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7-Phenyl-imidazoquinolin-4(5*H*)-one derivatives as selective and orally available mPGES-1 inhibitors

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ABSTRACT

To identify compounds with strong mPGES-1 inhibitory activity and clear in vitro ADME profile, we optimized the lead compound **1** by carrying our substitutions at the C(7)- and C(8)-positions. Replacement of the bromine atom of **1** with various substituents led to identification of the phenyl group as the best C(7)-substituent giving strong inhibitory activity with good in vitro ADME profile. Further SAR examination on both the C(2)- and the C(7)-phenyl groups provided compound **39** as the best candidate for further development. Compound **39** exhibited strong mPGES-1 inhibitory activity (IC_{50} = 4.1 nM), potent cell-based functional activity (IC_{50} = 33 nM) with good mPGES-1 selectivity (over 700-fold), excellent in vitro ADME profile, and good oral absorption in rat PK study.

1. Introduction

Prostaglandin E_2 (PGE_2), a well known lipid mediator, is biosynthesized in three steps from membrane phospholipids by sequential enzymatic action[1] and plays a central role in mediating inflammation, pain, and fever.[2] The biosynthetic pathway of PGE_2 involves release of arachidonic acid (AA) from membrane phospholipids by phospholipase A_2 (PLA_2) and conversion of AA to PGH_2 by cyclooxygenase (COX)-1 and -2 followed by production of PGE_2 from PGH_2 mainly by microsomal prostaglandin E_2 synthase-1 (mPGES-1), a terminal enzyme in this pathway.[3] mPGES-1 is an inducible synthase released in response to inflammatory stimuli, such as IL-1β, TNF-α, and LPS, and is functionally coupled to COX-2.[4] Studies using mPGES-1 knockout mice have indicated that mPGES-1 might be a promising target for suppression of increased PGE_2 levels. In fact, LPS-induced production of PGE_2 was completely suppressed in peritoneal macrophages derived from mPGES-1 knockout mice.[5] In addition, it has been shown that the symptoms of various inflammatory diseases, such as collagen induced arthritis, pain hypersensitivity, and neuropathic pain, could be significantly relieved by suppression of PGE_2 production in knockout mice.[6] As for side effects, mPGES-1 knockout mice exhibited no gastrointestinal toxicity, such as that seen in patients under long term use of non-steroidal anti inflammatory drugs (NSAIDs) which are COX-1/2 inhibitors, and no thrombogenesis, which is a crucial adverse effect of selective COX-2 inhibitors.[7] Based on these findings, selective mPGES-1 inhibitors are expected to be useful in the treatment of various PGE_2-/mPGES-1-related disorders,[8] without the crucial side effects of NSAIDs and COX-2 inhibitors.

In addition to the reported MF-63 (Merck Frosst) and PF-4693627 (Pfizer) mPGES-1 inhibitors,[9a,b] we have found a series of imidazoquinoline derivatives as novel mPGES-1 inhibitors.[10a] Optimization of these compounds with substituents at the C(2)-, C(4)-, N(1)-, N(3)-, and N(5)-positions led to the identification of compound **1** as a strong mPGES-1 inhibitor (IC_{50} = 9.1 nM)[10a,b] (Fig. 1). Compound **1** showed good in vitro ADME profile, that is high membrane permeability (Pe),[11] good metabolic stability (MS), and sufficient solubility in fed state simulated intestinal fluid (FaSSIF),[12] and was therefore expected to have good pharmacokinetic (PK) in vivo. However, compound **1** showed strong CYP 2C9 inhibition with an IC_{50} value of 0.7 μM. Further optimization of **1** led to compound **2**, which showed minimal inhibition of CYP, including CYP 2C9 (IC_{50} = >30 μM). Thus we conducted optimization work to identify strong mPGES-1 inhibitors with clear in vitro ADME profiles by focusing on substitutions at the C(7) and C(8)-positions of **1**.

2. Chemistry

The synthetic route of **2** and **5**–**8** is shown in Scheme 1. The starting materials **3a**–**3e** were synthesized as described in our previous report.[10a] Oxidation of **3a**–**3e** with *m*CPBA followed by chlorination with phosphorous oxychloride gave **4a**–**4e** in 47–65% yield. Reaction of **4a**–**4e** with hydrochloric acid provided the corresponding imidazoquinolin-4(5*H*)-one derivatives **2** and **5**–**8**

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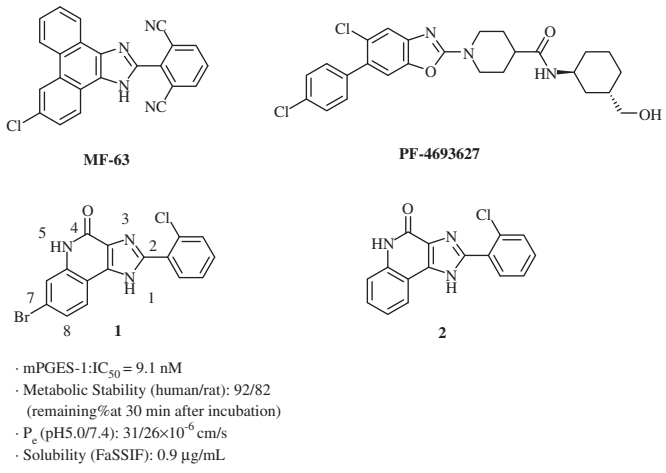


Figure 1. Structure of reported mPGES-1 inhibitors and compounds **1** and **2**.

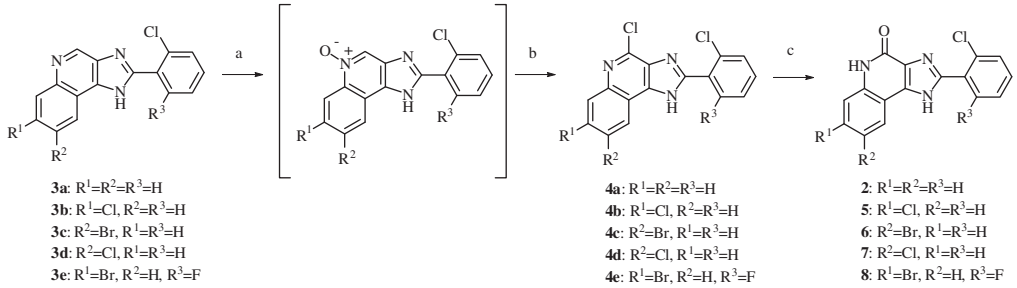
in 79–92%. Synthesis of the C(7)-substituted derivatives **9**–**28** is outlined in Scheme 2. The C(7)-alkyl derivatives **9**–**16** were prepared by Negishi coupling reaction with appropriate alkyl zinc reagents and **1**. The reaction proceeded without protecting the hydrogen atoms on the N(5) and imidazole part. Starting from **1** and **8**, the C(7)-aryl or heteroaryl derivatives **17**–**28** were prepared by Suzuki coupling reaction with appropriate boronic acid reagents in the presence of palladium catalyst. Compounds **36**–**39**, 2,6-disubstituted phenyl derivatives, were synthesized as shown in Scheme 3. Nitration of **29**[13] with 70% nitric acid in acetic acid gave **30** in 51%. Suzuki coupling reaction of **30** with phenyl boronic acid afforded **31** in 83%. Compound **31** was reacted with phosphorous oxychloride to give **32** in 97%. Compound **32** was converted to the 4-amino compound **33** with 28% aqueous ammonia. Catalytic hydrogenation of the nitro group in **33**, followed by ring closure reaction with appropriate benzaldehydes using sodium pyrosulfate provided **35a**–**35d**. Hydrolysis of **35a**–**35d** with hydrochloric acid gave **36**–**39** in 90–93%.

3. Results and discussion

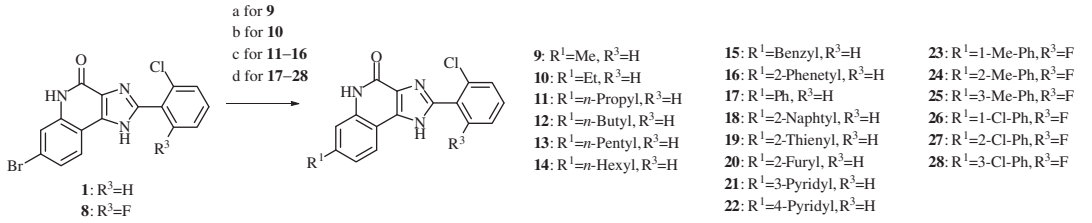
We initially investigated the effect of a substitution at the C(7)-position of **1** as shown in Table 1. Replacement of the bromine atom with a hydrogen atom (compound **2**) resulted in large loss of mPGES-1 inhibitory activity. Similarly, the chlorinated **5** showed threefold less mPGES-1 inhibitory activity than **1**. As for in vitro ADME, compounds **2** and **5** exhibited no inhibition of CYP2C9 (IC_{50} = >30 μM) and kept good MS. Next we placed a bromine or chlorine atom at the C(8)-position, however, the obtained compound **6** or **7**, respectively, exhibited remarkably low mPGES-1 inhibitory activity compared to the corresponding C(7)-substituted derivatives (**1** and **5**). Thus, we considered C(7)-position as a better position for further optimization. The order of compounds mPGES-1 inhibitory activity was bromine **1** > chlorine **5** > hydrogen **2**, suggesting that appropriate hydrophobicity or bulkiness of the substituent was important for strong inhibitory activity. In order to verify this hypothesis, we prepared and evaluated various C(7)-substituted compounds. The methyl derivative **9** inhibited mPGES-1 with an IC_{50} value of 241 nM, which was 25-fold less than that of **1**. Compound **9** mPGES-1 inhibitory activity could be improved by elongation of the alkyl chain, that is ethyl (**10**; 98 nM), *n*-propyl (**11**; 47 nM), and *n*-butyl (**12**; 17 nM). However, further elongation of the alkyl chain resulted in decreased inhibitory activity (*n*-pentyl (**13**) and *n*-hexyl (**14**)), leaving the *n*-butyl group as the most suitable substituent. Since there was no clear relationship between the inhibitory activity and *c*log*P*, we assumed that size of the compound was an important factor for potent inhibitory activity. In term of CYP inhibition, the prepared alkyl compounds had clear profiles against 4 types of CYP enzymes, including 2C9. Although we could overcome the problem of CYP 2C9 inhibition, the mechanism by which alkyl compounds spare CYP enzymes is still unclear. Among the prepared alkyl compounds, **12** was identified as the most potent, even though its mPGES-1 inhibitory activity and MS in human were inferior to those of the lead compound **1**.

Next, we prepared and evaluated C(7)-aryl compounds. A summary of the results is shown in Table 2. The phenyl derivative **17** inhibited mPGES-1 with an IC_{50} value (7.9 nM) of comparable to that of **1** and showed no MS and CYP inhibition concerns. These results encouraged us to investigate this compound in details. The benzyl derivative **15**, the 2-phenethyl **16**, and the 2-naphtyl **18** resulted in slight loss of inhibitory activity compared to the phenyl **17**, indicating that the phenyl group should be placed directly in the imidazoquinoline core and that the size of the aryl group is important for strong mPGES-1 inhibitory activity and good MS. Next, we replaced the phenyl group with the other 5- or 6-membered heteroaryl groups. The 2-thienyl derivative **19** and the 2-furyl **20** exhibited threefold loss of inhibitory activity compared to **17**. The 3-pyridyl and the 4-pyridyl derivatives **21** and **22** showed over 100-fold loss of inhibitory activity. These results suggested that basic substituents were not acceptable and that the hydrophobic aryl group without a hetero-atom was suitable as for C(7)-substituent. As a result, we examined the SAR of a C(7)-substituent and identified the bromine atom and the phenyl group as best substituents. We speculate that these groups have a suitable molecular size that allows them to fit well in mPGES-1 enzyme. In particular, the phenyl group was considered to be the best substituent in terms of inhibitory activity, CYP inhibition, and MS.

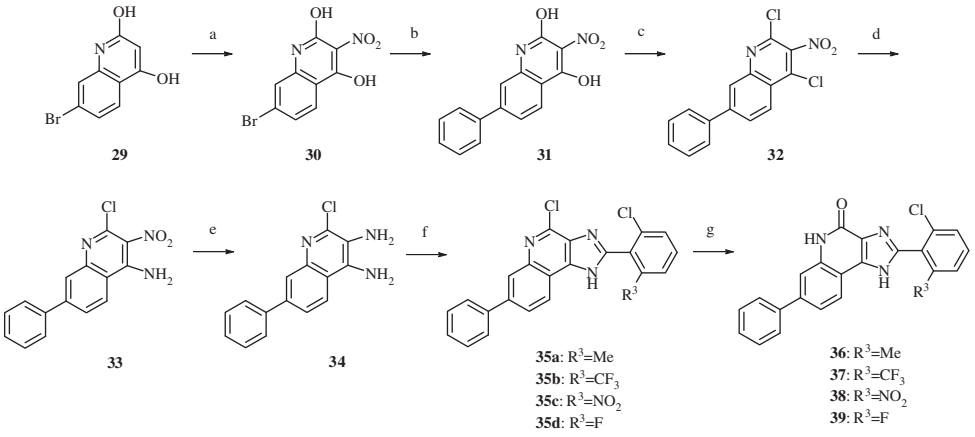
In a previous paper, we examined the SAR of substituents at the C(2)-position of the imidazoquinoline core and identified the 2-chlorophenyl group as the best substituent.[10a] On the other hand, Merck Frosst researchers have reported that mPGES-1 inhibitory activity could be enhanced (twofold) by replacement of the 2-chlorophenyl with 2-fluoro-6-chlorophenyl group at the 2-position of the phenanthrene-imidazole template.[9a] The structural similarity of the phenanthrene-imidazole template and **1** led us to prepare



Scheme 1. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, rt, 4 h; (b) $POCl_3$, reflux, 2 h, 47–65% in two steps; (c) 5 M HCl aq, EtOH/H_2O, reflux, 3 h, 79–92%.

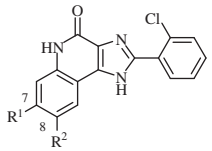


Scheme 2. Reagents and conditions: (a) 2.0 M MeZnCl in THF, $Pd(P^tBu_3)_2$ THF/NMP, rt, 1 h, 67%; (b) 2.0 M Et_2Zn in *n*-hexane, $Pd(P^tBu_3)_2$, THF/NMP, 0 °C, 0.5 h, 82%; (c) 0.5 M R^1-ZnBr in THF, $Pd(P^tBu_3)_2$, THF/NMP, 45 °C, 0.5 h, 48–85%; (d) R^1-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, THF/H_2O, reflux, 3–6 h, 61–73%.



Scheme 3. Reagents and conditions: (a) 70% HNO_3, AcOH, 60 °C, 1.5 h, 51%; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DMF/H_2O, 80 °C, 5 h, 83%: (c) $POCl_3$, reflux, 2 h, 97%; (d) 28% NH_3 aq, CH_3CN, 50 °C, 6.5 h, 80%; (e) 5% Pt/C, H_2, AcOEt/MeOH, rt, 6 h, 96%; (f) benzaldehyde reagents, $Na_2S_2O_7$, NMP, 140 °C, 6 h, 53–69%; (g) 5 M HCl aq, EtOH/H_2O, reflux, 3 h, 90–93%.

Table 1
Effects of the substituents (R^1 and R^2)

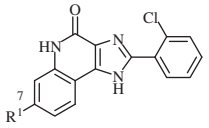


Compound	R^1	R^2	*c*log*P*	mPGES-1 IC_{50} (nM)	CYP inhibition IC_{50} (μM)				MS[a] (%)
					2C9	2C19	2D6	3A4	Human/rat
1	Br	H	4.41	9.1	0.7	20	>30	24	93/82
2	H	H	3.49	891	>30	>30	>30	>30	82/94
5	Cl	H	4.26	27	>30	>30	>30	>30	83/84
6	H	Br	4.41	198	>30	>30	>30	>30	74/84
7	H	Cl	4.26	434	>30	>30	>30	>30	55/90
9	Me	H	3.99	241	>30	>30	>30	>30	74/64
10	Et	H	4.52	98	21	>30	>30	>30	45/40
11	*n*-Propyl	H	5.05	47	24	>30	>30	>30	60/82
12	*n*-Butyl	H	5.58	17	>30	>30	>30	>30	64/83
13	*n*-Pentyl	H	6.11	53	>30	>30	>30	>30	6.0/52
14	*n*-Hexyl	H	6.64	70	>30	>30	>30	>30	3.5/47

[a] Metabolic stability (MS) was evaluated as a remaining % after the incubation with hepatic microsomes and NADPH for 30 min.

and evaluate compounds with *ortho*-disubstituted phenyl group at the C(2)-position. The results are shown in Table 3. Introduction of a fluorine atom, giving compound **39**, resulted in twofold stronger inhibitory activity than the *mono*-chlorine derivative **17** (IC_{50} = 4.1 nM). On the other hand, a methyl group (**36**), a trifluoromethyl group (**37**), or a nitro group (**38**) produced a slight loss of inhibitory activity compared to **17**. These results indicated that small electron withdrawing groups are suitable to enhance the inhibitory activity. As for in vitro ADME, compound **39** showed a profile similar to that of **17**. To obtain compounds with pico molar inhibitory activity, we finally investigated the effect of substituents on the C(7)-phenyl group of **39**. A methyl group as an electron-donating group, and a chlorine group as an electron-withdrawing group, were introduced to the *ortho*, *meta*, and *para*-positions (**23**–**28**), respectively. In both cases, the rank order of potency was *meta* > *para* > *ortho*. Among the compounds prepared, the *meta*-methyl **24** and the *meta*-chlorine **27** exhibited comparable or stronger inhibitory activity than **39**. Compound **24** showed weak MS, but not compound **27**. Since the results shown in Tables 1 and 2 indicated that the suitable molecular size for the C(7)-substituent

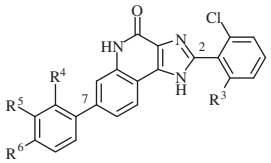
Table 2
Effects of the substituent (R^1)



Compound	R^1	*c*log*P*	mPGES-1 IC_{50} (nM)	CYP inhibition IC_{50} (μM)				MS[a] (%)
				2C9	2C19	2D6	3A4	Human/rat
12	*n*-Butyl	5.58	17	>30	>30	>30	>30	64/83
17	Phenyl	5.38	7.9	>30	>30	>30	>30	>97/>97
15	Benzyl	5.56	17	5.2	>30	>30	>30	60/40
16	2-Phenetyl	5.94	21	>30	>30	>30	>30	4.0/47
18	2-Naphtyl	6.56	32	>30	>30	>30	>30	78/84
19	2-Thienyl	5.24	21	>30	>30	>30	>30	84/60
20	2-Furyl	4.77	22	>30	>30	>30	>30	0.3/40
21	3-Pyridiyl	3.88	908	25	23	>30	24	49/53
22	4-Pyridyl	3.88	1128	>30	>30	>30	>30	17/49

[a] Metabolic stability (MS) was evaluated as a remaining % after the incubation with hepatic microsomes and NADPH for 30 min.

Table 3
Effects of the substituents (R^3–R^6)



Compound	R^3	R^4	R^5	R^6	mPGES-1 IC_{50} (nM)	CYP inhibition IC_{50} (μM)				MS[a] (%)
						2C9	2C19	2D6	3A4	Human/rat
17	H	H	H	H	7.9	>30	>30	>30	>30	>97/>97
36	Me	H	H	H	12	>30	>30	>30	>30	91/86
37	CF_3	H	H	H	12	9.8	7.2	>30	7.5	91/96
38	NO_2	H	H	H	10	20	>30	>30	>30	89/95
39	F	H	H	H	4.1	>30	>30	>30	>30	>97/95
23	F	Me	H	H	9.9	17	>30	>30	>30	>97/90
24	F	H	Me	H	4.5	9.0	>30	1.6	>30	7.3/7.9
25	F	H	H	Me	8.3	>30	>30	>30	>30	17/6.7
26	F	Cl	H	H	4.3	21	>30	>30	>30	>97/89
27	F	H	Cl	H	2.5	>30	>30	>30	>30	>97/>97
28	F	H	H	Cl	3.3	>30	>30	>30	>30	>97/>97

[a] Metabolic stability (MS) was evaluated as a remaining % after the incubation with hepatic microsomes and NADPH for 30 min.

Table 4
In vitro ADME profiles of **1**, **17**, **27**, and **39**

Compound	mPGES-1 IC_{50} (nM)	MS (%)	CYP inhibition IC_{50} (μM)				PAMPA Pe ($\times 10^{-6}$ cm/s)	Solubility (μg/mL) in FaSSIF
		Human/rat	2C9	2C19	2D6	3A4	pH5.0/pH7.4	
1	9.1	93/82	0.7	20	>30	24	>30/26	0.9
17	7.9	>97/>97	>30	>30	>30	>30	>30/>30	1.0
27	2.5	>97/>97	>30	>30	>30	>30	29/>30	0.5
39	4.1	>97/95	>30	>30	>30	>30	30/>30	1.0

Table 5
In vitro potency and selectivity of **39**

mPGES-1 IC_{50} (nM)	PGE_2 release IC_{50} (nM)	COX-1 IC_{50} (nM)	COX-2 IC_{50} (nM)	TXS IC_{50} (nM)	LTC4S IC_{50} (nM)
4.1	33	>10,000	>10,000	>3000	>3000

Table 6
Rats PK parameters of **39**

Dose (mg/kg)	Route	CL (mL/min/kg)	V_{dss} (L/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	AUC (ng h/mL)	BA (%)
1	iv	23	1.4	0.8	—	728	—
10	po	—	—	1.0	472	1395	19

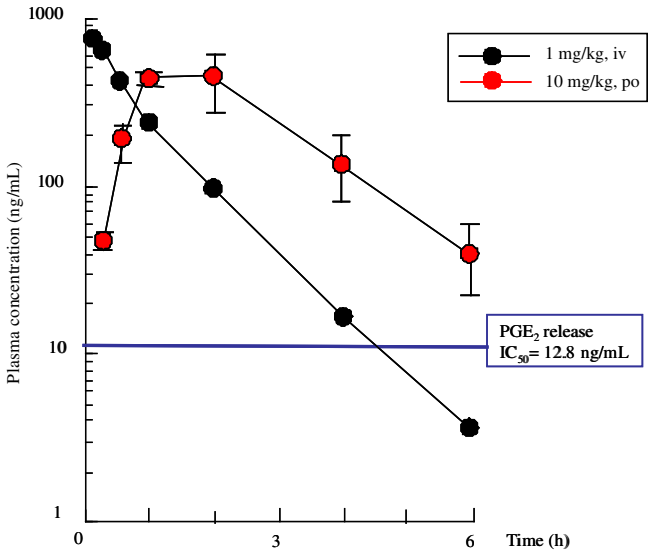


Figure 2. Time course of plasma concentration of **39** in rats.

was limited and that basic aryl or hetero aryl group gave decreased inhibitory activity, we stopped further SAR work and considered **27** and **39** to be preferable compounds.

To select candidates for in vivo study, we performed further in vitro ADME experiments, that is parallel artificial membrane permeability assay (PAMPA)[11] and solubility in FaSSIF,[12] with the potent compounds **1**, **17**, **27**, and **39**. The detailed profiles of these compounds are shown in Table 4. All compounds showed no concerns related to MS, CYP inhibition, or membrane permeability (Pe). However, the solubility of compound **27** was lower than that of **17** or **39**, and the inhibitory activity of **17** was twofold weaker than that of **39**. Thus, we selected **39** as the best compound and evaluated its cell-based activity, that is A549 cells were stimulated with IL-1α, and the generated amount of PGE_2 was measured (Table 5). Compound **39** inhibited PGE_2 release with an IC_{50} value of 33 nM (=12.8 ng/mL). In addition, **39** exhibited good mPGES-1 selectivity with no inhibition toward COX-1 and -2, thromboxane synthase (TXS), and leukotriene C4 synthase (LTC4S). In fact, **39** had over 700-fold selectivity toward mPGES-1 (Table 5).

Finally we conducted in vivo rats PK study with compound **39**. The results are shown in Table 6 and Fig. 2. Compound **39** was intravenously (1 mg/kg) or orally (10 mg/kg) administered to male rats. Intravenous administration of **39** resulted in low clearance (CL) and distribution at steady state (V_{dss}). In addition, when administrated orally, the maximum concentration (C_{max}) of **39** reached 472 ng/mL with an area under the curve (AUC) of 1395 ng h/mL. This translated to a 19% bioavailability. As shown in Fig. 2, plasma concentration of **39** (12.8 ng/mL) in cell based assay remained high for more than 6 h, suggesting that oral administration of compound **39** can be efficacious in vivo. Based on this good PK and in vitro profile, compound **39** is now considered as a promising mPGES-1 inhibitor worthy of further development.

4. Conclusion

By optimizing the lead compound **1** at the C(7)- and C(8)-positions, we identified compounds with strong mPGES-1 inhibitory activity and clear in vitro ADME profile. In term of inhibitory activity, substitution at the C(7)-position was better than that at the C(8)-position. Replacement of the bromine atom in **1** with a hydrophobic group, particularly a phenyl group giving compound **17** maintained mPGES-1 inhibitory activity with no CYP 2C9 inhibition, which was the main concern with compound **1**. Further SAR examination on both the C(2) and C(7)-phenyl groups of **17** gave two promising compounds **27** and **39**. We selected compound **39** for further development, since it showed strong inhibitory activity (IC_{50} = 4.1 nM) and excellent in vitro ADME profile (good MS, PAMPA, no CYP inhibition, and sufficient solubility). The functional activity of **39** was confirmed by cell-based assay, where this compound exhibited good mPGES-1 selectivity (over 700-fold). Rat PK study revealed that compound **39** has good oral absorption, making it suitable for further development as mPGES-1 inhibitor.

5. Experimental

5.1. General

Nuclear magnetic resonance spectra (NMR) were recorded on a JEOL JMN-LA300 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 JIR-SPX60 spectrometer as ATR. 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.

5.1.1. 2-(2-Chlorophenyl)imidazo[4,5-*c*]quinoline (3a)

A mixture of quinoline-3,4-diamine[14] (80.0 mg, 0.503 mmol), 2-chlorobenzaldehyde (142.0 mg, 1.01 mmol), and sodium pyrosulfate (287.0 mg, 1.51 mmol) in *N*,*N*-dimethylformamide (DMF) (5.0 mL) was stirred at 140 °C for 3 h. After cooling to rt, water and ethyl acetate (AcOEt) were added and then the mixture was extracted with AcOEt twice, and the combined extracts were washed with water and brine, dried over sodium sulfate (Na_2SO_4). After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1:1) and triturated with hexane/diisopropyl ether (IPE) to afford **3a** (127.0 mg, 90%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.59 (1H, s), 8.55–8.59 (1H, m), 8.22–8.25 (1H, m), 7.96 (1H, d, J = 7.5 Hz), 7.83–7.91 (2H, m), 7.75 (1H, dd, J = 1.5, 7.7 Hz), 7.58–7.69 (2H, m); mp 170–172 °C; IR (ATR) ν 2895, 1620, 1595, 1522, 1466, 1416, 1352, 1284, 1234, 1190, 1155, 1076, 1055, 1043 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{11}ClN_3$ $(M+H)^+$: 280.0636, found: 280.0633; HPLC; 97.1% (rt; 1.12 min).

5.1.2. 7-Chloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (3b) and 8-chloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (3d)

The title compounds **3b** and **3d** were synthesized from 7-chloroquinoline-3,4-diamine[14] and 6-chloroquinoline-3,4-diamine[14] in 92% and 89% yield according to the procedure to prepare **3a**, respectively. Compound **3b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.89 (1H, br s), 9.24 (1H, s), 8.42 (1H, d, J = 8.8 Hz), 8.12 (1H, d, J = 2.2 Hz), 7.89 (1H, d, J = 5.9 Hz), 7.65–7.71 (2H, m), 7.49–7.59 (2H, m); mp 225–226 °C; IR (ATR) ν 1628, 1560, 1487, 1475, 1358, 1311, 1261, 1188, 1072, 1051 cm^{-1}; HRMS (ESI+) m/z calcd

for $C_{16}H_{10}Cl_2N_3$ $(M+H)^+$: 314.0246, found: 314.0236; Anal. Calcd for $C_{16}H_9Cl_2N_3O{\cdot}1.00H_2O$; C, 57.85; H, 3.34; N, 12.65. Found: C, 57.76; H, 3.32; N, 12.66. Compound **3d**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.48 (1H, s), 8.59 (1H, s), 8.21 (1H, d, J = 9.0 Hz), 7.97 (1H, dd, J = 2.5, 6.9 Hz), 7.83 (1H, dd, J = 2.4, 9.0 Hz), 7.73–7.76 (1H, m), 7.58–7.67 (2H, m); mp 150–152 °C; IR (ATR) ν 1622, 1597, 1423, 1342, 1236, 1080, 1045 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}Cl_2N_3$ $(M+H)^+$: 314.0246, found: 314.0245; HPLC; 96.3% (rt; 1.48 min).

5.1.3. 7-Bromo-2-(2-chloro-6-fluorophenyl)imidazo[4,5-*c*]quinoline (3e)

The title compound **3e** was synthesized from 7-bromoquinoline-3,4-diamine[10a] and 2-chloro-6-fluorobenzaldehyde in 90% yield according to the procedure to prepare **3a**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.34 (1H, s), 8.31–8.36 (2H, m), 7.88 (1H, d, J = 8.8 Hz), 7.68–7.76 (1H, m), 7.61 (1H, d, J = 8.1 Hz), 7.53 (1H, t, J = 8.8 Hz); mp 129–131 °C; IR (ATR) ν 1456, 1319, 1250, 1198, 1062, 1024 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_9BrClFN_3$ $(M+H)^+$: 375.9647, found: 375.9652; HPLC; 99.0% (rt; 1.37 min).

5.1.4. 8-Bromo-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (3c)

To a solution of 6-bromo-4-chloro-3-nitroquinoline[15] (465.0 mg, 1.62 mmol) in CH_3CN (16.0 mL) was added 28% NH_3 aq (1.1 mL, 16.2 mmol) at rt and then the mixture was stirred at 50 °C for 1 h. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with AcOEt twice. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2/1) and triturated with IPE to afford 6-bromo-3-nitroquinolin-4-amine (401.7 mg, 93%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.15 (1H, s), 9.04 (2H, br s), 8.88 (1H, d, J = 2.0 Hz), 7.94 (1H, dd, J = 2.2, 8.8 Hz), 7.78 (1H, d, J = 8.8 Hz); mp 289 (dec); IR (ATR) ν 3385, 3072, 1628, 1566, 1525, 1466, 1375, 1325, 1252, 1201, 1146, 1119, 1072 cm^{-1}; HRMS (ESI+) m/z calcd for $C_9H_7BrN_3O_2$ $(M+H)^+$: 267.9716, found: 267.9711; HPLC; 95.5% (rt; 0.65 min).

A mixture of 6-bromo-3-nitroquinolin-4-amine (340.0 mg, 1.27 mmol), reducing iron powder (283.3 mg, 5.07 mmol), and ammonium chloride (271.2 mg, 5.07 mmol) in EtOH/H_2O (10.0/2.0 mL) was stirred at reflux for 2 h. After cooling to rt, the reaction mixture was filtrated with Celite® and the filtrate was evaporated in vacuo. The residue was washed with H_2O and triturated with IPE to afford 6-bromoquinoline-3,4-diamine (292.0 mg, 97%) as a yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.28 (0.5H, br s), 8.67 (1H, s), 8.27 (1.5H, br s), 8.15 (1H, s), 7.81 (2H, s), 5.58 (2H, br s); IR (ATR) ν 3319, 3186, 2933, 1686, 1630, 1578, 1566, 1489, 1430, 1376, 1346, 1294, 1269, 1236, 1200, 1119, 1072 cm^{-1}; mp 291 °C (dec); HRMS (ESI+) m/z calcd for $C_9H_9BrN_3$ $(M+H)^+$: 237.9974, found: 237.9960; HPLC; 98.9% (rt; 0.69 min).

The title compound **3c** was synthesized from prepared 6-bromoquinoline-3,4-diamine in 79% yield according to the procedure to prepare **3a**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.48 (1H, s), 8.75 (1H, s), 8.12 (1H, d, J = 9.0 Hz), 7.92–7.98 (2H, m), 7.73–7.76 (1H, m), 7.58–7.67 (2H, m); mp 153–155 °C; IR (ATR) ν 3093, 1618, 1595, 1421, 1340, 1234, 1045 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}BrClN_3$ $(M+H)^+$: 357.9741, found: 357.9740; HPLC; 99.4% (rt; 1.54 min).

5.1.5. 4-Chloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (4a)

To a solution of **3a** (50.0 mg, 0.179 mmol) in CH_2Cl_2 (10.0 mL) was added *m*-chloroperoxybenzoic acid (*m*CPBA) (61.7 mg, 0.357 mmol) at 0 °C and then the mixture was stirred at rt for 4 h. To the reaction mixture, saturated aqueous sodium thiosulfate and saturated aqueous sodium carbonate (Na_2CO_3) were added and then the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. To the obtained residue was added phosphorous oxychloride (2.0 mL) at rt and the reaction mixture was stirred at reflux for 2 h. The reaction mixture was evaporated in vacuo and then $CHCl_3$ and saturated aqueous Na_2CO_3 were added at 0 °C. The mixture was extracted with $CHCl_3$ twice and the combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5/1) and triturated with IPE/$CHCl_3$ to afford **4a** (31.2 mg, 56% in two steps) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.27 (1H, br s), 8.41–8.44 (1H, m), 8.04–8.07 (1H, m), 7.89 (1H, dd, J = 2.3, 7.1 Hz), 7.71–7.75 (3H, m), 7.54–7.65 (2H, m); mp 164–166 °C; IR (ATR) ν 2761, 1506, 1362, 1329, 1311, 1279, 1240, 1194, 1157, 1053, 1022 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}Cl_2N_3$ $(M+H)^+$: 314.0246, found: 314.0240; HPLC; 99.7% (rt; 1.97 min).

5.1.6. 4,7-Dichloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (4b), 8-bromo-4-chloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (4c), 4,8-dichloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinoline (4d), and 7-bromo-4-chloro-2-(2-chloro-6-fluorophenyl)imidazo[4,5-*c*]quinoline (4e)

The title compounds **4b**–**4e** were synthesized from **3b**–**3e** in 63%, 47%, 65%, and 52% yield according to the procedure to prepare **4a**, respectively. Compound **4b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.38 (1H, br s), 8.44 (1H, d, J = 8.6 Hz), 8.14 (1H, d, J = 2.0 Hz), 7.89 (1H, dd, J = 1.9, 7.4 Hz), 7.79 (1H, dd, J = 2.1, 8.7 Hz), 7.73 (1H, dd, J = 1.3, 7.9 Hz), 7.55–7.67 (2H, m); mp 254–256 °C; IR (ATR) ν 2951, 2825, 1628, 1603, 1562, 1537, 1487, 1475, 1433, 1392, 1358, 1311, 1261, 1188, 1122, 1072, 1051 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_9Cl_3N_3$ $(M+H)^+$: 347.9857, found: 347.9847; Anal. Calcd for $C_{16}H_8BrCl_2N_3{\cdot}0.25H_2O$; C, 48.34; H, 2.16; N, 10.57. Found: C, 48.20; H, 2.10; N, 10.49. Compound **4c**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.26 (1H, br s), 8.71 (1H, s), 8.01 (1H, d, J = 9.0 Hz), 7.86–7.92 (2H, m), 7.74 (1H, dd, J = 1.5, 7.9 Hz), 7.56–7.67 (2H, m); mp 254–256 °C; IR (ATR) ν 3433, 3062, 1564, 1506, 1454, 1369, 1356, 1313, 1265, 1242, 1211, 1194, 1130, 1099, 1072, 1038 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_9BrCl_2N_3$ $(M+H)^+$: 391.9351, found: 391.9351; HPLC; 96.5% (rt; 2.62 min). Compound **4d**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.27 (1H, br s), 8.55 (1H, s), 8.09 (1H, d, J = 9.0 Hz), 7.91 (1H, d, J = 5.7 Hz), 7.72–7.79 (2H, m), 7.57–7.67 (2H, m); mp 246–247 °C; IR (ATR) ν 3433, 1568, 1456, 1360, 1311, 1242, 1215, 1130, 1082, 1059, 1039 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_9Cl_3N_3$ $(M+H)^+$: 347.9857, found: 347.9857; HPLC; 99.3% (rt; 2.53 min). Compound **4e**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.67 (1H, br s), 8.31 (1H, d, J = 1.5 Hz), 8.27 (1H, d, J = 8.8 Hz), 7.92 (1H, d, J = 8.8 Hz), 7.70–7.78 (1H, m), 7.63 (1H, d, J = 8.1 Hz), 7.55 (1H, d, J = 8.8 Hz); mp 271–273 °C; IR (ATR) ν 2873, 1456, 1360, 1308, 1263, 1255, 1188, 1130, 1065, 1051 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_8BrCl_2FN_3$ $(M+H)^+$: 409.9257, found: 409.9261; HPLC; 97.2% (rt; 2.56 min).

5.1.7. 2-(2-Chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (2)

A mixture of **4a** (18.0 mg, 0.0573 mmol) and 5 M HCl aq (0.11 mL, 0.573 mmol) in EtOH/H_2O (1.0/0.1 mL) was stirred at reflux for 3 h. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) and triturated with IPE/$CHCl_3$ to afford **2** (15.5 mg, 91%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.44 (1H, br s), 8.05 (1H, d, J = 8.1 Hz), 7.82–7.85 (1H, m), 7.60–7.63 (1H, m), 7.43–7.52 (2H, m), 7.35–7.40 (2H, m), 7.19–7.24 (1H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.8, 150.2, 141.2, 136.4, 132.1, 131.9, 131.0, 130.6, 130.2, 128.8, 127.4, 127.1, 126.4, 121.6, 115.8,

115.1; mp 292–294 °C; IR (ATR) ν 3005, 1670, 1624, 1554, 1340, 1315, 1271, 1246, 1456, 1429, 1047 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{11}ClN_3O$ $(M+H)^+$: 296.0585, found: 296.0587; Anal. Calcd for $C_{16}H_{10}ClN_3O{\cdot}1.75H_2O$; C, 58.72; H, 4.16; N, 12.84. Found: C, 59.01; H, 3.98; N, 12.84.

5.1.8. 7-Chloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (5), 8-bromo-2-(2-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (6), 8-chloro-2-(2-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (7), and 7-bromo-2-(2-chloro-6-fluorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (8)

The title compounds **5**–**8** were synthesized from **4b**–**4e** in 90%, 86%, 79%, and 92% yield according to the procedure to prepare **2**, respectively. Compound **5**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.85 (1H, br s), 8.13 (1H, d, J = 8.6 Hz), 7.80 (1H, dd, J = 1.9, 7.4 Hz), 7.68 (1H, dd, J = 1.5, 7.9 Hz), 7.52–7.61 (2H, m), 7.50 (1H, d, J = 2.0 Hz), 7.33 (1H, dd, J = 2.0, 8.4 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.8, 148.8, 139.7, 137.6, 132.5, 132.3, 132.2, 131.8, 130.3, 129.0, 127.5, 125.7, 123.6, 122.2, 115.4, 112.9; mp 340–342 °C; IR (ATR) ν 3007, 1670, 1595, 1549, 1479, 1454, 1427, 1385, 1309, 1240, 1167, 1086, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}Cl_2N_3O$ $(M+H)^+$: 330.0195, found: 330.0191; Anal. Calcd for $C_{16}H_9Cl_2N_3O{\cdot}1.25H_2O$; C, 54.49; H, 3.29; N, 11.91. Found: C, 54.25; H, 2.99; N, 11.66. Compound **6**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.77 (1H, br s), 8.24 (1H, s), 7.80 (1H, dd, J = 2.5, 7.1 Hz), 7.67 (1H, dd, J = 1.6, 7.8 Hz), 7.50–7.62 (3H, m), 7.40 (1H, d, J = 8.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.6, 149.3, 135.6, 132.2, 132.1, 131.6, 130.7, 130.3, 129.4, 127.5, 123.9, 118.3, 116.2, 113.9; mp 339–341 °C; IR (ATR) ν 3309, 3149, 3080, 3005, 2895, 1670, 1616, 1545, 1456, 1427, 1400, 1385, 1306, 1244, 1068, 1047 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}BrClN_3O$ $(M+H)^+$: 373.9690, found: 373.9691; Anal. Calcd for $C_{16}H_9BrClN_3O{\cdot}0.75H_2O$; C, 49.51; H, 2.73; N, 10.83. Found: C, 49.72; H, 2.95; N, 10.64. **7**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.77 (1H, br s), 8.09 (1H, s), 7.80 (1H, dd, J = 2.4, 7.0 Hz), 7.67 (1H, dd, J = 1.6, 7.6 Hz), 7.50–7.60 (2H, m), 7.44–7.49 (2H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.4, 149.3, 135.3, 132.2, 131.6, 130.3, 129.4, 128.0, 127.7, 127.5, 126.0, 120.9, 117.9; mp 354–355 °C; IR (ATR) ν 3309, 3149, 3084, 3005, 2902, 1670, 1622, 1545, 1454, 1427, 1404, 1387, 1306, 1240, 1078, 1047 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_{10}Cl_2N_3O$ $(M+H)^+$: 330.0195, found: 330.0196; Anal. Calcd for $C_{16}H_9Cl_2N_3O{\cdot}1.25H_2O$; C, 54.49; H, 3.29; N, 11.91. Found: C, 54.57; H, 3.28; N, 11.91. **8**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.11 (0.6H, br s), 12.75 (0.4H, br s), 11.81 (1H, br s), 7.96 (1H, d, J = 8.8 Hz), 7.63–7.70 (2H, m), 7.56 (1H, d, J = 8.1 Hz), 7.42–7.50 (2H, m); mp >350 °C; IR (ATR) ν 2904, 1718, 1647, 1610, 1450, 1425, 1381, 1313, 1246, 1180, 1167, 1078 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{16}H_9BrClFN_3O$ $(M+H)^+$: 391.9596, found: 391.9601; HPLC; 98.1% (rt; 1.82 min).

5.1.9. 2-(2-Chlorophenyl)-7-methylimidazo[4,5-*c*]quinolin-4(5*H*)-one (9)

To a solution of **1** (20.0 mg, 0.0534 mmol) and bis(tri-*tert*-butylphosphine)palladium(0) ($Pd(P^tBu_3)_2$) (5.50 mg, 0.0107 mmol) in tetrahydrofuran (THF)/*N*-methylpyrrolidone (NMP) (1.0/0.5 mL) was added 2.0 M MeZnCl in THF solution (0.080 mL, 0.160 mmol) at 0 °C under an atmosphere of nitrogen and then the mixture was stirred at rt for 1 h. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with AcOEt twice. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1/1) and triturated with IPE/$CHCl_3$ to afford **9** (10.9 mg, 67%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.63 (1H, br s), 8.03 (1H, d, J = 8.1 Hz), 7.85 (1H, d, J = 7.0 Hz), 7.72 (1H, d, J = 7.7 Hz), 7.55–7.64 (2H, m), 7.30 (1H, s), 7.15 (1H, d, J = 8.4 Hz), 2.45 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.3, 148.3, 141.0, 137.9, 136.7, 132.2, 132.1, 131.4, 130.2, 129.6, 127.4, 123.3, 121.6, 115.9, 111.8, 21.3; mp 294–296 °C; IR (ATR) ν 2918, 1645, 1560, 1535, 1446, 1429, 1385, 1321, 1279, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{17}H_{13}ClN_3O$ $(M+H)^+$: 310.0742, found: 310.0741; Anal. Calcd for $C_{17}H_{12}ClN_3O{\cdot}0.25H_2O$; C, 65.86; H, 3.89; N, 13.55. Found: C, 65.90; H, 4.09; N, 13.25.

5.1.10. 2-(2-Chlorophenyl)-7-ethylimidazo[4,5-*c*]quinolin-4(5*H*)-one (10)

To a solution of **1** (20.0 mg, 0.0534 mmol) and $Pd(P^tBu_3)_2$ (5.50 mg, 0.0107 mmol) in THF/NMP (1.0/0.5 mL) was added 2.0 M Et_2Zn in hexane solution (0.080 mL, 0.160 mmol) at 0 °C under an atmosphere of nitrogen 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. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1/1) and triturated with IPE/$CHCl_3$ to afford **10** (14.2 mg, 82%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.70 (1H, br s), 11.60 (1H, br s), 7.99 (1H, d, J = 8.0 Hz), 7.80 (1H, dd, J = 2.0, 7.3 Hz), 7.65–7.67 (1H, m), 7.50–7.58 (2H, m), 7.27 (1H, s), 7.14 (1H, dd, J = 1.4, 8.2 Hz), 2.69 (2H, q, J = 7.3 Hz), 1.23 (3H, t, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 149.5, 144.5, 136.7, 132.1, 131.3, 130.2, 129.7, 127.3, 122.1, 121.7, 114.6, 28.3, 15.4; mp 291–293 °C; IR (ATR) ν 3091, 2953, 1653, 1635, 1578, 1466, 1434, 1390, 1375, 1234, 1188, 1101, 1057, 1039 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{18}H_{15}ClN_3O$ $(M+H)^+$: 324.0898, found: 324.0891; Anal. Calcd for $C_{18}H_{14}ClN_3O{\cdot}1.00H_2O$; C, 63.25; H, 4.72; N, 12.29. Found: C, 62.93; H, 4.48; N, 12.07.

5.1.11. 2-(2-Chlorophenyl)-7-(*n*-propyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (11)

To a solution of **1** (20.0 mg, 0.0534 mmol) and $Pd(P^tBu_3)_2$ (5.50 mg, 0.0107 mmol) in THF/NMP (1.0/0.5 mL) was added 0.5 M *n*-propyl-ZnBr in THF solution (0.32 mL, 0.160 mmol) at 45 °C under an atmosphere of nitrogen 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. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1/1) and triturated with IPE/$CHCl_3$ to afford **11** (13.3 mg, 74%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.70 (1H, br s), 11.56 (1H, br s), 7.98 (1H, d, J = 8.1 Hz), 7.78 (1H, dd, J = 2.0, 7.3 Hz), 7.64–7.67 (1H, m), 7.49–7.58 (2H, m), 7.24 (1H, s), 7.11 (1H, dd, J = 1.4, 8.2 Hz), 2.62 (2H, t, J = 7.5 Hz), 1.62 (2H, dt, J = 7.3, 14.8 Hz), 0.91 (3H, t, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 142.5, 136.7, 132.2, 131.4, 130.2, 129.8, 127.4, 122.6, 121.7, 115.3, 37.4, 24.0, 13.7; mp 284–285 °C; IR (ATR) ν 2954, 1649, 1535, 1448, 1338, 1248, 1180, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{19}H_{17}ClN_3O$ $(M+H)^+$: 338.1055, found: 338.1056; Anal. Calcd for $C_{19}H_{16}ClN_3O$; C, 67.56; H, 4.77; N, 12.44. Found: C, 67.58; H, 4.93; N, 12.24.

5.1.12. 7-(*n*-Butyl)-2-(2-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (12), 2-(2-chlorophenyl)-7-(*n*-pentyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (13), 2-(2-chlorophenyl)-7-(*n*-hexyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (14), 7-benzyl-2-(2-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (15), and 2-(2-chlorophenyl)-7-(2-phenethyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (16)

The title compounds **12**–**16** were synthesized from **1** in 85%, 57%, 48%, 72%, and 68% yield according to the procedure to prepare

11, respectively. Compound **12**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.73 (0.5H, s), 13.56 (0.5H, s), 11.57 (0.5H, s), 11.41 (0.5H, s), 7.98 (1H, d, J = 8.1 Hz), 7.78 (1H, d, J = 7.2 Hz), 7.63–7.67 (1H, m), 7.50–7.64 (2H, m), 7.25 (1H, s), 7.11 (1H, d, J = 8.1 Hz), 2.66 (2H, t, J = 7.5 Hz), 1.55–1.65 (2H, m), 1.32 (2H, dt, J = 7.3, 21.4 Hz), 0.90 (3H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.8, 155.1, 149.6, 146.9, 144.4, 142.4, 136.6, 132.2, 131.4, 130.1, 127.3, 122.7, 121.6, 115.3, 114.0, 109.5, 35.0, 33.1, 21.8, 13.8; mp 281–283 °C; IR (ATR) ν 2954, 1647, 1533, 1448, 1329, 1248, 1180, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{20}H_{19}ClN_3O$ $(M+H)^+$: 352.1211, found: 352.1211; Anal. Calcd for $C_{20}H_{18}ClN_3O{\cdot}0.5H_2O$; C, 66.57; H, 5.31; N, 11.65. Found: C, 66.66; H, 5.18; N, 11.49. Compound **13**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.47 (1H, br s), 7.97 (1H, d, J = 8.1 Hz), 7.78–7.83 (1H, m), 7.63–7.66 (1H, m), 7.47–7.61 (2H, m), 7.23 (1H, s), 7.09 (1H, dd, J = 1.5, 8.1 Hz), 2.67 (2H, t, J = 7.7 Hz), 1.56–1.65 (2H, m), 1.26–1.35 (4H, m), 0.86 (3H, t, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 142.5, 136.6, 132.1, 132.0, 131.1, 130.2, 127.3, 122.4, 121.6, 115.2, 35.3, 30.9, 30.6, 22.0, 13.9; mp 268–270 °C; IR (ATR) ν 2956, 1649, 1539, 1456, 1329, 1250, 1180, 1051 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{21}H_{21}ClN_3O$ $(M+H)^+$: 366.1368, found: 366.1376; Anal. Calcd for $C_{21}H_{20}ClN_3O{\cdot}0.25H_2O$; C, 68.10; H, 5.58; N, 11.35. Found: C, 67.83; H, 5.49; N, 11.29. Compound **14**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.77 (0.5H, br s), 13.61 (0.5H, br s), 11.62 (0.5H, br s), 11.45 (0.5H, br s), 7.98 (1H, d, J = 7.3 Hz), 7.76–7.81 (1H, m), 7.63–7.69 (1H, m), 7.47–7.57 (2H, m), 7.24 (1H, d, J = 7.3 Hz), 7.11 (1H, d, J = 8.1 Hz), 2.62–2.68 (2H, m), 1.58–1.62 (2H, m), 1.24–1.28 (6H, m), 0.85 (3H, t, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.7, 151.3, 147.0, 144.4, 135.7, 131.9, 130.4, 129.7, 128.6, 128.4, 126.9, 124.6, 122.4, 121.2, 115.8, 115.0, 36.1, 32.1, 31.3, 29.3, 22.5, 13.9; mp 267–269 °C; IR (ATR) ν 2925, 1647, 1248, 1180, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{23}ClN_3O$ $(M+H)^+$: 380.1524, found: 380.1530; HPLC; 100% (rt; 2.74 min). Compound **15**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.77 (0.5H, s), 13.61 (0.5H, s), 11.61 (0.5H, s), 11.44 (0.5H, s), 8.00 (1H, d, J = 7.9 Hz), 7.75–7.80 (1H, m), 7.63–7.70 (1H, m), 7.50–7.55 (2H, m), 7.17–7.33 (6H, m), 7.14 (1H, d, J = 7.9 Hz), 4.03 (2H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.8, 155.0, 149.7, 147.0, 144.2, 141.8, 140.9, 136.9, 135.7, 132.2, 131.3, 130.1, 129.7, 128.8, 128.5, 127.3, 126.1, 123.1, 121.8, 115.8, 114.3, 109.7, 41.2; mp 268–270 °C; IR (ATR) ν 2920, 1655, 1635, 1429, 1394, 1340, 1313, 1267, 1240, 1101, 1043 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{23}H_{17}ClN_3O$ $(M+H)^+$: 386.1055, found: 386.1055; HPLC; 98.5% (rt; 2.19 min). Compound **16**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.52 (1H, br s), 7.98 (1H, d, J = 8.1 Hz), 7.79 (1H, dd, J = 2.0, 7.0 Hz), 7.65 (1H, d, J = 7.2 Hz), 7.49–7.58 (2H, m), 7.14–7.29 (7H, m), 2.94 (4H, br s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.3, 154.7, 152.5, 145.7, 141.6, 141.3, 136.7, 132.2, 131.4, 130.2, 129.8, 128.5, 128.3, 127.4, 125.9, 122.6, 121.6, 115.4, 112.5, 110.6, 37.3, 36.9; mp 188–202 °C (amorphous solid); IR (ATR) ν 3010, 1647, 1635, 1248, 1180, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{24}H_{19}ClN_3O$ $(M+H)^+$: 400.1211, found: 400.1211; Anal. Calcd for $C_{24}H_{18}ClN_3O{\cdot}0.75H_2O$; C, 69.73; H, 4.75; N, 10.17. Found: C, 69.66; H, 4.67; N, 9.89.

5.1.13. 2-(2-Chlorophenyl)-7-phenylimidazo[4,5-*c*]quinolin-4(5*H*)-one (17)

A mixture of **1** (100.0 mg, 0.267 mmol), phenyl boronic acid (48.8 mg, 0.401 mmol), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (30.9 mg, 0.0267 mmol) and Na_2CO_3 (141.4 mg, 1.34 mmol) in THF/H_2O (3.0/0.3 mL) was stirred at reflux for 6 h. After cooling to rt, water and AcOEt were added and the mixture was extracted with AcOEt twice. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) and triturated with IPE/$CHCl_3$ to afford **17** (72.2 mg, 73%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.99 (1H, br s), 8.06 (1H, d, J = 8.3 Hz), 8.00 (1H, dd, J = 1.8, 7.5 Hz), 7.66–7.69 (2H, m), 7.62 (1H, d, J = 1.7 Hz), 7.45–7.51 (3H, m), 7.30–7.43 (4H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.7, 149.0, 140.4, 137.0, 136.4, 132.0, 131.3, 130.2, 129.0, 128.4, 127.2, 126.5, 121.8, 120.0, 116.5, 113.2; mp 335–337 °C; IR (ATR) ν 2950, 1653, 1635, 1419, 1313, 1265, 1244, 1159, 1101, 1039 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{15}ClN_3O$ $(M+H)^+$: 372.0898, found: 372.0898; Anal. Calcd for $C_{22}H_{14}ClN_3O{\cdot}0.50H_2O$; C, 69.38; H, 3.97; N, 11.03. Found: C, 69.08; H, 3.81; N, 10.88.

5.1.14. 2-(2-Chlorophenyl)-7-(naphthalen-2-yl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (18), 2-(2-chlorophenyl)-7-(thiophen-2-yl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (19), 2-(2-chlorophenyl)-7-(furan-2-yl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (20), 2-(2-chlorophenyl)-7-(pyridin-3-yl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (21), and 2-(2-chlorophenyl)-7-(pyridin-4-yl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (22)

The title compounds **18**–**22** were synthesized from **1** with corresponding boronic acid reagents in 71%, 64%, 68%, 63%, and 61% yield according to the procedure to prepare **17**, respectively. Compound **18**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.75 (1H, br s), 11.71 (1H, br s), 8.26 (1H, s), 8.22 (1H, d, J = 8.1 Hz), 8.02–8.08 (2H, m), 7.95–7.98 (1H, m), 7.81–7.87 (3H, m), 7.74 (1H, d, J = 8.1 Hz), 7.63–7.69 (1H, m), 7.55–7.60 (4H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 139.7, 137.6, 137.2, 137.1, 133.3, 132.4, 132.2, 131.4, 130.2, 129.7, 129.0, 128.7, 128.3, 127.6, 127.4, 126.6, 126.4, 125.5, 125.0, 124.8, 123.6, 122.4, 121.1, 118.2, 114.1; mp 167–192 °C (amorphous solid); IR (ATR) ν 3012, 1653, 1637, 1425, 1387, 1269, 1244, 1211, 1173, 1049 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{26}H_{17}ClN_3O$ $(M+H)^+$: 422.1055, found: 422.1055; HPLC; 98.4% (rt; 2.57 min). Compound **19**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.14 (1H, br s), 8.02 (1H, d, J = 8.3 Hz), 7.92–7.95 (1H, m), 7.65 (1H, d, J = 1.7 Hz), 7.52–7.56 (3H, m), 7.47–7.49 (1H, m), 7.38–7.41 (2H, m), 7.16 (1H, dd, J = 3.6, 5.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 143.6, 136.5, 133.0, 132.0, 131.5, 130.2, 129.3, 128.6, 126.8, 125.5, 123.4, 122.0, 118.7, 111.9; mp 245–247 °C; IR (ATR) ν 3001, 1653, 1448, 1429, 1387, 1331, 1271, 1242, 1159, 1045 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{20}H_{13}ClN_3OS$ $(M+H)^+$: 378.0462, found: 378.0469; HPLC; 98.7% (rt; 2.10 min). Compound **20**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.87 (0.5H, br s), 13.69 (0.5H, br s), 11.78 (0.5H, br s), 11.62 (0.5H, br s), 8.10 (1H, d, J = 8.3 Hz), 7.76–7.82 (3H, m), 7.61–7.65 (2H, m), 7.50–7.59 (2H, m), 7.00 (1H, d, J = 2.9 Hz), 6.64 (1H, dd, J = 1.7, 3.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.8, 155.0, 152.6, 150.0, 147.5, 144.0, 143.4, 136.9, 132.2, 131.4, 130.2, 129.6, 128.8, 127.3, 122.3, 118.0, 115.2, 112.3, 110.1, 106.7; mp 182–215 °C (amorphous solid); IR (ATR) ν 2991, 1655, 1425, 1396, 1313, 1271, 1246, 1169, 1047, 1020 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{20}H_{13}ClN_3O_2$ $(M+H)^+$: 362.0691, found: 362.0691; HPLC; 98.0% (rt; 1.94 min). Compound **21**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.91 (1H, br s), 11.75 (1H, br s), 8.92 (1H, d, J = 2.4 Hz), 8.62 (1H, dd, J = 1.7, 4.8 Hz), 8.20 (1H, d, J = 8.3 Hz), 8.08–8.12 (1H, m), 7.82 (1H, dd, J = 2.2, 7.0 Hz), 7.74 (1H, d, J = 1.5 Hz), 7.51–7.69 (5H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 148.8, 147.6, 137.1, 136.7, 135.2, 134.3, 132.2, 131.5, 130.2, 129.6, 127.4, 124.1, 122.6, 120.9, 114.0; mp 266–285 °C (amorphous solid); IR (ATR) ν 3010, 1662, 1448, 1425, 1383, 1350, 1323, 1238, 1194, 1174, 1126, 1049, 1026 cm^{-1}; Anal. Calcd for $C_{21}H_{13}ClN_4O{\cdot}1.00H_2O$; C, 64.54; H, 3.87; N, 14.34. Found: C, 64.30; H, 3.78; N, 14.11. Compound **22**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.94 (1H, br s), 11.80 (1H, br s), 8.20–8.23 (2H, m), 8.22 (1H, d, J = 8.3 Hz), 7.80–7.83 (2H, m), 7.66–7.75 (4H, m), 7.51–7.61 (2H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 150.1, 146.9, 137.0, 136.6, 132.2, 131.5, 130.2, 129.5, 127.4, 122.6, 121.3, 120.7, 114.1; mp 245–275 °C

(amorphous solid); IR (ATR) ν 3012, 1662, 1635, 1601, 1448, 1425, 1389, 1325, 1244, 1227, 1173, 1047 cm^{-1}; Anal. Calcd for $C_{21}H_{13}ClN_4O\cdot1.00H_2O$; C, 64.54; H, 3.87; N, 14.34. Found: C, 64.51; H, 3.61; N, 13.96.

5.1.15. 2-(2-Chloro-6-fluorophenyl)-7-(3-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (27)

A mixture of **8** (50.0 mg, 0.127 mmol), 3-chlorophenyl boronic acid (29.8 mg, 0.191 mmol), $Pd(PPh_3)_4$ (14.7 mg, 0.0127 mmol), and Na_2CO_3 (67.0 mg, 0.635 mmol) in THF/H_2O (2.0/0.2 mL) was stirred at reflux for 3 h. After cooling to rt, water and AcOEt were added and the mixture was extracted with AcOEt twice. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1) twice and triturated with IPE/$CHCl_3$ to afford **27** (35.2 mg, 65%) as a white solid. Compound **27**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.08 (0.5H, br s), 13.99 (0.5H, br s), 11.81 (0.6H, br s), 11.62 (0.4H, br s), 8.15 (0.6H, d, J = 8.3 Hz), 8.06 (0.4H, d, J = 8.3 Hz), 7.70–7.74 (2H, m), 7.61–7.68 (3H, m), 7.52–7.57 (2H, m), 7.44–7.51 (2H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7 (d, $^1J_{C-F}$ = 248.0 Hz), 157.7, 154.9, 144.1, 141.9, 141.4, 138.2, 136.9, 134.5, 133.9, 133.0 (d, $^3J_{C-F}$ = 9.3 Hz), 131.0, 127.6, 126.5, 125.8, 125.5, 122.4, 121.1, 118.9 (d, $^2J_{C-F}$ = 18.5 Hz), 114.9 (d, $^2J_{C-F}$ = 21.6 Hz), 114.1, 111.1; mp 351–353 °C; IR (ATR) ν 3005, 1653, 1624, 1597, 1539, 1452, 1429, 1379, 1323, 1250, 1167, 1099, 1084, 1012 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{13}Cl_2FN_3O$ $(M+H)^+$: 424.0414, found: 424.0414; Anal. Calcd for $C_{22}H_{12}Cl_2FN_3O\cdot0.25H_2O$; C, 61.63; H, 2.94; N, 9.80. Found: C, 61.52; H, 2.95; N, 9.74.

5.1.16. 2-(2-Chloro-6-fluorophenyl)-7-(2-methylphenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (23), 2-(2-chloro-6-fluorophenyl)-7-(3-methylphenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (24), 2-(2-chloro-6-fluorophenyl)-7-(4-methylphenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (25), 2-(2-chloro-6-fluorophenyl)-7-(2-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (26), and 2-(2-chloro-6-fluorophenyl)-7-(4-chlorophenyl)imidazo[4,5-*c*]quinolin-4(5*H*)-one (28)

The title compounds **23**–**26** and **28** were synthesized from **8** with corresponding boronic acid reagents in 67%, 70%, 71%, 61%, and 68% yield according to the procedure to prepare **27**, respectively. Compound **23**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.02 (1H, br s), 11.80 (0.5H, br s), 11.63 (0.5H, br s), 8.00–8.09 (1H, m), 7.63–7.68 (1H, m), 7.55–7.58 (1H, m), 7.45–7.50 (1H, m), 7.40 (1H, s), 7.24–7.34 (5H, m), 2.26 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7 (d, $^1J_{C-F}$ = 248.6 Hz), 157.7, 155.0, 144.0, 141.5, 141.0, 140.6, 136.3, 134.8, 134.5, 133.0 (d, $^3J_{C-F}$ = 9.3 Hz), 130.5, 129.5, 127.6, 126.1, 125.8, 123.3, 121.5, 119.1 (d, $^2J_{C-F}$ = 19.1 Hz), 116.3, 114.9 (d, $^2J_{C-F}$ = 22.8 Hz), 110.2, 20.2; mp 336–338 °C; IR (ATR) ν 3005, 1653, 1626, 1533, 1452, 1429, 1338, 1254, 1163 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{23}H_{16}ClFN_3O$ $(M+H)^+$: 404.0960, found: 404.0960; Anal. Calcd for $C_{23}H_{15}ClFN_3O\cdot0.25H_2O$; C, 67.65; H, 3.83; N, 10.29. Found: C, 67.92; H, 3.79; N, 10.21. Compound **24**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.05 (0.5H, br s), 13.96 (0.5H, br s), 11.79 (0.5H, br s), 11.61 (0.5H, br s), 8.13 (0.6H, d, J = 7.9 Hz), 8.04 (0.4H, d, J = 7.9 Hz), 7.37–7.72 (8H, m), 7.22 (1H, d, J = 7.0 Hz), 2.40 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7 (d, $^1J_{C-F}$ = 246.7 Hz), 157.7, 155.0, 144.1, 141.3, 140.5, 139.7, 138.3, 136.9, 134.5, 133.0 (d, $^3J_{C-F}$ = 9.9 Hz), 129.0, 128.5, 127.4, 125.8, 123.9, 122.2, 121.0, 119.2 (d, $^2J_{C-F}$ = 26.5 Hz), 114.9 (d, $^2J_{C-F}$ = 22.8 Hz), 113.9, 110.5, 21.2; mp 260–295 °C (amorphous solid); IR (ATR) ν 3005, 1653, 1626, 1533, 1452, 1427, 1379, 1323, 1252, 1186, 1163, 1097, 1058 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{23}H_{16}ClFN_3O$ $(M+H)^+$: 404.0960, found: 404.0961; Anal. Calcd for $C_{23}H_{15}ClFN_3O\cdot0.25H_2O$; C, 67.65; H, 3.83; N, 10.29. Found: C, 67.37; H, 3.83; N, 10.02. Compound **25**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.04 (0.5H, br s), 13.95 (0.5H, br s), 11.80 (0.5H, br s), 11.62 (0.5H, br s), 8.12 (0.6H, d, J = 8.3 Hz), 8.02 (0.4H, d, J = 8.3 Hz), 7.44–7.71 (7H, m), 7.32 (2H, d, J = 7.9 Hz), 2.36 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7 (d, $^1J_{C-F}$ = 247.4 Hz), 157.6, 154.9, 143.9, 141.2, 140.2, 139.7, 137.2, 136.8, 134.5, 132.8 (d, $^3J_{C-F}$ = 9.3 Hz), 129.6, 126.5, 125.8, 122.2, 120.7, 119.1 (d, $^2J_{C-F}$ = 22.2 Hz), 114.8 (d, $^2J_{C-F}$ = 20.4 Hz), 113.5, 110.3, 20.6; mp 275–291 °C (amorphous solid); IR (ATR) ν 3012, 1653, 1626, 1541, 1454, 1429, 1381, 1325, 1252, 1184, 1167, 1113, 1059, 1020 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{23}H_{16}ClFN_3O$ $(M+H)^+$: 404.0960, found: 404.0961; Anal. Calcd for $C_{23}H_{15}ClFN_3O\cdot0.25H_2O$; C, 67.65; H, 3.83; N, 10.29. Found: C, 67.59; H, 3.87; N, 10.03. Compound **26**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.07 (0.6H, br s), 14.00 (0.4H, br s), 11.87 (0.5H, br s), 11.69 (0.5H, br s), 8.14 (0.6H, d, J = 8.1 Hz), 8.05 (0.4H, d, J = 8.1 Hz), 7.55–7.68 (3H, m), 7.41–7.51 (5H, m), 7.33 (1H, dd, J = 1.7, 8.3 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.8 (d, $^1J_{C-F}$ = 248.0 Hz), 157.6, 155.0, 144.0, 139.4, 138.8, 138.3, 136.1, 134.5, 133.1 (d, $^3J_{C-F}$ = 9.3 Hz), 131.5, 131.3, 130.0, 129.5, 127.7, 125.8, 123.4, 121.5, 119.2 (d, $^2J_{C-F}$ = 18.5 Hz), 116.7, 114.9 (d, $^2J_{C-F}$ = 21.6 Hz), 110.0; mp 334–336 °C; IR (ATR) ν 3005, 1653, 1628, 1533, 1452, 1425, 1385, 1327, 1248, 1165, 1126, 1074, 1038 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{13}Cl_2FN_3O$ $(M+H)^+$: 424.0414, found: 424.0414.; Anal. Calcd for $C_{22}H_{12}Cl_2FN_3O$; C, 62.28; H, 2.85; N, 9.90. Found: C, 62.00; H, 2.92; N, 9.82. Compound **28**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.07 (1H, br s), 11.83 (0.5H, br s), 11.66 (0.5H, br s), 8.12 (1H, br s), 7.63–7.80 (4H, m), 7.56–7.61 (4H, m), 7.44–7.51 (1H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7 (d, $^1J_{C-F}$ = 248.6 Hz), 157.5, 154.9, 144.0, 141.6, 138.4, 137.0, 136.9, 134.4 (d, $^3J_{C-F}$ = 3.7 Hz), 132.9 (d, $^3J_{C-F}$ = 9.3 Hz), 132.7, 129.0, 128.4, 125.8, 122.3, 120.8, 119.0 (d, $^2J_{C-F}$ = 18.7 Hz), 114.9 (d, $^2J_{C-F}$ = 20.8 Hz), 113.8, 109.3; mp 342–344 °C; IR (ATR) ν 2997, 1653, 1568, 1533, 1479, 1450, 1421, 1379, 1244, 1163, 1090, 1011 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{13}Cl_2FN_3O$ $(M+H)^+$: 424.0414, found: 424.0414; Anal. Calcd for $C_{22}H_{12}Cl_2FN_3O\cdot0.25H_2O$; C, 61.63; H, 2.94; N, 9.80. Found: C, 61.59; H, 2.92; N, 9.76.

5.1.17. 7-Bromo-3-nitroquinoline-2,4-diol (30)

A suspension of 7-bromoquinoline-2,4-diol (**29**)[13] (5.00 g, 20.8 mmol), 70% nitric acid (2.80 mL, 31.2 mmol) in acetic acid (50.0 mL) was stirred at 60 °C for 1.5 h. After cooling to rt, IPE (200 mL) was added and stirred at 1 h. The precipitated solid was filtrated to afford **30** (2.90 g, 51%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.66 (1H, br s), 7.90 (1H, d, J = 8.6 Hz), 7.43 (1H, d, J = 1.8 Hz), 7.37 (1H, dd, J = 1.5, 8.6 Hz); mp 290 °C (dec); IR (ATR) ν 3190, 1672, 1599, 1429, 1317, 1302, 1223, 1196, 1163, 1122, 1068 cm^{-1}; HRMS (ESI+) m/z calcd for $C_9H_6BrN_2O_4$ $(M+H)^+$: 284.9505, found: 284.9509; HPLC; 99.1% (rt; 1.08 min).

5.1.18. 3-Nitro-7-phenylquinoline-2,4-diol (31)

A mixture of **30** (2.90 g, 10.2 mmol), phenyl boronic acid (2.48 g, 20.4 mmol), $Pd(PPh_3)_4$ (1.18 g, 1.02 mmol), and Na_2CO_3 (4.31 g, 40.7 mmol) in DMF/H_2O (30.0/10.0 mL) was stirred at 80 °C for 5 h. After cooling to rt, water and AcOEt were added and the mixture was extracted with AcOEt twice. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1/1) and triturated with IPE/$CHCl_3$ to afford **31** (2.38 g, 83%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.14 (1H, s), 7.92 (1H, d, J = 8.1 Hz), 7.60–7.63 (2H, m), 7.45–7.50 (2H, m), 7.35–7.40 (1H, m), 7.29 (1H, d, J = 1.7 Hz), 7.24 (1H, dd, J = 1.7, 7.7 Hz); mp 348 °C (dec); IR (ATR) ν 1539, 1506, 1485, 1394, 1358, 1313, 1288, 1252, 1173, 1161, 1047, 1032 cm^{-1}; HRMS

(ESI+) *m/z* calcd for $C_{15}H_{11}N_2O_4$ $(M+H)^+$: 283.0713, found: 283.0717; HPLC; 97.5% (rt; 1.80 min).

5.1.19. 2,4-Dichloro-3-nitro-7-phenylquinoline (32)

suspension of **31** (2.00 g, 7.09 mmol) in phosphorous oxychloride (10.0 mL, 70.9 mmol) was stirred at reflux for 2 h. After cooling to 0 °C, cooled water was dropped and then the precipitated solid was filtrated. The solid was purified by silica gel column chromatography (hexane/AcOEt = 5/1) and triturated with IPE/$CHCl_3$ to afford **32** (2.23 g, 97%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.45 (1H, d, J = 1.5 Hz), 8.40 (1H, d, J = 8.8 Hz), 8.31 (1H, dd, J = 1.5, 8.8 Hz), 7.94–7.97 (2H, m), 7.48–7.60 (3H, m); mp 168–170 °C; IR (ATR) ν 3421, 3253, 1637, 1599, 1302, 1277 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_9Cl_2N_2O_2$ $(M+H)^+$: 319.0036, found: 319.0020; HPLC; 97.1% (rt; 3.54 min).

5.1.20. 2-Chloro-3-nitro-7-phenylquinolin-4-amine (33)

To a solution of **32** (2.20 g, 6.89 mmol) in CH_3CN (50.0 mL) was added 28% NH_3 aq (3.34 mL, 55.2 mmol) at rt and then the mixture was stirred at 50 °C for 6.5 h. To the reaction mixture, water and AcOEt were added and then the mixture was extracted with AcOEt twice. The combined extracts were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 2/1) and triturated with IPE to afford **33** (1.65 g, 80%) as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.53 (1H, d, J = 8.8 Hz), 8.23 (2H, br s), 8.05 (1H, d, J = 1.5 Hz), 7.96 (1H, dd, J = 2.2, 8.8 Hz), 7.86–7.89 (2H, m), 7.42–7.55 (3H, m); mp 213–215 °C; IR (ATR) ν 3363, 1618, 1602, 1574, 1547, 1524, 1477, 1454, 1443, 1419, 1313, 1281 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_{11}ClN_3O_2$ $(M+H)^+$: 300.0534, found: 300.0520; HPLC; 97.0% (rt; 2.59 min).

5.1.21. 2-Chloro-7-phenylquinoline-3,4-diamine (34)

A mixture of **33** (1.08 g, 3.60 mmol) and 5% Pt/C (300.0 mg) in AcOEt/MeOH (30.0/30.0 mL) was stirred under an atmosphere of hydrogen at rt for 6 h. The reaction mixture was filtrated with Celite® and the solvent of the filtrate was removed in vacuo. The residue was triturated with $CHCl_3$/MeOH to afford **34** (935.0 mg, 96%) as a pale gray solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.11 (1H, d, J = 8.8 Hz), 7.86 (1H, d, J = 1.5 Hz), 7.78 (2H, d, J = 7.3 Hz), 7.68 (1H, dd, J = 2.2, 8.8 Hz), 7.48 (2H, t, J = 7.3 Hz), 7.37 (1H, t, J = 7.3 Hz), 6.39 (2H, br s), 4.85 (2H, br s); mp 220–222 °C; IR (ATR) ν 3361, 3275, 3213, 1387, 1319, 1138, 1093 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_{13}ClN_3$ $(M+H)^+$: 270.0793, found: 270.0777; HPLC; 95.0% (rt; 1.29 min).

5.1.22. 4-Chloro-2-(2-chloro-6-fluorophenyl)-7-phenylimidazo[4,5-*c*]quinoline (35d)

A mixture of **34** (50.0 mg, 0.185 mmol), 2-chloro-6-fluorobenzaldehyde (44.1 mg, 0.278 mmol), and sodium pyrosulfate (52.8 mg, 0.278 mmol) in NMP (2.0 mL) was stirred at 140 °C for 6 h. After cooling to rt, 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. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1/1) and triturated with hexane/AcOEt to afford **35d** (52.2 mg, 69%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (1H, d, J = 8.1 Hz), 8.26 (1H, d, J = 1.5 Hz), 7.70 (1H, d, J = 8.8 Hz), 7.58 (2H, d, J = 7.3 Hz), 7.37 (2H, t, J = 7.3 Hz), 7.26–7.31 (1H, m), 7.02–7.07 (1H, m), 6.91 (1H, d, J = 8.1 Hz), 6.61–6.68 (1H, m); mp 186–188 °C; IR (ATR) ν 1327, 1250, 1205, 1182, 1132, 1065 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{13}Cl_2FN_3$ $(M+H)^+$: 408.0465, found: 408.0466; HPLC; 98.9% (rt; 2.74 min).

5.1.23. 42–44 4-Chloro-2-(2-chloro-6-methylphenyl)-7-phenylimidazo[4,5-*c*]quinoline (35a), 4-chloro-2-(2-chloro-6-(trifluoromethyl)phenyl)-7-phenylimidazo[4,5-*c*]quinoline (35b), and 4-chloro-2-(2-chloro-6-nitrophenyl)-7-phenylimidazo[4,5-*c*]quinoline (35c)

The title compounds **35a**–**35c** were synthesized from **34** with corresponding benzaldehydes in 67%, 62%, and 53% yield according to the procedure to prepare **35d**, respectively. Compound **35a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28–8.33 (2H, m), 7.75 (1H, d, J = 8.1 Hz), 7.63 (2H, d, J = 7.3 Hz), 7.40 (2H, t, J = 7.3 Hz), 7.29–7.34 (1H, m), 6.98–7.18 (3H, m), 2.01 (3H, s); mp 176–178 °C; IR (ATR) ν 1456, 1325, 1265, 1203, 1180, 1130, 1059 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{16}Cl_3N_3$ $(M+H)^+$: 404.0716, found: 404.0718; HPLC; 97.8% (rt; 2.82 min). Compound **35b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.51 (0.5H, br s), 9.83 (0.5H, br s), 8.55–8.59 (0.4H, m), 8.30–8.39 (0.6H, m), 7.83–8.05 (1H, m), 7.70–7.77 (4H, m), 7.54–7.64 (2H, m), 7.35–7.48 (3H, m); mp 124–126 °C; IR (ATR) ν 1456, 1311, 1205, 1174, 1132, 1068 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{13}Cl_2N_3F_3$ $(M+H)^+$: 458.0433, found: 458.0436; HPLC; 98.7% (rt; 2.90 min). Compound **35c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20–8.25 (2H, m), 7.74 (2H, d, J = 8.1 Hz), 7.58 (2H, d, J = 7.3 Hz), 7.27–7.45 (5H, m); mp 168–170 °C; IR (ATR) ν 1269, 1203, 1068 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{13}Cl_2N_4O_2$ $(M+H)^+$: 435.0410, found: 435.0387; HPLC; 97.8% (rt; 2.68 min).

5.1.24. 2-(2-Chloro-6-methylphenyl)-7-phenylimidazo[4,5-*c*]quinolin-4(5*H*)-one (36), 2-(2-chloro-6-(trifluoromethyl)phenyl)-7-phenylimidazo[4,5-*c*]quinolin-4(5*H*)-one (37), 2-(2-chloro-6-nitrophenyl)-7-phenylimidazo[4,5-*c*]quinolin-4(5*H*)-one (38), and 2-(2-chloro-6-fluorophenyl)-7-phenylimidazo[4,5-*c*]quinolin-4(5*H*)-one (39)

The title compounds **36**–**39** were synthesized from **35a**–**35d** in 91%, 91%, 90%, and 93% yield according to the procedure to prepare **2**, respectively. Compound **36**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.84 (1H, br s), 11.87 (0.5H, br s), 11.70 (0.5H, br s), 8.21 (0.6H, d, J = 8.1 Hz), 8.10 (0.4H, d, J = 8.1 Hz), 7.75–7.79 (3H, m), 7.65 (1H, dd, J = 1.5, 8.1 Hz), 7.54–7.61 (4H, m), 7.45–7.51 (2H, m), 3.41 (3H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.9, 155.1, 149.2, 144.0, 140.5, 139.8, 136.9, 133.6, 131.1, 130.3, 129.2, 128.7, 127.8, 126.8, 122.3, 122.1, 120.9, 115.4, 113.9, 110.6, 19.9; mp 281–283 °C; IR (ATR) ν 3012, 1653, 1624, 1417, 1379, 1327, 1273, 1178, 1163 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{17}ClN_3O$ $(M+H)^+$: 386.1055, found: 386.1055; HPLC; 98.1% (rt; 2.13 min). Compound **37**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.09 (0.5H, br s), 14.05 (0.5H, br s), 11.94 (0.6H, br s), 11.76 (0.4H, br s), 8.02–8.21 (3H, m), 7.89–7.98 (1H, m), 7.75–7.81 (3H, m), 7.65–7.68 (1H, m), 7.56–7.62 (2H, m), 7.45–7.51 (1H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.8, 155.1, 146.3, 143.9, 139.9, 139.8, 137.0, 136.1, 135.3, 133.6, 132.4, 131.2, 129.2, 128.4 (q, $^2J_{C-F}$ = 55.5 Hz), 127.9, 126.8, 125.3 (q, $^3J_{C-F}$ = 5.6 Hz), 124.8, 122.9 (q, $^1J_{C-F}$ = 276.2 Hz), 122.3, 121.1, 115.3, 113.9, 110.6; mp 218–220 °C; IR (ATR) ν 3032, 1653, 1387, 1311, 1205, 1176, 1134, 1076 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{14}ClF_3N_3O$ $(M+H)^+$: 440.0772, found: 440.0772; HPLC; 98.9% (rt; 2.27 min). Compound **38**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.05 (1H, br s), 11.66 (1H, br s), 8.13 (1H, d, J = 8.1 Hz), 8.03 (1H, d, J = 8.1 Hz), 7.98 (1H, d, J = 8.1 Hz), 7.81 (1H, t, J = 8.4 Hz), 7.63–7.65 (2H, m), 7.61 (1H, s), 7.51 (1H, d, J = 8.1 Hz), 7.42–7.47 (2H, m), 7.31–7.36 (1H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.0, 150.5, 144.3, 140.1, 139.6, 137.0, 135.4, 134.7, 132.8, 129.2, 127.9, 126.8, 124.8, 123.6, 122.3, 121.0, 113.9, 113.4; mp 205–207 °C; IR (ATR) ν 3000, 1653, 1541, 1375, 1340, 1169, 1103 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{14}ClF_3N_4O_3$ $(M+H)^+$: 417.0749, found: 417.0749; HPLC; 100% (rt; 2.09 min). Compound **39**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.06 (0.5H, br s), 13.98 (0.5H, br s), 11.84 (0.6H, br s), 11.66

(0.4H, br s), 8.02–8.18 (1H, m), 7.63–7.73 (4H, m), 7.57–7.61 (2H, m), 7.48–7.54 (3H, m), 7.38–7.43 (1H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.8 (d, $^{1}J_{C-F}$ = 248.0 Hz), 157.7, 155.1, 144.1, 141.2, 139.9, 139.7, 137.0, 134.5 (d, $^{4}J_{C-F}$ = 3.7 Hz), 132.5 (d, $^{3}J_{C-F}$ = 9.9 Hz), 129.2, 127.9, 126.8, 125.9, 122.3, 121.0, 119.1 (d, $^{2}J_{C-F}$ = 18.5 Hz), 115.0 (d, $^{2}J_{C-F}$ = 21.6 Hz), 113.9, 110.2; mp 329–331 °C; IR (ATR) ν 3003, 1653, 1624, 1452, 1425, 1387, 1325, 1252, 1182, 1163 cm^{-1}; HRMS (ESI+) m/z calcd for $C_{22}H_{14}ClFN_3O$ $(M+H)^+$: 390.0804, found: 390.0804; Anal. Calcd for $C_{22}H_{13}ClFN_3O\cdot0.25H_2O$; C, 67.01; H, 3.45; N, 10.66. Found: C, 66.89; H, 3.38; N, 10.67.

5.2. Biological assay

5.2.1. mPGES-1 inhibition assay

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 rt 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 rt 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.[16]

5.2.2. Inhibition assay of IL-1α-induced PGE_2 production, COX-1, COX-2, TXS, and LTC4S

These assays were performed by Eurofins Panlabs, Inc.

5.3. In vitro pharmacokinetic study

5.3.1. Measurement of metabolic stability (MS)

The metabolic stability (MS) was evaluated as a remaining rate (%) by the incubation of the test compound with hepatic microsomes (Xenotech LLC) and nicotinamide adenine dinucleotide phosphate (NADPH) for 30 min at 37 °C. The value was determined by quantitating the remaining substrate using LC/MS/MS. The initial concentration of each compound was 1.0 μM.

5.3.2. CYP inhibition assay

CYP inhibition was evaluated after incubation for 10 min with the test compound and human liver microsomes (Xenotech LLC) and NADPH. As a positive control, Diclofenac, (*S*)-Mephenytoin, Bufuralol and Midazolam were used. The IC_{50} values were determined by quantitating the each metabolite using LC/MS/MS.

5.3.3. Parallel artificial membrane permeability assay (PAMPA)

PAMPA was evaluated by measuring the distribution of the compound after incubation with donor plate (System Solution Concentrate, pION Inc., pH: 5.0 and 7.4) and acceptor plate (Acceptor Sink Buffer, pION Inc.) for 4 h. The distribution was determined by measuring the ultraviolet absorption and the corresponding permeability coefficients were calculated using published method.[11]

5.4. In vivo rat pharmacokinetic study

Test compound (1 mg/kg, dissolved in 5% glucose/0.1 M HCl = 9/1) was dosed intravenously to the fasted male rats (n = 3). Test compound (10 mg/kg, suspended in 0.5% methyl cellulose solution) was dosed orally to the fasted male rats (n = 3). After dosing, blood samples (250 μL) were collected from the jugular vein using a heparinized syringe at the selected time points (iv: pre-dosing, 5, 15, 30 min, 1, 2, 4, 6, 24 h; po: 15 and 30 min, 1, 2, 4, 6, and 24 h, respectively). The blood samples were ice-chilled and then centrifuged at 12,000 rpm for 2 min at rt to obtain plasma, which was preserved at −70 °C in a freezer. The AUC, C_{max}, V_{dss}, and CL were obtained by measuring the time course of the plasma concentration of the test compound. BA was calculated according to the following equation:

$$\mathrm{BA}\ (\%) = (\mathrm{AUC_{po}}/D_{po})/(\mathrm{AUC_{iv}}/D_{iv}) \times 100$$

where AUC_{po}: AUC after oral dosing; AUC_{iv}: AUC after intravenous dosing; D_{po}; dosage of oral administration; D_{iv}; dosage of intravenous administration.

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