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Discovery of a 7-arylaminobenzimidazole series as novel CRF_1 receptor antagonists

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ABSTRACT

A promising lead compound **1** of a benzimidazole series has been identified as a corticotropin-releasing factor 1 (CRF_1) receptor antagonist. In this study, we focused on replacement of a 7-alkylamino group of **1**, predicted to occupy a large lipophilic pocket of a CRF_1 receptor, with an aryl group. During the course of this examination, we established new synthetic approaches to 2,7-diarylaminobenzimidazoles. The novel synthesis of 7-arylaminobenzimidazoles culminated in the identification of compounds exhibiting inhibitory activities comparable to the alkyl analog **1**. A representative compound, *p*-methoxyanilino analog **16g**, showed potent CRF binding inhibitory activity against a human CRF_1 receptor and human CRF_1 receptor antagonistic activity (IC_{50} = 27 nM, 56 nM, respectively). This compound exhibited ex vivo ^{125}I-Tyr^0 (^{125}I-CRF) binding inhibitory activity in mouse frontal cortex, olfactory bulb, and pituitary gland at 20 mg/kg after oral administration. In this report, we discuss the structure–activity-relationship of these 7-arylamino-1*H*-benzimidazoles and their synthetic method.

1. Introduction

Corticotropin-releasing factor (CRF) is a 41-amino acid neuropeptide and mediates its actions through two G_s-coupled G protein-coupled receptor subtypes, CRF_1 and CRF_2.[1,2] CRF is considered to be the main regulator of the hypothalamus–pituitary–adrenocortical (HPA) axis via CRF_1 receptors.[3,4] After exposure to stress, secretion of CRF increases in the neurons of the paraventricular nucleus of the hypothalamus and stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland.[5,6] In healthy individuals not suffering from life-threatening events, a negative feedback system against the activation of the HPA-axis is operating; in contrast, the system collapses in patients with stress-related disorders. Moreover, CRF plays an important role in the brain as a neurotransmitter that mediates stress-related behaviors.[4,7]

In our previous study, we designed unique benzazole derivatives with a single-atom linker between the core and the pendant phenyl group as novel CRF_1 receptor antagonists.[8] Initial structure-activity-relationship (SAR) studies revealed that lead compound **1** shown in Figure 1 demonstrated potent in vitro CRF_1 receptor binding activity with an IC_{50} value of 12 nM[8] and ex vivo CRF binding inhibitory activity in the brain after oral administration in mice. Compound **1** has a di-alkylamino moiety located in a para orientation of the hydrogen-bonding acceptor (HBA) of the *N*-methylbenzimidazole core to fit into a large lipophilic pocket of the CRF_1 receptor. We were also interested in placing an alkyl-arylamino group at the same position of the benzimidazole core and whether it would bind more effectively in the lipophilic pocket. In addition, previous SAR studies indicated that a normal propyl group can be replaced with an isopropyl group[8] and the branched alkyl group can be expected to effectively occupy the large three-dimensional pocket compared with a linear group. Therefore, compounds in which these alkyl groups were replaced with an aryl group and a branched alkyl group were designed and examined.

Abbreviations: CRF, corticotropin-releasing factor; HPA, hypothalamus–pituitary–adrenocortical; ACTH, adrenocorticotropic hormone; SAR, structure–activity-relationship; HBA, hydrogen-bonding acceptor; CDI, *N*,*N*′-carbonyldiimidazole; *o*-biphenylPCy_2, *o*-biphenyl(dicyclohexyl)phosphine; S-Phos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; X-Phos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; PMB, *p*-methoxybenzyl; CHO, Chinese hamster ovary.

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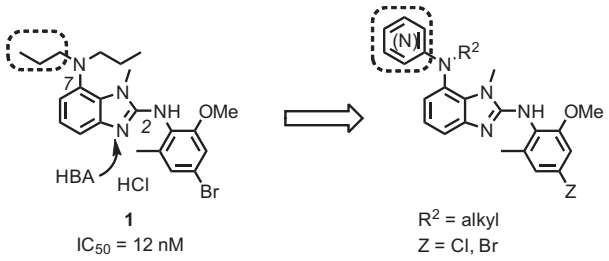


Figure 1. Design of a novel 7-arylaminobenzimidazole series.

Flexible alignment of 7-isopropylphenylaminobenzimidazole **16** with the lead compound **1** was performed using MOE.[9] It was found that the aryl group of compound **16**, exemplified as a yellow circle in Figure 2, overlapped well with the corresponding alkyl chain of compound **1** as well as the other key functional groups including an HBA and a pendant aryl group exemplified as white circles. In addition, the aryl group of compound **16** might be able to accommodate three-dimensionally compared with the alkyl group of compound **1**. That means that the aryl group would occupy unknown space and enhance potency. This superimposition study suggested that the newly designed compounds should exhibit potent inhibitory activity.

The aryl amino series, having diverse size of substituents with electron-deficient or electron-donating characteristics, was targeted for SAR studies. In this study, another anilino group at the 2-position was fixed in 4-chloro or bromo-2-methoxy-6-methylanilines, because 7-dialkylamino-1*H*-benzimidazoles having these groups exhibited potent and comparable CRF_1 receptor binding activity.[8] We also investigated novel synthetic methods to prepare 2,7-diarylaminobenzimidazoles. In this report, the synthesis and the biological activities of a novel series of 7-arylamino-1*H*-benzimidazoles, as well as SAR study results are discussed.

2. Results and discussion

2.1. Chemistry

Synthesis of the 7-anilinobenzimidazole derivatives is illustrated in Schemes 1–6 and Table 1. Preparation of 7-amino-1,3-dihydro-2*H*-benzimidazol-2-one **5** was performed from commercially available 2-chloro-1,3-dinitrobenzene **2** as described in Scheme 1. The chlorobenzene **2** was treated with methylamine to afford the corresponding *N*-methylaniline **3**, which was followed by reduction to give triamine **4**. The key intermediate **5** was provided by cyclization of the triamine **4** with *N*,*N*′-carbonyldiimidazole (CDI).

Our initial efforts were focused on preparation of the desired 7-arylaminobenzimidazoles **6** by a palladium-catalyzed coupling reaction of 7-aminobenzimidazole **5** and aryl halide (ArX) as described in Table 1. The coupling reaction of *p*-bromoanisole, *p*-chlorobromobenzene, and 2-bromo-5-methylpyridine using tris(dibenzylideneacetone)dipalladium and *o*-biphenyl(dicyclohexyl) phosphine (*o*-biphenylPCy_2) afforded the desired compounds **6a**, **6e**, and **6k**, respectively (entries 2, 7, and 16), while the reaction of *p*-bromophenyl methyl sulfone and *p*-bromobenzonitrile failed (entries 8 and 11). The phosphine ligands with a bulky biphenyl group, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos), have been reported to increase the activity and stability of the catalytic system in comparison with simpler phosphine ligands such as 2-(dicyclohexylphosphino)-2′-methylbiphenyl.[10,11] In our case, using S-Phos as a ligand also provided the desired coupled compounds having the methylsulfonyl and the cyano group, **6f** and **6h** (entries 9 and 12). The yield of the reaction with *p*-bromoanisole also increased when X-Phos was used instead of *o*-biphenylPCy_2 (entries 2 vs 3). To summarize these results, bulkier phosphine ligands, S-Phos or X-Phos, worked better than *o*-biphenylPCy_2 in these coupling reactions with both electron-rich and electron-deficient phenyl halides, and were especially effective for the reaction of electron-deficient phenyl halides when no desired compounds coupled by *o*-biphenylPCy_2 were provided. The chemistry also worked well with meta substituents, as exemplified with compounds **6** wherein an alkoxy, an alkyl and a sulfonyl group, **6b**, **6d**, **6g**, and **6j** (entries 4, 6, 10, and 15), as well as a pyridine analog **6l** (entry 17) were obtained in 20–67% yields. While the reaction of neutral type of bromobenzene with X-Phos mainly gave the diphenyl adduct **7** (entry 1), and *m*-cyano analog **6i** could not be prepared even with *m*-iodobenzonitrile (entry 14), *p*-iodobenzonitrile provided the target compound **6h** (entry 13). Therefore, the reactants were reversed such that 7-arylaminobenzimidazole **5** was replaced with 7-bromo-1,3-dihydro-2*H*-benzimidazol-2-one **8** and subsequently coupled with an aniline, as illustrated in Scheme 2. The 7-bromobenzimidazole **8** was prepared from the 7-aminobenzimidazole **5** by a modified Sandmeyer reaction using copper(II) bromide and *tert*-butylnitrate. A desired monophenylamino coupled compound **6m** was obtained in good yield by the optimized coupling reaction of 7-bromo analog **8** with X-Phos by microwave irradiation. Furthermore, this condition also enabled the reaction of **8** and *m*-aminobenzonitrile to provide the desired product **6i** in 37% yield, a significant improvement relative to original attempt (<5%) described in Table 1 (entry 14).

7-Arylaminobenzimidazol-2-ones **6** with both electron-donating and electron-withdrawing groups were easily converted to 2-chloro-1,3-dihydro-2*H*-benzimidazoles **9** using phosphorus oxychloride, and the common precursors **10** were smoothly synthesized from the 2-chlorobenzimidazoles **9** with isopropylbromide in good yields as shown in Scheme 3. However, chlorination of electron-rich 7-aminobenzimidazol-2-ones **6**, according to substitution pattern of an aryl group at the 7-*N*-position, gave no desired 2-chlorobenzimidazoles **9**. The electron-rich 7-aminobenzimidazole core might be

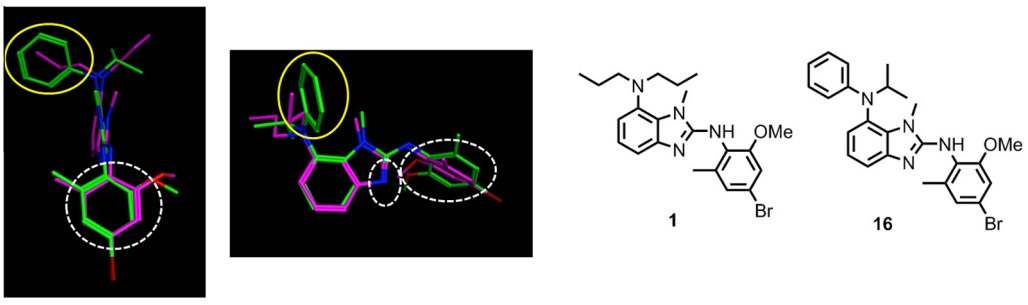
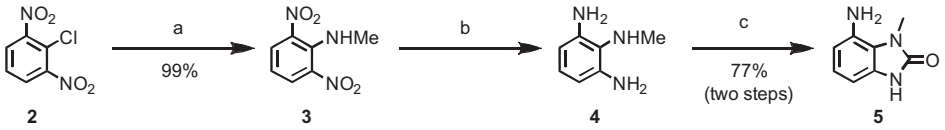
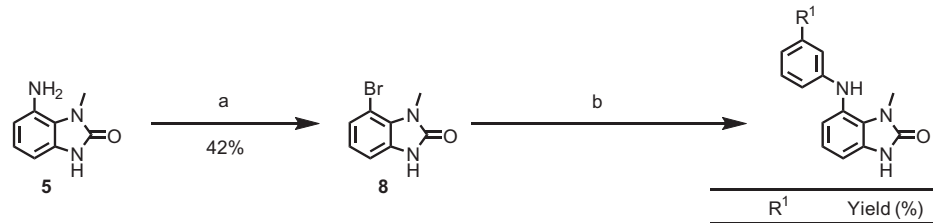


Figure 2. Superimposition of **1** (pink) and **16** (green).

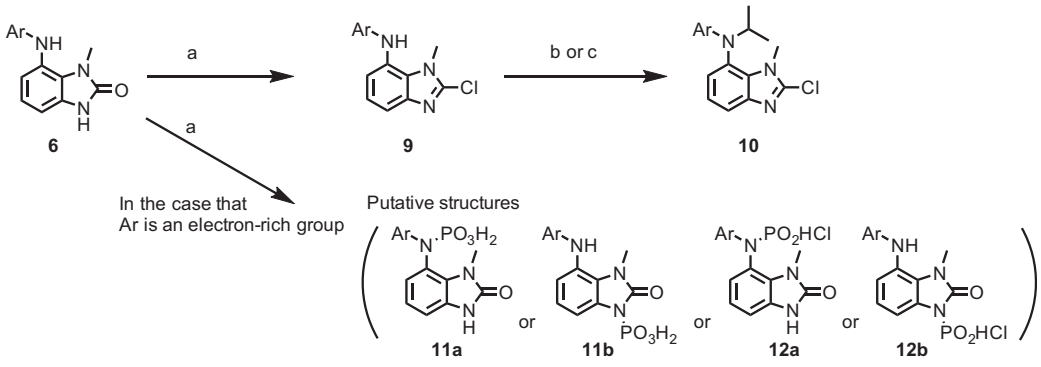


Scheme 1. Reagents and conditions: (a) $MeNH_2$, MeOH, rt; (b) H_2, Pd–C, THF, rt; (c) CDI, THF, rt.



	R^1	Yield (%)
6m	H	64
6i	CN	37

Scheme 2. Reagents and conditions: (a) $CuBr_2$, ^{t}BuONO, DMF, rt; (b) aniline or 3-cyanoaniline, Pd_2dba_3, S-Phos or X-Phos, NaO^{t}Bu, 1,4-dioxane, microwave irradiation, 100–120 °C.



6 → 9

	Ar	Yield (%)
9a	C_6H_5	32
9b	*m*-$MeOC_6H_4$	44
9c	*m*-^{i}PrOC_6H_4	58
9d	*p*-NCC_6H_4	45
9e	*m*-NCC_6H_4	38
9f	*m*-$NCMe_2CC_6H_4$	81
9g	6-MeO-3-pyridyl	41

9 → 10

	Ar	Yield (%)
10a	C_6H_5	85
10b	*m*-$MeOC_6H_4$	70
10c	*m*-^{i}PrOC_6H_4	66
10d	*p*-NCC_6H_4	87
10e	*m*-NCC_6H_4	75
10f	*m*-$NCMe_2CC_6H_4$	59
10g	6-MeO-3-pyridyl	90

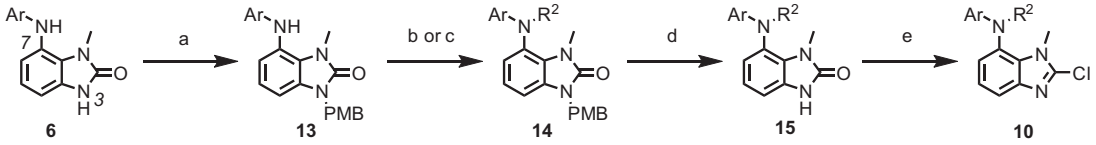
Scheme 3. Reagents and conditions: (a) $POCl_3$, 100 °C; (b) ^{i}PrBr or ^{i}PrI, NaH, (^{n}Bu$_4$NI,) DMF, rt; (c) ^{i}PrI, NaH, DMF, rt.

formed with phosphorus oxychloride to afford a stable complex **11** or **12**. As such, an alternative route was envisioned wherein benzimidazol-2-ones **6** would be converted to the 2-chlorobenzimidazoles **10** as described in Scheme 4. The key point was selection of a stable protective group under the conditions of the first three steps, regioselective protection of the benzimidazol-2-ones **6** at the 3-position, alkylation or acylation at the 7-*N*-position, and removal of the protective group. A *p*-methoxybenzyl (PMB)-protecting group was thus selected and introduced at the 3-position of the benzimidazol-2-ones **6**. Subsequent alkylation or acylation at the 7-*N*-position was performed without issue on an electron-rich 7-aminobenzimidazole analog bearing *p*-alkoxy phenyl groups, **14b** and **14c**. The PMB group in the 7-*N*-alkylated or 7-*N*-acylated compounds **14** could be removed by heating in TFA. Finally, chlorination by phosphorus oxychloride successfully gave the desired 2-chlorobenzimidazoles **10**. This route was also acceptable for other analogs with electron-deficient aryl group such as **13d** and **13e** and hetero aromatic analog **13f**, suggesting that this route was more amenable to the synthesis of more diverse compounds in comparison to the route described in Scheme 3.

Coupling reaction of the resulting 2-chlorobenzimidazoles **10** and 4-halogeno-2-methoxy-6-methylanilines **17** gave the target compounds **16** by heating or under microwave irradiation (Scheme 5).

A *m*-cyano group in compound **16n** was subsequently converted to a carboxamide in **16p** by oxidation with hydrogen peroxide under basic conditions (Scheme 6). Methyl ester **16o** was also prepared from **16n** with methanol under acidic conditions. Hydrolysis of the methyl ester **16o** provided to the corresponding carboxylic acid **16x** and was subsequently condensed with methylamine or dimethylamine to afford **16q** and **16r**, respectively. The 2-carbamoyl-2-propyl analog **16s** was prepared from the corresponding carboxylic acid **16y** obtained from the cyano analog **16v** in a method similar to that for preparing the amide analogs, **16q** and **16r**.

As mentioned above, we established novel synthetic methods for preparing 2,7-diarylaminobenzimidazoles, employing two key



6 → 13

	Ar	Yield (%)
13a	*p*-ClC$_6$H$_4$	>99
13b	*p*-MeOC$_6$H$_4$	95
13c	*p*-*i*PrOC$_6$H$_4$	67
13d	*p*-MeSO$_2$C$_6$H$_4$	49
13e	*m*-MeSO$_2$C$_6$H$_4$	71
13f	5-Me-2-pyridyl	87

13 → 14

	Ar	R^2	Yield (%)
14a	*p*-ClC$_6$H$_4$	*i*Pr	62
14b	*p*-MeOC$_6$H$_4$		80
14c	*p*-*i*PrOC$_6$H$_4$		71
14d	*p*-MeSO$_2$C$_6$H$_4$		84
14e	*m*-MeSO$_2$C$_6$H$_4$		73
14f	5-Me-2-pyridyl		74
14g	*p*-ClC$_6$H$_4$	CH$_2$CMe$_3$	32
14h		COMe	89
14i		CH$_2$CH$_2$OMe	81
14j		CH$_2$-3-tetrahydrofuranyl	60

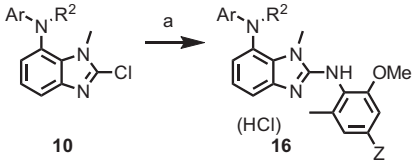
14 → 15

	Ar	R^2	Yield (%)
15a	*p*-ClC$_6$H$_4$	*i*Pr	88
15b	*p*-MeOC$_6$H$_4$		>99
15c	*p*-*i*PrOC$_6$H$_4$		-
15d	*p*-MeSO$_2$C$_6$H$_4$		75
15e	*m*-MeSO$_2$C$_6$H$_4$		-
15f	5-Me-2-pyridyl		39
15g	*p*-ClC$_6$H$_4$	CH$_2$CMe$_3$	80
15h		COMe	73
15i		CH$_2$CH$_2$OMe	71
15j		CH$_2$-3-tetrahydrofuranyl	91

15 → 10

	Ar	R^2	Yield (%)
10l	*p*-ClC$_6$H$_4$	*i*Pr	72
10m	*p*-MeOC$_6$H$_4$		78
10n	*p*-*i*PrOC$_6$H$_4$		18 (2 steps)
10o	*p*-MeSO$_2$C$_6$H$_4$		47
10p	*m*-MeSO$_2$C$_6$H$_4$		23 (2 steps)
10q	5-Me-2-pyridyl		64
10r	*p*-ClC$_6$H$_4$	CH$_2$CMe$_3$	73
10s		COMe	69
10t		CH$_2$CH$_2$OMe	80
10u		CH$_2$-3-tetrahydrofuranyl	56

Scheme 4. Reagents and conditions: (a) PMBCl, K_2CO_3, (^{n}Bu$_4$NI,) DMF, rt–70 °C; (b) R_2Br or R_2I or R_2OMs, K_2CO_3 or NaH, (^{n}Bu$_4$NI,) DMF, rt–70 °C; (c) Ac_2O, pyridine, 120 °C; (d) TFA, 65–70 °C; (e) $POCl_3$, 80–100 °C.



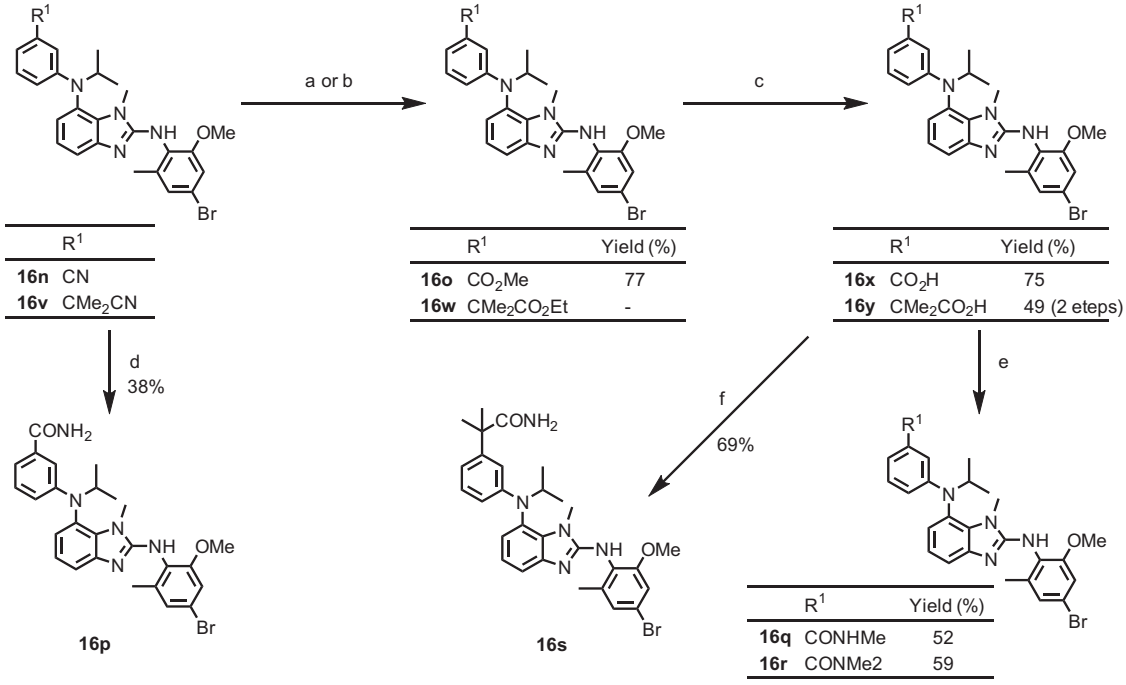
	Ar	R^2	HCl	Z	Yield (%)
16a	*p*-ClC$_6$H$_5$	*i*Pr		Cl	53
16b		CH$_2$CMe$_3$	HCl	Cl	22
16c		COMe	HCl	Cl	53
16d		CH$_2$CH$_2$OMe	HCl	Cl	33
16e		CH$_2$-3-tetrahydrofuranyl		Cl	53
16f	C$_6$H$_5$	*i*Pr		Cl	27
16g	*p*-MeOC$_6$H$_4$			Cl	65
16h	*m*-MeOC$_6$H$_4$			Br	10
16i	*p*-*i*PrOC$_6$H$_4$			Cl	36
16j	*m*-*i*PrOC$_6$H$_4$			Cl	26
16k	*p*-MeSO$_2$C$_6$H$_4$			Br	36
16l	*m*-MeSO$_2$C$_6$H$_4$			Br	64
16m	*p*-NCC$_6$H$_4$			Br	9.5
16n	*m*-NCC$_6$H$_4$			Br	69
16t	6-MeO-3-pyridyl			Cl	32
16u	5-Me-2-pyridyl			Cl	41
16v	*m*-NCMe$_2$CC$_6$H$_4$			Br	74

Scheme 5. Reagents and conditions: (a) i) 4-halogeno-2-methoxy-6-methylaniline **17** (NMP), (microwave irradiation), 100–120 °C, (ii) 2 M HCl/Et_2O).

approaches. The first involved selection of an appropriately bulky phosphine ligand, S-Phos or X-Phos, in the palladium-catalyzed coupling reactions of 7-aminobenzimidazole **5** or 7-bromobenzimidazole **8**. The second strategy was to adopt the alternate synthetic route described in Scheme 4, to prepare 2-chlorobenaimidaole **10**, based on the electron density of the benzimidazole core **6**, thus avoiding the difficulties presented by the route shown in Scheme 3.

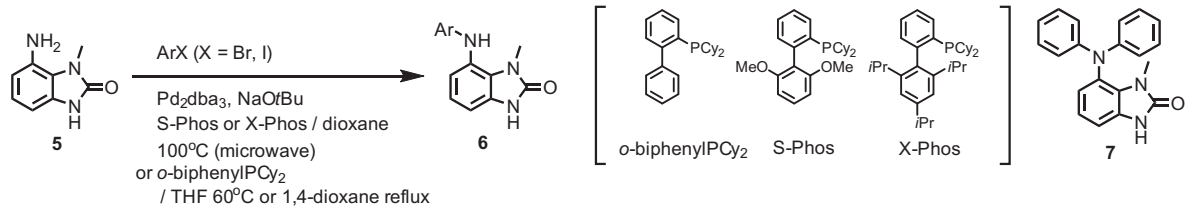
2.2. Human CRF_1 receptor binding study

The synthesized compounds **16a**–**u** were screened for their ovine ^{125}I-CRF binding inhibitory activity to human CRF_1 receptors expressed in Chinese hamster ovary (CHO) cellular membranes. This SAR study initiated from *p*-chloroanilino derivatives because a phenyl ring with a substituent at the para position is advantageous for metabolic stability.[12] The results of the 7-(*p*-chloroanilino) series are listed in Table 2. The isopropyl analog **16a** exhibited potent CRF_1 receptor binding activity comparable to 7-(dialkylamino)benzimidazole **1** with an IC_{50} value of 12 nM. It was revealed that the 7-(*p*-chloroanilino) group was able to access the lipophilic pocket and demonstrated the feasibility of replacing an alkyl group of **1** with an aromatic moiety. In addition, the compounds could be further diversified via introduction of an alkyl group of the 7-(*p*-chloroanilino) series, because they still retained



Scheme 6. Reagents and conditions: (a) i) HCl, MeOH, rt; ii) H_2O, THF; (b) EtOH, H_2SO_4, reflux; (c) NaOH, THF, (MeOH,) H_2O, rt–70 °C; (d) H_2O_2, NaOH, EtOH, H_2O, reflux; (e) $MeNH_2$ or Me_2NH, HBTU, $^iPr_2NEt$, THF, rt; (f) NH_4OH, WSC, HOBt, DMF, rt.

Table 1
Effect of phosphine ligands on Pd-catalyzed coupling reaction of 7-amino-1-methylbenzimidazol-2-one with aryl halides



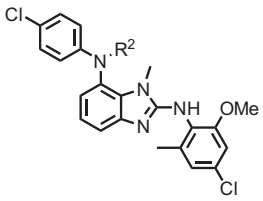
Entry	Ar	Phosphine ligand	**6** Yield (%)	Compd No.
1	C_6H_4	X-Phos	—[b]	**7**
2	*p*-$MeOC_6H_4$	*o*-biphenylPCy_2	42	**6a**
3	*p*-$MeOC_6H_4$	X-Phos	61	**6a**
4	*m*-$MeOC_6H_4$[a]	X-Phos	57	**6b**
5	*p*-*i*PrOC_6H_4	X-Phos	22	**6c**
6	*m*-*i*PrOC_6H_4	X-Phos	20	**6d**
7	*p*-ClC_6H_4	*o*-biphenylPCy_2	44	**6e**
8	*p*-$MeSO_2C_6H_4$	*o*-biphenylPCy_2	—[b]	-
9	*p*-$MeSO_2C_6H_4$	S-Phos	61	**6f**
10	*m*-$MeSO_2C_6H_4$	S-Phos	65	**6g**
11	*p*-NCC_6H_4	*o*-biphenylPCy_2	—[b]	-
12	*p*-NCC_6H_4	S-Phos	19	**6h**
13	*p*-NCC_6H_4[a]	S-Phos	74	**6h**
14	*m*-NCC_6H_4[a]	S-Phos	<5	**6i**
15	*m*-$NCMe_2CC_6H_4$	X-Phos	67	**6j**
16	5-Me-2-pyridyl	*o*-biphenylPCy_2	41	**6k**
17	6-MeO-3-pyridyl	X-Phos	32	**6l**

[a] X = I.
[b] No identification of desired compounds.

potency. The methoxyethyl analog **16d** (IC_{50} = 50 nM) exhibited a little less CRF_1 receptor binding activity than isopropyl analog **16a** (IC_{50} = 25 nM). The series with bulkier alkyl groups such as neopentyl or (tetrahydrofuranyl)methyl analogs, **16b** and **16e**, showed less potent activity than **16a** and **16d**, respectively, suggesting that the tolerable position for a bulky group is limited. The acetyl-substituted analog **16c** was six-fold less potent than the isopropyl analog **16a**. Compounds having a lipophilic group in R^2 exhibited greater potency as opposed to polar groups in binding to the CRF_1 receptors.

Effects of substitution with different sizes and diverse electronic characteristics of the 7-*N*-aryl groups are shown in Table 3. The

Table 2
Effects of alkyl groups at the 7-*N*-position on *h*CRF_1 receptor binding activity

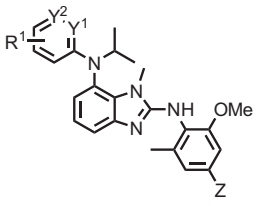


Compound No.	Additive	R^2	Binding[a] (IC_{50}, nM)
16a			25 (20–31)
16b	HCl		4400 (2600–7200)
16c	HCl		160 (100–240)
16d	HCl		50 (30–85)
16e			220 (160–310)
1	HCl		12 (7.7–17)

[a] IC_{50} values and 95% confidential intervals were calculated from the concentration–response curves.

chloro- and methoxy-analogs, **16a**, **16g**, and **16h**, were as potent as the non-substituted phenyl analog **16f** and the lead compound **1** with IC_{50} values of the binding activity of 10^{-8} M order. Compounds having bulkier substituents at the meta position of the 7-anilino moiety showed 3–12-fold more potent binding activity than the *p*-substituted compounds, for instance, the isopropyloxy analogs, **16i** versus **16j**, and the methylsulfonyl analogs, **16k** versus **16l**. On the other hand, compounds substituted by smaller groups showed almost equal activity, for instance, the methoxy analogs,

Table 3
Effects of alkyl groups at the 7-*N*-position on *h*CRF_1 receptor binding activity



Compound No.	R^1	Y^1	Y^2	Z	Binding[a] (IC_{50}, nM)
16a	*p*-Cl	CH	CH	Cl	25 (20–31)
16f	H	CH	CH	Cl	13 (8.7–20)
16g	*p*-MeO	CH	CH	Cl	27 (18–39)
16h	*m*-MeO	CH	C	Br	52 (38–69)
16i	*p*-*i*PrO	CH	CH	Cl	1800 (920–3500)
16j	*m*-*i*PrO	CH	C	Cl	580 (280–1200)
16k	*p*-$MeSO_2$	CH	CH	Br	1100 (570–2200)
16l	*m*-$MeSO_2$	CH	C	Br	90 (62–130)
16m	*p*-NC	CH	CH	Br	84 (63–110)
16n	*m*-NC	CH	C	Br	69 (48–100)
16p	*m*-H_2NCO	CH	C	Br	120 (84–160)
16q	*m*-MeHNCO	CH	C	Br	53 (41–69)
16r	*m*-Me_2NCO	CH	C	Br	75 (56–101)
16s	*m*-$H_2NCOCMe_2$	CH	C	Br	120 (76–190)
16t	6-MeO	CH	N	Cl	25 (18–33)
16u	5-Me	N	CH	Cl	69 (50–94)
1					12 (7.7–17)

[a] IC_{50} values and 95% confidential intervals were calculated from the concentration–response curves.

Table 4
Ex vivo ^{125}I-CRF binding inhibitory activity[a]

	Frontal cortex (%)	Olfactory bulb (%)	Pituitary (%)
Vehicle	0	0	0
16g	80	82	89
1	79	72	65

[a] The values are% inhibition of ovine ^{125}I-CRF binding to mouse frontal cortex, olfactory bulb, and pituitary homogenates. Tissues were collected by decapitation 1 h after oral administration of 20 mg/kg of test compounds (n = 10), respectively. Homogenates of each brain area were prepared from 10 brains for each compound.

16g versus **16h**, and the cyano analogs, **16m** versus **16n**. These results suggest that the binding pocket of CRF_1 receptor for the *para* site is not so large in comparison with that for the meta site. Regarding the meta position, electron-donating substituents such as a methoxy (**16h**) and electron-withdrawing groups such as methylsulfonyl (**16l**) and cyano (**16n**) exhibited potent binding activity with IC_{50} values of 52, 90, and 69 nM, respectively. Neutral groups such as a carboxamide (**16p**), amides (**16q** and **16r**), or an alkyl (**16s**) group on the 7-anilino group also showed activity with IC_{50} values of 53–120 nM. These results indicate that binding activity is independent of the electron density of the 7-anilino groups and the size of substituents at the meta position, except for isopropyl analog **16j**. Furthermore, it was revealed that polar groups were acceptable in this region of the binding pocket of CRF_1 receptors. Pyridyl analogs **16t** and **16u**, with IC_{50} values of 25 and 69 nM, respectively, were as potent as the phenyl analogs **16f** and **16g**.

As demonstrated in the SAR studies noted above, introduction of aniline groups in place of the alkyl groups in compound **1** in the benzimidazole series gave compounds exhibiting high potency in binding to the CRF_1 receptors. The results of the SAR studies suggested that the binding activity was independent of the electron density of the anilino group and the size of substituents at the meta position of the anilino group. On the other hand, the binding pocket of CRF_1 receptor for the *para* site of the anilino group is small in comparison with that for the meta site. Polar groups such as pyridyl moiety instead of an anilino one and amide substituents on the anilino group were also tolerable. Small and lipophilic alkyl groups as R^2 were better than bulky or polar groups in binding to CRF_1 receptors.

Among these 7-*N*-arylbenzimidazoles, compound **16g** demonstrated better mouse metabolic stability as well as potent activity in the CRF_1 receptor-binding assay. Compound **16g** also inhibited luciferase levels responding to *c*AMP released by human CRF with IC_{50} values of 56 (40–77) nM in vitro CRF_1 antagonistic activity, indicating that compound **16g** behaves as a CRF_1 receptor antagonist.

2.3. Ex vivo binding study in mice

The penetration into the brain and the CRF_1 receptor binding activity of compound **16g** one hour after 20 mg/kg oral administration was evaluated in ex vivo studies in mice. The results are listed in Table 4. Compound **16g** significantly inhibited ^{125}I-CRF binding in frontal cortex, olfactory bulb, and pituitary gland. The inhibitory rates of **16g** were around 80%, which showed activity as potent as that of compound **1**. These results suggested that compound **16g** was orally administered, well absorbed, and easily penetrated into the brain.

3. Conclusion

In this study, a novel series of 7-arylamino-1*H*-benzimidazole was synthesized and evaluated as CRF_1 receptor antagonists. The aromatic groups at the 7-*N*-position of the benzimidazole were

introduced by palladium-catalyzed coupling reactions of 7-aminobenzimidazole **5** or 7-bromobenzimidazole **8** in the presence of bulky phosphine ligands, S-Phos or X-Phos. The synthetic route of the key intermediates, 2-chlorobenzimidazole **10**, can be selected depending on the electron density of the benzimidazole core. These investigations successfully provided a novel synthetic method for preparing 2,7-diarylaminobenzimidazoles. The synthesized target compounds were evaluated in an in vitro CRF_1 receptor-binding assay and the SAR study was examined. The results suggested that diverse substituents on the anilino group at the 7-position were tolerable for binding activity, and small alkyl groups at the 7-*N*-position were better than bulky groups. It was revealed that an aryl group at the 7-*N*-position of a benzimidazole core could replace an alkyl group and occupy the lipophilic pocket of the CRF_1 receptor. The selected compound having potent human CRF_1 receptor binding inhibition activity, **16g**, also showed human CRF_1 antagonistic activity in cAMP accumulation assay. Furthermore, this compound exhibited ex vivo CRF binding inhibitory activity in mice, suggesting that this compound can be well absorbed orally and easily penetrate the brain. It was found that the novel benzimidazole series with an aryl group as well as an alkyl group at the 7-*N*-position resulted in compounds exhibiting potent activity as CRF_1 receptor antagonists.

4. Experimental

4.1. General

All reactions were performed using commercially available starting materials, reagents and solvents, without further purification. Reactions were monitored using thin-layer chromatography with silica gel 60 F_{254} plates (Merck) or liquid chromatography–mass spectrometry (LC/MS). LC/MS analysis was performed using three methods. The first method was performed using an HP-1100 (Agilent Technologies) separations module [CAPCELL PAK UG-120 ODS (2.0 × 50 mm I.D., Shiseido Co., Ltd, Japan); 0.1% TFA in a distilled H_2O/MeCN gradient; UV detection at 220 nm or 254 nm]. MS spectra were recorded using a Micromass ZMD with electrospray ionization. The second method was performed using a Shimadzu LC-20AD separations module [L-column2 ODS (3.0 × 50 mm I.D., CERI, Japan); 5 mM $AcONH_4$ in an ultrapure H_2O/MeCN gradient; UV detection at 220 nm or 254 nm]. MS spectra were recorded using a Shimadzu LCMS-2020 system with electrospray ionization. The third method was performed using a Waters 2795 separations module [L-column2 ODS (3.0 × 50 mm I.D., CERI, Japan); 0.05% TFA in an ultrapure H_2O/MeCN gradient; UV detection at 220 nm or 254 nm]. MS spectra were recorded using a Waters ZQ2000 with electrospray ionization. Magnesium sulfate or sodium sulfate was used as a desiccant for organic extracts. Chromatographic purification was performed using a silica gel column (Kieselgel 60, 0.063–0.22 mm, Merck) or Purif-Pack (SI 60 μm or NH 60 μm, Fuji Silysia, Ltd). Preparative TLC purification was performed using a TLC plate (silica gel 60, Merck). Preparative HPLC purification was performed using a Gilson pumping system with a photodiode array detector (Hewlett Packard 1100 series) [YMC ODS-A (20 × 50 mm I.D.); 0.1% TFA in a distilled H_2O/MeCN gradient; UV detection at 220 nm]. Separations were achieved using a YMC packed column. Synthesized compounds were analyzed as described below. Melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. LC/MS analysis for the detection of mass ion peaks was performed as described above. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Varian Mercury-300 (300 MHz) and a Bruker DPX-300 (300 MHz) NMR system. Chemical shifts are shown in parts per million (ppm), and tetramethylsilane was used as an internal standard. Abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet, dd = doublets of a doublet, br = broad, and br s = broad singlet. Coupling constants (*J* values) are given in hertz (Hz). The acidic protons of diketones, carboxylic acids, alcohols, or anilines were not frequently observed in the ^{1}H NMR spectra. ^{13}C NMR spectra were recorded on a Bruker Avance II + 600 (600 MHz). Chemical shifts are given in parts per million (ppm), with tetramethylsilane used as an internal standard. The purities were assessed using elemental analyses or analytical HPLC. Elemental analyses were performed by Takeda Analytical Research Laboratories, Ltd. HPLC analyses were performed using a Varian ProStar [YMC ODS-AQ (4.6 × 150 mm I.D.); 1% *i*-PrOH and 10 mM NH_4OAc in a distilled H_2O/MeCN gradient; UV detection at 220 nm or 254 nm] or a Shimadzu UFLC instrument [L-column2 ODS (3.0 × 50 mm, I.D.); 0.1% TFA in a distilled H_2O/MeCN gradient; UV detection at 220 nm]. HPLC analysis showed %purity in terms of the area under the curve of a main peak.

4.2. Synthesis

4.2.1. *N*-Methyl-2,6-dinitroaniline (3)

To a suspension of 2-chloro-1,3-dinitrobenzene (200 g, 987 mmol) in methanol (300 mL) was added methylamine (40% solution in methanol; 314 mL, 2960 mmol), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate and saturated aqueous sodium hydrogen carbonate. The aqueous layer was separated and extracted with ethyl acetate. The organic layer was washed with water, brine, passed through celite and concentrated in vacuo to give the title compound (191.8 g, 99%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.89 (3H, d, J = 5.4 Hz), 6.76 (1H, t, J = 8.1 Hz), 8.18 (2H, d, J = 8.1 Hz), 8.49 (1H, br s).

4.2.2. N^2-Methylbenzene-1,2,3-triamine (4)

To a solution of compound **3** (31.6 g, 150 mmol) in tetrahydrofuran with stabilizer (470 mL) was added palladium on carbon (3.5 g), and the mixture was stirred at room temperature for 7 h under hydrogen pressure. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give the title compound, which was used without purification. ^{1}H NMR ($CDCl_3$) δ 1.83–1.87 (3H, m), 3.72–3.77 (5H, m), 6.22 (2H, d, J = 7.8 Hz), 6.75 (1H, t, J = 7.8 Hz).

4.2.3. 7-Amino-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (5)

To a solution of compound **4** (42.0 g, 306 mmol) in tetrahydrofuran (450 mL) was added CDI (25.5 g, 158 mmol), and the mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuo, and the residual solid was washed with dichloromethane to give the title compound (20.1 g, 77%) as a solid. ^{1}H NMR (DMSO-d_6) δ 3.50 (3H, br s), 4.84 (2H, s), 6.29 (1H, dd, J = 7.8, 0.9 Hz), 6.34 (1H, dd, J = 7.8, 0.9 Hz), 6.67 (1H, t, J = 8.1 Hz).

4.2.4. 7-[(4-Methoxyphenyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (6a) (entry 2)

To a mixture of compound **5** (0.183 g, 1.12 mmol), *o*-biphenylPCy$_2$ (0.037 g, 0.11 mmol), sodium *tert*-butoxide (0.237 g, 2.47 mmol) and tris(dibenzylidineacetone)dipalladium (0.041 g, 0.045 mmol) in tetrahydrofuran (6 mL) was added 4-bromoanisole (0.14 mL, 1.12 mmol) and heated to 60 °C for 18 h. The reaction mixture was diluted with ethyl acetate, and passed through celite. The filtrate was purified by silica gel column chromatography eluting with a 97% methanol/dichloromethane mixture to give the title compound (0.126 g, 42%) as a tan powder.

4.2.5. 7-[(4-Methoxyphenyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (6a) (entry 3)

To a mixture of compound **5** (2.00 g, 12.3 mmol), X-Phos (0.292 g, 0.613 mmol), sodium *tert*-butoxide (2.94 g, 30.6 mmol) and tris(dibenzylidineacetone)dipalladium (0.224 g, 0.245 mmol) in 1,4-dioxane (25 mL) was added 4-bromoanisole (1.6 mL, 12.9 mmol) and heated to 100 °C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was powdered from diethyl ether to give the title compound (2.02 g, 61%). MS calcd: 269; Found: 270 (M+H). ^{1}H NMR (DMSO-d_6) δ 3.29 (3H, s), 3.66 (3H, s), 6.62 (2H, d, J = 8.8 Hz), 6.70–6.83 (4H, m), 6.91 (1H, t, J = 7.8 Hz), 7.30 (1H, s), 10.85 (1H, s).

4.2.6. 7-[(3-Methoxyphenyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (6b)

Compound **6b** (0.283 g, 57%) was prepared from 3-iodoanisole (0.230 mL, 1.93 mmol) in a manner similar to that described in compound **6a** (entry 3). Solid. ^{1}H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.65 (3H, s), 6.15–6.19 (2H, m), 6.25–6.28 (1H, m), 6.77–6.84 (2H, m), 6.96 (1H, t, J = 7.8 Hz), 7.02 (1H, t, J = 7.8 Hz), 7.67 (1H, s), 10.93 (1H, s).

4.2.7. 1-Methyl-7-[[4-(1-methylethyl)oxyphenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (6c)

Compound **6c** (0.370 g, 22%) was prepared from 1-bromo-4-(1-methylethoxy)benzene (0.801 mL, 6.43 mmol) in a manner similar to that described in compound **6a** (entry 3). Solid. ^{1}H NMR (DMSO-d_6) δ 1.20 (6H, d, J = 6.3 Hz), 3.30 (3H, s), 4.34–4.44 (1H, m), 6.58–6.62 (2H, m), 6.71–6.81 (4H, m), 6.88–6.94 (1H, m), 7.33 (1H, s).

4.2.8. 1-Methyl-7-[[3-(1-methylethyl)oxyphenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (6d)

Compound **6d** (0.370 g, 20%) was prepared from 1-bromo-3-[(1-methylethyl)oxy]benzene (1.38 g, 6.44 mmol) in a manner similar to that described in compound **6a** (entry 3). Solid. ^{1}H NMR ($CDCl_3$) δ 1.29 (6H, d, J = 6.4 Hz), 3.49 (3H, s), 4.42–4.52 (1H, m), 5.32 (1H, br s), 6.15–6.17 (1H, m), 6.22–6.27 (1H, m), 6.34–6.39 (1H, m), 6.85–6.90 (1H, m), 6.94–7.12 (3H, m), 9.37 (1H, br s).

4.2.9. 7-[(4-Chlorophenyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (6e)

To a mixture of compound **5** (5.00 g, 30.6 mmol), *o*-biphenylPCy$_2$ (0.537 g, 1.53 mmol), sodium *tert*-butoxide (7.40 g, 2.50 mmol) and tris(dibenzylidineacetone)dipalladium (0.56 g, 0.61 mmol) and 1,4-dioxane (80 mL) were added 4-chlorobromobenzene (6.16 g, 32.2 mmol), and the mixture was refluxed for 22 h. The reaction mixture was cooled, poured into water (200 mL) and adjusted to pH 8 with saturated aqueous ammonium chloride. The precipitate was filtered, washed with water and dried. Recrystallization from ethanol gave the title compound (3.69 g, 44%) as a tan crystal. MS calcd: 273; Found: 274 (M+H).

4.2.10. 1-Methyl-7-[(4-methylsulfonyl)phenylamino]-1,3-dihydro-2*H*-benzimidazol-2-one (6f)

To a mixture of compound **5** (0.300 g, 1.84 mmol), S-Phos (0.0377 g, 0.0919 mmol), sodium *tert*-butoxide (0.350 g, 3.70 mmol), tris(dibenzylidineacetone)dipalladium (0.170 g, 0.180 mmol) and 1,4-dioxane (0.5 mL) was added 4-bromophenylmethylsulfone (0.520 g, 2.20 mmol), and the mixture was refluxed for 4 h. The reaction mixture was cooled, poured into water, and extracted with ethyl acetate and ethyl acetate-tetrahydrofuran. The organic layer was concentrated in vacuo. The resulting solid was washed with ethyl acetate to give the title compound (0.357 g, 61%) as crystals. ^{1}H NMR ($CDCl_3$) δ 3.09 (3H, s), 3.25 (3H, s), 6.70 (2H, d, J = 8.6 Hz), 6.83 (1H, d, J = 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.64 (2H, d, J = 8.6 Hz), 8.53 (1H, s), 11.01 (1H, s).

4.2.11. 1-Methyl-7-[(3-methylsulfonyl)phenylamino]-1,3-dihydro-2*H*-benzimidazol-2-one (6g)

Compound **6g** (0.545 g, 65%) was prepared from 3-bromophenylmethylsulfone (0.590 g, 1.35 mmol) in a manner similar to that described in compound **6f**. ^{1}H NMR (DMSO-d_6) δ 3.13 (3H, s), 3.29 (3H, s), 6.82–6.91(3H, m), 7.01 (1H, t, J = 8.0 Hz), 7.13 (1H, s), 7.18 (1H, d, J = 8.0 Hz), 7.38 (1H, t, J = 8.0 Hz), 8.23 (1H, s), 11.00 (1H, br s).

4.2.12. 4-[(1-Methyl-2-oxo-1,3-dihydro-2*H*-benzimidazol-7-yl)amino]benzonitrile (6h) (entry 13)

Compound **6h** (0.036 g, 74%) was prepared from 4-iodobenzonitrile (0.051 g, 0.22 mmol) in a manner similar to that described in compound **6f**. ^{1}H NMR (DMSO-d_6) δ 3.23 (3H, s), 6.69 (2H, d, J = 8.8 Hz), 6.82 (1H, d, J = 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.52 (2H, d, J = 8.8 Hz), 8.55 (1H, s), 11.01 (1H, s).

4.2.13. 3-[(1-Methyl-2-oxo-1,3-dihydro-2*H*-benzimidazol-7-yl)amino]benzonitrile (6i)

Compound **6i** (0.043 g, 37%) was prepared from compound **8** (0.100 g, 0.44 mmol), the preparation is described below, and 3-aminobenzonitrile (0.062 g, 0.53 mmol) in a manner similar to that described in compound **6f**. ^{1}H NMR ($CDCl_3$) δ 3.45 (3H, s), 5.53 (1H, s), 6.84–6.89 (3H, m), 7.02–7.10 (4H, m), 9.03 (1H, s).

4.2.14. 2-Methyl-2-{3-[(3-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl)amino]phenyl}propanenitrile (6j)

Compound **6j** (0.930 g, 67%) was prepared from 2-(3-bromophenyl)-2-methylpropanenitrile (1.11 g, 4.95 mmol) in a manner similar to that described in compound **6a** (entry 3). Solid. MS calcd: 306; Found: 307 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.70 (6H, s), 3.50 (3H, s), 5.47 (1H, s), 6.52 (1H, dd, J = 8.4, 2.1 Hz), 6.80–6.95 (2H, m), 6.95–7.15 (2H, m), 7.17 (1H, d, J = 8.1 Hz), 9.37(1H, s).

4.2.15. 1-Methyl-7-(5-methylpyridin-2-ylamino)-1,3-dihydro-2*H*-benzimidazol-2-one (6k)

Compound **6k** (1.29 g, 41%) was prepared from 2-bromo-5-methylpyridine (2.21 g, 12.0 mmol) in a manner similar to that described in compound **6e**. MS calcd: 254; Found: 255 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 3.32 (3H, s), 6.44 (1H, d, J = 8.4 Hz), 6.75–6.90 (2H, m), 6.90–7.00 (1H, m), 7.33 (1H, d, J = 8.4 Hz), 7.83 (1H, s), 8.20 (1H, s), 10.88 (1H, s).

4.2.16. 7-[(6-Methoxypyridin-3-yl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (6l)

Compound **6l** (0.525 g, 32%) was prepared from 5-bromo-2-methoxypyridine (0.833 mL, 6.43 mmol) in a manner similar to that described in compound **6a** (entry 3). Solid. ^{1}H NMR (DMSO-d_6) δ 3.34 (3H, s), 3.76 (3H, s), 6.67–6.72 (2H, m), 6.77 (1H, d, J = 7.2 Hz), 6.92 (1H, t, J = 7.8 Hz), 7.10–7.13 (1H, m), 7.43 (1H, s), 7.60–7.61 (1H, m), 10.92 (1H, br s).

4.2.17. 7-Anilino-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (6m)

Compound **6m** (0.402 g, 64%) was prepared from compound **8** (0.600 g, 2.64 mmol), the preparation is described below, and aniline (0.253 mL, 2.77 mmol) in a manner similar to that described in compound **6a** (entry 3). MS calcd: 239; Found: 240 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.48 (3H, s), 5.35 (1H, s), 6.64–6.67 (2H, m), 6.83 (1H, t, J = 7.2 Hz), 6.85–6.89 (1H, m), 6.97 (1H, t, J = 6.6 Hz), 7.03 (1H, t, J = 7.8 Hz), 7.17–7.23 (2H, m), 9.23 (1H, br s).

4.2.18. 7-Bromo-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (8)

To a suspension of compound **5** (6.10 g, 37.4 mmol) and copper (II) bromide (4.20 g, 19.0 mmol) in *N*,*N*-dimethylformamide (30 mL) was added *tert*-butyl nitrite (5.43 mL, 41.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 8 h. The reaction mixture was passed through celite, and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The resulting solid was washed with ethanol-diethyl ether to give the title compound (3.53 g, 42%). ^{1}H NMR (DMSO-d_6) δ 3.56 (3H, s), 6.91 (1H, t, J = 8.0 Hz), 6.98 (1H, d, J = 8.0 Hz), 7.15 (1H, d, J = 8.0 Hz), 11.17 (1H, s).

4.2.19. 4-[(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)amino] benzonitrile (9d)

A mixture of compound **6h** (0.137 g, 0.518 mmol) and phosphorous oxychloride (1.5 mL) was refluxed for 3 h. The mixture was concentrated in vacuo. The residue was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 25% ethyl acetate/hexane mixture to give the title compound (0.066 g, 45%). MS calcd: 282; Found: 283 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 5.97 (1H, s), 6.62 (2H, d, J = 8.6 Hz), 7.09 (1H, d, J = 7.8 Hz), 7.28 (1H, t, J = 7.8 Hz), 7.46 (2H, d, J = 8.6 Hz), 7.66 (1H, d, J = 7.8 Hz).

4.2.20. 2-Chloro-1-methyl-*N*-phenyl-1*H*-benzimidazol-7-amine (9a)

Compound **9a** (0.138 g, 32%) was prepared from compound **6m** (0.400 g, 1.67 mmol) in a manner similar to that described in compound **9d**. MS calcd: 257; Found: 258 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 5.20 (1H, br s), 6.61–6.65 (2H, m), 6.82–6.87 (1H, m), 7.04 (1H, d, J = 7.5 Hz), 7.16–7.25 (3H, m), 7.57 (1H, t, J = 7.5 Hz).

4.2.21. 2-Chloro-*N*-(3-methoxyphenyl)-1-methyl-1*H*-benzimidazol-7-amine (9b)

Compound **9b** (0.336 g, 44%) was prepared from compound **6b** (0.715 g, 2.66 mmol) in a manner similar to that described in compound **9d**. Oil. ^{1}H NMR ($CDCl_3$) δ 3.73 (3H, s), 3.82 (3H, s), 5.48 (1H, br s), 6.15–6.17 (1H, m), 6.21–6.24 (1H, m), 6.38–6.42 (1H, m), 7.03–7.13 (2H, m), 7.22 (1H, t, J = 7.8 Hz), 7.57–7.60 (1H, m).

4.2.22. 2-Chloro-1-methyl-*N*-(3-(1-methylethyl)oxyphenyl)-1*H*-benzimidazol-7-amine (9c)

Compound **9c** (0.180 g, 58%) was prepared from compound **6d** (0.295 g, 0.992 mmol) in a manner similar to that described in compound **9d**. Oil. ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, d, J = 6.0 Hz), 3.82 (3H, s), 4.39–4.49 (1H, m), 5.43 (1H, br s), 6.12–6.14 (1H, m), 6.19–6.22 (1H, m), 6.37–6.40 (1H, m), 7.03–7.11 (2H, m), 7.22 (1H, t, J = 8.4 Hz), 7.56–7.59 (1H, m).

4.2.23. 3-[(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)amino] benzonitrile (9e)

Compound **9e** (0.557 g, 38%) was prepared from compound **6i** (1.38 g, 5.22 mmol) in a manner similar to that described in compound **9d**. MS calcd: 282; Found: 283 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s), 5.76 (1H, s), 6.83–6.86 (2H, m), 7.07–7.12 (2H, m), 7.26–7.30 (2H, m), 7.65 (1H, dd, J = 8.0, 0.8 Hz).

4.2.24. 2-[3-[(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)amino] phenyl]-2-methylpropanenitrile (9f)

Compound **9f** (0.789 g, 81%) was prepared from compound **6j** (0.920 g, 3.00 mmol) in a manner similar to that described in compound **9d**. Oil. MS calcd: 324; Found: 325 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.69 (6H, s), 3.83 (3H, s), 5.58 (1H, s), 6.46 (1H, dd, J = 8.4, 2.4 Hz), 6.85–6.95 (1H, m), 7.00–7.12 (2H, m), 7.16 (1H, d, J = 8.1 Hz), 7.20–7.30 (1H, m), 7.59 (1H, d, J = 8.1 Hz).

4.2.25. 2-Chloro-*N*-(6-methoxypyridin-3-yl)-1-methyl-1*H*-benzimidazol-7-amine (9g)

Compound **9g** (0.228 g, 41%) was prepared from compound **6l** (0.520 g, 1.92 mmol) in a manner similar to that described in compound **9d**. Oil. ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 3.88 (3H, s), 5.45 (1H, br s), 6.63–6.66 (1H, m), 6.93–6.95 (1H, m), 7.01–7.05 (1H, m), 7.17 (1H, t, J = 8.4 Hz), 7.47–7.50 (1H, m), 7.64–7.65 (1H, m).

4.2.26. 2-Chloro-1-methyl-*N*-(1-methylethyl)-*N*-phenyl-1*H*-benzimidazol-7-amine (10a)

To a suspension of compound **9a** (0.130 g, 0.504 mmol) in *N*,*N*-dimethylformamide (2.5 mL) was added sodium hydride (60% dispersion in oil; 0.202 g, 5.04 mmol) at 0 °C, and the mixture was stirred at room temperature for 5 min. 2-Iodopropane (0.504 mL, 5.04 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 20% ethyl acetate/hexane mixture to give the title compound (0.128 g, 85%) as a syrup. MS calcd: 299; Found: 300 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, br s), 1.40 (3H, br s), 3.63 (3H, s), 4.35–4.44 (1H, m), 6.49 (2H, dd, J = 8.7, 0.9 Hz), 6.68–6.73 (1H, m), 7.05 (1H, dd, J = 7.5, 0.9 Hz), 7.13–7.18 (2H, m), 7.30 (1H, t, J = 8.1 Hz), 7.69 (1H, dd, J = 8.1, 0.9 Hz).

4.2.27. 2-Chloro-*N*-(3-methoxyphenyl)-1-methyl-*N*-(1-methylethyl)-1*H*-benzimidazol-7-amine (10b)

Compound **10b** (0.368 g, 70%) was prepared from compound **9b** (0.336 g, 1.17 mmol) in a manner similar to that described in compound **10a**. Oil. ^{1}H NMR ($CDCl_3$) δ 0.83–0.94 (3H, m), 1.36–1.44 (3H, m), 3.64 (3H, s), 3.71 (3H, s), 4.26–4.39 (1H, m), 6.06–6.12 (2H, m), 6.26–6.29 (1H, m), 7.01–7.15 (2H, m), 7.28 (1H, t, J = 7.2 Hz), 7.67 (1H, d, J = 6.9 Hz).

4.2.28. 2-Chloro-1-methyl-*N*-(1-methylethyl)-*N*-[3-(1-methylethyl)oxyphenyl]-1*H*-benzimidazol-7-amine (10c)

Compound **10c** (0.0690 g, 66%) was prepared from compound **9c** (0.0930 g, 0.294 mmol) in a manner similar to that described in compound **10a**. Oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 6.6 Hz), 1.27 (6H, d, J = 6.0 Hz), 1.40 (3H, d, J = 6.6 Hz), 3.65 (3H, s), 4.30–4.40 (1H, m), 4.37–4.47 (1H, m), 6.01–6.06 (2H, m), 6.25–6.28 (1H, m), 7.00–7.06 (2H, m), 7.28 (1H, t, J = 7.8 Hz), 7.66–7.69 (1H, m).

4.2.29. 4-[(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)(1-methylethyl) amino]benzonitrile (10d)

To a suspension of compound **9d** (0.064 g, 0.226 mmol), tetrabutylammonium iodide (0.0084 g, 0.023 mmol) and sodium hydride (90% dry; 0.0181 g, 0.679 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was added 2-bromopropane (0.0723 mL, 0.679 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 50% ethyl acetate/hexane mixture to give the title compound (0.064 g, 87%). MS calcd: 324; Found: 325 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, d, J = 6.6 Hz), 1.43 (3H, d, J = 6.6 Hz), 3.58 (3H, s), 4.30–4.43 (1H, m), 6.49 (2H, d, J = 8.2 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.42 (2H, d, J = 8.2 Hz), 7.75 (1H, d, J = 8.0 Hz).

4.2.30. 3-[(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)(1-methylethyl)amino]benzonitrile (10e)

Compound **10e** (0.480 g, 75%) was prepared from compound **9e** (0.556 g, 1.97 mmol) in a manner similar to that described in compound **10d**. MS calcd: 324; Found: 325 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 6.4 Hz), 1.41 (3H, d, J = 6.4 Hz), 3.61 (3H, s), 4.30–4.38 (1H, m), 6.62 (1H, d, J = 8.0 Hz), 6.78 (1H, s), 6.98 (1H, d, J = 8.0 Hz), 7.01 (1H, d, J = 8.0 Hz), 7.20 (1H, t, J = 8.0 Hz), 7.33 (1H, t, J = 8.0 Hz), 7.74 (1H, d, J = 8.0 Hz).

4.2.31. 2-[3-[(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)(1-methylethyl)amino]phenyl]-2-methylpropanenitrile (10f)

Compound **10f** (0.520 g, 59%) was prepared from compound **9f** (0.780 g, 2.13 mmol) in a manner similar to that described in compound **10a**. Solid. Mp 105–106 °C. MS calcd: 366; Found: 367 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 7.2 Hz), 1.42 (3H, d, J = 7.2 Hz), 1.66 (6H, s), 3.64 (3H, s), 4.35–4.50 (1H, m), 6.24 (1H, d, J = 7.2 Hz), 6.76 (1H, d, J = 7.2 Hz), 6.78 (1H, s), 7.05 (1H, d, J = 8.0 Hz), 7.10 (1H, t, J = 7.2 Hz), 7.31 (1H, t, J = 8.0 Hz), 7.70 (1H, d, J = 8.0 Hz).

4.2.32. 2-Chloro-*N*-(6-methoxypyridin-3-yl)-1-methyl-*N*-(1-methylethyl)-1*H*-benzimidazol-7-amine (10g)

Compound **10g** (0.221 g, 90%) was prepared from compound **9g** (0.228 g, 0.790 mmol) in a manner similar to that described in compound **10a**. Oil. ^{1}H NMR ($CDCl_3$) δ 0.98–1.43 (6H, m), 3.72 (3H, s), 3.85 (3H, s), 4.24–4.34 (1H, m), 6.58 (1H, dd, J = 9.0, 0.9 Hz), 6.79 (1H, dd, J = 9.0, 3.3 Hz), 7.05 (1H, dd, J = 7.5, 0.9 Hz), 7.28 (1H, t, J = 7.5 Hz), 7.53 (1H, d, J = 3.3 Hz), 7.67 (1H, dd, J = 7.5, 0.9 Hz).

4.2.33. 4-[(4-Chlorophenyl)amino]-1-(4-methoxybenzyl)-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (13a)

A mixture of compound **6e** (0.270 g, 1.00 mmol), 4-methoxybenzyl chloride (0.17 mL, 1.20 mmol), potassium carbonate (0.210 g, 1.50 mmol) and *N*,*N*-dimethylformamide (1 mL) was stirred at 70 °C for 100 min. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 15% ethyl acetate/hexane mixture to give the title compound (0.39 g, >99%) as a powder. MS calcd: 393; Found: 394 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.49 (3H, s), 3.78 (3H, s), 5.02 (2H, s), 5.30 (1H, s), 6.56 (2H, d, J = 8.4 Hz), 6.80–6.95 (4H, m), 6.97 (1H, t, J = 8.0 Hz), 7.13 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.0 Hz).

4.2.34. 1-(4-Methoxybenzyl)-4-[(4-methoxyphenyl)amino]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (13b)

A mixture of compound **6a** (1.53 g, 5.68 mmol), 4-methoxybenzyl chloride (0.924 mL, 6.82 mmol), potassium carbonate (1.57 g, 11.4 mmol), tetrabutylammonium iodide (0.0315 mg, 0.085 mmol) and *N*,*N*-dimethylformamide (20 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water and concentrated in vacuo. The residue was powdered from diethyl ether to give the title compound (2.10 g, 95%) as a powder. MS calcd: 389; Found: 390 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.53 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 5.01 (2H, s), 5.20 (1H, br s), 6.64–6.68 (2H, m), 6.71–6.70 (4H, m), 6.84–6.95 (3H, m), 7.28–7.31 (2H, m).

4.2.35. 1-(4-Methoxybenzyl)-3-methyl-4-[[4-(1-methylethyl)oxyphenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (13c)

Compound **13c** (0.860 g, 67%) was prepared from compound **6c** (0.920 g, 3.09 mmol) in a manner similar to that described in compound **13b**. Solid. ^{1}H NMR ($CDCl_3$) δ 1.29 (6H, d, J = 6.0 Hz), 3.53 (3H, s), 3.76 (3H, s), 4.34–4.46 (1H, m), 5.01 (2H, s), 5.19 (1H, br s), 6.62–6.66 (2H, m), 6.71–6.95 (7H, m), 7.28–7.31 (2H, m).

4.2.36. 1-(4-Methoxybenzyl)-3-methyl-4-[[(4-methylsulfonyl)phenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (13d)

Compound **13d** (0.595 g, 49%) was prepared from compound **6f** (0.887 g, 2.80 mmol) in a manner similar to that described in compound **13b**. ^{1}H NMR ($CDCl_3$) δ 3.00 (3H, s), 3.47 (3H, s), 3.77 (3H, s), 5.01 (2H, s), 6.31 (1H, s), 6.69 (1H, d, J = 8.8 Hz), 6.84–6.89 (4H, m), 7.01 (1H, t, J = 8.0 Hz), 7.29 (2H, d, J = 8.8 Hz), 7.69 (2H, d, J = 8.8 Hz).

4.2.37. 1-(4-Methoxybenzyl)-3-methyl-4-[[(3-methylsulfonyl)phenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (13e)

Compound **13e** (0.980 g, 71%) was prepared from compound **6g** (1.00 g, 3.15 mmol) in a manner similar to that described in compound **13b**. ^{1}H NMR ($CDCl_3$) δ 3.03 (3H, s), 3.50 (3H, s), 3.78 (3H, s), 5.03 (2H, s), 5.63 (1H, s), 6.81–6.87 (5H, m), 7.00 (1H, t, J = 8.0 Hz), 7.29–7.35 (5H, m).

4.2.38. 1-(4-Methoxybenzyl)-3-methyl-4-(5-methylpyridin-2-ylamino)-1,3-dihydro-2*H*-benzimidazol-2-one (13f)

Compound **13f** (1.60 g, 87%) was prepared from compound **6k** (1.25 g, 4.92 mmol) in a manner similar to that described in compound **13b**. Oil. MS calcd: 374; Found: 375 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.21 (3H, s), 3.52 (3H, s), 3.78 (3H, s), 5.02 (2H, s), 6.22 (1H, s), 6.28 (1H, d, J = 8.4 Hz), 6.80–6.90 (2H, m), 6.90 (1H, d, J = 8.0 Hz), 6.98 (1H, t, J = 8.0 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.25-.35 (1H, m), 7.98 (1H, s).

4.2.39. 4-[(4-Chlorophenyl)(1-methylethyl)amino]-1-(4-methoxybenzyl)-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (14a)

To a mixture of compound **13a** (0.118 g, 0.30 mmol), 2-bromopropane (0.056 mL, 0.60 mmol), tetrabutylammonium iodide (one spatula) and *N*,*N*-dimethylformamide (2 mL) was added sodium hydride (90% dry; 0.016 g, 0.60 mmol). The mixture was stirred at 60 °C for 6 h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 20–33% ethyl acetate/hexane gradient mixture to give the title compound (0.0806 g, 62%) as an oil. MS calcd: 435; Found: 436 (M+H). ^{1}H NMR($CDCl_3$) δ 0.96 (3H, d, J = 6.0 Hz), 1.33 (3H, d, J = 6.0 Hz), 3.30 (3H, s), 3.79 (3H, s), 4.20–4.35 (1H, m), 5.02 (2H, s), 6.40 (2H, d, J = 9.2 Hz), 6.77 (1H, d, J = 8.0 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.92 (1H, d, J = 8.0 Hz), 7.05 (1H, d, J = 8.0 Hz), 7.09 (2H, d, J = 9.2 Hz), 7.32 (2H, d, J = 8.4 Hz).

4.2.40. 4-[(4-Chlorophenyl)(2,2-dimethylpropyl)amino]-1-(4-methoxybenzyl)-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (14g)

To a solution of compound **13a** (0.118 g, 0.300 mmol), neopentyl iodide (0.119 g, 0.600 mmol) in *N*,*N*-dimethylformamide (3 mL) was added sodium hydride (90% dry; 0.016 g, 0.600 mmol), and the mixture was stirred at 60 °C for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 20% ethyl acetate/hexane mixture to give the title compound (0.045 g, 32%). MS calcd: 463; Found: 464 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, s), 3.28 (3H, s), 3.37 (1H, d, J = 14.8 Hz), 3.79–3.82 (4H, m), 4.95–5.10 (2H, m), 6.52 (2H, d, J = 8.8 Hz), 6.80–6.90 (3H, m), 6.95–7.05 (2H, m), 7.05 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 8.4 Hz).

4.2.41. 1-(4-Methoxybenzyl)-4-[4-(methoxyphenyl)(1-methylethyl)amino]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (14b)

Compound **14b** (1.80 g, 80%) was prepared from compound **13b** (2.02 g, 1.35 mmol) and 2-iodopropane (7.18 mL) according to the method described in the preparation of compound **14g**. MS calcd: 431; Found: 432 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.80–1.30 (6H, m), 3.36 (3H, s), 3.73 (3H, s), 3.79 (3H, s), 4.20–4.35 (1H, m), 5.02 (2H, s), 6.46 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 8.8 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.85–6.95 (3H, m), 7.01 (1H, t, J = 8.0 Hz), 7.32 (2H, d, J = 8.8 Hz).

4.2.42. 1-(4-Methoxybenzyl)-3-methyl-4-[(1-methylethyl)[4-(1-methylethyl)oxyphenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (14c)

Compound **14c** (0.674 g, 71%) was prepared from compound **13c** (0.860 g, 2.06 mmol) and 2-iodopropane (2.06 mL, 20.6 mmol) in a manner similar to that described in compound **14g**. Solid. ^{1}H NMR ($CDCl_3$) δ 1.04–1.33 (6H, m), 1.27 (6H, d, J = 6.0 Hz), 3.35 (3H, s), 3.79 (3H, s), 4.19–4.29 (1H, m), 4.29–4.39 (1H, m), 5.02 (2H, s), 6.41–6.45 (2H, m), 6.70–6.76 (2H, m), 6.79–6.82 (1H, m), 6.85–6.89 (3H, m), 7.00 (1H, t, J = 7.5 Hz), 7.32 (2H, d, J = 8.7 Hz).

4.2.43. 1-(4-Methoxybenzyl)-3-methyl-4-[(1-methylethyl)[4-(methylsulfonyl)phenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (14d)

Compound **14d** (0.545 g, 84%) was prepared from compound **13d** (0.590 g, 1.35 mmol) in a manner similar to that described in compound **14a**. ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, d, J = 6.2 Hz), 1.26 (3H, d, J = 6.2 Hz), 3.01 (3H, s), 3.25 (3H, s), 3.79 (3H, s), 4.32–4.39 (1H, m), 5.01 (1H, d, J = 15.4 Hz), 5.06 (1H, d, J = 15.4 Hz), 6.56 (2H, d, J = 8.8 Hz), 6.77 (1H, d, J = 8.0 Hz), 6.84–6.89 (2H, m), 6.98 (1H, d, J = 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.32 (2H, d, J = 8.8 Hz), 7.68 (2H, d, J = 8.8 Hz).

4.2.44. 1-(4-Methoxybenzyl)-3-methyl-4-[(1-methylethyl)[3-(methylsulfonyl)phenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (14e)

Compound **14e** (0.782 g, 73%) was prepared from compound **13e** (0.977 g, 2.23 mmol) in a manner similar to that described in compound **14a**. ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, d, J = 6.4 Hz), 1.37 (3H, d, J = 6.4 Hz), 3.03 (3H, s), 3.28 (3H, s), 3.79 (3H, s), 4.34–4.39 (1H, m), 5.04 (2H, s), 6.57 (1H, d, J = 8.0 Hz), 6.77 (1H, d, J = 8.0 Hz), 6.89 (2H, d, J = 8.6 Hz), 6.96 (1H, d, J = 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.18–7.29 (3H, m), 7.32 (2H, d, J = 8.6 Hz).

4.2.45. 1-(4-Methoxybenzyl)-3-methyl-4-[(1-methylethyl)(5-methylpyridin-2-yl)amino]-1,3-dihydro-2*H*-benzimidazol-2-one (14f)

Compound **14f** (0.254 g, 74%) was prepared from compound **13f** (0.310 g, 0.828 mmol) and 2-bromopropane (1.31 mL, 1.66 mmol) in a manner similar to that described in compound **14g**. Oil. MS calcd: 416; Found: 417 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 6.8 Hz), 1.35 (3H, d, J = 6.8 Hz), 2.17 (3H, s), 3.27 (3H, s), 3.79 (3H, s), 4.95–5.10 (1H, m), 5.02 (2H, s), 5.86 (1H, d, J = 8.8 Hz), 6.83 (1H, d, J = 8.0 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.93 (1H, d, J = 8.4 Hz), 7.06 (1H, t, J = 8.4 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.8 Hz), 8.04 (1H, s).

4.2.46. *N*-(4-Chlorophenyl)-*N*-[1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl]acetamide (14h)

A mixture of compound **13a** (0.393 g, 1.00 mmol), pyridine (0.1 mL) and acetic anhydride (10 mL) was heated at 120 °C for 4 days. The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated sodium bicarbonate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 40–50% ethyl acetate/hexane gradient mixture to give the title compound (0.388 g, 89%) as an oil. MS calcd: 435; Found: 436 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.05 (3H, s), 3.47 (3H, s), 3.79 (3H, s), 4.99 (1H, d, J = 15.6 Hz), 5.05 (1H, d, J = 15.6 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.80–6.90 (1H, m), 6.90–7.10 (2H, m), 7.31 (2H, d, J = 8.4 Hz), 7.20–7.40 (4H, m).

4.2.47. 4-[(4-Chlorophenyl)(2-methoxyethyl)amino]-1-(4-methoxybenzyl)-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (14i)

Compound **14i** (0.560 g, 81%) was prepared from compound **13a** (0.601 g, 1.53 mmol) and 2-bromoethyl methyl ether (0.215 mL, 2.29 mmol) in a manner similar to that described in compound **14a**. MS calcd: 451; Found: 452 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.29 (6H, s), 3.55–3.65 (2H, m), 3.79 (3H, s), 3.70–4.00 (2H, m), 4.95–5.10 (2H, m), 6.49 (2H, d, J = 8.4 Hz), 6.80–6.95 (4H, m), 7.04 (1H, t, J = 8.0 Hz), 7.10 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz).

4.2.48. 4-[(4-Chlorophenyl)(tetrahydrofuran-3-ylmethyl)amino]-1-(4-methoxybenzyl)-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (14j)

Compound **14j** (0.220 g, 60%) was prepared from compound **13a** (0.300 g, 0.762 mmol) and (tetrahydrofuran-3-yl)methyl methanesulfonate (0.310 g, 1.50 mmol) in a manner similar to that described in compound **14a**. Oil. MS calcd: 477; Found: 478 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.50–1.65 (1H, m), 1.95–2.10 (1H, m), 2.60–2.75 (1H, m), 3.26 (3H, s), 3.20–3.60 (2H, m), 3.79 (3H, s), 3.65–3.95 (4H, m), 4.95–5.10 (2H, m), 6.48 (2H, d, J = 8.8 Hz), 6.80–6.95 (4H, m), 7.02 (1H, t, J = 8.0 Hz), 7.11 (2H, d, J = 8.8 Hz), 7.32 (2H, d, J = 8.8 Hz).

4.2.49. 7-[(4-Methoxyphenyl)(1-methylethyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (15b)

To a mixture of compound **14b** (1.80 g, 4.17 mmol) and trifluoroacetic acid (45 mL) was stirred at 65 °C for 4 days. The reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with aqueous sodium bicarbonate and water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 50% ethyl acetate/hexane mixture and preparative HPLC to give the title compound (0.408 g, 31%) as an oil. MS calcd: 311; Found: 312 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.90–1.20 (6H, br), 3.33 (3H, s), 3.73 (3H, s), 4.23–4.28 (1H, m), 6.47–6.69 (2H, m), 6.75–6.80 (3H, m), 6.71–7.07 (2H, m), 8.94 (1H, s).

4.2.50. 7-[(4-Chlorophenyl)(1-methylethyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (15a)

Compound **15a** (0.558 g, 88%) was prepared from compound **14a** (0.880 g, 2.03 mmol) in a manner similar to that described in compound **15b**. Oil. MS calcd: 315; Found: 316 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, d, J = 6.4 Hz), 1.36 (3H, d, J = 6.4 Hz), 3.28 (3H, s), 4.20–4.35 (1H, m), 6.43 (2H, d, J = 8.8 Hz), 6.78–6.85 (1H, m), 7.05–7.20 (4H, m), 9.09 (1H, s).

4.2.51. 1-Methyl-7-[(1-methylethyl)[4-(methylsulfonyl)phenyl]amino]-1,3-dihydro-2*H*-benzimidazol-2-one (15d)

Compound **15d** (0.333 g, 75%) was prepared from compound **14d** (0.590 g, 1.23 mmol) in a manner similar to that described in compound **15b**. ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, d, J = 6.3 Hz), 1.41 (3H, d, J = 6.3 Hz), 3.01 (3H, s), 3.21 (3H, s), 4.33–4.39 (1H, m), 6.56 (2H, d, J = 8.8 Hz), 6.80–6.83 (1H, m), 7.14–7.26 (2H, m), 7.69 (2H, d, J = 8.8 Hz), 9.67 (1H, s).

4.2.52. 1-Methyl-7-[(1-methylethyl)(5-methylpyridin-2-yl) amino]-1,3-dihydro-2*H*-benzimidazol-2-one (15f)

Compound **15f** (0.070 g, 39%) was prepared from compound **14f** (0.250 g, 0.600 mmol) in a manner similar to that described in compound **15b**. MS calcd: 296; Found: 297 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, d, J = 6.8 Hz), 1.37 (3H, d, J = 6.8 Hz), 2.16 (3H, s), 3.26 (3H, s), 5.00–5.15 (1H, m), 5.90 (1H, d, J = 8.4 Hz), 6.87 (1H, t, J = 4.0 Hz), 7.00–7.15 (3H, m), 8.06 (1H, s), 9.58 (1H, s).

4.2.53. 7-[(4-Chlorophenyl)(2,2-dimethylpropyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (15g)

Compound **15g** (0.052 g, 80%) was prepared from compound **14g** (0.088 g, 0.190 mmol) in a manner similar to that described in compound **15b**. MS calcd: 343; Found: 344 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.96 (9H, s), 3.25 (3H, s), 3.40 (1H, d, J = 16.0 Hz), 3.83 (1H, d, J = 16.0 Hz), 6.54 (2H, d, J = 8.2 Hz), 6.96 (1H, d, J = 6.0 Hz), 7.04 (1H, d, J = 8.2 Hz), 7.10–7.20 (3H, m), 8.06 (1H, s).

4.2.54. *N*-(4-Chlorophenyl)-*N*-[3-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-4-yl]acetamide (15h)

Compound **15h** (0.200 g, 73%) was prepared from compound **14h** (0.380 g, 0.872 mmol) in a manner similar to that described in compound **15b**. ^{1}H NMR ($CDCl_3$) δ 2.07 (3H, s), 3.44 (3H, s), 6.85–6.95 (1H, m), 7.05–7.15 (2H, m), 7.25–7.30 (4H, m), 9.25 (1H, br s).

4.2.55. 7-[(4-Chlorophenyl)(2-methoxyethyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (15i)

Compound **15i** (0.404 g, 71%) was prepared from compound **14i** (0.550 g, 1.22 mmol) in a manner similar to that described in compound **15b**. MS calcd: 331; Found: 332 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.26 (3H, s), 3.30 (3H, s), 3.55–3.70 (2H, m), 3.70–4.00 (2H, m), 6.51 (2H, d, J = 8.8 Hz), 6.90 (1H, d, J = 8.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 7.05–7.20 (3H, m), 8.81 (1H, s).

4.2.56. 7-[(4-Chlorophenyl)(tetrahydrofuran-3-ylmethyl)amino]-1-methyl-1,3-dihydro-2*H*-benzimidazol-2-one (15j)

Compound **15j** (0.150 g, 91%) was prepared from compound **14j** (0.220 g, 0.460 mmol) in a manner similar to that described in compound **15b**. MS calcd: 357; Found: 358 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.80–2.00 (2H, m), 2.60–2.80 (1H, m), 3.25 (3H, s), 3.45–3.60 (2H, m), 3.60–4.00 (4H, m), 5.50 (2H, d, J = 8.8 Hz), 6.80–7.00 (1H, m), 7.05 (1H, t, J = 8.0 Hz), 7.05–7.20 (3H, m), 9.68 (1H, s).

4.2.57. 2-Chloro-*N*-(4-chlorophenyl)-1-methyl-*N*-(1-methylethyl)-1*H*-benzimidazol-7-amine (10l)

A mixture of compound **15a** (0.042 g, 0.130 mmol) and phosphorous oxychloride (1.5 mL) was stirred at 80 °C for 1.5 h. The mixture was concentrated in vacuo. The residue was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 17% ethyl acetate/hexane mixture to give the title compound (0.032 g, 72%) as an oil. MS calcd: 333; Found: 334 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 6.0 Hz), 1.39 (3H, d, J = 6.0 Hz), 3.63 (3H, s), 4.30–4.40 (1H, m), 6.40 (2H, d, J = 8.8 Hz), 7.03 (1H, d, J = 8.0 Hz), 7.09 (2H, d, J = 8.8 Hz), 7.30 (1H, t, J = 8.0 Hz), 7.70 (1H, d, J = 8.0 Hz).

4.2.58. 2-Chloro-*N*-(4-methoxyphenyl)-1-methyl-*N*-(1-methylethyl)-1*H*-benzimidazol-7-amine (10m)

Compound **10m** (0.394 g, 78%) was prepared from compound **15b** (0.480 g, 1.54 mmol) in a manner similar to that described in compound **10l**. MS calcd: 329; Found: 330 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.20–1.22 (6H, m), 3.69 (3H, s), 3.73 (3H, s), 4.28–4.37 (1H, m), 6.43–6.49 (2H, m), 6.72–6.78 (2H, m), 7.04–7.07 (1H, m), 7.28 (1H, t, J = 7.8 Hz), 7.64–7.67 (1H, m).

4.2.59. 2-Chloro-1-methyl-*N*-(1-methylethyl)-*N*-[4-(1-methylethyl)oxyphenyl]-1*H*-benzimidazol-7-amine (10n)

Compound **10n** (0.0943 g, 18% in two steps) was prepared from compound **15c**, prepared from compound **14c** (0.674 g, 1.47 mmol) in a manner similar to that described in compound **15b**, in a manner similar to that described in compound **10l**. Oil. ^{1}H NMR ($CDCl_3$) δ 1.00–1.38 (6H, m), 1.28 (6H, d, J = 6.0 Hz), 3.68 (3H, s), 4.30–4.39 (2H, m), 6.40–6.45 (2H, m), 6.71–6.77 (2H, m), 7.04–7.07 (1H, m), 7.27 (1H, t, J = 7.8 Hz), 7.64–7.67 (1H, m).

4.2.60. 2-Chloro-1-methyl-*N*-(1-methylethyl)-*N*-[4-(methylsulfonyl)phenyl]-1*H*-benzimidazol-7-amine (10o)

Compound **10o** (0.148 g, 47%) was prepared from compound **15d** (0.300 g, 0.835 mmol) in a manner similar to that described in compound **10l**. ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 6.6 Hz), 1.45 (3H, d, J = 6.6 Hz), 3.02 (3H, s), 3.60 (3H, s), 4.38–4.46 (1H, m), 6.55–6.57 (2H, m), 7.02–7.05 (1H, m), 7.34–7.38 (1H, m), 7.65–7.79 (3H, m).

4.2.61. 2-Chloro-1-methyl-*N*-(1-methylethyl)-*N*-[3-(methylsulfonyl)phenyl]-1*H*-benzimidazol-7-amine (10p)

Compound **15e**, used for the next step without further purification, was prepared from compound **14e** (0.780 g, 1.63 mmol) in a manner similar to that described in compound **15b**. MS calcd: 359; Found: 360 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, d, J = 6.2 Hz), 1.39 (3H, d, J = 6.2 Hz), 3.03 (3H, s), 3.24 (3H, s), 4.33–4.40 (1H, m), 6.58 (1H, d, J = 8.0 Hz), 6.81–6.83 (1H, m), 7.12–7.29 (5H, m), 9.54 (1H, s). Compound **10p** (0.153 g, 23% in two steps) was prepared from compound **15e** in a manner similar to that described in compound **10l**. MS calcd: 377; Found: 378 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 6.6 Hz), 1.42 (3H, d, J = 6.6 Hz), 3.05 (3H, s), 3.62 (3H, s), 4.40–4.47 (1H, m), 6.46–6.49 (1H, m), 7.03 (1H, d, J = 8.0 Hz), 7.24–7.27 (3H, m), 7.33 (1H, t, J = 8.0 Hz), 7.74 (1H, d, J = 8.0 Hz).

4.2.62. 2-Chloro-1-methyl-*N*-(1-methylethyl)-*N*-(5-methylpyridin-2-yl)-1*H*-benzimidazol-7-amine (10q)

Compound **10q** (0.048 g, 64%) was prepared from compound **15f** (0.070 g, 0.236 mmol) in a manner similar to that described in compound **10l**. Crystal. MS calcd: 314; Found: 315 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 6.8 Hz), 1.40 (3H, d, J = 6.8 Hz), 2.17 (3H, s), 3.61 (3H, s), 5.10–5.20 (1H, m), 5.79 (1H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.31 (1H, t, J = 8.0 Hz), 7.70 (1H, d, J = 8.0 Hz), 8.07 (1H, s).

4.2.63. 2-Chloro-*N*-(4-chlorophenyl)-*N*-(2,2-dimethylpropyl)-1-methyl-1*H*-benzimidazol-7-amine (10r)

Compound **10r** (0.053 g, 73%) was prepared from compound **15g** (0.050 g, 0.145 mmol) in a manner similar to that described in compound **10l**. MS calcd: 361; Found: 362 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, s), 3.47 (1H, d, J = 14.8 Hz), 3.62 (3H, s), 3.93 (1H, d, J = 14.8 Hz), 6.51 (2H, d, J = 8.8 Hz), 7.08 (2H, d, J = 8.8 Hz), 7.20–7.40 (2H, m), 7.60 (1H, d, J = 8.0 Hz).

4.2.64. *N*-(2-Chloro-1-methyl-1*H*-benzimidazol-7-yl)-*N*-(4-chlorophenyl)acetamide (10s)

Compound **10s** (0.146 g, 69%) was prepared from compound **15h** (0.200 g, 0.633 mmol) in a manner similar to that described in compound **10l**. MS calcd: 333; Found: 334 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.05 (3H, s), 3.78 (3H, s), 7.05–7.25 (1H, m), 7.25–7.45 (5H, m), 7.75 (1H, d, J = 8.0 Hz).

4.2.65. 2-Chloro-*N*-(4-chlorophenyl)-*N*-(2-methoxyethyl)-1-methyl-1*H*-benzimidazol-7-amine (10t)

Compound **10t** (0.240 g, 80%) was prepared from compound **15i** (0.285 g, 0.859 mmol) in a manner similar to that described in compound **10l**. MS calcd: 349; Found: 350 (M+H). ^{1}H NMR ($CDCl_3$) δ 3.27 (3H, s), 3.50–3.65 (2H, m), 3.62 (3H, s), 3.80–4.00 (2H, m), 6.50 (2H, d, J = 8.6 Hz), 7.05–7.20 (3H, m), 7.31 (1H, t, J = 8.0 Hz), 7.65 (1H, d, J = 8.0 Hz).

4.2.66. 2-Chloro-*N*-(4-chlorophenyl)-1-methyl-*N*-(tetrahydrofuran-3-ylmethyl)-1*H*-benzimidazol-7-amine (10u)

Compound **10u** (0.089 g, 56%) was prepared from compound **15j** (0.150 g, 0.419 mmol) in a manner similar to that described in compound **10l**. Oil. MS calcd: 375; Found: 376 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.50–1.70 (1H, m), 1.95–2.10 (1H, m), 2.60–2.75 (1H, m), 3.59 (3H, s), 3.50–3.65 (2H, m), 3.65–3.80 (2H, m), 3.80–4.00 (2H, m), 6.49 (2H, d, J = 8.8 Hz), 7.05–7.20 (3H, m), 7.32 (1H, t, J = 8.0 Hz), 7.66 (1H, d, J = 8.0 Hz).

4.2.67. 4-Chloro-2-methoxy-6-methylaniline (17a)

To a solution of 4-chloro-2-methylaniline (98.8 g, 697 mmol) in acetonitrile (400 mL) was added *N*-bromosuccinimide (137 g, 767 mmol), and the mixture was stirred at 0 °C for 90 min. The reaction mixture was concentrated in vacuo. The residue was diluted with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo to give 2-bromo-4-chloro-6-methylaniline (154 g, >99%) as a brown powder. MS calcd: 219; Found: 220 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.18 (3H, s), 4.04 (2H, br s), 6.99 (1H, d, J = 1.2 Hz), 7.29 (1H, d, J = 1.2 Hz). To a solution of 2-bromo-4-chloro-6-methylaniline (45.0 g, 204 mmol) in methanol (30 mL) were added sodium methoxide (28% solution in methanol, 225 mL) and copper iodide (44.7 g, 234 mmol), and the mixture was stirred at 100 °C for 2 h. The reaction mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 0–10% ethyl acetate/hexane gradient mixture to give the title compound (26.4 g, 75%) as a brown solid. MS calcd: 171; Found: 172 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.13 (3H, s), 3.70 (2H, br s), 3.82 (3H, s), 6.66 (1H, d, J = 2.1 Hz), 6.69 (1H, d, J = 2.1 Hz).

4.2.68. 4-Bromo-2-methoxy-6-methylaniline (17b)

To a solution of 2-methoxy-6-methylaniline (25.0 g, 182 mmol) in acetic acid (30 mL) and methanol (60 mL) was added a solution of bromine (9.34 mL, 182 mmol) in acetic acid (60 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with diethyl ether and dissolved in ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and concentrated in vacuo to give the title compound (20.7 g, 53%) as a brown solid. MS calcd: 215; Found: 216 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.14 (3H, s), 3.83 (3H, s), 6.80 (1H, s), 6.84 (1H, s).

4.2.69. 4-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]benzonitrile (16m)

A mixture of compound **10d** (0.050 g, 0.154 mmol) and compound **17b** (0.100 g, 0.460 mmol) was stirred at 120 °C for 3 days. The mixture was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate and water and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a 33% ethyl acetate/hexane mixture. The desired fraction was concentrated in vacuo, and the residual solid was washed with diethyl ether-hexane to give the title compound (0.0074 g, 9.5%). Solid. MS calcd: 503; Found: 504 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, d, J = 6.6 Hz), 1.42 (3H, d, J = 6.6 Hz), 2.18 (3H, s), 3.49 (3H, s), 3.81 (3H, s), 4.34–4.40 (1H, m), 5.82 (1H, s), 6.55 (2H, d, J = 8.6 Hz), 6.80 (1H, d, J = 7.8 Hz), 6.93 (1H, s), 7.06 (1H, s), 7.16 (1H, t, J = 7.8 Hz), 7.42 (2H, d, J = 8.6 Hz), 7.55 (1H, d, J = 7.8 Hz). HPLC: >99% purity.

4.2.70. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-N^7-(4-chlorophenyl)-1-methyl-N^7-(1-methylethyl)-1*H*-benzimidazole-2,7-diamine (16a)

Compound **16a** (0.148 g, 53%) was prepared from compound **10l** (0.200 g, 0.598 mmol) and compound **17a** (0.310 g, 1.80 mmol) in a manner similar to that described in compound **16m**. Solid. MS calcd: 468; Found: 469 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, d, J = 4.5 Hz), 1.39 (3H, d, J = 4.5 Hz), 2.19 (3H, s), 3.55 (3H, s), 3.81 (3H, s), 4.25–4.40 (1H, m), 5.81 (1H, s), 6.47 (2H, d, J = 8.8 Hz), 6.78 (1H, s), 6.81 (1H, d, J = 8.0 Hz), 6.90 (1H, s), 7.10 (1H, d, J = 8.8 Hz), 7.13 (1H, t, J = 8.0 Hz), 7.51 (1H, d, J = 8.0 Hz).

4.2.71. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-N^7-(4-chlorophenyl)-N^7-(2,2-dimethylpropyl)-1-methyl-1*H*-benzimidazole-2,7-diamine Hydrochloride (16b)

A mixture of compound **10r** (0.039 g, 0.106 mmol) and compound **17a** (0.055 g, 0.320 mmol) was stirred at 120 °C for 26 h. The reaction mixture was dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate and water and concentrated in vacuo. The residue was purified by preparative HPLC. The fraction was concentrated in vacuo. The residue was dissolved in methanol (5 mL), treated with 2 M hydrochloride in diethyl ether (2 mL) and concentrated in vacuo to give the title compound (0.012 g, 22%). Solid. MS calcd: 496; Found: 497 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.93 (9H, s), 2.38 (3H, s), 3.10 (3H, s), 3.42 (1H, d, J = 14.8 Hz), 3.62 (3H, s), 3.90 (1H, d, J = 14.8 Hz), 6.51 (2H, d, J = 8.0 Hz), 6.73 (1H, s), 6.87 (1H, s), 7.10 (2H, d, J = 8.0 Hz), 7.20–7.40 (1H, m), 7.42 (1H, s), 10.47 (1H, s), 13.35 (1H, s).

4.2.72. *N*-[2-[(4-Chloro-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl]-*N*-(4-chlorophenyl)acetamide hydrochloride (16c)

Compound **16c** (0.116 g, 53%) was prepared from compound **10s** (0.145 g, 0.434 mmol) in a manner similar to that described in compound **16b**. Colorless solid. Mp: 176–178 °C. MS calcd: 468; Found: 469 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 2.37 (3H, s), 3.48 (3H, s), 3.65 (3H, s), 6.76 (1H, s), 6.82 (1H, s), 7.00–7.20 (1H, m), 7.20–7.30 (2H, m), 7.30–7.45 (3H, m), 7.50–7.65 (1H, m), 10.80 (1H, s). HPLC: >96% purity.

4.2.73. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-N^7-(4-chlorophenyl)-N^7-(2-methoxyethyl)-1-methyl-1*H*-benzimidazole-2,7-diamine Hydrochloride (16d)

Compound **16d** (0.059 g, 33%) was prepared from compound **10t** (0.120 g, 0.343 mmol) in a manner similar to that described in compound **16b**. Colorless solid. Mp: 131–133 °C. MS calcd: 484; Found: 485 (M+H). ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 3.07 (3H, s), 3.25 (3H, s), 3.50–3.60 (2H, br), 3.61 (3H, s), 3.80–4.00 (2H, m), 6.49 (2H, d, J = 8.0 Hz), 6.71 (1H, s), 6.86 (1H, s), 7.12 (2H, d, J = 8.0 Hz), 7.14 (1H, d, J = 8.0 Hz), 7.35–7.50 (2H, m), 10.59 (1H, s). HPLC: >98% purity.

4.2.74. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-N^7-(4-chlorophenyl)-1-methyl-N^7-(tetrahydrofuran-3-ylmethyl)-1*H*-benzimidazole-2,7-diamine (16e)

Compound **16e** (0.061 g, 53%) was prepared from compound **10u** (0.085 g, 0.226 mmol) and compound **17a** (0.12 g, 0.680 mmol) in a manner similar to that described in compound

16m. Colorless crystal. Mp: 212–214 °C. MS calcd: 510; Found: 511 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.50–1.70 (1H, m), 2.00–2.15 (1H, m), 2.18 (3H, s), 2.65–2.80 (1H, m), 3.51 (3H, s), 3.50–3.70 (2H, m), 3.81 (3H, s), 3.65–4.00 (4H, m), 5.81 (1H, s), 6.56 (2H, d, J = 8.0 Hz), 6.79 (1H, s), 6.85–7.00 (2H, m), 7.13 (2H, d, J = 8.0 Hz), 7.10–7.20 (1H, m), 7.47 (1H, d, J = 6.8 Hz). Anal. Calcd for $C_{27}H_{28}N_4O_2Cl_2$: C, 63.41; H, 5.52; N, 10.95. Found: C, 63.28; H, 5.57; N, 10.68.

4.2.75. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-N^7-(4-methoxyphenyl)-1-methyl-N^7-(1-methylethyl)-1*H*-benzimidazole-2,7-diamine (16g)

A mixture of compound **10m** (0.291 g, 0.881 mmol), compound **17a** (0.454 g, 2.64 mmol) and *N*-methyl-2-pyrrolidinone (0.3 mL) was stirred at 120 °C for 18 h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 50% ethyl acetate/hexane mixture. The desired fraction was concentrated in vacuo. The residue was powdered from diethyl ether to give the title compound (0.359 g, 65%) as a colorless powder. mp: 213–214 °C. MS calcd: 464; Found: 465 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.21–1.27 (6H, m), 2.18 (3H, s), 3.61 (3H, s), 3.74 (3H, s), 3.81 (3H, s), 4.25–4.35 (1H, m), 5.82 (1H, br s), 6.50–6.54 (2H, m), 6.74–6.78 (3H, m), 6.83–6.89 (2H, m), 7.11 (1H, t, J = 7.5 Hz), 7.47 (1H, d, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6) δ 155.4, 153.3, 150.8, 144.1, 142.9, 137.9, 132.7, 129.9, 126.5, 126.0, 122.0, 121.7, 121.0, 114.7, 114.6, 109.6, 55.9, 55.1, 48.2, 29.9, 20.6, 17.7. HPLC: 97% purity.

4.2.76. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-1-methyl-N^7-(1-methylethyl)-N^7-phenyl-1*H*-benzimidazole-2,7-diamine (16f)

Compound **16f** (0.0427 g, 27%) was prepared from compound **10a** (0.111 g, 0.367 mmol) in a manner similar to that described in compound **16g**. Colorless solid. Mp: 230–231 °C. MS calcd: 434; Found: 435(M+H). ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, br s), 1.39 (3H, br s), 2.18 (3H, s), 3.56 (3H, s), 3.80 (3H, s), 4.32–4.42 (1H, m), 5.82 (1H, br s), 6.56 (2H, d, J = 8.4 Hz), 6.67–6.71 (1H, m), 6.77–6.78 (1H, m), 6.84 (1H, d, J = 7.5 Hz), 6.88–6.89 (1H, m), 7.10–7.19 (3H, m), 7.49 (1H, d, J = 7.5 Hz). Anal. Calcd for $C_{25}H_{27}N_4OCl{\cdot}0.3H_2O$: C, 68.19; H, 6.32; N, 12.72. Found: C, 68.19; H, 6.22; N, 12.51. HPLC: 96% purity.

4.2.77. N^2-(4-Bromo-2-methoxy-6-methylphenyl)-N^7-(3-methoxyphenyl)-1-methyl-N^7-(1-methylethyl)-1*H*-benzimidazole-2,7-diamine (16h)

A mixture of compound **10b** (0.100 g, 0.303 mmol), compound **17b** (0.197 g, 0.910 mmol) and *N*-methyl-2-pyrrolidinone (1.0 mL) was stirred at 120 °C for 2 h under microwave irradiation. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by preparative HPLC. The desired fraction was diluted with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was crystallized from diethyl ether to give the title compound (0.0155 g, 10%) as a solid. MS calcd: 508; Found: 509 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, d, J = 6.6 Hz), 1.39 (3H, d, J = 6.6 Hz), 2.17 (3H, s), 3.56 (3H, s), 3.72 (3H, s), 3.81 (3H, s), 4.30–4.36 (1H, m), 5.85 (1H, br s), 6.14–6.16 (2H, m), 6.26–6.28 (1H, m), 6.83 (1H, d, J = 7.8 Hz), 6.91–6.92 (1H, m), 7.04–7.15 (2H, m), 7.26 (1H, s), 7.48–7.61 (1H, m).

4.2.78. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-1-methyl-N^7-(1-methylethyl)-N^7-[4-(1-methylethyl)oxyphenyl]-1*H*-benzimidazole-2,7-diamine (16i)

Compound **16i** (0.0266 g, 36%) was prepared from compound **10n** (0.0543 g, 0.152 mmol) in a manner similar to that described in compound **16g**. Solid. mp: 202–203 °C. MS Calcd: 492; Found: 493 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.09–1.28 (6H, m), 1.29 (6H, d, J = 6.6 Hz), 2.18 (3H, s), 3.60 (3H, s), 3.81 (3H, s), 4.25–4.41 (2H, m), 5.82 (1H, br s), 6.48–6.51 (2H, m), 6.72–6.78 (3H, m), 6.84–6.89 (2H, m), 7.11 (1H, t, J = 7.8 Hz), 7.47 (1H, d, J = 7.8 Hz).

4.2.79. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-1-methyl-N^7-(1-methylethyl)-N^7-[3-(1-methylethyl)oxyphenyl]-1*H*-benzimidazole-2,7-diamine (16j)

Compound **16j** (0.0237 g, 26%) was prepared from compound **10c** (0.0670 g, 0.187 mmol) in a manner similar to that described in compound **16g**. Solid. Mp: 192–193 °C. MS calcd: 492; Found: 493 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, d, J = 6.6 Hz), 1.25–1.29 (6H, m), 1.39 (3H, d, J = 6.6 Hz), 2.18 (3H, s), 3.56 (3H, s), 3.80 (3H, s), 4.28–4.47 (2H, m), 5.82 (1H, br s), 6.10–6.13 (2H, m), 6.23–6.26 (1H, m), 6.77–6.78 (1H, m), 6.84 (1H, d, J = 7.8 Hz), 6.88–6.89 (1H, m), 7.07 (1H, t, J = 9.0 Hz), 7.11 (1H, t, J = 8.1 Hz), 7.48 (1H, d, J = 8.1 Hz).

4.2.80. N^2-(4-Bromo-2-methoxy-6-methylphenyl)-1-methyl-N^7-(1-methylethyl)-N^7-[4-(methylsulfonyl)phenyl]-1*H*-benzimidazole-2,7-diamine (16k)

Compound **16k** (0.0555 g, 36%) was prepared from compound **10o** (0.104 g, 0.275 mmol) in a manner similar to that described in compound **16m**. Colorless solid. Mp: 154–155 °C. MS calcd: 556; Found: 557 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, d, J = 6.4 Hz), 1.44 (3H, d, J = 6.4 Hz), 2.19 (3H, s), 3.01 (3H, s), 3.49 (3H, s), 3.81 (3H, s), 4.38–4.46 (1H, m), 5.83 (1H, s), 6.61 (2H, d, J = 8.8 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.93 (1H, s), 7.06 (1H, s), 7.17 (1H, t, J = 8.0 Hz), 7.55 (1H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.8 Hz). Anal. Calcd for $C_{26}H_{29}N_4O_3SBr$: C, 56.01; H, 5.24; N, 10.05. Found: C, 56.18; H, 5.49; N, 9.68.

4.2.81. N^2-(4-Bromo-2-methoxy-6-methylphenyl)-1-methyl-N^7-(1-methylethyl)-N^7-[3-(methylsulfonyl)phenyl]-1*H*-benzimidazole-2,7-diamine (16l)

Compound **16l** (0.143 g, 64%) was prepared from compound **10p** (0.150 g, 3.97 mmol) in a manner similar to that described in compound **16m**. Colorless solid. Mp: 240–242 °C. MS calcd: 556; Found: 557 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, d, J = 6.2 Hz), 1.42 (3H, d, J = 6.2 Hz), 2.18 (3H, s), 3.05 (3H, s), 3.53 (3H, s), 3.81 (3H, s), 4.39–4.45 (1H, m), 5.83 (1H, s), 6.58 (1H, d, J = 7.8 Hz), 6.80 (1H, d, J = 7.8 Hz), 6.92 (1H, s), 7.05 (1H, s), 7.16 (1H, t, J = 7.8 Hz), 7.22–7.29 (3H, m), 7.53 (1H, d, J = 7.8 Hz). Anal. Calcd for $C_{26}H_{29}N_4O_3SBr$: C, 56.01; H, 5.24; N, 10.05. Found: C, 55.96; H, 5.31; N, 9.87. HPLC: >99% purity.

4.2.82. 3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]benzonitrile (16n)

Compound **16n** (0.507 g, 69%) was prepared from compound **10e** (0.475 g, 1.46 mmol) in a manner similar to that described in compound **16m**. Purple solid. Mp: 248–250 °C. MS calcd: 503; Found: 504 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, J = 6.4 Hz), 1.40 (3H, t, J = 6.4 Hz), 2.20 (3H, s), 3.52 (3H, s), 3.81 (3H, s), 4.29–4.35 (1H, m), 5.84 (1H, s), 6.71 (1H, d, J = 7.6 Hz), 6.79 (1H, d, J = 7.6 Hz), 6.83 (1H, s), 6.93 (1H, s), 6.96 (1H, d, J = 7.6 Hz), 7.06 (1H, s), 7.14–7.22 (2H, m), 7.54 (1H, d, J = 7.6 Hz). Anal. Calcd for $C_{26}H_{26}N_5OBr{\cdot}0.5H_2O$: C, 60.82; H, 5.30; N, 13.64. Found: C, 61.03; H, 5.20; N, 13.29.

4.2.83. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-N^7-(6-methoxypyridin-3-yl)-1-methyl-N^7-(1-methylethyl)-1*H*-benzimidazole-2,7-diamine (16t)

Compound **16t** (0.0319 g, 32%) was prepared from compound **10g** (0.070 g, 0.212 mmol) in a manner similar to that described

in compound **16g**. Colorless solid. Mp: 215–216 °C. MS calcd: 465; Found: 466 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.10–1.35 (6H, m), 2.19 (3H, s), 3.63 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 4.21–4.33 (1H, m), 5.83 (1H, br s), 6.57–6.60 (1H, m), 6.78–6.91 (4H, m), 7.11 (1H, t, J = 8.1 Hz), 7.47 (1H, d, J = 8.1 Hz), 7.58–7.59 (1H, m). HPLC: 97% purity.

4.2.84. N^2-(4-Chloro-2-methoxy-6-methylphenyl)-1-methyl-N^7-(1-methylethyl)-N^7-(5-methylpyridin-2-yl)-1*H*-benzimidazole-2,7-diamine (16u)

Compound **16u** (0.028 g, 41%) was prepared from compound **10q** (0.047 g, 0.149 mmol) and compound **17a** (0.077 g, 0.449 mmol) in a manner similar to that described in compound **16m**. Colorless solid. Mp: 245–246 °C. MS Calcd: 449; Found: 450 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, d, J = 6.8 Hz), 1.39 (3H, d, J = 6.8 Hz), 2.18 (6H, s), 3.53 (3H, s), 3.80 (3H, s), 5.10–5.20 (1H, m), 5.91 (1H, d, J = 8.8 Hz), 5.90 (1H, br s), 6.78 (1H, s), 6.87 (1H, d, J = 8.0 Hz), 6.89 (1H, s), 7.11 (1H, d, J = 8.0 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.51 (1H, d, J = 8.0 Hz), 8.07 (1H, s). Anal. Calcd for $C_{25}H_{28}N_5OCl$: C, 66.73; H, 6.27; N, 15.56. Found: C, 66.51; H, 6.36; N, 15.40.

4.2.85. 2-[3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]phenyl]-2-methylpropanenitrile (16v)

Compound **16v** (0.270 g, 74%) was prepared from compound **10f** (0.250 g, 0.680 mmol) and compound **17b** (0.440 g, 2.04 mmol) in a manner similar to that described in compound **16g**. Solid. Mp: 227–229 °C. MS calcd: 545; Found: 546 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, d, J = 6.6 Hz), 1.42 (3H, d, J = 6.6 Hz), 1.65 (3H, s), 1.67 (3H, s), 2.16 (3H, s), 3.55 (3H, s), 3.81 (3H, s), 4.35–4.50 (1H, m), 5.82 (1H, s), 6.35 (1H, d, J = 6.9 Hz), 6.75–6.80 (2H, m), 6.83 (1H, d, J = 8.4 Hz), 6.92 (1H, s), 7.09 (1H, s), 7.05–7.20 (2H, m), 7.52 (1H, d, J = 8.1 Hz).

4.2.86. Methyl 3-[[2-[(4-bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]benzoate (16o)

To a solution of compound **16n** (0.337 g, 0.668 mmol) in methanol (5 mL) was bubbled hydrogen chloride gas for 10 min., and the mixture was stirred at room temperature for 15 h. After hydrogen chloride and the solvent were removed in vacuo, the residue was diluted with tetrahydrofuran and water. The mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 3% methanol/dichloromethane mixture to give the title compound (0.359 g, 77%) as a solid. MS calcd: 536; Found: 537 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, d, J = 6.2 Hz), 1.41 (3H, d, J = 6.2 Hz), 2.18 (3H, s), 3.54 (3H, s), 3.81(3H, s), 3.88 (3H, s), 4.41–4.47 (1H, m), 5.81 (1H, s), 6.56 (1H, d, J = 8.0 Hz), 6.83 (1H, d, J = 8.0 Hz), 6.92 (1H, s), 7.05 (1H, s), 7.13–7.17 (2H, m), 7.37 (1H, d, J = 8.0 Hz), 7.42 (1H, s), 7.52 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{27}H_{29}N_4O_3Br$: C, 60.34; H, 5.44; N, 10.42. Found: C, 60.34; H, 5.40; N, 10.57.

4.2.87. 3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]benzamide (16p)

To a solution of compound **16n** (0.090 g, 0.178 mmol) in ethanol (1 mL) were added 30% aqueous hydrogen peroxide (0.064 mL, 0.624 mmol) and 10 N aqueous sodium hydroxide (0.00428 mL, 0.0428 mmol), and the mixture was refluxed for 24 h. Addition of 30% aqueous hydrogen peroxide (0.064 mL, 0.624 mmol) and 10 N aqueous sodium hydroxide (0.00428 mL, 0.0428 mmol) was followed by refluxing for 60 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine and concentrated in vacuo. The resulting solid was collected by filtration and washed with dichloromethane to give the title compound (0.016 g). The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography eluting with a 5% methanol/dichloromethane mixture. The desired fraction was concentrated in vacuo. The resulting solid was washed with dichloromethane to give the title compound (0.014 g). The filtrate was concentrated in vacuo, and the residue was crystallized from dichloromethane to give the title compound (0.006 g) as a crystal. Total: 0.035 g, 38%. MS calcd: 521; Found: 522 (M+H). ^{1}H NMR (DMSO-d_6) δ 0.93 (3H, d, J = 5.8 Hz), 1.31 (3H, d, J = 5.8 Hz), 2.08 (3H, s), 3.47 (3H, s), 3.74 (3H, s), 4.43–4.48 (1H, m), 5.95 (1H, s), 6.49 (1H, d, J = 6.8 Hz), 6.69 (1H, d, J = 8.0 Hz), 7.03–7.19 (6H, m), 7.25 (1H, s), 7.84 (1H, s), 7.93 (1H, s). Anal. Calcd for $C_{26}H_{28}N_5O_2Br{\cdot}0.3H_2O$: C, 59.16; H, 5.46; N, 13.27. Found: C, 59.40; H, 5.43; N, 12.89.

4.2.88. 3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]benzoic acid (16x)

A mixture of compound **16o** (0.266 g, 0.495 mmol), 1 N aqueous sodium hydroxide (3 mL) and tetrahydrofuran (3 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water and adjusted to pH 4.5 with hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 10% methanol/dichloromethane mixture to give the title compound (0.195 g, 75%) as a solid. MS calcd: 522; Found: 523 (M+H). ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 6.0 Hz), 1.32 (3H, d, J = 6.0 Hz), 2.08 (3H, s), 3.47 (3H, s), 3.73 (3H, s), 4.40–4.45 (1H, m), 6.70–6.74 (2H, m), 6.92–7.10 (4H, m), 7.10–7.23 (3H, m), 7.95 (1H, s), 12.72 (1H, s).

4.2.89. 3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]-*N*-methylbenzamide (16q)

To a suspension of compound **16x** (0.080 g, 0.153 mmol) in tetrahydrofuran (1 mL), were added *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) (0.120 g, 0.310 mmol) and diisopropylethylamine (0.027 mL, 0.153 mmol), and the mixture was stirred at room temperature for 30 min. Addition of 2 M methylamine in tetrahydrofuran (0.11 mL, 0.23 mmol) was followed by stirring at room temperature for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 10% methanol/dichloromethane mixture. The desired fraction was concentrated in vacuo. The resulting crystals were washed with dichloromethane-diethyl ether to give the title compound (0.043 g, 52%). Colorless solid. Mp: 261–263 °C. MS calcd: 535; Found: 536 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J = 6.2 Hz), 1.40 (3H, d, J = 6.2 Hz), 2.18 (3H, s), 2.98 (3H, d, J = 4.8 Hz), 3.53 (3H, s), 3.80 (3H, s), 4.42–4.49 (1H, m), 5.86 (1H, br s), 5.98 (1H, br s), 6.53 (1H, d, J = 8.0 Hz), 6.83 (1H, d, J = 8.0 Hz), 6.92 (1H, s), 6.96 (1H, d, J = 8.0 Hz), 7.05 (1H, s), 7.12–7.16 (3H, m), 7.51 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{27}H_{30}N_5O_2Br{\cdot}0.5H_2O$: C, 59.45; H, 5.73; N, 12.84. Found: C, 59.65; H, 5.56; N, 12.83. HPLC: 96% purity.

4.2.90. 3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]-*N*,*N*-dimethylbenzamide (16r)

To a suspension of compound **16x** (0.080 g, 0.153 mmol) in tetrahydrofuran (1 mL) were added HBTU (0.120 g, 0.310 mmol)

and diisopropylethylamine (0.040 mL, 0.23 mmol), and the mixture was stirred at room temperature for 30 min. Addition of 2 M dimethylamine in tetrahydrofuran (0.11 mL, 0.23 mmol) was followed by stirring at room temperature for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was and concentrated in vacuo. The resulting crystals were washed with ethyl acetate to give the title compound (0.050 g, 59%). Colorless solid. Mp: 271–272 °C. MS calcd: 549; Found: 550 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J = 6.6 Hz), 1.39 (3H, d, J = 6.6 Hz), 2.19 (3H, s), 2.91 (3H, s), 3.06 (3H, s), 3.56 (3H, s), 3.81 (3H, s), 4.34–4.43 (1H, m), 5.82 (1H, s), 6.52 (1H, d, J = 8.0 Hz), 6.92 (1H, s), 6.72 (1H, d, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz), 6.92 (1H, s), 7.04 (1H, s), 7.12 (1H, d, J = 8.0 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.51 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{28}H_{32}N_5O_2Br$: C, 61.09; H, 5.86; N, 12.72. Found: C, 60.94; H, 5.77; N, 12.65. HPLC: 96% purity.

4.2.91. 2-[3-[[2-[(4-Bromo-2-methoxy-6-methylphenyl)amino]-1-methyl-1*H*-benzimidazol-7-yl](1-methylethyl)amino]phenyl]-2-methylpropanamide (16s)

A mixture of compound **16v** (0.100 g, 0.183 mmol), ethanol (10 mL) and concentrated sulfuric acid (4 mL) was refluxed for 48 h. The reaction mixture was poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was dissolved in methanol (5 mL) and tetrahydrofuran (2 mL), followed by addition of 8 N aqueous sodium hydroxide (1 mL). After stirring at 70 °C for 3 h, the reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 5% methanol/dichloromethane mixture to give compound **16y** (0.051 g, 49%) as a solid. MS Calcd: 564; Found: 565 (M+H). To a solution of compound **16y** (0.047 g, 0.081 mmol) in *N*,*N*-dimethylformamide (0.5 mL) were added 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (WSC) (0.029 g, 0.166 mmol) and 1-hydroxybenzotriazole monohydrate (HOBT) (0.029 g, 0.166 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane and aqueous ammonia, and the mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 5% methanol/dichloromethane mixture to give the title compound (0.032 g, 69%) as a colorless solid. Mp: 234–236 °C. MS calcd: 564; Found: 565 (M+H). ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, d, J = 6.3 Hz), 1.40 (3H, d, J = 6.3 Hz), 1.58 (6H, s), 2.16 (3H, s), 3.52 (3H, s), 3.81 (3H, s), 4.30–4.45 (1H, m), 5.15–5.30 (2H, m), 5.75–5.90 (1H, m), 6.37 (1H, d, J = 7.5 Hz), 6.63 (1H, s), 6.73 (1H, d, J = 8.1 Hz), 6.83 (1H, d, J = 7.5 Hz), 6.92 (1H, s), 7.04 (1H, s), 7.05–7.20 (2H, m), 7.50 (1H, d, J = 7.8 Hz). Anal. Calcd for $C_{29}H_{34}N_5O_2Br$: C, 61.70; H, 6.07; N, 12.41. Found: C, 61.35; H, 6.02; N, 12.17.

4.3. In vitro study

4.3.1. Measurement of the rate of inhibition of CRF_1 binding

A receptor-binding experiment was performed using a human CRF_1 receptor expressing a CHO cell membrane fraction and ovine CRF, ^{125}I-Tyr^0 (^{125}I-CRF). Various concentrations of a test compound were incubated with 1 μg of the CHO membrane fraction and 50 pM of ^{125}I-CRF in binding assay buffer [50 mM Tris–HCl, 5 mM EDTA, 10 mM $MgCl_2$, 0.05% CHAPS, 0.1% BSA, 0.5 mM PMSF, 0.1 μg/mL pepstatin, and 20 μg/mL leupeptin (pH 7.5)]. For measuring non-specific binding (NSB), 0.1 μM of unlabeled human urocortin was incubated with 1 μg of the CHO cell membrane fraction and 50 pM of ^{125}I-CRF in binding assay buffer. The reaction was performed at rt for 1.5 h, the membrane was collected on a glass filter (UniFilter plate GF-C/Perkin Elmer) using suction filtration and a cell harvester (Perkin Elmer), and it was washed with ice-cold 50 mM Tris–HCl (pH 7.5). After drying the glass filter, a liquid scintillation cocktail (Microscinti; Perkin Elmer) was added, and the radioactivity of ^{125}I-CRF remaining on the glass filter was measured using a TopCount (Perkin Elmer). The percent inhibition was calculated using the following equation:

$$\%\text{Inhibition} = (\text{Bound} - \text{NSB})/(\text{TB} - \text{NSB}) \times 100,$$

where Bound is the radioactivity when a compound is added, TB is the total binding radioactivity, and NSB is the non-specifically bound radioactivity. IC_{50} values and 95% confidence intervals were calculated using GraphPad Prism software.

4.3.2. CRF_1 antagonistic activity

CRF_1 antagonistic activity was obtained by measuring inhibition of adenylate cyclase using a CRE-luciferase reporter assay. CHO cells expressing the human CRF_1 receptor and the CRE-luciferase gene were added to the wells of a 96-well plate (40,000 cells/well) and incubated for 24 h. After cultivation, the culture medium was removed, and the cells were treated for 4 h with various drug concentrations in 100 μL of assay buffer [20 mM HEPES, Ham F-12, and 0.1% BSA (pH 7.2)] containing 1 nM human CRF. After exposure to the test compounds, the cells were lysed and luciferase activity was measured using a Steady-Glo® luciferase assay system (Promega). Light emission was detected using an ARVO-SX (Wallac). IC_{50} values and 95% confidence intervals were calculated using GraphPad Prism software.

4.4. Ex vivo study

4.4.1. Preparation of brain membrane homogenates

Mice were sacrificed by decapitation, and their brains were rapidly removed and homogenized at 4 °C using a Physcotron homogenizer (setting, 10 s) in lysis buffer [50 mM Tris–HCl (pH 7.0), 10 mM $MgCl_2$, 2 mM EDTA, and 100 KU/mL aprotinin]. The frontal cortex was diluted with lysis buffer to a final concentration of 5 mg wet tissue/mL. The olfactory bulb was homogenized in 5 mL of lysis buffer and diluted to 1/5 with lysis buffer. The pituitary was homogenized in 2.5 mL of lysis buffer and diluted with lysis buffer to a final concentration of 5 mg wet tissue/mL.

Animals were handled according to the procedures approved by the Animal Experiment Ethics Committee of Takeda Pharmaceutical Company Ltd.

4.4.2. Drugs

The compounds were suspended in 0.5% methyl cellulose (MC; ShinEtsu) in water and administered orally in a volume of 10 mL/kg for use in the ex vivo binding assay described below.

4.4.3. Ex vivo binding assay in mice

Test compounds or the corresponding vehicle was orally administered to mice (10 per group) 1 h before decapitation and organ (frontal cortex, olfactory bulb, and pituitary) removal. The tissues were homogenized in ice-cold lysis buffer using a Physcotron homogenizer and diluted as described above. ^{125}I-CRF (ovine) binding was performed with membrane homogenates in the presence of 100 pM of ^{125}I-CRF (ovine) in lysis buffer containing 0.1% BSA, 0.5% DMSO, and 0.05% CHAPS in a final volume of 200 μL. After incubation at rt for 2 h, the incubation mixture was filtered on a Whatman GF/C filter presoaked in 0.3% polyethylenimine. The filters were washed six times with ice-cold wash buffer (PBS containing 0.05% CHAPS and 0.01% Triton X-100) and dried. Radioactivity was determined using a gamma scintillation counter.

The results were expressed as an inhibitory rate of ^{125}I-CRF (ovine) binding, with in vitro determination of NSB using 1 μM of compound **1**.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2016.08.005. These data include MOL files and InChiKeys of the most important compounds described in this article.

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