 125.2, 123.6, 121.0, 120.8, 118.2, 114.8, 73.3, 65.5, 17.1, −1.5; mp 218–219 °C; IR (ATR) ν 2862, 1659, 1589, 1543, 1458, 1387, 1377, 1333, 1319, 1246, 1215, 1151, 1095, 1078, 1038 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{24}BrClN_3O_2Si$ (M+H)$^+$: 504.0504, found: 504.0504; Anal. Calcd for $C_{22}H_{23}BrClN_3O_2$ Si; C, 52.34; H, 4.59; N, 8.32. Found: C, 52.50; H, 4.63; N, 8.37.

4.1.13. *tert*-Butyl 7-bromo-2-(2-chlorophenyl)-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-3-carboxylate (16)

A mixture of **1** (250.0 mg, 0.667 mmol) and DMAP (40.7 mg, 0.334 mmol) in THF (10.0 mL) was stirred at 50 °C for 5 min and then Boc_2O (284.2 mg, 2.00 mmol) was added and the reaction mixture was sttired at 50 °C for 1 h. After cooling to room temperature, the solvent of the mixture was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1:1) and triturated with IPE to afford **16** (241.0 mg, 72%) as a white amorphous solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.72 (1H, s), 8.16 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 1.7 Hz), 7.57 (1H, dd, J = 1.4, 6.9 Hz), 7.49–7.53 (2H, m), 7.40–7.47 (2H, m), 1.51 (9H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.4, 151.8, 146.2, 145.8, 137.5, 133.9, 131.6, 131.5, 130.1, 129.5, 126.9, 126.3, 124.4, 123.1, 120.4, 118.6, 114.7, 87.1, 27.3; mp 165–180 °C; IR (ATR) ν 2862, 2359, 1761, 1655, 1591, 1547, 1454, 1387, 1365, 1336, 1317, 1261, 1188, 1147, 1095, 1066, 1045 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{21}H_{18}BrClN_3O_3$ (M+H)$^+$: 474.0215, found: 474.0215; Anal. Calcd for $C_{21}H_{17}BrClN_3O_3$; C, 53.13; H, 3.61; N, 8.85. Found: C, 53.35; H, 3.79; N, 8.62.

4.1.14. 7-Bromo-2-(2-chlorophenyl)-5-methyl-3-((2-(trimethylsilyl)ethoxy)methyl)-*3H*-imidazo[4,5-*c*]quinolin-4(*5H*)-one (17)

To a solution of **15** (100.0 mg, 0.198 mmol) in DMF (1.0 mL) was added K_2CO_3 (53.5 mg, 0.396 mmol) and MeI (0.026 mL, 0.396 mmol) at room temperature and then the mixture was stirred for 2 h. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30:1) and triturated with IPE to afford **17** (96.6 mg, 94%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (1H, d, J = 8.3 Hz), 8.03 (1H, d, J = 1.7 Hz), 7.83–7.88 (2H, m), 7.80 (1H, dd, J = 2.2, 7.6 Hz), 7.68–7.81 (2H, m), 5.88 (2H, s), 3.90 (3H, s), 3.53 (2H, t, J = 8.3 Hz), 0.85 (2H, t, J = 8.3 Hz), 0.00 (9H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.5, 151.8, 142.3, 138.4, 133.3, 132.5, 132.2, 129.8, 128.5, 127.4, 125.5, 123.8, 122.0, 120.2, 118.4, 115.5, 73.3, 65.5, 29.1, 17.1, −1.53; mp 205–218 °C; IR (ATR) ν 2947, 2893, 1655, 1568, 1554, 1470, 1456, 1439, 1398, 1346, 1309, 1246, 1221, 1151, 1119, 1093, 1080, 1055, 1003 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{23}H_{26}BrClN_3O_2Si$ $(M+H)^+$: 518.0661, found: 518.0660. HPLC: 98.74%.

4.1.15. *tert*-Butyl 7-bromo-2-(2-chlorophenyl)-5-methyl-4-oxo-4,5-dihydro-*3H*-imidazo[4,5-*c*]quinoline-3-carboxylate (18)

To a solution of **16** (65.0 mg, 0.137 mmol) in DMF (1.0 mL) was added K_2CO_3 (37.0 mg, 0.274 mmol) and MeI (0.018 mL, 0.274 mmol) at room temperature and then the mixture was stirred for 2 h. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1:1) and triturated with IPE to afford **18** (61.6 mg, 92%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.11 (1H, d, J = 8.3 Hz), 7.89 (1H, d, J = 1.7 Hz), 7.61–7.70 (3H, m), 7.51–7.58 (2H, m), 3.73 (3H, s), 1.34 (9H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.9, 150.5, 145.6, 142.8, 139.1, 132.8, 132.3, 131.9, 129.3, 129.2, 127.3, 125.5, 124.3, 122.8, 120.0, 118.4, 114.6, 86.6, 29.6, 26.6; mp 323–325 °C; IR (ATR) ν 1761, 1670, 1570, 1450, 1432, 1396, 1371, 1358, 1309, 1284, 1261, 1238, 1196, 1147, 1117, 1080, 1055, 1001 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{20}BrClN_3O_3$ $(M+H)^+$: 488.0371, found: 488.0372. HPLC: 98.83%.

4.1.16. 7-Bromo-2-(2-chlorophenyl)-5-methyl-imidazo[4,5-*c*]quinolin-4(*5H*)-one (4)

To a solution of **16** (30.0 mg, 0.0632 mmol) and K_2CO_3 (13.0 mg, 0.0948 mmol) in DMF (1.0 mL) was added MeI (0.006 mL, 0.0948 mmol) at room temperature and then the mixture was stirred for 2 h. After the methylation was completed, MeOH (3.0 mL) and 1 M NaOHaq. (0.6 mL) were added and then the mixture was vigorously stirred for 30 min. To the reaction mixture, AcOEt and water were added and then the mixture was extracted with AcOEt twise, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) and triturated with IPE to afford **4** (22.7 mg, 92% in two steps) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.11 (1H, d, J = 8.4 Hz), 7.84 (1H, d, J = 1.7 Hz), 7.79 (1H, dd, J = 1.8, 7.5 Hz), 7.66 (1H, dd, J = 1.4, 7.8 Hz), 7.50–7.60 (3H, m), 3.74 (3H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.4, 155.2, 149.4, 138.5, 132.6, 132.2, 131.6, 130.2, 129.3, 127.4, 125.1, 123.8, 121.6, 118.4, 116.5, 113.8, 29.2; mp 316–318 °C; IR (ATR) ν 3080, 1676, 1647, 1605, 1558, 1473, 1458, 1421, 1400, 1329, 1198, 1147, 1057 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{12}BrClN_3O$ $(M+H)^+$: 387.9847, found: 387.9842; Anal. Calcd for $C_{17}H_{11}BrClN_3O\cdot1.00H_2O$; C, 50.21; H, 3.22; N, 10.33. Found: C, 50.00; H, 2.82; N, 10.12.

4.1.17. 7-Bromo-2-(2-chlorophenyl)-5-ethyl-imidazo[4,5-*c*]quinolin-4(*5H*)-one (19)

The title compound **19** was synthesized from **16** in 92% yield using EtI according to the procedure to prepare **4** from **16**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.92 (0.5H, br s), 8.13 (1H, d, J = 8.3 Hz), 7.87 (1H, s), 7.78 (1H, dd, J = 1.9, 7.2 Hz), 7.66 (1H, d, J = 7.5 Hz), 7.49–7.59 (3H, m), 4.41 (2H, q, J = 7.0 Hz), 1.24 (3H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.1, 150.0, 137.3, 132.2, 131.5, 130.2, 129.5, 127.4, 125.0, 124.1, 121.7, 117.9, 36.5, 13.0; mp 274–276 °C; IR (ATR) ν 2848, 1664, 1599, 1587, 1541, 1427, 1392, 1381, 1371, 1333, 1321, 1205, 1153, 1068, 1041 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{14}BrClN_3O$ $(M+H)^+$: 402.0003, found: 402.0003; Anal. Calcd for $C_{18}H_{13}BrClN_3O\cdot0.25H_2O$; C, 53.10; H, 3.34; N, 10.32. Found: C, 53.16; H, 3.26; N, 10.29.

4.1.18. 5-Benzyl-7-bromo-2-(2-chlorophenyl)-imidazo[4,5-*c*]quinolin-4(*5H*)-one (20)

The title compound **20** was synthesized from **16** in 90% yield using BnBr according to the procedure to prepare **4** from **16**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.03 (0.7H, br s), 8.13 (1H, d, J = 8.3 Hz), 7.82 (1H, dd, J = 2.0, 7.2 Hz), 7.68 (1H, dd, J = 1.5, 7.7 Hz), 7.64 (1H, d, J = 1.5 Hz), 7.49–7.60 (3H, m), 7.30–7.35 (2H, m), 7.20–7.26 (3H, m), 5.67 (2H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 149.7, 148.1, 137.6, 136.9, 132.2, 131.6, 130.2, 129.5, 128.8, 128.0, 127.4, 127.1, 126.4, 125.3, 124.1, 121.3, 118.8, 115.6, 44.5; mp 294–295 °C; IR (ATR) ν 2846, 1668, 1591, 1543, 1454, 1421, 1390, 1373, 1360, 1335, 1321, 1190, 1151, 1103, 1072, 1049 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{16}BrClN_3O$ $(M+H)^+$: 464.0160, found: 464.0160; Anal. Calcd for $C_{23}H_{15}BrClN_3O$; C, 59.44; H, 3.25; N, 9.04. Found: C, 59.18; H, 3.31; N, 9.03.

4.1.19. 7-Bromo-2-(2-chlorophenyl)-imidazo[4,5-*c*]quinolin-4-amine (21)

A mixture of **7** (80.0 mg, 0.203 mmol) and NH_4Cl (109 mg, 2.03 mmol) and *i*-Pr_2EtN (0.328 mL, 2.03 mmol) in *N*-methylpyrrolidone (NMP) (1.5 mL) was stirred at 150 °C for 1 h under microwave irradiation. After cooling to room temperature, water and AcOEt were added. The mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) and triturated with $CHCl_3$ to afford **21** (36.0 mg, 48%) as a pale brown solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.63 (0.4H, br s), 8.05 (1H, d, J = 8.4 Hz), 7.85 (1H, br s), 7.68–7.72 (2H, m), 7.51–7.61 (2H, m), 7.38 (1H, dd, J = 1.9, 8.5 Hz), 6.93 (2H, br s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.5, 147.5, 145.8, 132.4, 131.9, 131.5 130.2, 129.9, 127.5, 127.4, 123.7, 123.1, 119.9; mp 283–285 °C; IR (ATR) ν 3477, 3437, 3302, 3142, 1651, 1579, 1522, 1471, 1448, 1390, 1273, 1105, 1086, 1063, 1043 cm^{-1}; MS (ESI) m/z calcd for $C_{16}H_{11}BrClN_4$ $(M+H)^+$: 372.9850, found: 372.9850; Anal. Calcd for $C_{16}H_{10}BrClN_4\cdot0.75H_2O$; C, 49.64; H, 2.99; N, 14.47. Found: C, 49.57; H, 2.72; N, 14.24.

4.1.20. 7-Bromo-2-(2-chlorophenyl)-*N*-methyl-imidazo[4,5-*c*]quinolin-4-amine (22)

A mixture of **7** (100.0 mg, 0.254 mmol) and 2 M methylamine in THF (0.640 mL, 1.27 mmol) in NMP (3.0 mL) was stirred at 140 °C for 0.5 h under microwave irradiation. After cooling to room temperature, water and AcOEt were added. The mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent

was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1:1) and triturated with hexane/IPE to afford **22** (82.0 mg, 78%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.66 (0.6H, s), 7.81 (1H, br s), 7.78 (1H, s), 7.67–7.70 (1H, m), 7.51–7.60 (2H, m), 7.37 (2H, d, J = 8.4 Hz), 3.04 (3H, d, J = 4.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.8, 147.2, 145.9, 133.3, 132.2, 132.0, 131.4, 130.2, 129.9, 128.0, 127.4, 123.5, 123.0, 119.9, 113.4, 27.3; mp 233–234 °C; IR (ATR) ν 3435, 3373, 2964, 1630, 1591, 1581, 1524, 1514, 1450, 1435, 1414, 1392, 1377, 1267, 1246, 1217, 1130, 1117, 1065, 1043 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{17}H_{13}BrClN_4$ $(M+H)^+$: 387.0007, found: 387.0008; Anal. Calcd for Anal. Calcd for $C_{17}H_{12}BrClN_4$; C, 52.67; H, 3.12; N, 14.45. Found: C, 52.95; H, 3.17; N, 14.40.

4.1.21. 7-Bromo-2-(2-chlorophenyl)-*N,N*-dimethyl-imidazo[4,5-*c*]quinolin-4-amine (23)

The title compound **23** was synthesized from **7** in 99% yield using 2 M dimethylamine in THF according to the procedure to prepare **22**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.73 (0.8H, s), 8.07 (1H, d, J = 8.4 Hz), 7.84–7.88 (1H, m), 7.76 (1H, d, J = 1.8 Hz), 7.66–7.70 (1H, m), 7.52–7.59 (2H, m), 7.37 (1H, dd, J = 2.0, 8.4 Hz), 3.55 (6H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.6, 146.0, 145.1, 135.5, 132.1, 131.9, 131.3, 130.4, 129.5, 128.2, 127.8, 127.4, 123.6, 122.9, 120.2, 112.9, 38.8; mp 194–195 °C; IR (ATR) ν 3435, 2926, 2359, 1618, 1583, 1568, 1525, 1450, 1416, 1373, 1267, 1201, 1097, 1061, 1036, 1001 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{18}H_{15}BrClN_4$ $(M+H)^+$: 401.0163, found: 401.0163; Anal. Calcd for $C_{18}H_{14}BrClN_4$; C, 53.82; H, 3.51; N, 13.95. Found: C, 53.66; H, 3.50; N, 13.75.

4.1.22. 7-Bromo-2-(2-chlorophenyl)-4-(methylthio)-imidazo[4,5-c]quinoline (24)

A mixture of **7** (50.0 mg, 0.127 mmol) and sodium thiomethoxide (NaSMe, 50.8 mg, 0.635 mmol) in NMP (1.0 mL) was stirred at 80 °C for 1 h under microwave irradiation. After cooling to room temperature, water and AcOEt were added. The mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30:1) and triturated with AcOEt to afford **24** (41.0 mg, 80%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.06 (0.7H, s), 8.27 (1H, d, J = 8.6 Hz), 8.18 (1H, d, J = 1.3 Hz), 7.85 (1H, dd, J = 1.7, 7.0 Hz), 7.69–7.75 (2H, m), 7.53–7.64 (2H, m), 2.72 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.7, 148.8, 144.5, 135.1, 132.8, 132.4, 132.1, 131.8, 130.3, 130.1, 129.5, 128.0, 127.6, 123.7, 120.4, 115.0, 11.2; mp 214–215 °C; IR (ATR) ν 3433, 2929, 2360, 1620, 1568, 1497, 1452, 1443, 1362, 1308, 1286, 1257, 1234, 1207, 1194, 1055, 1036 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{17}H_{12}BrClN_3S$ $(M+H)^+$: 403.9618, found: 403.9611; Anal. Calcd for $C_{17}H_{11}BrClN_3S$; C, 50.45; H, 2.74; N, 10.38. Found: C, 50.52; H, 2.78; N, 10.37.

4.1.23. 7-Bromo-2-(2-chlorophenyl)-4-(ethylthio)-imidazo[4,5-c]quinoline (25)

The title compound **25** was synthesized in 94% yield from **7** using sodium thioethoxide (NaSEt) according to the procedure to prepare **24**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.06 (0.6H, s), 8.27 (1H, d, J = 8.6 Hz), 8.15 (1H, d, J = 1.7 Hz), 7.85 (1H, dd, J = 1.9, 7.1 Hz), 7.69–7.75 (2H, m), 7.53–7.64 (2H, m), 3.40 (2H, q, J = 7.3 Hz), 1.41 (3H, t, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 149.0, 144.5, 132.4, 132.2, 131.8, 130.4, 130.1, 129.5, 128.0, 127.6, 123.7, 120.4, 22.4, 14.9; mp 129–133 °C (dec); IR (ATR) ν 2927, 2362, 1703, 1624, 1560, 1491, 1473, 1429, 1360, 1309, 1263, 1190, 1066, 1053 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{18}H_{14}BrClN_3S$ $(M+H)^+$: 417.9775, found: 417.9769; Anal. Calcd for $C_{18}H_{13}BrClN_3S$; C, 51.63; H, 3.13; N, 10.04. Found: C, 51.85; H, 3.41; N, 9.89.

4.1.24. 7-Bromo-2-(2-chlorophenyl)-imidazo[4,5-c]quinoline-4(5H)-thione (26)

A mixture of **7** (100 mg, 0.254 mmol) and sodium hydrosulfide hydrate ($NaSH/nH_2O$, 71.0 mg) in NMP (1.0 mL) was stirred at 100 °C for 0.5 h under microwave irradiation. After cooling to room temperature, water and AcOEt were added. The mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtrated, the solvent was removed in vacuo. The residue was triturated with $CHCl_3$ and water to afford **26** (42.0 mg, 42%) as a pale brown solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.92 (0.7H, br s), 13.44 (0.6H, br s), 8.11 (1H, d, J = 8.6 Hz), 7.96 (1H, d, J = 1.7 Hz), 7.79 (1H, d, J = 7.3 Hz), 7.66 (1H, d, J = 7.7 Hz), 7.48–7.60 (3H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 137.8, 132.4, 131.8, 130.0, 129.3, 127.3, 127.0, 123.9, 121.3, 119.1; mp 315–316 °C; IR (ATR) ν 3402, 2978, 2362, 1626, 1587, 1574, 1446, 1427, 1387, 1338, 1277, 1225, 1207, 1194, 1101, 1082, 1070, 1043 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}BrClN_3S$ $(M+H)^+$: 389.9462, found: 389.9454; Anal. Calcd for $C_{16}H_9BrClN_3S{\cdot}0.25H_2O$; C, 48.63; H, 2.42; N, 10.63. Found: C, 48.93; H, 2.57; N, 10.33.

4.2. Biological assays

The test compound in DMSO (final 1%) was added to 15 mg/mL microsome in 100 mM Tris–HCl at pH 8.0, 5 mM EDTA, 500 mM phenol, 1 mM GSH, 10 mM Hematin. The microsome was prepared from mPGES-1 and COX-1 co-transfected HEK293 cells. Next, the mixture was pre-incubated at room temperature for 30 min. The reaction was started by the addition of 12.5 mM arachidonic acid dissolved in 0.1 M KOH. The reaction mixture was incubated at room temperature for 60 min. The reaction was stopped by addition of 1 M HCl. The reaction mixture was neutralized by 1 M NaOH and PGE_2 levels were measured by HTRF. The IC_{50} values were calculated by a logistic regression method.[14]

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