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Design and synthesis of novel benzimidazole derivatives as phosphodiesterase 10A inhibitors with reduced CYP1A2 inhibition

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ABSTRACT

A novel class of phosphodiesterase 10A (PDE10A) inhibitors with reduced CYP1A2 inhibition were designed and synthesized starting from 2-{[(1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline (**1**). Introduction of an isopropyl group at the 2-position and a methoxy group at the 5-position of the benzimidazole ring of lead compound **1** resulted in the identification of 2-{[(2-isopropyl-5-methoxy-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline (**25b**), which exhibited potent PDE10A inhibitory activity with reduced CYP1A2 inhibitory activity compared to compound **1**.

1. Introduction

Schizophrenia is a chronic and devastating psychiatric disorder that is estimated to affect approximately 1% of the world's population.[1] Current antipsychotic drugs are effective in treating positive symptoms of schizophrenia such as hallucination and delusion, but have a only limited efficacy on negative symptoms such as social withdrawal, and cognitive impairments. In addition, these existing antipsychotics frequently induce adverse effects such as extrapyramidal syndrome, weight gain, diabetes and QT prolongation,[2] highlighting the unmet medical needs for drugs less prone to such side effects.

Cyclic nucleotide phosphodiesterases (PDEs) are enzymes that regulate intracellular signaling by hydrolyzing cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). The PDE superfamily of enzymes is classified into 11 families, namely PDE1–PDE11, in mammals. PDE10A enzyme is a dual substrate (cAMP/cGMP) phosphodiesterase that is highly expressed in the brain, particularly in the medium spiny neurons of the mammalian striatum.[3] Inhibition of PDE10A may enhance the intracellular second messenger signaling and striatal output suggested to be impaired in the schizophrenic patients.[4] Furthermore, papaverine and MP-10 (Fig. 1) which were reported as potent selective PDE10A inhibitors, showed potent efficacies in several rodent behavioral models of psychiatric disorders.[5] Especially a couple of literatures suggested that these PDE10A inhibitors also have pharmacological effects in animal models of cognitive deficits and negative symptoms in schizophrenia.[5d,e] Thus, PDE10A inhibitors have gathered attention as a new therapeutic approach for the treatment of schizophrenia.[6]

Our high-throughput screening approach identified new benzimidazole analog **1** (Fig. 1) as a PDE10A inhibitor with an IC_{50} value of 309 nM, but this lead compound **1** also had potent inhibitory activity against human cytochrome P450 1A2 (CYP1A2). Since CYP1A2 metabolizes some clinically used drugs such as theophylline,[7] propranolol,[8] and clozapine,[9] the inhibition of CYP1A2 can cause unfavorable drug-drug metabolizing interaction.

Before the modification of lead compound **1**, we focused our attention on the structural similarity between MP-10 and compound **1**. That is, both MP-10 and our lead compound **1** contain the quinolin-2-ylmethoxy unit, and the quinoline ring in MP-10 was reported to occupy the PDE10A selectivity pocket and form a hydrogen bond to Tyr693 of PDE10A enzyme.[5e] Therefore, we attempted to modify the 1-phenyl-benzimidazol moiety of compound **1** to increase PDE10A inhibitory activity and avoid CYP1A2 inhibition on the assumption that the quinoline ring of compound **1** occupied the selectivity pocket of PDE10A, as in the case of MP-10.

In this paper, we report the synthesis and the successful development of novel PDE10A inhibitors with reduced CYP1A2 inhibitory activity.

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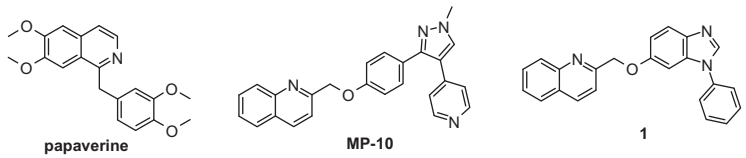


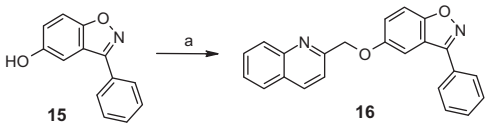
Figure 1. Structures of papaverine, MP-10, and compound **1**.

2. Chemistry

The synthesis of target compounds is shown in Schemes 1–6. The ipso-substitution reaction of reagent **2** with aniline followed by alkylation yielded compound **4**, which was converted to diamine **6** by reduction of the nitro group. Cyclization of diamine **6** with various orthoesters, carboxylic acids, acid chloride, carboxilic acid anhydride, or phosgene iminium chloride gave phenyl benzimidazole derivatives **1** and **7a–i**. 5-Fluoro-benzimidazole analogue **8** was also synthesized from 2,5-difluoro-4-nitrophenol **3** using a similar procedure (Scheme 1).

Scheme 2 shows the synthesis of indole and indazole derivatives **14a** and **14b**. Pd-catalyzed coupling between compound **9** and bromobenzene generated compound **10**, which after deprotection afforded intermediate **13a**. Hydroxyindazole derivative **13b** was synthesized via a cyclization reaction between benzaldehyde **11** and phenylhydrazine followed by the deprotection of methoxy group. Compounds **13a** and **13b** were reacted with 2-(chloromethyl)quinoline to give **14a** and **14b**, respectively. Benzoxazole analogue **16** was also synthesized in a similar manner from its precursor **15** as described in Scheme 3.[10]

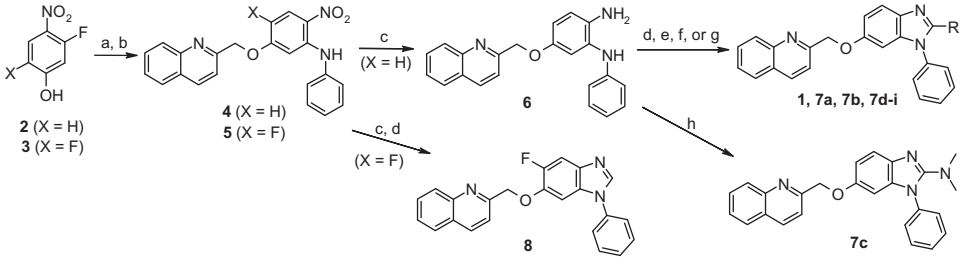
Azabenzimidazole analogue **21** was prepared in five steps as outlined in Scheme 4. Ipso-substitution of chloropyridine **17** with aniline gave compound **18**. Reduction of the nitro group followed by cyclization with orthoester yielded intermediate **19**. Deprotection of the methoxy group of **19** gave compound **20**, which was alkylated under Mitsunobu-type condition to afford compound **21**.



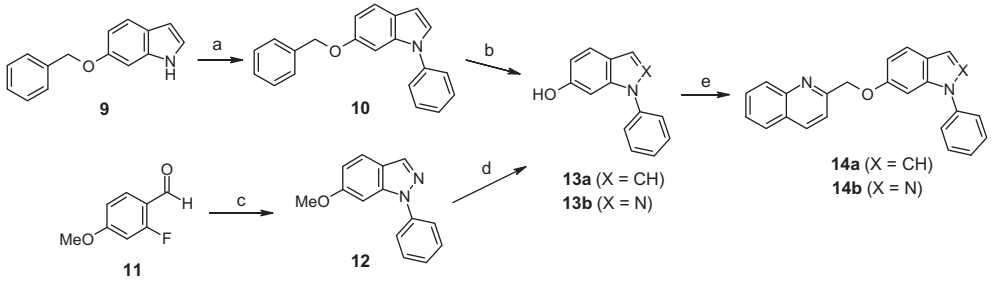
Scheme 3. Reagents and conditions: (a) 2-(chloromethyl)quinoline hydrochloride, KI, K_2CO_3, DMF.

5-Methoxybenzimidazole analogues **25a** and **25b** were prepared using the synthesis depicted in Scheme 5. Compound **22**[11] was converted to amine intermediate **23** using a Buchwald–Hartwig cross coupling reaction. Reduction of compound **23** followed by cyclization with orthoesters yielded benzimidazole derivatives **24a** and **24b**. Deprotection of the benzyl group and subsequent alkylation generated compounds **25a** and **25b**.

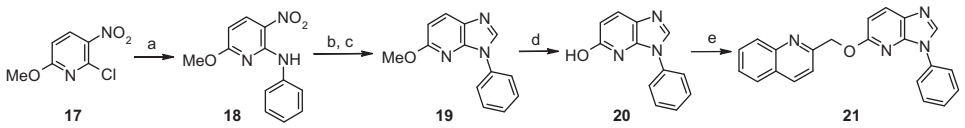
The synthesis of 1-substituted benzimidazole analogues **31a–i** and **32** are shown in Scheme 6. Phenol **26** was reacted with 2-(chloromethyl)quinoline to give compound **27**, which was converted to the intermediate **30** using Buchwald-Hartwig coupling or Ullmann coupling when the R group is an aromatic ring. Intermediate **30** with cyclohexyl ring or 4-pyridylmethyl group as the R group were prepared using an ipso-substitution reaction between amine and compound **29**, which was synthesized by the alkylation of phenol **28**. Reduction of the nitro group of compounds **30a–i** gave diamines, followed by cyclization with orthoformic acid methyl ester yielded benzimidazole analogues **31a–i**. Intermediate



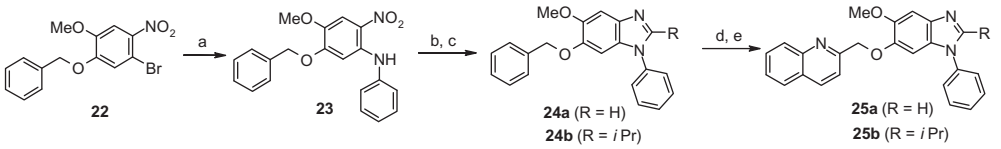
Scheme 1. Reagents and conditions: (a) aniline; (b) 2-(chloromethyl)quinoline hydrochloride, KI, K_2CO_3, DMF; (c) Fe, NH_4Cl, EtOH, H_2O; (d) $RC(OMe)_3$ or $RC(OEt)_3$, $TsOH{\cdot}H_2O$, THF; (e) RCOCl, pyridine, THF then AcOH; (f) RCO_2H, WSC·HCl, HOBt, DMF then AcOH; (g) $(RCO)_2O$, THF then AcOH; (h) phosgene iminium chloride, 1,2-dichloroethane.



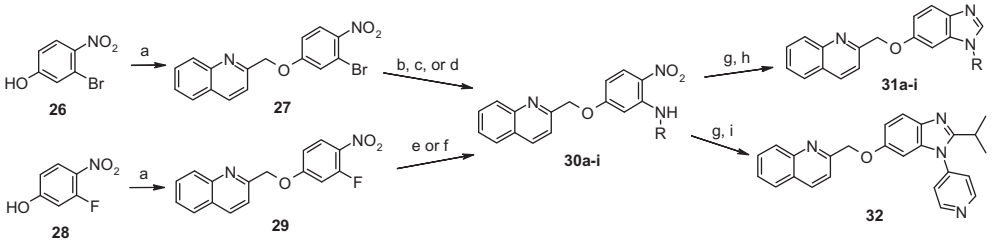
Scheme 2. Reagents and conditions: (a) bromobenzene, $Pd(OAc)_2$, Xphos, K_3PO_4, toluene; (b) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, H_2O, THF; (c) phenylhydrazine, Cs_2CO_3, NMP; (d) BBr_3, CH_2Cl_2; (e) 2-(chloromethyl)quinoline hydrochloride, K_2CO_3, KI, DMF.



Scheme 4. Reagents and conditions: (a) aniline, K_2CO_3, DMF; (b) $Pd(OH)_2/C$, H_2, EtOH–DMF; (c) $HC(OEt)_3$, $TsOH{\cdot}H_2O$, THF; (d) pyridine hydrochloride; (e) 2-quinolinylmethanol, ADDP, nBu$_3$P, THF.



Scheme 5. Reagents and conditions: (a) aniline, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene; (b) Fe, NH_4Cl, EtOH, H_2O; (c) $HC(OEt)_3$ or iPrCH(OMe)$_3$, $TsOH{\cdot}H_2O$, THF; (d) anisole, TFA; (e) 2-(chloromethyl)quinoline hydrochloride, Cs_2CO_3, KI, DMF.



Scheme 6. Reagents and conditions: (a) 2-(chloromethyl)quinoline hydrochloride, KI, K_2CO_3, DMF; (b) R-NH_2, $Pd_2(dba)_3$, BINAP, tBuONa, toluene; (c) R-NH_2, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, toluene or NMP; (d) R-NH_2, CuI, N,N'-dimethylethylenediamine, K_3PO_4, DMSO; (e) R-NH_2, K_2CO_3, DMF; (f) R-NH_2, DMF; (g) Fe, NH_4Cl, EtOH, H_2O; (h) $HC(OMe)_3$, $TsOH{\cdot}H_2O$, THF; (i) iPrC(OMe)$_3$, $TsOH{\cdot}H_2O$, THF.

30b was also converted to isopropyl benzimidazole analogue **32** using a similar procedure.

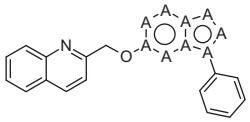
3. Results and discussion

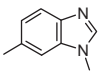
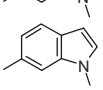
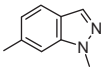
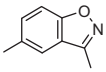
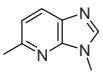
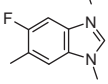
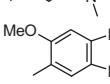
PDE10A inhibitory potencies of newly synthesized compounds were tested using in vitro inhibition of human recombinant PDE10A catalyzed cAMP hydrolysis. The lead compound **1** had moderate PDE10A inhibitory activity with an IC_{50} of 309 nM but displayed potent CYP1A2 inhibitory activity with an IC_{50} value of 0.38 μM.

To determine the optimal ring of the core heterocycle, the benzimidazole ring of compound **1** was replaced with other 5,6-membered hetroaromatic ring (Table 1). Indole, indazole and benzisoxazole analogues showed no PDE10A inhibitory activity up to 1000 nM concentration (**14a**, **14b**, and **16**), which suggested that the nitrogen atom at the 3-position of the benzimidazole ring is important for PDE10A inhibitory activity. Imidazopyridine analogue **21** had improved PDE10A inhibitory activity, although the CYP1A2 inhibition of **21** was extremely potent. The introduction of fluorine atom into the 5-position of the benzimidazole ring led to a slight decrease in activity (**8**), but the methoxy group at the 5-position contributed to a slight increase in PDE10A inhibitory activity with decreased CYP1A2 inhibition (**25a**).

We also optimized substituents at the 2-position of the benzimidazole ring of compound **1** (Table 2). Although the introduction of the electron-withdrawing trifluoromethyl group resulted in a loss of activity (**7a**), the electron-donating methoxymethyl and dimethylamino groups caused an increase in activity (**7b** and **7c**). When we added several alkyl groups to the structure, PDE10A inhibitory activities increased in order of steric bulkiness up to the size of the isopropyl group (**7d**–**g**). However, the introduction of bulkier substituents such as n-propyl or isobutyl groups led to a decrease in activity (**7h** and **7i**) compared with isopropyl analogue **7g**. The X-ray co-crystal structure of compound **7g** in the catalytic domain of PDE10A enzyme confirmed that the quinolinyl

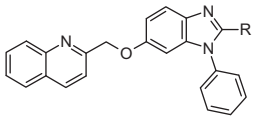
Table 1
PDE10A potency and CYP1A2 inhibition for core heterocycles



Compd	A	PDE10A IC_{50} (nM)	CYP1A2 IC_{50} (μM)
1		309	0.38
14a		>1000	NT[a]
14b		>1000	NT[a]
16		>1000	NT[a]
21		89	<0.31
8		494	NT[a]
25a		214	7.9

[a] Not tested.

Table 2
Effect of *C*-2 substituents on PDE10A potency and CYP1A2 inhibition



Compd	R	PDE10A IC_{50} (nM)	CYP1A2 IC_{50} (μM)
1	H	309	0.38
7a	CF_3	>1000	NT[a]
7b	CH_2OMe	166	5.1
7c	NMe_2	152	7.3
7d	Me	305	0.63
7e	Et	208	1.6
7f	Cyclopropyl	180	3.3
7g	Isopropyl	92	2.8
7h	*n*-Propyl	299	3.3
7i	Isobutyl	849	NT[a]

[a] Not tested.

nitrogen atom formed a hydrogen bond to Tyr693 of PDE10A enzyme as in the case with MP-10, and the isopropyl group was found to occupy a hydrophobic pocket in the catalytic domain of PDE10A (Fig 2). The benzimidazole ring of **7g** was sandwiched by Phe729 and Phe696, and it formed π–π stacking interaction with Phe729 and CH–π interaction with Phe696. In addition, the *N*-1 phenyl ring probably formed CH–π interaction with Ile692. As for the CYP1A2 inhibition of our compounds, any substituent at the 2-position was effective in reducing inhibition. We assumed that the substituents at the 2-position may directly block the interaction between the benzimidazole and CYP1A2 enzyme. We also assumed that the co-planer structure between the benzimidazole and the phenyl ring might cause the CYP1A2 inhibition,[12] therefore substituents at the 2-position increase the dihedral angle between the benzimidazole and the phenyl ring to attenuate CYP1A2 inhibition.

The influence of the phenyl ring on the 1-position of the benzimidazole ring of compound **1** was then investigated (Table 3). Nonaromatic cyclohexyl analogue **31a** lost PDE10A inhibitory activity. The replacement of the phenyl ring with 4-pyridyl ring resulted in a threefold increase in activity (**31b**), but the insertion of the methylene unit between the benzimidazole ring and 4-pyridyl moiety of compound **31b** was found to be detrimental to activity (**31c**; IC_{50} >1000 nM). We also examined other heteroaromatic rings. Although analogues including pyrazole (**31d** and **31e**), pyridazine (**31f**), and 2-pyrimidine (**31g**) had decreased activity,

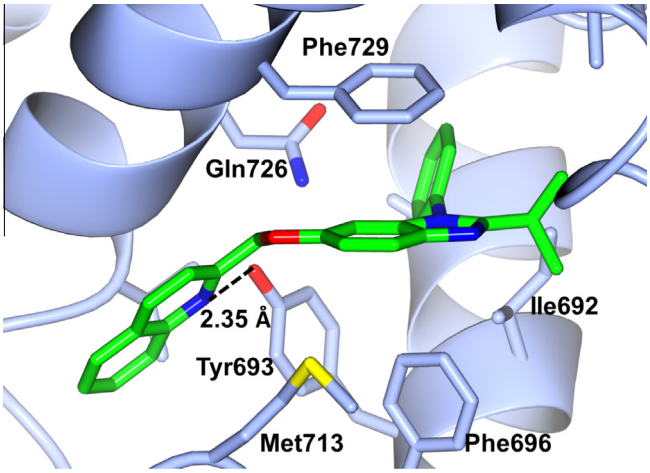
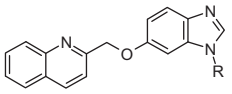


Figure 2. Crystal structure of **7g** (green) bound to the PDE10A (PDB code 3WI2).

4-pyrimidyl analogue **31h** had similar potency to 4-pyridyl analogue **31b**. The pyridyl nitrogen atom of **31b** and pyrimidyl *N*-1 nitrogen atom of **31h** may form a hydrogen bond to a water molecule inside the PDE10A catalytic site, as in the case with MP-10.[5e] Fortunately, the CYP1A2 inhibitory activities of **31b** and **31h** were twofold weaker than that of compound **1**. The thiazole derivative **31i** showed the most potent PDE10A inhibitory activity in Table 3, but also had extremely potent CYP1A2 inhibitory activity (IC_{50} <0.31 μM). The logarithm of the calculated partition coefficient between *n*-octanol and water (*C*log*P*) of compounds **31i**, **31b** and **31h** was 3.60, 1.92 and 1.87, respectively.[13] Thus, the higher *C*log*P* value of **31i** compared with those of **31b** and **31h** may contribute to the strong CYP1A2 inhibition.[14]

We successfully obtained compounds **25a**, **7g** and **31b**, which had increased PDE10A inhibitory activities with reduced CYP1A2 inhibition compared to lead compound **1**. We therefore decided to combine the methoxy group found in **25a** with the isopropyl group found in **7g**, which gave successful results regarding PDE10A inhibitory activity (**25b**, IC_{50} = 25 nM) and CYP1A2 inhibition (IC_{50} = 18 μM), as shown in Table 4. Compound **25b** had reduced CYP1A2 inhibitory activity, even compared with MP-10 that showed moderate CYP1A2 inhibitory activity in our assay (IC_{50} = 3.2 μM). We also combined the 4-pyridyl group found in **31b** with the isopropyl group found in **7g**. Unfortunately, PDE10A inhibitory activity of the combined compound **32** was reduced to one-sixth of that of compounds **31b** and **7g**, and was also weaker than even that of lead compound **1**. Although the reason for the reduced activity of **32** is unclear, the isopropyl group may cause the

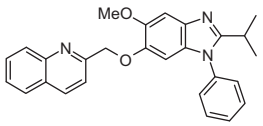
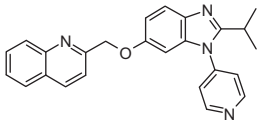
Table 3
Effect of *N*-1 substituents on PDE10A potency and CYP1A2 inhibition



Compd	R	PDE10A IC_{50} (nM)	CYP1A2 IC_{50} (μM)
1		309	0.38
31a		>1000	NT[a]
31b		99	0.80
31c		>1000	NT[a]
31d		774	NT[a]
31e		>1000	NT[a]
31f		>1000	NT[a]
31g		>1000	NT[a]
31h		72	0.70
31i		16	<0.31

[a] Not tested.

Table 4
Combination effect on PDE10A potency and CYP1A2 inhibition

Compd	Structure	PDE10A IC_{50} (nM)	CYP1A2 IC_{50} (μM)
25b		25	18
32		601	NT[a]

[a] Not tested.

pyridyl nitrogen atom to locate at an unsuitable position for a possible hydrogen bond to a water molecule inside the PDE10A catalytic domain.

We succeeded in finding novel benzimidazole derivatives such as **25b** with improved PDE10A inhibitory potency and reduced CYP1A2 inhibition. Further optimization and biological evaluation of benzimidazole analogues is being conducted at present.

4. Conclusions

Here, on the assumption that the quinoline ring of lead compound **1** occupied the selectivity pocket of PDE10A, the phenyl benzimidazole moiety of **1** was modified to increase PDE10A inhibitory activity and avoid CYP1A2 inhibition. Accordingly, the isopropyl group at the 2-position of the benzimidazole ring increased PDE10A inhibitory activity with reduced CYP1A2 inhibition, and the quinolinyl nitrogen atom of **7g** was found to form a hydrogen bond to Tyr693 of PDE10A enzyme, as in the case of MP-10. The methoxy group at the 5-position of the benzimidazole ring was also effective in increasing PDE10A inhibitory activity and avoiding CYP1A2 inhibition. The combination of the isopropyl group at the 2-position and the methoxy group at the 5-position resulted in success, and led to compound **25b** being a relatively potent PDE10A inhibitor with reduced CYP1A2 inhibition.

5. Experimental section

5.1. Chemistry

^{1}H NMR spectra were recorded on a Varian VNS-400, JEOL JNM-LA400, or JEOL JNM-AL400 and the chemical shifts were expressed in δ (ppm) values with trimethylsilane as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, dd = doublet of doublets, and br = broad peak). Mass spectra (MS) were recorded on Thermo Electron LCQ Advantage or Agilent 6140. Elemental analyses were performed using Yanaco MT-6 (C, H, N), Elementar Vario EL III (C, H, X), and Dionex ICS-3000 (S, halogene) and were within ±0.4% of theoretical values.

5.1.1. 2-Nitro-*N*-phenyl-5-(quinolin-2-ylmethoxy)aniline (4)

A mixture of 3-fluoro-4-nitrophenol (**2**, 10.0 g, 63.7 mmol) and aniline (17.0 mL, 187 mmol) was stirred at 140 °C for 3 h. After cooling at room temperature, the mixture was diluted with EtOAc and washed with 1 M hydrochloric acid. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was washed with hexane–EtOAc to give 3-anilino-4-nitrophenol (9.14 g, 62%) as a red solid. To a mixture of the above-obtained 3-anilino-4-nitrophenol and 2-(chloromethyl)quinoline hydrochloride (9.35 g, 43.7 mmol) in DMF (200 mL) were added K_2CO_3 (12.1 g, 87.3 mmol) and potassium iodide (659 mg, 3.97 mmol), and the mixture was stirred at 60 °C for 3 h. After cooling at room temperature, the mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was washed with hexane–EtOAc to give **4** (12.1 g, 82%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 5.38 (s, 2H), 6.61–6.65 (m, 2H), 7.11–7.23 (m, 5H), 7.56 (d, 1H, J = 8.5 Hz), 7.61–7.66 (m, 1H), 7.77–7,82 (m, 1H), 7.93 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 8.0 Hz), 8.12–8.16 (m, 1H), 8.40 (d, 1H, J = 8.5 Hz), 8.58 (s, 1H); MS (ESI) m/z 372 $[M+H]^+$.

5.1.2. 4-Fluoro-2-nitro-*N*-phenyl-5-(quinolin-2-ylmethoxy) aniline (5)

Compound **5** was prepared from 2,5-difluoro-4-nitrophenol (**3**) and aniline in a manner similar to that described for compound **4**, with a yield of 66% as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 2H), 6.69 (d, 1H, J = 7.4 Hz), 6.98–7.02 (m, 2H), 7.13–7.17 (m, 3H), 7.58–7.62 (m, 2H), 7.73–7.79 (m, 1H), 7.86 (d, 1H, J = 8.1 Hz), 7.95 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 11.4 Hz), 8.22 (d, 1H, J = 8.5 Hz), 9.65 (br s, 1H); MS (ESI) m/z 390 $[M+H]^+$.

5.1.3. N^2-Phenyl-4-(quinolin-2-ylmethoxy)benzene-1,2-diamine (6)

To a mixture of **4** (12.1 g, 32.6 mmol) and iron powder (9.10 g, 163 mmol) in EtOH (200 mL) and water (75 mL) was added NH_4Cl (871 mg, 16.3 mmol), and the mixture was refluxed for 3 h. After cooling at room temperature, the mixture was diluted with $CHCl_3$ and filtered through celite pad, and the filtrate was concentrated in vacuo. The residue was partitioned between water and EtOAc, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give **6** (10.9 g, 98%) as a brown solid. ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 2H), 5.28 (s, 2H), 5.30 (br s, 1H), 6.63–6.67 (m, 1H), 6.72–6.90 (m, 5H), 7.14–7.20 (m, 2H), 7.51–7.57 (m, 1H), 7.65 (d, 1H, J = 8.5 Hz), 7.69–7.75 (m, 1H), 7.80–7,84 (m, 1H), 8.05 (d, 1H, J = 8.3 Hz), 8.17 (d, 1H, J = 8.5 Hz); MS (APCI/ESI) m/z 342 $[M+H]^+$.

5.1.4. 2-{[(1-Phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline dihydrochloride (1)

To a solution of **6** (230 mg, 0.67 mmol) in THF (6 mL) were added triethyl orthoformate (0.25 mL, 1.50 mmol) and *p*-toluenesulfonic acid monohydrate (13 mg, 0.07 mmol), and the mixture was refluxed for 2 h. The mixture was then cooled at room temperature and concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate and $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (10–50% EtOAc in hexane) to give a brown oil, which was dissolved in $CHCl_3$ (5 mL) and 4 M HCl/EtOAc (0.43 mL, 1.72 mmol) was added to the solution. The mixture was concentrated in vacuo, and the residue was washed with diisopropylether to give **1** (239 mg, 84%) as a pale pink solid. ^{1}H

NMR (DMSO-d_6) δ 5.61 (s, 2H), 7.42–7.45 (m, 2H), 7.66–7.79 (m, 6H), 7.86 (d, 1H, J = 8.5 Hz), 7.88–7.93 (m, 2H), 8.09–8.16 (m, 2H), 8,64 (d, 1H, J = 8.5 Hz), 9.76 (s, 1H); MS (ESI) m/z 352 $[M+H]^+$; Anal. Calcd for $C_{23}H_{17}N_3O{\cdot}2HCl{\cdot}3.0H_2O$: C, 57.75; H, 5.27; N, 8.78; F, 14.82. Found: C, 58.03; H, 5.24; N, 8.78; F, 14.56.

5.1.5. 2-{[(2-Methyl-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl} quinoline dihydrochloride (7d)

Compound **7d** was prepared from **6** and triethyl orthoacetate in a manner similar to that described for compound **1**, with a yield of 55% as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 2.64 (s, 3H), 5.51 (s, 2H), 7.06 (d, 1H, J = 2.2 Hz), 7.38 (dd, 1H, J = 9.1, 2.3 Hz), 7.64–7.76 (m, 6H), 7.79 (d, 1H, J = 8.6 Hz), 7.84 (d, 1H, J = 8.6 Hz), 7.86–7.92 (m, 1H), 8.07 (dd, 2H, J = 8.7, 8.7 Hz), 8.58 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 366 $[M+H]^+$; Anal. Calcd for $C_{24}H_{19}N_3O{\cdot}2HCl{\cdot}3.9H_2O$: C, 56.68; H, 5.71; N, 8.26; F, 13.94. Found: C, 56.81; H, 5.60; N, 8.20; F, 13.81.

5.1.6. 2-{[(2-Ethyl-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl} quinoline dihydrochloride (7e)

Compound **7e** was prepared from **6** and triethyl orthopropionate in a manner similar to that described for compound **1**, with a yield of 47% as a pale pink solid. ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3H, J = 7.5 Hz), 2.94 (q, 2H, J = 7.5 Hz), 5.49 (s, 2H), 7.02 (d, 1H, J = 2.3 Hz), 7.39 (dd, 1H, J = 9.0, 2.3 Hz), 7.64–7.80 (m, 7H), 7.83–7.91 (m, 2H), 8.02–8.09 (m, 2H), 8.56 (d, 1H, J = 8.5 Hz); MS (ESI+) m/z 380 $[M+H]^+$; Anal. Calcd for $C_{25}H_{21}N_3O{\cdot}2HCl{\cdot}1.7H_2O$: C, 62.17; H, 5.51; N, 8.70; F, 14.68. Found: C, 62.33; H, 5.49; N, 8.57; F, 14.58.

5.1.7. 2-{[(2-Isopropyl-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl} quinoline dihydrochloride (7g)

Compound **7g** was prepared from **6** and trimethyl orthoisobutyrate in a manner similar to that described for compound **1**, with a yield of 81% as a pale orange solid. ^{1}H NMR (DMSO-d_6) δ 1.37 (d, 6H, J = 6.9 Hz), 3.06–3.18 (m, 1H), 5.48 (s, 2H), 6.98 (s, 1H), 7.40 (d, 1H, J = 9.0 Hz), 7.67–7.80 (m, 7H), 7.83–7.90 (m, 2H), 8.00–8.08 (m, 2H), 8.55 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 394 $[M+H]^+$; Anal. Calcd for $C_{26}H_{23}N_3O{\cdot}2HCl{\cdot}1.1H_2O{\cdot}0.1CHCl_3$: C, 62.93; H, 5.52; N, 8.44; Cl, 16.74. Found: C, 62.85; H, 5.58; N, 8.36; Cl 16.45.

5.1.8. 2-({[1-Phenyl-2-(trifluoromethyl)-1*H*-benzimidazol-6-yl] oxy}methyl)quinoline hydrochloride (7a)

To a solution of **6** (101 mg, 0.30 mmol) in THF (3 mL) cooled with ice-water bath was added trifluoroacetic anhydride (60 μL, 0.43 mmol), and the mixture was stirred at room temperature for 30 min. The mixture was concentrated in vacuo, and the residue was dissolved in acetic acid (3 mL) and stirred at 90 °C for 6 h. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between EtOAc and saturated aqueous sodium bicarbonate, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0–30% EtOAc in $CHCl_3$) to give a yellow solid, which was then dissolved in $CHCl_3$ (5 mL), and 4 M HCl/EtOAc (0.29 mL, 1.16 mmol) was added to the solution. The mixture was concentrated to give **7a** (29 mg, 22%) as a orange solid. ^{1}H NMR (DMSO-d_6) δ 5.41 (s, 2H), 6.83 (d, 1H, J = 2.1 Hz), 7.23 (dd, 1H, J = 8.9, 2.2 Hz), 7.52 (d, 2H, J = 7.0 Hz), 7.60–7.70 (m, 4H), 7.75 (d, 1H, J = 8.5 Hz), 7.82–7.88 (m, 2H), 7.99 (d, 1H, J = 8.5 Hz), 8.04 (d, 1H, J = 8.2 Hz), 8.51 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 420 $[M+H]^+$; Anal. Calcd for $C_{24}H_{16}F_3N_3O{\cdot}HCl{\cdot}0.6C_4H_8O_2{\cdot}0.05CHCl_3$: C, 61.72; H, 4.28; N, 8.16; Cl, 7.92; F, 11.07. Found: C, 61.52; H, 3.98; N, 8.04; Cl, 8.14; F, 10.69.

5.1.9. 2-({[2-(Methoxymethyl)-1-phenyl-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline dihydrochloride (7b)

To a solution of **6** (341 mg, 1.00 mmol) and methoxyacetic acid (90 μL, 1.20 mmol) in DMF (15 mL) were added 1H-benzotriazol-1-ol (135 mg, 1.00 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (230 mg, 1.20 mmol), and the mixture was stirred at room temperature for 17 h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in acetic acid (10 mL) and refluxed for 1 h before cooling at room temperature. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and saturated aqueous sodium bicarbonate. The organic layer was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give the free form of the title compound, which was then dissolved in EtOH (10 mL), and 4 M HCl/EtOAc (1.00 mL, 4.00 mmol) was added to the mixture. The mixture was concentrated in vacuo, and the residue was recrystalized from EtOH–Et_2O to give **7b** (288 mg, 62%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 3.34 (s, 3H), 4.70 (s, 2H), 5.46 (s, 2H), 7.05 (d, 1H, J = 2.1 Hz), 7.33 (dd, 1H, J = 9.0, 2.3 Hz), 7.59–7.71 (m, 6H), 7.75 (d, 1H, J = 8.6 Hz), 7.80 (d, 1H, J = 8.9 Hz), 7.82–7.88 (m, 1H), 7.99 (d, 1H, J = 8.4 Hz), 8.04 (d, 1H, J = 8.9 Hz), 8.51 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 396 $[M+H]^+$; Anal. Calcd for $C_{25}H_{21}N_3O_2{\cdot}2HCl{\cdot}0.5H_2O$: C, 62.90; H, 5.07; N, 8.80; Cl, 14.85. Found: C, 62.80; H, 5.08; N, 8.85; Cl, 14.73.

5.1.10. 2-{[(1-Phenyl-2-propyl-1*H*-benzimidazol-6-yl)oxy] methyl}quinoline dihydrochloride (7h)

Compound **7h** was prepared from **6** and butyric acid in a manner similar to that described for compound **7b**, with a yield of 49% as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 0.87 (t, 3H, J = 7.4 Hz), 1.66–1.76 (2H, m), 2.89 (t, 2H, J = 7.6 Hz), 5.43 (s, 2H), 7.02 (d, 1H, J = 2.2 Hz), 7.36 (dd, 1H, J = 9.0, 2.3 Hz), 7.62–7.77 (m, 7H), 7.80–7.86 (m, 2H), 7.94 (d, 1H, J = 8.4 Hz), 8.01 (d, 1H, J = 7.9 Hz), 8.45 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 394 $[M+H]^+$; Anal. Calcd for $C_{26}H_{23}N_3O{\cdot}2HCl{\cdot}0.4H_2O$: C, 65.94; H, 5.49; N, 8.87; Cl, 14.97. Found: C, 66.04; H, 5.43; N, 8.91; Cl, 14.96.

5.1.11. 2-{[(2-Isobutyl-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl} quinoline dihydrochloride (7i)

Compound **7i** was prepared from **6** and 3-methylbutanoic acid in a manner similar to that described for compound **7b**, with a yield of 31% as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 0.84 (d, 6H, J = 6.7 Hz), 1.98–2.10 (m, 1H), 2.86 (d, 2H, J = 7.3 Hz), 5,47 (s, 2H), 7.03 (d, 1H, J = 2.2 Hz), 7.39 (dd, 1H, J = 9.0, 2.3 Hz), 7.66–7.79 (m, 7H), 7.83–7.89 (m, 2H), 8.00 (d, 1H, J = 8.5 Hz), 8.05 (d, 1H, J = 8.0 Hz), 8.54 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 408 $[M+H]^+$; Anal. Calcd for $C_{27}H_{25}N_3O{\cdot}1.9HCl{\cdot}0.6H_2O$: C, 66.51; H, 5.81; N, 8.62; Cl, 13.81. Found: C, 66.67; H, 5.69; N, 8.69; Cl, 13.53.

5.1.12. 2-{[(2-Cyclopropyl-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline dihydrochloride (7f)

To a solution of **6** (100 mg, 0.29 mmol) and pyridine (35 μL, 0.43 mmol) in THF (3 mL) cooled with ice-water bath was added cyclopropanecarbonyl chloride (30 μL, 0.33 mmol), and the mixture was stirred at room temperature for 30 min. The mixture was concentrated in vacuo, and the residue was dissolved in acetic acid (3 mL) and stirred at 90 °C for 18 h. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between EtOAc and saturated aqueous sodium bicarbonate, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (10–60% EtOAc in hexane) to give an oil, which was then dissolved in $CHCl_3$ (3 mL),

and 4 M HCl/EtOAc (0.29 mL, 1.16 mmol) was added to the mixture. The mixture was concentrated to give **7f** (26 mg, 19%) as a pale orange solid. ^{1}H NMR (DMSO-d_6) δ 1.19–1.26 (m, 2H), 1.43–1.49 (m, 2H), 1.98–2.06 (m, 1H), 5.46 (s, 2H), 7.01 (d, 1H, J = 2.2 Hz), 7.34 (dd, 1H, J = 9.0, 2.3 Hz), 7.65–7.77 (m, 8H), 7.82–7.88 (m, 1H), 8.00 (d, 1H, J = 8.5 Hz), 8.04 (d, 1H, J = 8.0 Hz), 8.51 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 392 $[M+H]^+$; Anal. Calcd for $C_{26}H_{21}N_3O{\cdot}2HCl{\cdot}3.0H_2O{\cdot}0.2C_4H_8O_2$: C, 60.05; H, 5.75; N, 7.84; Cl, 13.23. Found: C, 60.24; H, 5.78; N, 7.73; Cl, 13.01.

5.1.13. *N,N*-Dimethyl-1-phenyl-6-(quinolin-2-ylmethoxy)-1*H*-benzimidazol-2-amine dihydrochloride (7c)

To a solution of **6** (512 mg, 1.50 mmol) in 1,2-dichloroethane (10 mL) was added phosgene iminium chloride (366 mg, 2.25 mmol), and the mixture was stirred at 50 °C for 5 h. After cooling at room temperature, the mixture was partitioned between $CHCl_3$ and saturated aqueous sodium bicarbonate. The organic layer was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give the free form of the title compound, which was then dissolved in $CHCl_3$ (10 mL), and 4 M HCl/EtOAc (2.0 mL, 8.0 mmol) was added to the mixture. The mixture was concentrated in vacuo to give **7c** (488 mg, 70%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 2.93 (s, 6H), 5.37 (s, 2H), 6.66 (d, 1H, J = 2.3 Hz), 7.11 (dd, 1H, J = 8.7, 2.4 Hz), 7.47 (d, 1H, J = 8.8 Hz), 7.63–7.72 (m, 7H), 7.81–7.87 (m, 1H), 7.97–8.04 (m, 2H), 8.47 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 395 $[M+H]^+$; Anal. Calcd for $C_{25}H_{22}N_4O{\cdot}2HCl{\cdot}4.0H_2O$: C, 55.66; H, 5.98; N, 10.39; Cl, 13.14. Found: C, 55.68; H, 6.10; N, 10.10; Cl, 13.19.

5.1.14. 2-{[(5-Fluoro-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline dihydrochloride (8)

To a suspension of **5** (835 mg, 2.14 mmol) and NH_4Cl (57 mg, 1.07 mmol) in EtOH (15 mL) and water (4.5 mL) was added iron powder (599 mg, 10.7 mmol), and the mixture was refluxed for 1 h. After cooling at room temperature, the mixture was diluted with $CHCl_3$ and water, and then filtered through celite pad. The organic layer of the filtrate was dried over Na_2SO_4, filtered and concentrated in vacuo to give a brown syrup (790 mg). To a solution of the above-obtained brown syrup (300 mg) in THF (6 mL) were added triethyl *ortho*formate (0.35 mL, 2.08 mmol) and *p*-toluenesulfonic acid monohydrate (16 mg, 0.08 mmol), and the mixture was refluxed for 3 h. The mixture was cooled at room temperature and concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give a solid, which was suspended in EtOH (10 mL), and the mixture was treated with 4 M HCl/EtOAc (0.50 mL, 2.00 mmol). The precipitate was collected by filtration and washed with diethylether to give **8** (189 mg, 51%) as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ 5.67 (s, 2H), 7.51–7.68 (m, 5H), 7.73–7.82 (m, 3H), 7.93–8.00 (m, 2H), 8.18 (d, 1H, J = 8.3 Hz), 8.27 (d, 1H, J = 8.6 Hz), 8.80 (d, 1H, J = 8.6 Hz), 9.19 (s, 1H); MS (ESI+) m/z 370 $[M+H]^+$; Anal. Calcd for $C_{23}H_{16}FN_3O{\cdot}2HCl{\cdot}0.5H_2O$: C, 61.21; H, 4.24; N, 9.31; Cl, 15.71; F, 4.21. Found: C, 61.11; H, 4.27; N, 9.36; Cl, 15.69; F, 4.28.

5.1.15. 6-(Benzyloxy)-1-phenyl-1*H*-indole (10)

To a mixture of 6-(benzyloxy)-1*H*-indole (**9**, 2.23 g, 10.0 mmol), bromobenzene (1.88 g, 12.0 mmol), palladium(II) acetate (47 mg, 0.21 mmol) and 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl (Xphos, 239 mg, 0.50 mmol) in toluene (27 mL) was added K_3PO_4 (3.19 g, 15.0 mmol), and the mixture was stirred at 100 °C for 16 h under argon atmosphere. After cooling at room temperature, the mixture was diluted with EtOAc and washed with saturated aqueous sodium bicarbonate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give **10** (1.83 g, 61%) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 5.11 (s, 2H), 6.61 (d, 1H, J = 3.2 Hz), 6.87 (dd, 1H, J = 8.6, 2.3 Hz), 7.12 (d, 1H, J = 2.2 Hz), 7.29–7.47 (m, 6H), 7.49 (d, 1H, J = 3.2 Hz), 7.51–7.61 (m, 5H); MS (ESI) m/z 300 $[M+H]^+$.

5.1.16. 1-Phenyl-1*H*-indol-6-ol (13a)

To a mixture of **10** (1.83 g, 6.11 mmol) and ammonium formate (3.86 g, 61.1 mmol) in water (10 mL), MeOH (30 mL) and THF (30 mL) was added 20% $Pd(OH)_2$ on carbon (429 mg), and the mixture was refluxed for 3 h. After cooling at room temperature, the mixture was filtered through celite pad, and concentrated in vacuo. The residue was partitioned between EtOAc and water, and the organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (10–50% EtOAc in hexane) to give **13a** (1.28 g, quant) as a pale green oil. ^{1}H NMR (DMSO-d_6) δ 6.55 (d, 1H, J = 3.3 Hz), 6.65 (dd, 1H, J = 8.5, 2.1 Hz), 6.93 (d, 1H, J = 1.8 Hz), 7.35–7.43 (m, 3H), 7.52–7.59 (m, 4H), 9.09 (br s, 1H); MS (EI) m/z 209 $[M]^+$.

5.1.17. 6-Methoxy-1-phenyl-1*H*-indazole (12)

To a solution of 2-fluoro-4-methoxybenzaldehyde (**11**, 2.31 g, 15.0 mmol) in DMF (60 mL) were added phenylhydrazine (1.62 g, 15.0 mmol) and Cs_2CO_3 (9.77 g, 30.0 mmol), and the mixture was stirred at 150 °C for 3 h. After cooling at room temperature, the mixture was diluted with EtOAc, washed with saturated aqueous sodium bicarbonate and brine, and concentrated in vacuo. The residue was purified by silica gel column chromatography (5 to 20% EtOAc in hexane) to give **12** (640 mg, 19%) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 6.90 (dd, 1H, J = 8.8, 1.9 Hz), 7.18 (s, 1H), 7.40 (t, 1H, J = 7.4 Hz), 7.57–7.64 (m, 2H), 7.73–7.81 (m, 3H), 8.24 (s, 1H); MS (ESI) m/z 225 $[M+H]^+$.

5.1.18. 1-Phenyl-1*H*-indazol-6-ol (13b)

To a solution of **12** (1.36 g, 6.06 mmol) in CH_2Cl_2 (50 mL) cooled with ice-water bath was slowly added 1 M BBr_3 solution in CH_2Cl_2 (18.3 mL, 18.3 mmol), and the mixture was stirred at room temperature for 16 h. To the resultant mixture cooled with ice-water bath was slowly added saturated aqueous sodium bicarbonate and the mixture was extracted with $CHCl_3$. The organic layer was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0–10% MeOH in $CHCl_3$) to give **13b** (1.27 g, quant) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 6.78 (dd, 1H, J = 8.7, 1.7 Hz), 7.09 (s, 1H), 7.38 (t, 1H, J = 7.4 Hz), 7.58 (dd, 2H, J = 7.8, 7.8 Hz), 7.65–7.72 (m, 3H), 8.17 (s, 1H), 9.82 (s, 1H); MS (ESI) m/z 211 $[M+H]^+$.

5.1.19. 2-{[(3-Phenyl-1,2-benzoxazol-5-yl)oxy]methyl} quinoline hydrochloride (16)

To a mixture of 3-phenyl-1,2-benzoxazol-5-ol[10] (**15**, 140 mg, 0.66 mmol) and 2-(chloromethyl)quinoline hydrochloride (142 mg, 0.66 mmol) in DMF (5 mL) were added K_2CO_3 (202 mg, 1.46 mmol) and potassium iodide (110 mg, 0.66 mmol), and the mixture was stirred at 80 °C for 6 h. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$) to give a beige solid, which was dissolved in MeOH (5 mL) and 4 M HCl/EtOAc (0.25 mL, 1.00 mmol) was added to the solution. The mixture was concentrated in vacuo, and the residue was washed with 2-propanol to give **16** (98 mg, 38%) as a beige solid. ^{1}H NMR (DMSO-d_6) δ 5.59 (s, 2H), 7.21 (dd, 1H, J = 8.9, 2.5 Hz), 7.53 (d, 1H, J = 2.5 Hz), 7.58–7.66 (m, 3H), 7.71–7.77 (m, 2H), 7.87–7.95 (m, 2H), 8.11–8.23 (m, 4H), 8.68 (d, 1H, J = 8.6 Hz); MS (ESI) m/z 353 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}N_2O_2{\cdot}HCl{\cdot}0.2H_2O$: C,

70.39; H, 4.47; N, 7.14; Cl, 9.03. Found: C, 70.39; H, 4.58; N, 7.05; Cl, 9.07.

5.1.20. 2-{[(1-Phenyl-1*H*-indazol-6-yl)oxy]methyl}quinoline hydrochloride (14b)

Compound **14b** was prepared from **13b** in a manner similar to that described for compound **16**, with a yield of 23% as a brown solid. ^{1}H NMR (DMSO-d_6) δ 5.58 (s, 2H), 7.08 (dd, 1H, J = 8.7, 2.0 Hz), 7.38–7.42 (m, 2H), 7.55 (dd, 2H, J = 7.9, 7.9 Hz), 7.66–7.72 (m, 3H), 7.78–7.91 (m, 3H), 8.08 (d, 1H, J = 8.2 Hz), 8.13 (d, 1H, J = 8.5 Hz), 8.25 (s, 1H), 8.58 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 352 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}N_3O{\cdot}HCl{\cdot}0.1H_2O$: C, 70.89; H, 4.71; N, 10.78; Cl, 9.10. Found: C, 70.82; H, 4.68; N, 10.61; Cl, 8.90.

5.1.21. 6-Methoxy-3-nitro-*N*-phenylpyridin-2-amine (18)

To a mixture of 2-chloro-6-methoxy-3-nitropyridine (**17**, 10.0 g, 53.0 mmol) and aniline (7.25 mL, 79.6 mmol) in DMF (200 mL) was added K_2CO_3 (7.33 g, 53.0 mmol), and the mixture was stirred at 110 °C for 5 h. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between EtOAc and water, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was washed with hexane–EtOAc to give **18** (9.15 g, 70%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 6.38 (d, 1H, J = 9.1 Hz), 7.17 (t, 1H, J = 7.4 Hz), 7.37–7.43 (m, 2H), 7.72 (d, 2H, J = 7.7 Hz), 8.44 (d, 1H, J = 9.1 Hz), 10.45 (br s, 1H); MS (FAB) m/z 246 $[M+H]^+$.

5.1.22. 6-Methoxy-N^2-phenylpyridine-2,3-diamine (19)

To a stirred mixture of **18** (6.50 g, 26.5 mmol) in EtOH (100 mL) and DMF (25 mL) was added 20% $Pd(OH)_2$ on carbon (50% wet, 102 mg), and the mixture was stirred at room temperature for 16 h under 1 atm of hydrogen gas atmosphere. The mixture was filtered through celite pad, and the filtrate was concentrated in vacuo to give a black oil. To the above-obtained black oil in THF (30 mL) were added triethyl *ortho*formate (13.2 mL, 79.5 mmol) and *p*-toluenesulfonic acid monohydrate (5.55 g, 29.2 mmol), and the mixture was refluxed for 5 h. The mixture was cooled at room temperature and concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate and $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give **19** (5.97 g, quant) as a brown oil. ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3H), 6.81 (d, 1H, J = 8.6 Hz), 7.42–7.48 (m, 1H), 7.58–7.64 (m, 2H), 7.96–8.00 (m, 2H), 8.10 (d, 1H, J = 8.6 Hz), 8.68 (s, 1H); MS (ESI) m/z 226 $[M+H]^+$.

5.1.23. 3-Phenyl-3*H*-imidazo[4,5-*b*]pyridin-5-ol (20)

A mixture of **19** (5.97 g, 26.5 mmol) and pyridine hydrochloride (30.6 g, 265 mmol) was stirred at 200 °C for 2 h. After cooling at room temperature, the mixture was basified with saturated aqueous sodium bicarbonate and extracted with $CHCl_3$–MeOH for 10 times. The combined organic layer was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0–10% MeOH in $CHCl_3$) to give **20** (4.33 g, 77%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 6.63 (d, 1H, J = 8.6 Hz), 7.42–7.47 (m, 1H), 7.56–7.62 (m, 2H), 7.86–7.90 (m, 2H), 8.01 (d, 1H, J = 8.6 Hz), 8.54 (s, 1H), 10.84 (br s, 1H); MS (ESI) m/z 212 $[M+H]^+$.

5.1.24. 2-{[(3-Phenyl-3*H*-imidazo[4,5-b]pyridin-5-yl)oxy]methyl} quinoline dihydrochloride (21)

To a mixture of **20** (211 mg, 1.00 mmol) and 2-quinolinylmethanol (260 mg, 1.63 mmol) in THF (10 mL) were added 1,1′-(azodicarbonyl)dipiperidine (ADDP, 378 mg, 1.50 mmol) and tributylphosphine (0.37 mL, 1.50 mmol), and the mixture was stirred at 60 °C for 15 h. After cooling at room temperature, the mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give free form of the title compound, which was dissolved in $CHCl_3$ (10 mL) and 4 M HCl/EtOAc (1.0 mL, 4.0 mmol) was added to the solution. The mixture was concentrated in vacuo and the residue was recrystalized from EtOH–Et_2O to give a beige solid. ^{1}H NMR (DMSO-d_6) δ 5.88 (s, 2H), 7.19 (d, 1H, J = 8.8 Hz), 7.35–7.45 (m, 3H), 7.65–7.71 (m, 2H), 7.78–7.84 (m, 1H), 7.90 (d, 1H, J = 8.6 Hz), 7.99–8.05 (m, 1H), 8.19 (d, 1H, J = 8.2 Hz), 8.30 (d, 1H, J = 8.8 Hz), 8.33 (d, 1H, J = 8.5 Hz), 8.81 (d, 1H, J = 8.6 Hz), 9.13 (s, 1H); MS (ESI) m/z 353 $[M+H]^+$; Anal. Calcd for $C_{22}H_{16}N_4O{\cdot}2HCl{\cdot}2H_2O{\cdot}0.08CHCl_3$: C, 56.32; H, 4.73; N, 11.90; Cl, 16.86. Found: C, 56.32; H, 4.77; N, 11.87; Cl, 16.83.

5.1.25. 5-(Benzyloxy)-4-methoxy-2-nitro-*N*-phenylaniline (23)

To a mixture of 1-(benzyloxy)-5-bromo-2-methoxy-4-nitrobenzene[11] (**22**, 1.00 g, 2.96 mmol), aniline (413 mg, 4.44 mmol), tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$, 135 mg, 0.15 mmol) and (+/−)-2,2′-bis(diphenylphosphoino)-1,1′-binaphthyl (BINAP, 138 mg, 0.22 mmol) in toluene (20 mL) was added Cs_2CO_3 (1.93 g, 5.91 mmol), and the mixture was stirred at 85 °C for 2 h under an argon gas atmosphere. After cooling at room temperature, the mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (20–100% EtOAc in hexane) to give **23** (1.04 g, quant) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 5.08 (s, 2H), 6.58 (s, 1H), 6.66–6.70 (m, 1H), 7.02 (d, 2H, J = 7.7 Hz), 7.18–7.37 (m, 7H), 7.65 (s, 1H), 9.77 (br s, 1H); MS (ESI) m/z 351 $[M+H]^+$.

5.1.26. 6-(Benzyloxy)-5-methoxy-1-phenyl-1*H*-benzimidazole (24a)

To a suspension of **23** (3.10 g, 8.85 mmol) and NH_4Cl (47 mg, 0.89 mmol) in EtOH (55 mL) and water (17 mL) was added iron powder (2.47 g, 44.2 mmol), and the mixture was refluxed for 3 h. After cooling at room temperature, the mixture was diluted with $CHCl_3$ and water, and then filtered through celite pad. The organic layer of the filtrate was dried over $MgSO_4$, filtered and concentrated in vacuo to give a purple solid. To a solution of the above-obtained purple solid in THF (57 mL) were added triethyl *ortho*formate (3.67 mL, 22.1 mmol) and *p*-toluenesulfonic acid monohydrate (168 mg, 0.88 mmol), and the mixture was refluxed for 3 h. The mixture was then cooled at room temperature and concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give **24a** (1.92 g, 66%) as a red solid. ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 5.15 (s, 2H), 7.01 (s, 1H), 7.31–7.46 (m, 9H), 7.51–7.75 (m, 2H), 7.96 (s, 1H); MS (ESI) m/z 331 $[M+H]^+$.

5.1.27. 6-(Benzyloxy)-5-methoxy-1-phenyl-1*H*-benzimidazole (24b)

Compound **24b** was prepared from **23** and trimethyl orthoisobutyrate in a manner similar to that described for compound **24a**, with a yield of 37% as a pale brown solid. ^{1}H NMR ($CDCl_3$) δ 1.32 (d, 6H, J = 6.8 Hz), 3.04 (sep, 1H, J = 6.8 Hz), 3.93 (s, 3H), 5.03 (s, 2H), 6.59 (s, 1H), 7.25–7.41 (m, 8H), 7.49–7.58 (m, 3H); MS (ESI) m/z 373 $[M+H]^+$.

5.1.28. 2-{[(2-Isopropyl-5-methoxy-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline dihydrochloride (25b)

A mixture of **24b** (982 mg, 2.64 mmol) and anisole (5.71 mL, 52.5 mmol) in trifluoroacetic acid (37 mL) was stirred at 80 °C overnight. After cooling at room temperature, the mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give a purple solid (754 mg). To a mixture of the above-obtained purple solid

(250 mg) and 2-(chloromethyl)quinoline hydrochloride (227 mg, 1.06 mmol) in DMF (5 mL) were added Cs_2CO_3 (692 mg, 2.13 mmol) and potassium iodide (15 mg, 0.09 mmol), and the mixture was stirred at 60 °C for 2 h followed by 80 °C for 2 h. After cooling at room temperature, the mixture was diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–5% MeOH in $CHCl_3$ then NH silica gel, 0–40% EtOAc in hexane) to give the free form of the title compound, which was dissolved in EtOH (10 mL), and 4 M HCl/EtOAc (0.50 mL, 2.00 mmol) was added to the solution. The mixture was concentrated in vacuo and the residue was triturated with 2-propanol. The precipitate was collected by filtration and dried in vacuo to give **25b** (120 mg, 27%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 1.37 (d, 6H, J = 7.0 Hz), 3.09 (sep, 1H, J = 7.0 Hz), 3.95 (s, 3H), 5.44 (s, 2H), 7.06 (s, 1H), 7.39 (s, 1H), 7.63–7.79 (m, 7H), 7.85–7.91 (m, 1H), 7.98 (d, 1H, J = 8.5 Hz), 8.07 (d, 1H, J = 8.2 Hz), 8.57 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 424 $[M+H]^+$; Anal. Calcd for $C_{27}H_{25}N_3O_2{\cdot}2HCl{\cdot}0.5H_2O$: C, 64.16; H, 5.58; N, 8.31; Cl, 14.03. Found: C, 63.90; H, 5.75; N, 8.14; Cl, 14.04.

5.1.29. 2-{[(5-Methoxy-1-phenyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline dihydrochloride (25a)

Compound **25a** was prepared from **24a** in a manner similar to that described for compound **25b**, with a yield of 6.1% as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 3.96 (s, 3H), 5.55 (s, 2H), 7.45 (s, 1H), 7.48 (s, 1H), 7.68–7.76 (m, 6H), 7.80 (d, 1H, J = 8.5 Hz), 7.85–7.89 (m, 1H), 8.02–8.09 (m, 2H), 8.58 (1H, d, J = 8.5 Hz), 9.74 (s, 1H); MS (ESI) m/z 382 $[M+H]^+$; Anal. Calcd for $C_{24}H_{19}N_3O_2{\cdot}2HCl{\cdot}2.0H_2O{\cdot}0.2\ C_2H_6O$: C, 58.66; H, 5.29; N, 8.41; Cl, 14.19. Found: C, 58.73; H, 5.30; N, 8.33; Cl, 13.92.

5.1.30. 2-[(3-Bromo-4-nitrophenoxy)methyl]quinoline (27)

To a mixture of 3-bromo-4-nitrophenol (**26**, 4.91 g, 22.5 mmol), 2-(chloromethyl)quinoline hydrochloride (5.79 g, 27.0 mmol) and potassium iodide (374 mg, 2.25 mmol) in DMF (50 mL) was added K_2CO_3 (7.47 g, 54.1 mmol), and the mixture was stirred at 60 °C for 90 min. After cooling at room temperature, the mixture was diluted with EtOAc, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was washed with EtOAc–hexane to give **27** (6.89 g, 85%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.44 (s, 2H), 7.03–7.07 (m, 1H), 7.42 (d, 1H, J = 2.4 Hz), 7.55–7.62 (m, 2H), 7.74–7.80 (m, 1H), 7.85 (d, 1H, J = 8.3 Hz), 7.96 (d, 1H, J = 9.3 Hz), 8.09 (d, 1H, J = 8.8 Hz), 8.23 (d, 1H, J = 8.3 Hz); MS (ESI) m/z 359, 361 $[M+H]^+$.

5.1.31. 2-{[(1-Phenyl-1*H*-indol-6-yl)oxy]methyl}quinoline (14a)

Compound **14a** was prepared from **13a** in a manner similar to that described for compound **27**, with a yield of 18% as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 5.39 (s, 2H), 6.61 (dd, 1H, J = 3.3, 0.7 Hz), 6.95 (dd, 1H, J = 8.6, 2.2 Hz), 7.20 (d, 1H, J = 2.2 Hz), 7.35–7.39 (m, 1H), 7.44–7.52 (m, 5H), 7.56 (d, 1H, J = 8.6 Hz), 7.59–7.64 (m, 1H), 7.70 (d, 1H, J = 8.5 Hz), 7.78–7.82 (m, 1H), 7.96–8.04 (m, 2H), 8.39 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 351$[M+H]^+$; Anal. Calcd for $C_{24}H_{18}N_2O{\cdot}0.1H_2O$: C, 81.84; H, 5.21; N, 7.95. Found: C, 81.67; H, 5.20; N, 7.79.

5.1.32. 2-[(3-Fluoro-4-nitrophenoxy)methyl]quinoline (29)

Compound **29** was prepared from 3-fluoro-4-nitrophenol (**28**) in a manner similar to that described for compound **27**, with a yield of 98% as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.55 (s, 2H), 7.12 (dd, 1H, J = 9.3, 1.7 Hz), 7.35 (1H, dd, J = 13.6, 2.5 Hz), 7.61–7.67 (m, 1H), 7.70 (d, 1H, J = 8.6 Hz), 7.77–7.83 (m, 1H), 7.99–8.04 (m, 1H), 8.18 (dd, 1H, J = 9.1, 9.1 Hz), 8.46 (d, 1H, J = 8.5 Hz); MS (ESI) m/z 299 $[M+H]^+$.

5.1.33. *N*-Cyclohexyl-2-nitro-5-(quinolin-2-ylmethoxy)aniline (30a)

To a solution of **29** (895 mg, 3.00 mmol) in DMF (30 mL) was added cyclohexylamine (1.03 mL, 9.00 mmol), and the mixture was stirred at 80 °C for 6 h. After cooling at room temperature, the mixture was diluted with water. The precipitate was collected by filtration and dried in vacuo to give **30a** (1.12 g, 99%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.21–1.37 (m, 6H), 1.61–1.70 (m, 2H), 1.84–1.90 (m, 2H), 3.29–3.37 (m, 1H), 5.44 (s, 2H), 6.28 (d, 1H, J = 2.5 Hz), 6.32 (dd, 1H, J = 9.5, 2.6 Hz), 7.55–7.62 (m, 2H), 7.73–7.78 (m, 1H), 7.84 (d, 1H, J = 8.1 Hz), 8.08 (d, 1H, J = 8.5 Hz), 8.12 (d, 1H, J = 9.5 Hz), 8.21 (d, 1H, J = 8.5 Hz), 8.31 (br d, 1H, J = 7.1 Hz); MS (ESI) m/z 378 $[M+H]^+$.

5.1.34. *N*-[2-Nitro-5-(quinolin-2-ylmethoxy)phenyl]pyridin-4-amine (30b)

To a mixture of **27** (300 mg, 0.84 mmol), 4-aminopyridine (80 mg, 0.85 mmol), $Pd_2(dba)_3$ (38 mg, 0.04 mmol) and BINAP (52 mg, 0.08 mmol) in toluene (10 mL) was added sodium *tert*-butoxide (120 mg, 1.25 mmol), and the mixture was stirred at 85 °C for 2 h under argon gas atmosphere. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (40–100% EtOAc in $CHCl_3$) to give **30b** (224 mg, 72%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.43 (s, 2H), 6.69 (dd, 1H, J = 9.3, 2.7 Hz), 6.85–6.88 (m, 2H), 7.03 (d, 1H, J = 2.4 Hz), 7.56–7.63 (m, 2H), 7.77–7.82 (m, 1H), 7,87 (d, 1H, J = 7.8 Hz), 8.04 (d, 1H, J = 8.3 Hz), 8.19–8.25 (m, 4H), 9.62 (br s, 1H); MS (ESI) m/z 373 $[M+H]^+$.

5.1.35. 2-Nitro-*N*-(pyridin-4-ylmethyl)-5-(quinolin-2-ylmethoxy) aniline (30c)

To a solution of **29** (300 mg, 1.01 mmol) and 4-picolylamine (0.12 mL, 1.20 mmol) in DMF (3 mL) was added K_2CO_3 (209 mg, 1.50 mmol), and the mixture was stirred at 80 °C for 1 h. After cooling at room temperature, the mixture was partitioned between EtOAc and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give **30c** (370 mg, 95%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 4.47 (d, 2H, J = 6.0 Hz), 5.32 (s, 2H), 6.16 (d, 1H, J = 2.5 Hz), 6.42 (dd, 1H, J = 9.5, 2.5 Hz), 7.14–7.17 (m, 2H), 7.56–7.62 (m, 2H), 7.74–7.79 (m, 1H), 7.82–7.86 (m, 1H), 8.04 (d, 1H, J = 8.5 Hz), 8.14 (d, 1H, J = 8.5 Hz), 8.19 (d, 1H, J = 9.5 Hz), 8.42–8.45 (m, 2H), 8.70 (br t, 1H, J = 6.0 Hz); MS (ESI) m/z 387 $[M+H]^+$.

5.1.36. 1-Methyl-*N*-[2-nitro-5-(quinolin-2-ylmethoxy)phenyl]-1*H*-pyrazol-3-amine (30e)

To a mixture of **27** (160 mg, 0.45 mmol), 1-methyl-1*H*-pyrazol-3-amine (48 mg, 0.49 mmol), $Pd_2(dba)_3$ (38 mg, 0.024 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 27 mg, 0.047 mmol) in toluene (5 mL) was added Cs_2CO_3 (220 mg, 0.68 mmol), and the mixture was stirred at 85 °C for 2 h under an argon gas atmosphere. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (0–30% EtOAc in $CHCl_3$) to give **30b** (145 mg, 87%) as an orange solid. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 5.41 (s, 2H), 5.91 (d, 1H, J = 2.2 Hz), 6.51 (dd, 1H, J = 9.5, 2.7 Hz), 7.21 (d, 1H, J = 2.2 Hz), 7.48 (d, 1H, J = 2.6 Hz), 7.54–7.59 (m, 1H), 7.62 (d, 1H, J = 8.5 Hz), 7.73–7.78 (m, 1H), 7.83–7.86 (m, 1H), 8.06 (d, 1H, J = 8.6 Hz), 8.18–8.23 (m, 2H), 10.02 (s, 1H); MS (ESI) m/z 376 $[M+H]^+$.

5.1.37. 1-Methyl-*N*-[2-nitro-5-(quinolin-2-ylmethoxy)phenyl]-1*H*-pyrazol-4-amine (30d)

Compound **30d** was prepared from **29** and 1-methyl-1*H*-pyrazol-4-amine dihydrochloride in a manner similar to that described

for compound **30e**, with a yield of 30% as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 5.31 (s, 2H), 6.44 (dd, 1H, J = 9.5, 2.6 Hz), 6.52 (d, 1H, J = 2.6 Hz), 7.27 (s, 1H), 7.41 (s, 1H), 7.55–7.60 (m, 2H), 7.73–7.78 (m, 1H), 7.83–7.86 (m, 1H), 8.06 (d, 1H, J = 8.6 Hz), 8.17 (d, 1H, J = 9.5 Hz), 8.21 (d, 1H, J = 8.4 Hz), 9.26 (s, 1H); MS (ESI) m/z 376 $[M+H]^+$.

5.1.38. *N*-[2-Nitro-5-(quinolin-2-ylmethoxy)phenyl]pyrimidin-4-amine (30h)

To a mixture of **27** (500 mg, 1.39 mmol), 4-aminopyrimidine (199 mg, 2.09 mmol), $Pd_2(dba)_3$ (138 mg, 0.070 mmol) and Xantphos (81 mg, 0.14 mmol) in *N*-methylpyrrolidone (4 mL) was added Cs_2CO_3 (680 mg, 2.09 mmol), and the mixture was stirred at 160 °C for 10 min under microwave irradiation. After cooling at room temperature, the mixture was filtered through celite pad, and the filtrate was partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20–100% EtOAc in hexane then NH silica gel, 20–50% $CHCl_3$ in hexane) to give **30h** (97 mg, 19%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.53 (s, 2H), 6.75–6.80 (m, 2H), 7.75–7.61 (m, 1H), 7.66 (d, 1H, J = 8.5 Hz), 7.76–7.80 (m, 1H), 7.85 (d, 1H, J = 8.2 Hz), 8.10 (d, 1H, J = 8.6 Hz), 8.22–8.28 (m, 2H), 8.38 (d, 1H, J = 5.8 Hz), 8.70 (s, 1H), 8.77 (d, 1H, J = 2.7 Hz), 10.60 (br s, 1H); MS (ESI) m/z 374 $[M+H]^+$.

5.1.39. *N*-[2-Nitro-5-(quinolin-2-ylmethoxy)phenyl]pyrimidin-2-amine (30g)

Compound **30g** was prepared from **27** and pyrimidin-2-amine in a manner similar to that described for compound **30h**, with a yield of 44% as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.52 (s, 2H), 6.72 (dd, 1H, J = 9.4, 2.7 Hz), 6.86 (t, 1H, J = 4.8 Hz), 7.56–7.61 (m, 1H), 7.68 (d, 1H, J = 8.5 Hz), 7.74–7.80 (m, 1H), 7.84–7.87 (m, 1H), 8.10 (d, 1H, J = 8.5 Hz), 8.23 (d, 1H, J = 8.5 Hz), 8.27 (d, 1H, J = 9.4 Hz), 8.45 (d, 2H, J = 4.8 Hz), 8.83 (d, 1H, J = 2.7 Hz), 10.31 (br s, 1H); MS (ESI) m/z 374 $[M+H]^+$.

5.1.40. *N*-[2-Nitro-5-(quinolin-2-ylmethoxy)phenyl]-1,3-thiazol-2-amine (30i)

Compound **30i** was prepared from **27** and 1,3-thiazol-2-amine in a manner similar to that described for compound **30e**, with a yield of 90% as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 2H), 6.70 (dd, 1H, J = 9.4, 2.7 Hz), 6.85 (d, 1H, J = 3.7 Hz), 7.33 (d, 1H, J = 3.7 Hz), 7.56–7.61 (m, 1H), 7.67 (d, 1H, J = 8.5 Hz), 7.75–7.79 (m, 1H), 7.84–7.88 (m, 1H), 8.10 (d, 1H, J = 7.8 Hz), 8.22–8.27 (m, 2H), 8.52 (d, 1H, J = 2.7 Hz), 10.66 (s, 1H); MS (ESI) m/z 379 $[M+H]^+$.

5.1.41. *N*-[2-Nitro-5-(quinolin-2-ylmethoxy)phenyl]pyridazin-4-amine (30f)

To a mixture of **27** (500 mg, 1.39 mmol), 4-aminopyridazine (159 mg, 1.67 mmol) and K_3PO_4 (355 mg, 1.67 mmol) in DMSO (8 mL) were added CuI (318 mg, 1.67 mmol) and *N*,*N*′-dimethylethylenediamine (0.18 mL, 1.67 mmol), and the mixture was stirred at 110 °C for 30 min under an argon gas atmosphere. After cooling at room temperature, the mixture was diluted with water and 28% aqueous ammonia solution, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0–5% MeOH in $CHCl_3$) to give **30f** (138 mg, 27%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 5.47 (s, 2H), 6.80 (dd, 1H, J = 9.4, 2.6 Hz), 6.90 (dd, 1H, J = 5.9, 2.9 Hz), 7.07 (d, 1H, J = 2.6 Hz), 7.57–7.64 (m, 2H), 7.78–7.84 (m, 1H), 7.87 (d, 1H, J = 8.1 Hz), 8.05 (d, 1H, J = 8.6 Hz), 8.22–8.27 (m, 2H), 8.59 (br s, 1H), 9.08 (br s, 1H), 9.58 (s, 1H); MS (ESI) m/z 374 $[M+H]^+$.

5.1.42. 2-{[(1-Cyclohexyl-1*H*-benzimidazol-6-yl)oxy]methyl}quinoline dihydrochloride (31a)

Compound **31a** was prepared from **30a** in a manner similar to that described for compound **8**, with a yield of 22% as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 2.06–2.16 (m, 6H), 3.60–3.69 (m, 2H), 4.00–4.07 (m, 2H), 5.00–5.10 (m, 1H), 5.80 (s, 2H), 7.43 (dd, 1H, J = 9.1, 2.3 Hz), 7.78–7.85 (m, 2H), 7.99–8.04 (m, 2H), 8.08 (d, 1H, J = 2.3 Hz), 8.21 (d, 1H, J = 8.3 Hz), 8.36 (d, 1H, J = 8.6 Hz), 8.87 (d, 1H, J = 8.6 Hz), 9.80 (s, 1H); MS (ESI) m/z 358 $[M+H]^+$. Anal. Calcd for $C_{23}H_{23}N_3O{\cdot}2HCl{\cdot}3.1H_2O$: C, 56.82; H, 6.47; N, 8.64; Cl, 14.58. Found: C, 56.97; H, 6.81; N, 8.70; Cl, 14.54.

5.1.43. 2-({[1-(1-Methyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline dihydrochloride (31e)

To a suspension of **30e** (145 mg, 0.39 mmol) and NH_4Cl (13 mg, 0.24 mmol) in EtOH (9 mL) and water (3 mL) was added iron powder (110 mg, 1.97 mmol), and the mixture was refluxed for 1 h. After cooling at room temperature, the mixture was diluted with $CHCl_3$ and filtered through celite pad. The organic layer of the filtrate was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a black oil. To a solution of the above-obtained black oil in THF (5 mL) were added triethyl *ortho*formate (0.10 mL, 0.87 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol), and the mixture was refluxed for 2 h. The mixture was cooled at room temperature and partitioned between saturated aqueous sodium bicarbonate and $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0–50% EtOAc in $CHCl_3$) to give an oil, which was dissolved in $CHCl_3$ (5 mL) and the mixture was treated with 4 M HCl/EtOAc (0.40 mL, 1.60 mmol). The precipitate was collected by filtration and washed with 2-propanol to give **31e** (75 mg, 45%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 3.94 (s, 3H), 5.67 (s, 2H), 6.84 (d, 1H, J = 2.3 Hz), 7.40 (dd, 1H, J = 9.1, 2.4 Hz), 7.73–7.78 (m, 1H), 7.83–7.87 (m, 2H), 7.90–7.97 (m, 2H), 8.00 (d, 1H, J = 2.3 Hz), 8.14 (d, 1H, J = 8.2 Hz), 8.24 (d, 1H, J = 8.5 Hz), 8.71 (d, 1H, J = 8.5 Hz), 9.72 (s, 1H); MS (ESI) m/z 356 $[M+H]^+$. Anal. Calcd for $C_{21}H_{17}N_5O{\cdot}2HCl{\cdot}1.2H_2O$: C, 56.06; H, 4.79; N, 15.57; Cl, 15.76. Found: C, 56.10; H, 4.77; N, 15.51; Cl, 15.74.

5.1.44. 2-({[1-(Pyridin-4-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline trihydrochloride (31b)

Compound **31b** was prepared from **30b** in a manner similar to that described for compound **31e**, with a yield of 57% as a pink solid. ^{1}H NMR (DMSO-d_6) δ 5.69 (s, 2H), 7.26–7.31 (m, 1H), 7.72–7.78 (m, 2H), 7.81 (d, 1H, J = 8.9 Hz), 7.90–7.97 (m, 2H), 8.11–8.16 (m, 1H), 8.20–8.27 (m, 1H), 8.34–8.39 (m, 2H), 8.68–8.75 (m, 1H), 9.02–9.10 (m, 3H); MS (ESI) m/z 353 $[M+H]^+$. Anal. Calcd for $C_{22}H_{16}N_4O{\cdot}2.6HCl{\cdot}2.4H_2O$: C, 53.88; H, 4.81; N, 11.42; Cl, 18.80. Found: C, 54.15; H, 4.84; N, 11.44; Cl, 18.55.

5.1.45. 2-({[1-(Pyridin-4-ylmethyl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline trihydrochloride (31c)

Compound **31c** was prepared from **30c** in a manner similar to that described for compound **8**, with a yield of 36% as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 5.47 (s, 2H), 6.00 (s, 2H), 7.37 (dd, 1H, J = 9.0, 2.3 Hz), 7.59 (d, 1H, J = 2.3 Hz), 7.65–7.70 (m, 1H), 7.73 (d, 1H, J = 8.5 Hz), 7.75–7.79 (m, 2H), 7.81–7.87 (m, 2H), 8.00–8.07 (m, 2H), 8.49 (d, 1H, J = 8.5 Hz), 8.73–8.76 (m, 2H), 9.60 (s, 1H); MS (ESI) m/z 367 $[M+H]^+$. Anal. Calcd for $C_{23}H_{18}N_4O{\cdot}3.1HCl{\cdot}3.6H_2O$: C, 50.75; H, 5.24; N, 10.29; Cl, 20.19. Found: C, 50.66; H, 5.32; N, 10.30; Cl, 20.13.

5.1.46. 2-({[1-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline dihydrochloride (31d)

Compound **31d** was prepared from **30d** and in a manner similar to that described for compound **31e**, with a yield of 40% as a pale pink solid. ^{1}H NMR (DMSO-d_6) δ 4.00 (s, 3H), 5.59 (s, 2H), 7.39 (dd, 1H, J = 9.0, 2.4 Hz), 7.47 (d, 1H, J = 2.2 Hz), 7.67–7.72 (m, 1H), 7.82–7.91 (m, 3H), 8.00 (d, 1H, J = 0.7 Hz), 8.07–8.13 (m, 2H), 8.48 (s, 1H), 8.59 (d, 1H, J = 8.5 Hz), 9.59 (s, 1H); MS (ESI) m/z 356 $[M+H]^+$. Anal. Calcd for $C_{21}H_{17}N_5O{\cdot}2HCl{\cdot}0.1H_2O$: C, 58.64; H, 4.50; N, 16.28; Cl, 16.49. Found: C, 58.77; H, 4.50; N, 16.34; Cl, 16.28.

5.1.47. 2-({[1-(Pyridazin-4-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline trihydrochloride (31f)

Compound **31f** was prepared from **30f** and in a manner similar to that described for compound **8**, with a yield of 39% as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 5.68 (s, 2H), 7.28 (dd, 1H, J = 8.9, 2.4 Hz), 7.72–7.78 (m, 2H), 7.82 (d, 1H, J = 8.9 Hz), 7.92–7.98 (m, 2H), 8.15 (d, 1H, J = 8.1 Hz), 8.25 (d, 1H, J = 8.5 Hz), 8.28 (dd, 1H, J = 5.8, 2.8 Hz), 8.74 (d, 1H, J = 8.5 Hz), 9.14 (s, 1H), 9.52 (dd, 1H, J = 5.8, 1.0 Hz), 9.85 (dd, 1H, J = 2.8, 1.0 Hz); MS (ESI) m/z 354 $[M+H]^+$. Anal. Calcd for $C_{21}H_{15}N_5O{\cdot}3HCl{\cdot}1.7H_2O{\cdot}0.2C_2H_6O$: C, 51.14; H, 4.53; N, 13.93; Cl, 21.16. Found: C, 51.43; H, 4.54; N, 14.30; Cl, 20.78.

5.1.48. 2-({[1-(Pyrimidin-2-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline dihydrochloride (31g)

Compound **31g** was prepared from **30g** in a manner similar to that described for compound **8**, with a yield of 57% as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ 5.68 (s, 2H), 7.28 (dd, 1H, J = 8.9, 2.5 Hz), 7.57 (t, 1H, J = 4.9 Hz), 7.74–7.80 (m, 2H), 7.94–8.00 (m, 2H), 8.16 (d, 1H, J = 8.3 Hz), 8.29 (d, 1H, J = 8.5 Hz), 8.34 (d, 1H, J = 2.5 Hz), 8.76 (d, 1H, J = 8.5 Hz), 8.98 (d, 2H, J = 4.9 Hz), 9.34 (s, 1H); MS (ESI) m/z 354 $[M+H]^+$. Anal. Calcd for $C_{21}H_{15}N_5O{\cdot}2HCl{\cdot}1.6H_2O$: C, 55.42; H, 4.47; N, 15.39; Cl, 15.58. Found: C, 55.30; H, 4.61; N, 15.45; Cl, 15.76.

5.1.49. 2-({[1-(Pyrimidin-4-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline trihydrochloride (31h)

Compound **31h** was prepared from **30h** in a manner similar to that described for compound **8**, with a yield of 65% as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 5.64 (s, 2H), 7.24 (dd, 1H, J = 8.8, 2.5 Hz), 7.72–7.77 (m, 2H), 7.92–7.97 (m, 2H), 8.12–8.16 (m, 2H), 8.26 (d, 1H, J = 8.5 Hz), 8.27 (d, 1H, J = 2.5 Hz), 8.72 (d. 1H. J = 8.5 Hz), 8.97 (d, 1H, J = 5.8 Hz), 9.20 (d, 1H, J = 0.9 Hz), 9.22 (s, 1H); MS (ESI) m/z 354 $[M+H]^+$. Anal. Calcd for $C_{21}H_{15}N_5O{\cdot}2.6HCl{\cdot}2.6H_2O$: C, 50.95; H, 4.64; N, 14.15; Cl, 18.62. Found: C, 50.84; H, 4.48; N, 14.01; Cl, 18.57.

5.1.50. 2-({[1-(1,3-Thiazol-2-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline dihydrochloride (31i)

Compound **31i** was prepared from **30i** in a manner similar to that described for compound **31e**, with a yield of 25% as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 5.67 (s, 2H), 7.25 (dd, 1H, J = 8.9, 2.4 Hz), 7.73–7.83 (m, 4H), 7.93 (d, 1H, J = 2.4 Hz), 7.95–8.00 (m, 2H), 8.17 (d, 1H, J = 8.0 Hz), 8.28 (d, 1H, J = 8.5 Hz), 8.78 (d, 1H, J = 8.5 Hz), 8.98 (s, 1H); MS (ESI) m/z 359 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_4OS{\cdot}1.9HCl{\cdot}0.5H_2O$: C, 55.01; H, 3.90; N, 12.83; S, 7.34; Cl, 15.42. Found: C, 55.15; H, 3.99; N, 12.72; S, 7.15; Cl, 15.41.

5.1.51. 2-({[2-Isopropyl-1-(pyridin-4-yl)-1*H*-benzimidazol-6-yl]oxy}methyl)quinoline trihydrochloride (32)

Compound **32** was prepared from **30b** in a manner similar to that described for compound **31e**, with a yield of 56% as a pink solid. ^{1}H NMR (DMSO-d_6) δ 1.39 (d, 6H, J = 6.9 Hz), 3.20 (sep, 1H, J = 6.9 Hz), 5.58 (s, 2H), 7.21 (d, 1H, J = 2.2 Hz), 7.40 (dd, 1H, J = 8.9, 2.2 Hz), 7.77 (dd, 1H, J = 7.5, 7.5 Hz), 7.84–7.91 (m, 2H), 7.93–8.03 (m, 3H), 8.15 (d, 1H, J = 8.1 Hz), 8.20 (d, 1H, J = 8.5 Hz), 8.74 (d, 1H, J = 8.5 Hz), 9.06–9.10 (m, 2H); MS (ESI) m/z 395 $[M+H]^+$. Anal. Calcd for $C_{25}H_{22}N_4O{\cdot}3HCl{\cdot}1.2H_2O{\cdot}0.2C_3H_8O$: C, 57.21; H, 5.44; N, 10.42; Cl, 19.79. Found: C, 57.17; H, 5.26; N, 10.64; Cl, 19.64.

5.2. PDE10A enzyme assay protocol

5.2.1. Cloning and vector construction of *PDE10A2*

The full-length human *PDE10A2* was amplified by PCR using the 1st strand cDNA synthesized from the total RNA isolated from human neuroblastoma TGW cell line. The PCR products were cloned into a pCR2.1-TOPO vector (Invitrogen. Inc.) to confirm sequences. The confirmed plasmid was digested with restricted enzymes, BamHI/HindIII, and this digested product was inserted into a pFastBac1 vector (Invitrogen. Inc.).

5.2.2. Preparation of human PDE10A2 enzyme

Human PDE10A2 enzyme protein was expressed in a *Spodoptera frugiperda* Sf9 insect cell using the Bac-to-Bac Baculovirus Expression System (Invitrogen. Inc.). The infected Sf9 cells were collected by the centrifuge and removed medium. The collected cells were lysed by sonication in the lysis buffer (50 mM Tris–HCl [pH 8.0], 150 mM NaCl, 3 mM DTT, 0.1% NP-40, 20% Glycerol with protease inhibitors), The lysate was centrifuged and supernatant was collected to obtain the PDE10A2 enzyme solution. We confirmed the PDE10A2 expression by Western blot analysis.

5.2.3. PDE10A2 inhibition assay

Inhibition of compounds on human PDE10A enzyme activity was assessed by measuring the amount of cAMP by the Homogeneous Time-Resolved Fluorescence (HTRF) detection method. The assay was performed in 12 μL samples containing a optimal amount of the PDE10A enzyme, a buffer (40 mM Tris–HCl pH 7.5; 5 mM $MgCl_2$), 0.1 μM cAMP and various concentrations of compounds(0.1 nM to 10 μM). After compounds were preincubated for 30 min with the enzyme, the reaction was initiated by adding the substrate cAMP and the mixture was incubated for 60 min at room temperature with agitation. The reaction was terminated by the addition of the fluorescence acceptor (cAMP labeled with the dye d2) and the fluorescence donor (anti-cAMP antibody labeled with Cryptate, Cisbio). After 60 min, the fluorescence transfer corresponding to the amount of residual cAMP was measured at lex. 320 nm, lem. 620 nm and lem. 665 nm using an Envision plate reader (PerkinElmer) and signal ratio (665:620) was calculated. The ratio determined in the absence of enzyme was subtracted from all data. The obtained results were converted to activity relative to an uninhibited control (100%) and IC_{50} values were calculated using Prism software (GraphPad Software, Inc.).

5.3. CYP1A2 inhibition

Using a 96-well plate, 3-cyano-7-ethoxycoumarin (5 μM), each test compound (from 0.16 to 20 μM), and the enzyme (0.026 pmol) were incubated at 37 °C for 20 min in 100 μL of total volume of 100 mM phosphate buffer (pH 7.4) containing 8.2 μM $NADP^+$, 0.41 mM glucose-6-phosphate, 0.41 mM $MgCl_2$ and 0.4 Units/mL glucose-6-phosphate dehydrogenase. Thereafter, the reaction was stopped by adding 0.5 M 2-amino-2-hydroxymethyl-1,3-propanediol aqueous solution containing 80% acetonitrile, and the fluorescence intensity (excitation wavelength; 409 nm, fluorescence wavelength; 460 nm) was measured using a fluorescence plate reader. The residual activity was calculated based on the following formula, and concentration of each test compound by which the residual activity becomes 50% (IC_{50}) was obtained.

$$\text{The residual activity}(\%) = (C_1 - B_1)/(C_0 - B_1) \times 100$$

C_1: fluorescence intensity in the presence of test compound having known concentration, enzyme, and substrate.

C_0: fluorescence intensity in the absence of test compound and in the presence of enzyme and substrate.

B_1: fluorescence intensity of blank well.

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