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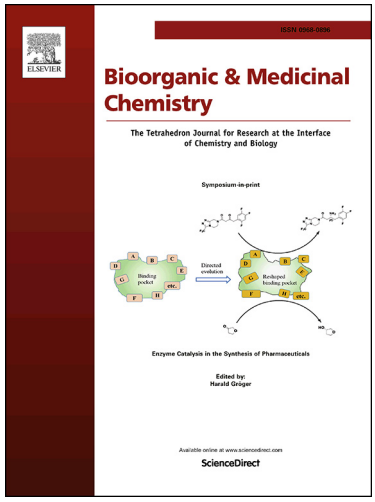

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PII: S0968-0896(18)31308-7
DOI: https://doi.org/10.1016/j.bmc.2018.09.006
Reference: BMC 14531

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 20 July 2018
Revised Date: 3 September 2018
Accepted Date: 5 September 2018

Please cite this article as: Shinozuka, T., Tsukada, T., Fujii, K., Tokumaru, E., Shimada, K., Onishi, Y., Matsui, Y., Wakimoto, S., Kuroha, M., Ogata, T., Araki, K., Ohsumi, J., Sawamura, R., Watanabe, N., Yamamoto, H., Fujimoto, K., Tani, Y., Mori, M., Tanaka, J., Discovery of DS-6930, a Potent Selective PPARγ Modulator. Part I: Lead Identification, *Bioorganic & Medicinal Chemistry* (2018), doi: https://doi.org/10.1016/j.bmc.2018.09.006

Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Discovery of DS-6930, a Potent Selective PPARγ Modulator. Part I: Lead Identification

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
PPARγ
DS-6930
benzimidazole

ABSTRACT

The lead identification of a novel potent selective PPARγ agonist, DS-6930 is reported. To avoid PPARγ-related adverse effects, a partial agonist was designed to prevent the direct interaction with helix 12 of PPARγ-LBD. Because the TZD group is known to interact with helix 12, the TZD in efatutazone (CS-7017) was replaced to discover novel PPARγ intermediate partial agonist **8i**. The optimization of **8i** yielded **13ac** with high potency *in vitro*. Compound **13ac** exhibited robust plasma glucose lowering effects comparable to those of rosiglitazone (3 mg/kg) in Zucker diabetic fatty rats. Upon toxicological evaluation, compound **13ac** (300 mg/kg) induced hemodilution to a lower extent than rosiglitazone; however, **13ac** elevated liver enzyme activities. X-ray crystallography revealed no direct interaction of **13ac** with helix 12, and the additional lipophilic interactions are also suggested to be related to the maximum transcriptional activity of **13ac**.

1. Introduction

Type 2 diabetes (T2DM) is a global epidemic that is a leading cause of death even in developing countries.[1] Out of the estimated 425 million people with diabetes, 90% suffer from T2DM.[1] It is an economically debilitating disorder that critically affects national healthcare budgets.[1] Commercially marketed drugs for T2DM include metformin, sulfonylureas, dipeptidyl peptidase-IV inhibitors, sodium-dependent glucose co-transporter 2 inhibitors, GLP-1 receptor agonists and peroxisome proliferator-activated receptor γ (PPARγ) agonists.[2,3] However, drugs with less adverse effects remain to be identified.[4] Thiazolidinedione (TZD)-based PPARγ full agonists, pioglitazone and rosiglitazone improve insulin sensitivity by restoring plasma insulin and glucose levels in T2DM patients.[5,6] However, they are associated with adverse effects, such as weight gain, peripheral edema, hepatotoxicity, bone fracture, carcinogenicity and cardiovascular risks.[6-10] These adverse effects limit their usage. If such adverse effects are avoided, PPARγ modulators present an attractive therapeutic approach.[11]

Although the particular mechanism of PPARγ agonism for antidiabetic efficacy is not fully elucidated, the inhibition of PPARγ phosphorylation by cyclin-dependent kinase 5 (Cdk5) is reported to be involved in the mechanism of antidiabetic efficacy of PPARγ modulators, rather than PPARγ transcriptional activity.[12] Furthermore, non-PPARγ agonists with PPARγ phosphorylation inhibitory activity exhibited potent *in vivo* efficacy in rodents,[13,14] suggesting that PPARγ phosphorylation is the underlying mechanism of antidiabetic efficacy, while PPARγ agonist activity is related to adverse effects.[15] We adopted an ordinary approach to tackle PPARγ-related adverse effects. We believe there is still scope for the development of safer PPARγ partial agonists by the regulation of cofactors. In this paper, we report the lead identification of a novel potent selective PPARγ agonist, DS-6930 (**I**, Figure 1) through conventional PPARγ reporter assays.

We carried out this study based on TZD-based PPARγ full agonists, such as rivoglitazone (CS-011, **II**, Figure 1)[16], efatutazone (CS-7017, **III**, Figure 1),[17] and non-TZD partial PPARγ agonist, (-)-cercosporamide derivative (**IV**, Figure 1)[18-20]. The stabilization of helix 12 dynamics of PPARγ-ligand binding domain (LBD) is known to play a critical role in the PPARγ transcriptional activity of PPARγ full agonists.[21,22] TZD moiety of PPARγ full agonists interacts directly with Tyr473 on helix 12.[21,22] On the other hand, (-)-cercosporamide derivative (**IV**) binds to PPARγ-LBD without direct interaction to helix12.[18-20] Such an interaction is proposed to partially activate the PPARγ receptor, which results in diminished PPARγ-related adverse effects through the selective recruitment of cofactors.[18-20,23-29] Several PPARγ partial agonists are known to lack the direct interaction with this helix.[23-29] INT131 showed partially activated PPARγ target genes without direct hydrogen bonding with helix 12.[23] The

absence of interaction between benzimidazolone-based PPARγ partial agonist and Tyr473 on helix 12 was also reported.[24,25] In both cases, mutagenesis studies on Tyr473 indicated that this residue was nonessential for the transcriptional activity.[23-25] Another study concluded that partial agonists activate PPARγ using a hexlix 12-independent mechanism.[29] Consequently, the avoidance of such interaction is expected to identify novel partial agonists. Efatutazone is known as one of the most potent full PPARγ agonists (EC_{50}: 0.038 nM). Derivatization of efatutazone would lead to the discovery of partial agonists with enough *in vitro* potency, even though replacement of the TZD group leads to a significant drop in the activity. Thus, to acquire potent partial PPARγ agonists with robust efficacy *in vivo*, our research initiated with modification of the TZD moiety of **III** to prevent the direct interaction with Tyr473 on helix 12.

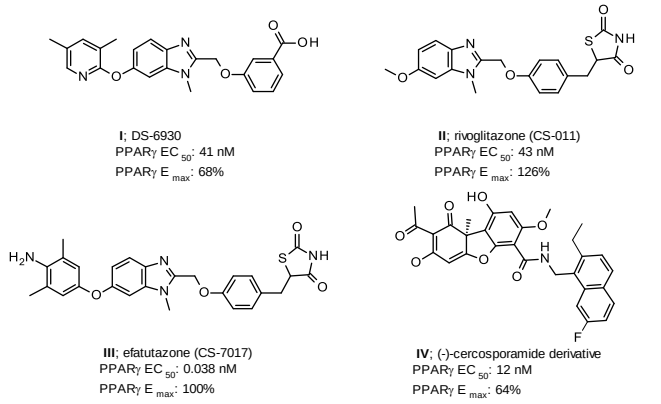
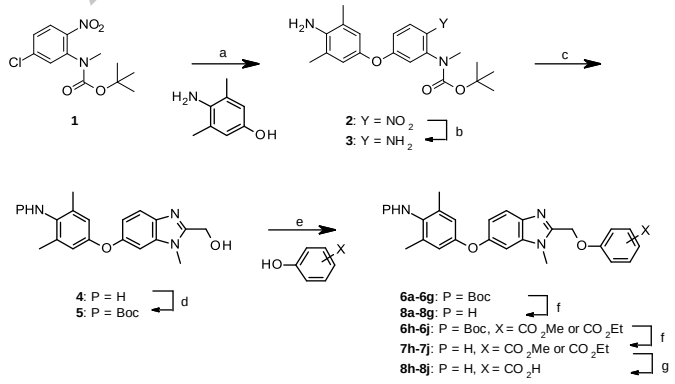


Figure 1. Structures of DS-6930 (**I**), rivoglitazone (CS-011, **II**), efatutazone (CS-7017, **III**) and (-)-cercosporamide derivative (**IV**) with PPARγ-agonist activities in COS-7 cells.

2. RESULTS and DISCUSSION

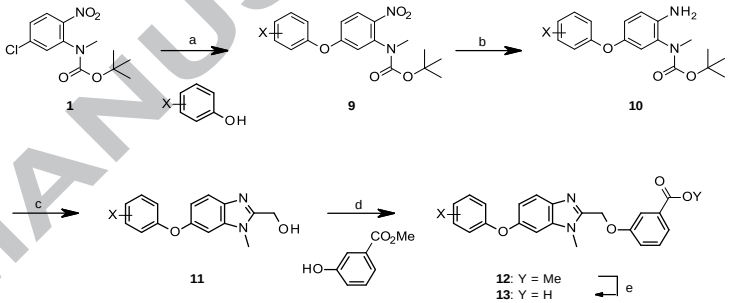
2.1. Chemical synthesis

4-Amino-3,5-dimethylphenoxy derivatives **8** (Table 1) were synthesized by nucleophilic aromatic substitution as a key step (Scheme 1). Nitrobenzene **1** was reacted with 4-amino-3,5-dimethylphenol to afford nitro ether **2**, and reduced under a hydrogenolytic condition to yield diamine **3**. Reacting the unpurified compound **3** with glycolic acid under an acidic condition afforded benzimidazole **4**. In this reaction scheme, the protection of the amino group of 4-amino-3,5-dimethylphenoxy moiety was not required due to the low nucleophilicity of the hindered amino group. However, the protection of this amino group was essential for the subsequent Mitsunobu reaction conducted with a variety of phenols to yield compounds **6**. Finally, BOC group was deprotected to afford target molecules **8a–8g**. Carboxylic acids **8h–8j** were synthesized by hydrolyzing esters **7h–7j**.



Scheme 1. Synthesis of Compounds **8**. Reagents and conditions: (a) NaH, DMA; (b) H_2, Pd/C, EtOH; (c) glycolic acid, HCl, 1,4-dioxane, 53% (3 steps); (d) Boc_2O, *i*-PrOH, 26%; (e) ADDP, PBu_3, toluene; (f) HCl, 1,4-dioxane, 67% (2 steps, **7h**), 63% (2 steps, **7i**), 67% (2 steps, **7j**), 53% (2 steps, **8a**), 53% (2 steps, **8b**), 87% (2 steps, **8c**), 92% (2 steps, **8d**), 68% (2 steps, **8e**), 83% (2 steps, **8f**), 92% (2 steps, **8g**); (g) NaOH, 1,4-dioxane, H_2O, 60 °C, 66% (**8h**), 61% (**8i**), 77% (**8j**).

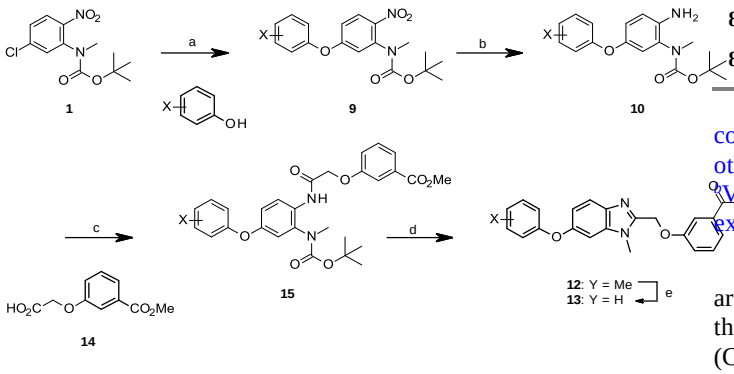
3-Benzoic acid derivatives **13** listed in Tables 2 and 3 were synthesized using the same synthetic scheme as that used for synthesizing compounds **8** (Scheme 2). Suitably substituted phenols were reacted with nitrobenzene **1** to provide corresponding nitro ethers **9**. After reducing nitro group, benzimidazoles **11** were obtained by the treatment of **10** with glycolic acid under an acidic condition. Because several diamines **10** indicated instability towards chromatographic purification, diamines **10** were converted to benzimidazoles **11** without purification. After Mitsunobu reaction of benzimidazoles **11** with methyl 3-hydroxybenzoate, the final saponification of methyl esters **12** gave desired carboxylic acids **13a-13ae**.



Scheme 2. Synthesis of Compounds **13a-13ae**. Reagents and conditions: (a) NaH, DMF, 80 °C, 99% (**9d**), 99% (**9g**), 99% (**9h**), 99% (**9i**), 56% (**9n**), 92% (**9r**), 69% (**9ab**), 99% (**9ac**), 99% (**9ad**), 99% (**9ae**); (b) Fe, NH_4Cl, EtOH, H_2O, reflux; (c) glycolic acid, HCl, 1,4-dioxane,H_2O, reflux, 73% (**11a**, 3 steps), 72% (**11b**, 3 steps), 80% (**11c**, 3 steps), 29% (**11d**, 2 steps), 72% (**11e**, 3 steps), 63% (**11f**, 3 steps), 88% (**11g**, 2 steps), 20% (**11h**, 2 steps), 78% (**11i**, 2 steps), 61% (**11j**, 3 steps), 89% (**11k**, 3 steps), 87% (**11l**, 3 steps), 75% (**11m**, 3 steps), 91% (**11n**, 2 steps), 57% (**11o**, 3 steps), 75% (**11p**, 3 steps), 76% (**11q**, 3 steps), 83% (**11r**, 2 steps), 60% (**11s**, 3 steps), 88% (**11t**, 3 steps), 69% (**11u**, 3 steps), 86% (**11v**, 3 steps), 85% (**11w**, 3 steps), 87% (**11x**, 3 steps), 70% (**11y**, 3 steps), 83% (**11z**, 3 steps), 77% (**11aa**, 3 steps), 58% (**11ab**, 2 steps), 57% (**11ac**, 2 steps), 49% (**11ad**, 2 steps), 45% (**11ae**, 2 steps); (d) ADDP, PBu_3, CH_2Cl_2, 66% (**12a**), 58% (**12b**), 86% (**12c**), 81% (**12d**), 81% (**12e**), 85% (**12f**), 83% (**12g**), 97% (**12h**), 44% (**12i**), 89% (**12j**), 65% (**12k**), 75% (**12l**), 81% (**12m**), 91% (**12n**), 81% (**12o**), 78% (**12p**), 84% (**12q**), 78% (**12r**), 60% (**12s**), 80% (**12t**), 86% (**12u**), 77% (**12v**), 65% (**12w**), 78% (**12x**), 49% (**12y**), 82% (**12z**), 80% (**12aa**), 74% (**12ab**), 99% (**12ac**), 32% (**12ad**), 67% (**12ae**); (e) NaOH, 1,4-dioxane, H_2O, reflux, 70% (**13a**), 68% (**13b**), 93% (**13c**), 37% (**13d**), 98% (**13e**), 60% (**13f**), 68% (**13g**), 84% (**13h**), 89% (**13i**), 89% (**13j**), 89% (**13k**), 86% (**13l**), 86% (**13m**), 81% (**13n**), 89% (**13o**), 86% (**13p**), 48% (**13q**), 91% (**13r**), 85% (**13s**), 82% (**13t**), 76% (**13u**), 89% (**13v**), 93% (**13w**), 48% (**13x**), 95% (**13y**), 94% (**13z**), 81% (**13aa**), 73% (**13ab**), 72% (**13ac**), 86% (**13ad**), 70% (**13ae**).

Bicyclic ring analogues **13af–13ah** listed in Table 3 were synthesized from amides **15** as intermediates (Scheme 3). Diamines **10** were coupled with [3-(methoxycarbonyl)phenoxy]acetic acid (**14**) under the usual condition to provide amides **15**. Benzimidazoles **12** were obtained

by the treatment of amides **15** with HCl. The saponification of methyl esters **12** provided carboxylic acids **13af-13ah**.

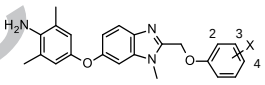


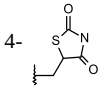
Scheme 3. Synthesis of Compounds **13af-13ah**. Reagents and conditions: (a) NaH, DMF, 80 °C, 27% (**9af**); (b) Fe, NH_4Cl, EtOH, H_2O, reflux; (c) WSC•HCl, HOBt•H_2O, CH_2Cl_2, 86% (**15af**, 2 steps), 94% (**15ag**, 3 steps), 93% (**15ah**, 3 steps); (d) HCl, EtOAc, 60 °C, 84% (**12af**), 47% (**12ag**), 79% (**12ah**); (e) NaOH, 1,4-dioxane, H_2O, reflux, 63% (**13af**), 74% (**13ag**), 98% (**13ah**).

2.2. In vitro activity, in vitro ADME properties and in vivo efficacy in KK/Ta mice

PPARγ transcriptional activities were evaluated by GAL4-PPAR-LBD reporter gene assays using COS-7 cells. The maximum transcriptional activity (E_{max}) of each test compound was calculated relative to that of rosiglitazone (100%). As shown in Table 1, PPARγ full agonist rosiglitazone exhibited EC_{50} = 396 nM. To prevent the direct interaction with Tyr473 on helix 12, the removal of TZD-methyl group from **III** was examined, which resulted in several thousand-fold reduction in potency *in vitro* (Compound **8a**, EC_{50} = 318 nM). As expected, **8a** closed to a partial agonist (E_{max} = 73%). Therefore, we decided to introduce several small functional groups to avoid the direct interaction with Tyr473. When methyl ketone, nitrile or carboxylic acid was introduced in the right-hand side benzene ring, 3-position was found to be optimal for the potency. 3-Subtituted ketone **8c** and nitrile **8f** exhibited 4.9- and 7.4-fold higher potencies, respectively, than that of **8a**. Compounds **8c** (E_{max} = 86%) and **8f** (E_{max} = 92%) assumed a full agonist, while 3-carboxylic acid derivative **8i** closed to a partial agonist (E_{max} = 73%). Accordingly, **8i** was further modified to enhance its potency *in vitro*.

Table 1. PPARγ Transcriptional Activities of Compounds **8**[a]



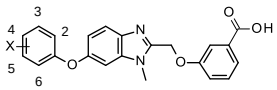
Compound	X	EC_{50} (nM)	E_{max} (%)
rosiglitazone		396 ± 133[b]	100
III	4- 	0.038	100
8a	H	318	73
8b	2-COMe	356	96
8c	3-COMe	65	86
8d	4-COMe	340	70
8e	2-CN	391	80
8f	3-CN	43	92
8g	4-CN	395	79
8h	2-CO_2H	6094	52
8i	3-CO_2H	299	73
8j	4-CO_2H	797	91

[a]Luciferase activity in COS-7 cells after treatment with the test compound. Values on single experiment run in octuplicate unless otherwise noted. HCl salts of all the test compounds were used. [b]Value represented as mean ± S.E.M. Value on five independent experiments run in octuplicate.

The modifications of left-hand side phenyl ring in compound **8i** are summarized in Table 2. The removal of all substituents from this phenyl ring only led to a 2.8-fold reduction in potency *in vitro* (Compound **13a**). This modification enhanced the maximum transcriptional activity due to unclear reasons (E_{max} = 90%). *In vitro* ADME profiling showed that this modification decreases solubility, while both compounds **8i** and **13a** exhibited high stability against human liver microsomes. SAR studies were performed to identify compounds with high potency and low maximum transcriptional activity. The introduction of a fluorine atom at positions 3 and 4 increased the potencies by several folds retaining the maximum transcriptional activities (Compounds **13c** and **13d**), while 2-fluoro derivative **13b** showed diminished potency. The microsomal stability of 3-fluoro-substituted compound **13c** was robust. Upon evaluation of selectivity over PPARα, fluoro-substituted compounds **13c** and **13d** were found to exhibit high selectivity over PPARα; both compounds caused less than 50% activation of PPARα at 10 μM. This series of compounds caused no PPARδ transcriptional activity at 10 μM (Data not shown). These compounds were then evaluated for preliminary in vivo efficacy. Plasma glucose (PG) lowering effects in hyperglycemic KK/Ta mice were assessed after they were administered 0.03% (ca. 30 mg/kg/day, assuming constant food intake) of the compounds through their diets. After 3 days, abilities to induce PG reduction (% change vs vehicle control) and body weight gain (% change vs vehicle control) as well as plasma concentrations of the test compounds were determined (n = 3). Both compounds **13c** and **13d** significantly reduced PG levels in KK/Ta mice (52.1 and 56.7%, respectively vs vehicle control). They also increased body weight by 3–4%, similar to full agonists.[30] Despite its modest potency *in vitro*, 3-fluoro derivative **13c** exhibited potent *in vivo* efficacy due to its high plasma concentration. Methyl substitution enhanced *in vitro* potency by over ten-fold, and all methyl substituted compounds **13e–13g** had EC_{50} values less than 100 nM. Among these methyl derivatives, 3- and 4-substituted compounds (**13f** and **13g**) significantly reduced PG levels in KK/Ta mice. 2-Methyl derivative **13e** failed to exhibit potent *in vivo* efficacy, despite showing *in vitro* potency and plasma exposure comparable to those of 3-methyl derivative **13f**.[31] Among methyl substituted derivatives, 2- and 3-substituted compounds (**13e** and **13f**) exhibited modest microsomal stability, while 4-derivative **13g** displayed high microsomal stability. A high *in vitro* potency was also observed in 3- or 4-chloro substituted compounds (**13h** and **13i**). 4-Chloro derivative **13i** indicated excellent selectivity over PPARα, while 3-chloro analogue **13h** exhibited remarkably enhanced PPARα activity. Methoxy substitutions were not found to be suitable for good *in vitro* potency (Compounds **13j–13l**), while 3-ethoxy derivative **13m** showed high *in vitro* potency. Nevertheless, **13m** failed to exhibit potent *in vivo* efficacy in KK/Ta mice. Because 3-substitution was one of the optimal substation patterns for *in vitro* potency, several 3-substituted derivatives were synthesized to find out 3-trifluoromethoxy and 3-trifluoromethyl substituted compounds **13n** and **13o**, which exhibited high potencies *in vitro* as well as *in vivo*. Similar to 3-chloro analogue **13h**, a diminished

selectivity over PPARα was observed in 3-trifluoromethyl derivative **13o**.

Table 2. PPAR Transcriptional Activities, *In Vitro* ADME Profiles and *In Vivo* Efficacies of Compounds **13**



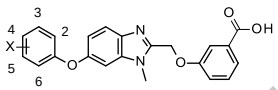
Compound	X	PPARγ EC_{50} (nM)[a]	PPARγ E_{max} (%)[a]	PPARα EC_{50} (nM)[b]	PPARα E_{max} (%)[b]	Log D[c]	Solubility (μg/mL)[d]	Human MS (%)[e]	In vivo efficacies in KK/Ta mice[f]		
									PG reduction (%)	Body weight gain (%)	Plasma concentration (μg/mL)
8i[i]	3-Me, 4-NH_2, 5-Me	299	73	NT[g]	NT[g]	1.4	11	88	NT[g]	NT[g]	NT[g]
13a[i]	H	845	90	NT[g]	NT[g]	1.8	2.0	100	NT[g]	NT[g]	NT[g]
13b	2-F	1434	125	>10000	21	1.7	12	NT[g]	NT[g]	NT[g]	NT[g]
13c	3-F	201	75	>10000	22	2.0	2.2	98	52.1 ± 9.1**	3.2 ± 0.97	1.74 ± 0.87
13d	4-F	122	75	>10000	29	2.0	19	NT[g]	56.7 ± 6.4**	3.4 ± 2.2	0.32 ± 0.092
13e	2-Me	56	80	>10000	16	2.4	2.2	62	26.9 ± 12.3	3.7 ± 0.69	0.10 ± 0.005
13f	3-Me	79	76	>10000	19	2.3	3.8	69	56.9 ± 0.85**	3.2 ± 1.2	0.090 ± 0.022
13g	4-Me	40	73	>10000	28	2.4	7.9	91	48.4 ± 9.7*	4.8 ± 1.1	0.51 ± 0.051
13h[i]	3-Cl	86	103	ND[h]	69	2.7	0	90	59.6 ± 3.1**	2.8 ± 1.4	0.19 ± 0.020
13i	4-Cl	126	62	>10000	8	2.6	2.0	NT[g]	34.4 ± 10.7*	4.1 ± 1.2	ND[h]
13j[i]	2-OMe	474	60	>10000	4	1.3	12	74	NT[g]	NT[g]	NT[g]
13k	3-OMe	235	92	>10000	30	1.8	5.4	68	NT[g]	NT[g]	NT[g]
13l	4-OMe	307	71	>10000	7	1.8	9.3	100	NT[g]	NT[g]	NT[g]
13m	3-OEt	40	56	>10000	37	2.4	0	NT[g]	22.0 ± 4.9	3.3 ± 3.1	ND[h]
13n	3-OCF_3	113	69	>10000	17	3.3	0.9	98	41.9 ± 4.1**	5.3 ± 2.3	0.37 ± 0.018
13o[i]	3-CF_3	23	81	ND[h]	56	2.8	0	85	45.1 ± 16.6*	3.8 ± 1.7	0.090 ± 0.031

[a]Luciferase activity in COS-7 cells after treatment with the test compound. Values on single experiment run in octuplicate. [b]PPARα activity (%) in COS-7 cells. Values on single experiment run in octuplicate. The maximum transcriptional activity (E_{max}) of the test compound is expressed relative to that of the reference compound as 100%.[32] [c]Distribution coefficients (Log D) were measured based on partition between 1-octanol and PBS (pH = 7.4). [d]Aqueous thermodynamic solubility at pH 6.8. Values on single experiment run in duplicate. [e]Human microsomal stability assessed based on test compound (%) remaining after 0.5 h of incubation with human liver microsomes. [f]PG reduction (% change in PG level vs vehicle control), body weight gain (% change in body weight vs vehicle control) and plasma concentration (μg/mL) of the test compounds in hyperglycemic KK/Ta mice after the oral administration of 0.03% (ca. 30 mg/kg/day, assuming constant food intake) of the test compounds through their diet on day 3 (n = 3). Data are represented as mean ± S.E.M. Statistical significance compared to vehicle treatment is denoted by *p < 0.05 and **p < 0.01 as determined by the Student T-test. The plasma concentration of the test compound was measured on day 3 (n = 3). Each value represents the mean ± S.D. [g]Not tested. [h]Not determined. [i]HCl salt.

To further enhance *in vitro* potency and *in vivo* efficacy, another substituent was introduced on the left-hand side phenyl ring as shown in Table 3. Initially, compounds were tested for synergic effects with difluoro derivatives. When another fluorine atom was introduced at positions 3, 4, 5, or 6 on benzene ring of 2-fluoro derivative **13b**, 2,3-, 2,4- and 2,5-substitution (Compounds **13p–13r**) indicated severalfold improved potencies, whereas 2,6-substituted compound **13s** did not exhibit an improved potency. Further enhancement of the potency was achieved in 3,4- and 3,5-substituted compounds (Compounds **13t** and **13u**). Among difluoro-substituted compounds, 2,5- and 3,4-difluoro derivatives (**13r** and **13t**) exhibited excellent *in vivo* efficacies in KK/Ta mice. In terms of PPARα selectivity, only 2,3-difluoro derivative **13p** indicated diminished selectivity. Because 2-methyl substitution significantly enhanced *in vitro* potency (Compound **13e** in Table 1), 2-methyl substituted 4- or 5-fluoro derivatives (**13v** and **13w**) were synthesized to find excellent potencies *in vitro* (EC_{50} = 22 and 39 nM, respectively). Compound **13v** exhibited potent PG reduction in KK/Ta mice, while **13w** did not. Although **13v** indicated robust *in vivo* efficacy, modest

microsomal stability was still an issue. 2-Fluoro-substituted 4-methyl and 5-methyl derivatives (Compounds **13x** and **13y**) showed less potencies *in vitro* with better microsomal stabilities than compounds **13v** and **13w**. Both **13x** and **13y** showed potent *in vivo* efficacies. To further enhance *in vitro* potencies of 3,4- and 3,5-substituted derivatives, a methyl group was incorporated. As expected, 3-fluoro-4-methyl derivative **13z** exhibited excellent potency *in vitro* (EC_{50} = 4.4 nM) with modest partial agonist affinity (E_{max} = 80%). Compound **13z** showed over 50% PG reduction *in vivo*. Moreover, the 3-fluoro-4-methyl substitution enhanced PPARγ potency without PPARα activation. 3-Methyl-4-fluoro derivative **13aa** and 3-fluoro-5-methyl derivative **13ab** also exhibited excellent potencies *in vitro*. Both compounds yielded the same plasma exposures in KK/Ta mice and reduced PG to the same extent. It should be noticed that **13aa** showed moderate microsomal stability (69%), while **13ab** possessed robust stability (100%). Because the incorporation of chloro group was expected to increase *in vitro* potency similar to methyl group (Compounds **13f** and **13h**, Table 2), a chloride atom was incorporated to yield compounds **13ac–13ae**; they exhibited excellent potencies *in vitro*. 3-Fluoro-4-chloro derivative **13ac** and 3-fluoro-5-chloro analogue **13ad** not only exhibited strong potencies *in vitro*, but also robust efficacies in KK/Ta mice. 3-Chloro-4-fluoro derivative **13ae** exhibited attenuated *in vitro* potency and *in vivo* efficacy. The enhancement of PPARα activity in **13ae** may relate to the 3-chloro substituent, because enhanced PPARα activity was observed in 3-chloro analogue **13h**. Because 3,4-disubstituted compounds possessed optimal characteristics, fused ring derivatives were synthesized. Dihydrobenzofurans **13af** and **13ag** retained high potencies *in vitro*. Compound **13ag** exhibited E_{max} = 95% due to unclear reasons. Although **13ag** exhibited potent *in vitro* potency as well as *in vivo* efficacy, a moderate microsomal stability was observed. The aromatization of **13ag** provided benzofuran **13ah**, which showed attenuated potency *in vitro* with high microsomal stability.

Table 3. PPAR Transcriptional Activities, *In Vitro* ADME Profiles and *In Vivo* Efficacies of Compounds **13**



Compound	X	PPARγ EC_{50} (nM)[a]	PPARγ E_{max} (%)[a]	PPARα EC_{50} (nM)[b]	PPARα E_{max} (%)[b]	Log D[c]	Solubility (μg/mL)[d]	Human MS (%)[e]	*In vivo* efficacies in KK/Ta mice[f]		
									PG reduction (%)	Body weight gain (%)	Plasma concentration (μg/mL)
13p	2-F, 3-F	230	86	ND[h]	52	2.1	0	88	35.8 ± 12.9	4.3 ± 1.4	ND[h]
13q	2-F, 4-F	143	77	>10000	17	1.9	11	100	37.6 ± 9.6*	3.7 ± 0.92	0.37 ± 0.074
13r	2-F, 5-F	134	79	>10000	36	1.9	5.7	98	51.2 ± 4.7**	3.3 ± 1.7	0.70 ± 0.67
13s	2-F, 6-F	1326	76	>10000	19	1.8	NT[g]	85	NT[g]	NT[g]	NT[g]
13t[i]	3-F, 4-F	118	71	>10000	39	2.0	0	100	56.0 ± 3.6**	3.4 ± 1.4	0.16 ± 0.017
13u	3-F, 5-F	95	54	>10000	33	2.3	10	NT[g]	39.5 ± 11.7*	4.4 ± 2.3	0.36 ± 0.11
13v	2-Me, 4-F	22	66	>10000	19	2.5	1.7	59	54.7 ± 5.0**	2.8 ± 2.9	0.19 ± 0.048
13w	2-Me, 5-F	39	84	>10000	17	2.5	0.6	64	26.4 ± 7.4	5.1 ± 2.7	ND[h]
13x	2-F, 4-Me	92	90	>10000	16	2.3	0.5	92	53.4 ± 10.1**	2.5 ± 3.1	0.55 ± 0.140
13y	2-F, 5-Me	139	111	>10000	37	2.4	11	83	49.4 ± 18.4*	1.6 ± 2.4	0.12 ± 0.039
13z	3-F, 4-Me	4.4	80	>10000	40	2.7	4.4	91	56.8 ± 1.2**	4.2 ± 1.8	0.47 ± 0.11
13aa[i]	3-Me, 4-F	62	61	>10000	28	2.3	0	69	49.4 ± 6.7**	3.5 ± 1.5	0.19 ± 0.010
13ab	3-F, 5-Me	21	84	>10000	29	2.7	0.5	100	58.3 ± 3.1**	1.7 ± 2.4	0.19 ± 0.041
13ac	3-F, 4-Cl	68 ± 28[j]	82 ± 4.0[j]	>10000[j]	32 ± 2.7[j]	2.7	0	100	43.2 ± 6.7**	4.4 ± 3.0	0.57 ± 0.23
13ad	3-F, 5-Cl	23	78	>10000	43	2.8	0.9	78	57.5 ± 4.2**	3.1 ± 2.9	0.37 ± 0.064
13ae[i]	3-Cl, 4-F	64	79	ND[h]	52	2.8	0	NT[g]	30.0 ± 14.4	3.7 ± 3.4	0.17 ± 0.021
13af[i]		87	60	>10000	8	1.7	7.6	87	NT[g]	NT[g]	NT[g]

13ag		21	95	>10000	12	2.0	16	62	41.6 ± 7.3**	4.8 ± 3.6	0.36 ±0.058
13ah		188	79	>10000	37	2.4	0.8	100	48.3 ± 10.5**	2.5 ± 1.7	0.38 ± 0.060

[a]Luciferase activity in COS-7 cells after treatment with the test compound. Values on single experiment run in octuplicate unless otherwise noted. [b]PPARα activity (%) in COS-7 cells. Values on single experiment run in octuplicate unless otherwise noted. The maximum transcriptional activity (E_{max}) of the test compound is expressed relative to that of the reference compound as 100%.[32] [c]Distribution coefficients (Log D) were measured after partition between 1-octanol and PBS (pH = 7.4). [d]Aqueous thermodynamic solubility at pH 6.8. Values on single experiment run in duplicate. [e]Human microsomal stability. Test compound (%) remaining after a 0.5 h of incubation with human liver microsomes. [f]PG reduction (% change in PG level vs vehicle control), body weight gain (% change in body weight vs vehicle control) and plasma concentration (μg/mL) of the test compounds in hyperglycemic KK/Ta mice after the oral administration of 0.03% (ca. 30 mg/kg/day assuming constant food intake) of compounds through their diet on day 3 (n = 3). Data are represented as mean ± S.E.M. Statistical significance compared to vehicle treatment is denoted by *p < 0.05 and **p < 0.01 as determined by the Student T-test. The plasma concentration of the test compound was measured on day 3 (n = 3). Each value represents the mean ± S.D. [g]Not tested. [h]Not determined. [i]HCl salt. [j]Values represented as mean ± S.E.M. Values on 13 independent experiments run in octuplicate.

2.3. In Vivo Efficacy in ZDF Rats

Several compounds were selected for further pharmacological profiling. These compounds were assessed for their abilities to reduce PG in Zucker diabetic fatty (ZDF) rats after administration at 3 mg/kg/day p.o. for 14 days as shown in Table 4 (n = 5). After this treatment duration, an additional administration was performed to evaluate PK parameters (Table 4). The administration of rosiglitazone reduced PG levels by 40.3% vs vehicle control. Compounds **13g** and **13r** indicated robust stability against rat liver microsomes, and were expected to exhibit potent efficacy in ZDF rats because both compounds already significantly reduced PG levels in KK/Ta mice. As expected, both compounds exhibited excellent efficacies in ZDF rats (58.6 and 61.2% PG reduction, respectively, vs vehicle control) with statistical significance. Administration of this series of compounds caused body weight gain (vs vehicle control) similar to the full agonist, rosiglitazone. Compounds **13g** and **13r** increased the body weight of ZDF rats by 13.0 and 9.5%, respectively, whereas rosiglitazone increased the body weight by 12.6%. Although compound **13v** exhibited potent PG reduction in KK/Ta mice (Table 3), **13v** suffered from poor efficacy in ZDF rats due to low plasma exposure. Compounds **13x**, **13z** and **13ag** also significantly reduced PG levels. Despite their similar effects on PG levels, compounds **13z** and **13ag** induced relatively high body weight gains (13.8 and 15.6%, respectively, vs vehicle control), while **13x** moderately increased the body weight (8.5% vs vehicle control). Note that compound **13ag** indicated a full agonist affinity. When compound **13ac** was administered at 0.3, 3 and 30 mg/kg, a clear PK/PD correlation was observed. In this assessment, body weight was also increased in a dose-dependent manner.

Table 4. Plasma Glucose (PG) Reduction (%) in Zucker Diabetic Fatty (ZDF) Rats After the Oral administration of the Test Compounds on Day 14 with PK parameters (n = 5)

Compound	Rat microsomal stability (%)[a]	*In vivo* efficacies in ZDF rats[b]			PK parameters in ZDF rats[c]		
		Dose (mg/kg)	PG reduction (%)	Body weight gain (%)	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0\text{-}24\,h}$ (h·μg/mL)
rosiglitazone	NT[d]	3	40.3 ± 16.2	12.6 ± 3.3*	ND[e]	ND[e]	ND[e]
13g	100	3	58.6 ± 8.8**	13.0 ± 2.4**	1.11 ± 0.11	2.00 ± 0.00	7.10 ± 0.75
13r	95	3	61.2 ± 10.1*	9.5 ± 1.5**	0.52 ± 0.05	2.00 ± 0.00	3.87 ± 0.29
13v	47	3	22.0 ± 17.9	11.9 ± 2.8*	0.042 ± 0.01	4.00 ± 0.00	0.42 ± 0.04
13x	98	3	61.7 ± 10.2*	8.5 ± 2.9*	0.30 ± 0.03	2.40 ± 0.89	3.16 ± 0.39
13z	100	3	59.3 ± 10.9**	13.8 ± 2.1**	0.79 ± 0.11	2.00 ± 0.00	5.53 ± 0.83
13ac	94	0.3	16.6 ± 12.9	2.3 ± 2.9	0.18 ± 0.13	6.80 ± 9.65	1.74 ± 0.43
13ac	94	3	43.8 ± 13.8**	12.4 ± 3.1**	0.92 ± 0.33	2.40 ± 0.89	6.75 ± 0.85
13ac	94	30	74.9 ± 0.8**	16.7 ± 1.5**	8.08 ± 1.78	2.00 ± 0.00	55.77 ± 16.70
13ag	79	3	69.7 ± 0.9**	15.6 ± 1.6**	0.080 ± 0.01	3.20 ± 1.10	0.85 ± 0.06

[a]Rat microsomal stability assessed based on test compound (%) remaining after 0.5 h of incubation with rat liver microsomes. [b]PG reduction (% change in PG level vs vehicle control) and body weight (% change in body weight vs vehicle control) in ZDF rats after the oral administration of 3 mg/kg of the test compounds in 0.5% methylcellulose on day 14. Data are represented as mean ± S.E.M. Statistical significance compared to vehicle treatment is denoted by *p < 0.05 and **p < 0.01 as determined by the Student T-test. [c]PK parameters were acquired after the administration of the test compounds to ZDF rats on day 15. Each value represents the mean ± S.D. [d]Not tested. [e]Not dertermined.

2.4. Monkey PK Profile

Based on pharmacological results in rodents, Compounds **13g**, **13r**, **13x**, **13z** and **13ac** were selected as candidates for further evaluation.[33] Monkey PK study was performed with these compounds as shown in Table 5. The selected compounds were orally administered to male cynomolgus monkeys at 3 mg/kg (n = 2-3). Total body clearance (CL), distribution volume at steady state (V_{ss}) and F value (%) were calculated after intravenous administration (1 mg/kg) of the compounds to the same monkeys.

All compounds exhibited ideal $T_{1/2}$ values for once daily administration in clinical studies. One of the reasons for this excellent half-life is the robust stability against monkey liver microsomes (Table 5). 4-Methyl-substituted derivatives **13g**, **13x** and **13z** exhibited higher *CL* values than other compounds. Moreover, **13g** and **13x** exhibited higher V_{ss} and lower *AUC* values; nevertheless, these PK parameters were acceptable for clinical candidate selection. Halogenated compounds **13r** and **13ac** exhibited excellent PK parameters with the lowest *CL* and V_{ss} as well as the highest *AUC* values, despite the dosage being only 3 mg/kg. Consequently, compound **13ac** with higher *in vitro* potency was selected for further toxicological evaluation.

Table 5. PK Parameters of the test Compounds in Cynomolgus Monkeys[a]

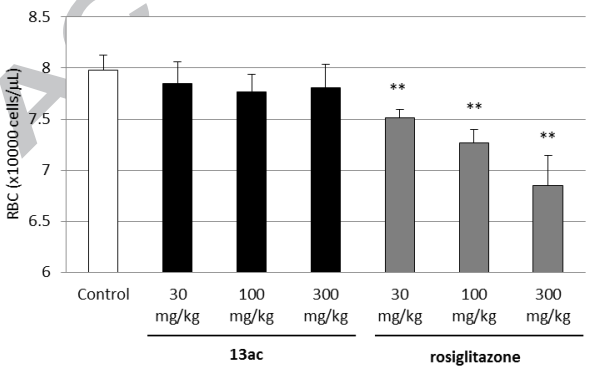
Compd	Monkey microsomal stability (%)[b]	C_{max} (μg/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{last} (h·μg/mL)	F (%)	CL (mL/min/kg)	V_{ss} (L/kg)
13g[c]	100	1.02 ± 0.12	1.00 ± 0.0	10.4 ± 3.1	4.87 ± 0.54	34 ± 3.9	3.58 ± 0.52	0.56 ± 0.14
13r[c]	100	5.63 ± 1.9	1.00 ± 0.0	16.1 ± 4.7	40.9 ± 7.0	65 ± 11	0.80 ± 0.014	0.39 ± 0.014
13x[c]	100	0.33 ± 0.0071	1.50 ± 0.71	16.1 ± 0.21	2.87 ± 0.071	24 ± 0.64	4.16 ± 0.62	1.23 ± 0.46
13z[c]	91	2.06 ± 0.11	1.50 ± 0.71	13.8 ± 9.6	8.44 ± 2.9	28 ± 9.8	1.80 ± 0.66	0.32 ± 0.028
13ac[d]	100	4.44 ± 1.5	1.67 ± 0.6	18.3 ± 6.6	40.2 ±4.3	25 ± 2.7	0.32 ± 0.035	0.20 ± 0.090

[a]The test compounds in 0.5% methylcellulose were administered to male cynomolgus monkeys at 3 mg/kg (p.o.). Total body clearance (*CL*), distribution volume at steady state (V_{ss}) and *F* value were calculated after intravenous (1 mg/kg) administration of the test compounds. Each value represents the mean ± S.D. [b]Monkey microsomal stability assessed based on test compound (%) remaining after 0.5 h of incubation with monkey liver microsomes. [c]n = 2. [d]n = 3.

*2.5. In Vivo Toxicological Evaluation of Compound **13ac***

In vivo toxicological results of **13ac** are summarized in Figure 2. Adverse effects were assessed after repeated oral administration of **13ac** (30, 100 and 300 mg/kg/day) to female Wistar–Imamichi rats for 28 days. Rosiglitazone administration served as control. TK parameters were obtained on day 28 from a satellite group of female rats as shown in Table 6 (n = 2).[34] At the pharmacologically effective dose of 0.3 mg/kg (C_{max}, 0.18 μg/mL, $AUC_{0-24\ h}$, 1.74 h·μg/mL), a high plasma exposure of **13ac** was observed. No death or clinical abnormalities were observed during the administration period in any test group. As shown in Figure 2a, rosiglitazone significantly (p < 0.01) reduced the number of red blood cells (RBCs) to cause hemodilution in a dose-dependent manner (5.9, 8.9 and 14.2% reduction at 30, 100 and 300 mg/kg, respectively).[35] On the other hand, no remarkable change in RBC counts was observed in **13ac**-administered groups. At 300 mg/kg, compound **13ac** affected RBC counts; however, they were not statistically significant. Similar results were obtained after hematocrit analysis (Figure 2b). The weight of the heart is reported to be associated with hemodilution.[18,24,36] The administration of rosiglitazone significantly increased the weight of the heart (% of body weight) at 30 mg/kg (p < 0.05) and higher doses (p < 0.01). Compound **13ac** significantly increased the weight of the heart (p < 0.05) at 300 mg/kg, which was the maximum dose studied (Figure 2c). The heart weight gain after the administration of **13ac** at 300 mg/kg (9.9%) was lower than that after rosiglitazone administration at 100 mg/kg (24.7%) with statistical significance (p < 0.05). These results clearly demonstrate that **13ac** causes PPARγ-related adverse effects; however, these effects are milder than those of rosiglitazone. Nevertheless, compound **13ac** elevated the activities of liver enzymes. As shown in Figure 2d, it elevated aspartate transaminase (AST) activity but without clear dose-dependency. Alanine transaminase (ALT) activity was also elevated (data not shown). These elevations in liver enzyme activities were not accompanied with any histopathological changes. Although these changes in liver enzyme activities by **13ac** were modest, **13ac** was considered hepatotoxic because rosiglitazone did not affect liver enzyme activities in this study. Therefore, further derivatization is deemed essential to avoid such adverse effects.

a)



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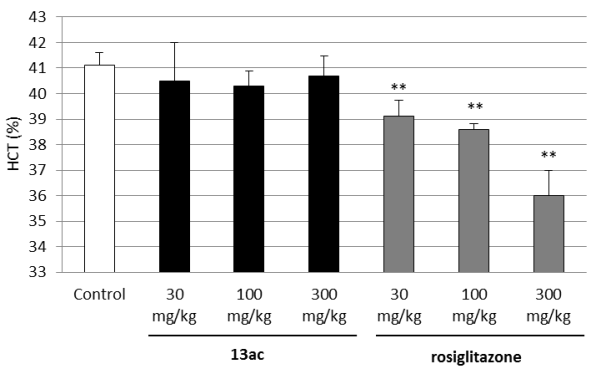

c)

d)

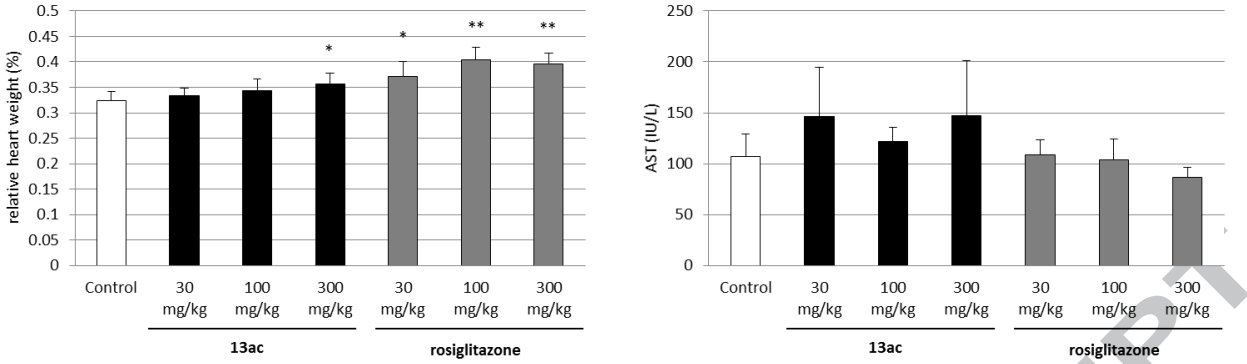

Figure 2. *In vivo* toxicological evaluation of compound **13ac**. (a) RBC numbers, (b) hematocrit (%), (c) heart weight (% of body weight), and (d) aspartate aminotransferase (AST) level in Wistar–Imamichi rats after repeated administration of **13ac** or rosiglitazone (30, 100 and 300 mg/kg) for 4 weeks. Data are represented as mean ± S.D. (n = 5). Statistical significance compared to vehicle treatment is denoted by *$p < 0.05$, **$p < 0.01$ as determined by the Student T-test.

Table 6. TK Parameters of **13ac** (n = 2)[a]

Dose (mg/kg/day)	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0\text{-}24\,h}$ (h·μg/mL)
30	9.1 ± 2.0	4.0 ± 0.0	93.7 ± 7.6
100	14.9 ± 3.2	5.0 ± 4.2	192 ± 26
300	22.6 ± 13	3.0 ± 1.4	190 ± 57

[a] TK parameters were acquired from a satellite group of female Wistar–Imamichi rats on day 28. Each value represents the mean ± S.D.

*2.6. X-ray crystal structure of **13ac** bound to PPARγ-LBD*

The binding mode of **13ac** to PPARγ-LBD was determined at 1.8 Å resolution with *R*cryst and *R*free values of 0.204 and 0.229, respectively (Figure 3). The overall structure adopted a canonical three-layered α-helical sandwich structure, which is typical of a nuclear receptor LBD (Figure 3a). Compound **13ac** utilizes the same ligand-binding pocket as rosiglitazone. As shown in Figure 3b, **13ac** forms hydrophobic and hydrophilic interactions with PPARγ-LBD, including two direct hydrogen bonds, two water-mediated hydrogen bonds and van der Waals contacts. The benzoic acid group of **13ac** forms direct hydrogen bonds with side chains of Tyr327 and Lys367 as well as a water-mediated hydrogen bond with Ser289. 1-Methylbenzimidazole moiety of **13ac** forms a water-mediated hydrogen bond with the main-chain nitrogen of Ser342. Additional lipophilic interactions of 4-chloro-3-fluorophenoxy group in **13ac** were observed. 4-Chloro-3-fluorophenoxy group occupies an additional binding site surrounded by a β-sheet, helix 2' and helix 3, and makes lipophilic contacts with Ile249, Leu255, Gly258, Glu259, Ile262, Arg280, Ile341 and Met348. Because such lipophilic interactions were not observed in rosiglitazone, they were considered responsible for the more potent pharmacological activities of **13ac** than rosiglitazone.

Typical PPARγ full agonists stabilize the PPARγ LBD in active conformation by interacting with Tyr473 on helix 12,[21,22] while several PPARγ partial agonists that selectively regulate the recruitment of cofactors lack the direct interaction with helix 12.[23,24,27] Full agonist rosiglitazone forms a tight direct hydrogen bond with Tyr473 (Figure 3c).[21,37] On the other hand, the crystal structure of PPARγ-LBD with **13ac** shows that this series of compounds also do not directly interact with helix12 (Figure 3d). Since modifications of the left-hand side phenoxy group provide compounds with a variety of agonist efficacy (Emax = 54-125%), the lipophilic interactions of substituted phenoxy group with β-sheet, helix 2' and helix 3 may relate to the magnitude of agonist efficacy. Therefore, avoiding the interaction with Tyr473 and the additional lipophilic interactions of substituted phenoxy group may relate to the maximum transcriptional activity of **13ac**.[38] The superior safety profile of **13ac** was caused due to this distinct binding mode through the selective recruitment of cofactors. It was later confirmed with the same molecular template DS-6930 (**I**, Figure 1), which is disclosed in a subsequent paper.

a) b)

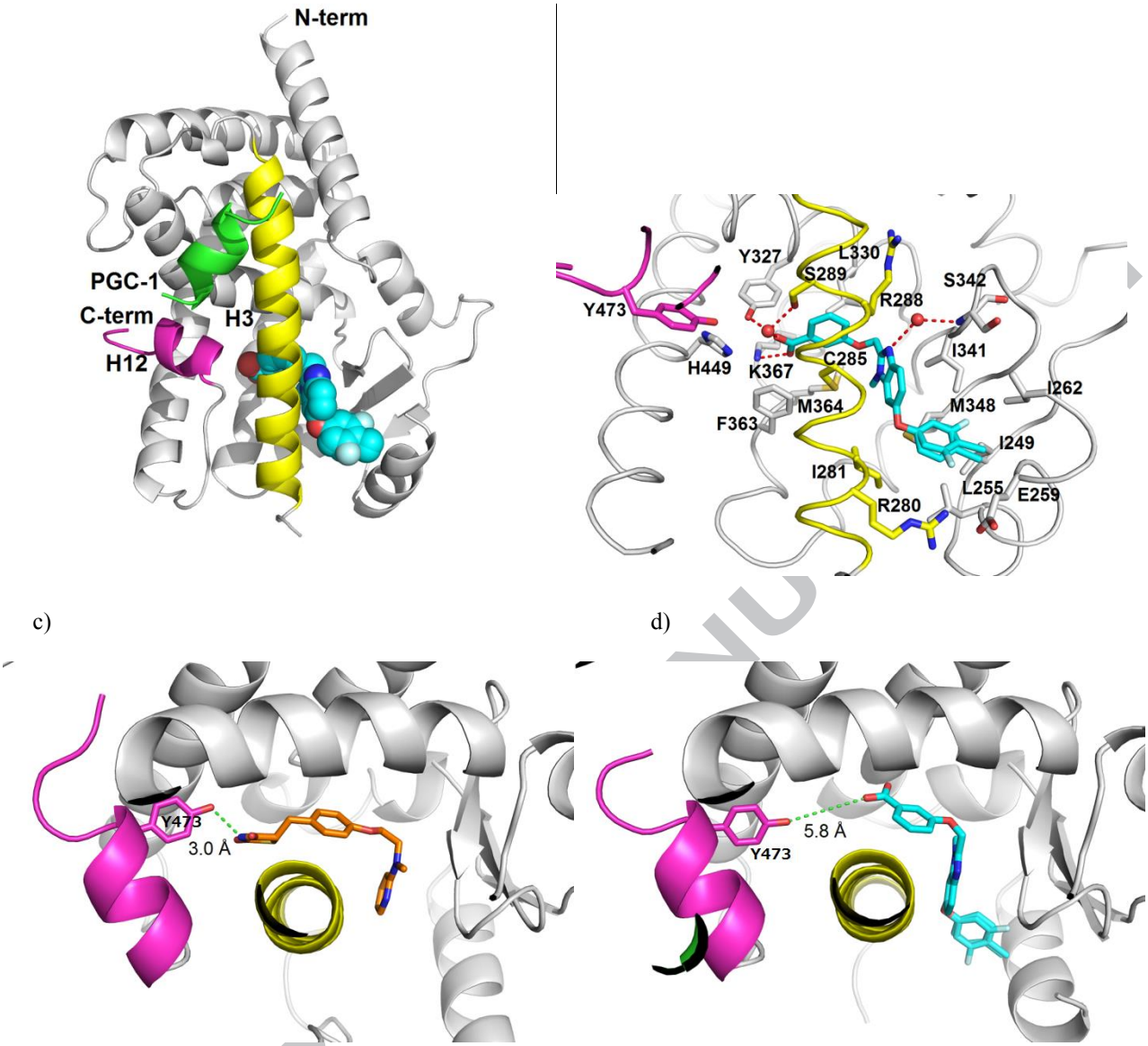

Figure 3. X-ray crystal structure of compound **13ac** bound to PPARγ-LBD (PDB 5Z5S). (a) Schematic representation of PPARγ-LBD with **13ac**. Helix 3 (residues 277–303) and helix 12 (residues 467–477) of PPARγ-LBD and PGC-1 peptide, respectively, are colored in yellow, magenta and green. Other parts of the PPARγ-LBD are colored in gray. The bound form of **13ac** is depicted as a CPK model with carbon atoms in cyan, oxygen atoms in red and nitrogen atoms in blue. (b) Details of the binding model of **13ac** to PPARγ-LBD. Residues of PPARγ-LBD involved in the binding of **13ac**, residue 473 on helix 12 and **13ac** are shown as stick models. Hydrogen bonds are marked as red dotted lines. (c) The binding mode of rosiglitazone to PPARγ-LBD. A tight hydrogen bond with Tyr473 was observed (PDB 2PRG). (d) The binding mode of **13ac** to PPARγ-LBD. **13ac** lacks the direct interaction with Tyr473.

3. CONCLUSIONS

By modifying TZD moiety of full agonist efatutazone (CS-7017), a novel PPARγ agonist **8i** was designed such that it lacks direct interaction with Tyr473 on helix 12 of PPARγ-LBD. The left-hand side benzene ring in compound **8i** was optimized to yield **13ac**, which exhibited high *in vitro* potency. The positions of halogen atoms dictated pharmacological activity; 3-chloro-4-fluoro analog **13ae** exhibited attenuated activity *in vitro* and *in vivo*. Compound **13ac** demonstrated robust PG lowering effects similar to rosiglitazone in ZDF rats, whereas **13ac** caused fewer PPARγ-related adverse effects, including hemodilution in Wistar–Imamichi rats. The analysis of the binding mode of compound **13ac** with PPARγ-LBD revealed no direct interaction between **13ac** and Tyr473 on helix 12. In addition, the lipophilic interactions of 4-chloro-3-fluorophenoxy group of **13ac** were observed. This binding mode is proposed to be the reason for robust pharmacological activities of **13ac** with fewer PPARγ-related adverse effects. Upon toxicological evaluation, compound **13ac** was found to cause modest hepatotoxicity. Therefore, we further sought to synthesize compounds with minimal hepatotoxicity, which will be reported in a proceeding paper.

4. EXPERIMENTAL SECTION

4.1. General Procedures

Starting reagents were purchased from commercial suppliers and were used without further purification unless otherwise specified. Chromatographic elution was carried under continuous monitoring by TLC using silica gel 60F254 (Merck & Co., Inc.) as the stationary phase; the mobile phase was the elution solvent used in column chromatography. A UV detector was used for detection. Silica gel SK-85 (230–400 mesh) or silica gel SK-34 (70–230 mesh), manufactured by Merck & Co., Inc., or Chromatorex NH

(200–350 mesh), manufactured by Fuji Silysia Chemical Ltd., was used as the column packing silica gel. ^{1}H NMR spectra were obtained on Varian Unity 400- and 500-MHz spectrometers. Spectra were recorded in the indicated solvent at ambient temperature; chemical shifts are reported in ppm (δ) relative to the solvent peak. Resonance patterns are represented with the following notations: br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). MS analysis was carried out by FAB, EI, or ESI. HRMS was carried out using an LC-MS system composed of a Waters Xevo Q-ToF MS and an Acquity UHPLC system. Elemental analyses were carried out on a Microcorder JM10 and a Dionex ICS-1500. The purity was assessed by reversed-phase HPLC analysis (column, Inertsil ODS-3, 4.6 × 250 mm; eluent, MeCN/0.1% Et3N•HCl aqueous solution; flow rate, 1 mL/min; wavelength, 254 nm). All assay compounds were ≥ 95% pure.

*4.2. General Procedure for S_NAr Reaction to Prepare **9** (General Procedure A)*

NaH (30.0 mmol) was added to a solution of **1** (8.60 g, 30.0 mmol) and substituted phenol (30.0 mmol) in DMF (150 mL) at room temperature under N_2, and the mixture was stirred at 80 °C for 10 h. Water was added to the cooled mixture, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to obtain purified compound **9**, or crude **9** was used directly for the next reaction without further purification.

*4.3. General Procedure for Reduction of Nitro Group, Followed by Benzimidazole Ring Annulation to Prepare **11** (General Procedure B)*

A solution of **9** (30.0 mmol), iron powder (8.37 g, 150 mmol) and NH_4Cl (0.803 g, 15.0 mmol) in water (80 mL) and EtOH (160 mL) was stirred under reflux for 5 h. The cooled reaction mixture was filtered through a pad of celite, and the filtrate was extracted with EtOAc several times. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude **10**. A solution of crude **10**, glycolic acid (3.42 g, 45.0 mmol) in 4 M HCl in 1,4-dioxane (200 mL) was stirred under reflux for 2 h. The cooled reaction mixture was poured slowly into 10% $NaHCO_3$ aqueous solution to precipitate a solid, which was collected by filtration, washed with EtOAc/hexane (1:1), and finally washed with water to obtain **11**.

*4.4. General Procedure for Mitsunobu Reaction, Followed by Deprotection to Prepare **7** or **8** (General Procedure C)*

A solution of **5** (1.00 mmol), PBu_3 (2.00 mmol), ADDP (2.00 mmol) and substituted phenol (1.50 mmol) in toluene (5 mL) was stirred for 10 h under N_2. After concentration of the reaction mixture under reduced pressure, the residue was purified by silica gel chromatography to obtain **6**. A solution of **6** in 4 M HCl in 1,4-dioxane (10 mL) was stirred for 2 h. The precipitated solid was collected by filtration and washed with EtOAc to obtain **7** or **8**.

*4.5. General Procedure for Mitsunobu Reaction to Prepare **12** (General Procedure D)*

A solution of **11** (1.00 mmol), PBu_3 (2.00 mmol), ADDP (2.00 mmol) and methyl 3-hydroxybenzoate (0.23 g, 1.5 mmol) in toluene (5 mL) was stirred for 10 h under N_2. After concentrating the reaction mixture under reduced pressure, the residue was purified by silica gel chromatography to obtain **12**.

*4.6. General Procedure for Hydrolysis to Prepare **8** or **13** (General Procedure E)*

A solution of **7** or **12** (0.400 mmol) in 1 M NaOH (10 mL, 10 mmol) and 1,4-dioxane (10 mL) was stirred at 60 °C for 2 h. Concentrated HCl (1.5 mL) was added to the cooled mixture, and the mixture was concentrated to obtain a residue. The resulting solid was washed with water, followed by EtOAc to obtain **8** or **13** as an HCl salt. Alternatively, the cooled reaction mixture was neutralized by adding an equimolar volume of 1 M HCl, and the precipitated solid was collected by filtration to provide the free form of **13**.

*4.7. General Procedure for Amidation to Prepare **15** (General Procedure F)*

A solution of crude **10** prepared from **9** (30.0 mmol), **14** (6.30 g, 30.0 mmol), HOBt•H_2O (4.05 g, 30.0 mmol) and WSC•HCl (5.73 g, 30.0 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 18 h under N_2. Water was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography to obtain **15**.

*4.8. General Procedure for Benzimidazole Ring Annulation of **15** to Prepare **12** (General Procedure G)*

A solution of **15** (32.8 mmol) in 4 M HCl in EtOAc (165 mL) was stirred at 60 °C for 4 h. After cooling the reaction mixture, the precipitated solid was collected by filtration to obtain **12** as an HCl salt.

*4.8.1. [6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**4**).*

NaH (55%, 4.02 g, 92.1 mmol) was added to a solution of **1** (26.4 g, 92.1 mmol) and 4-amino-3,5-dimethylphenol (12.6 g, mmol) in DMA (200 mL) at 0 °C under N_2, and the mixture was stirred at room temperature for 24 h. Water was added to the reaction mixture at 0 °C, and the mixture was extracted with EtOAc twice. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude **2**. A solution of crude **2** and Pd/C (10%, 7.60 g) in EtOH (500 mL) was stirred under H_2 at room temperature for 24 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to obtain crude **3**. A solution of crude **3**, glycolic acid (10.5 g, 138 mmol) in 4 M HCl in 1,4-dioxane (200 mL) was stirred under reflux for 2 h. The cooled reaction mixture was poured slowly into 10% $NaHCO_3$ aqueous solution, followed by extraction with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by recrystallization from EtOAc/*i*-Pr_2O to obtain **4** (14.7 g, 53%, 3 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.07 (6H, s), 3.72 (3H, s), 4.38 (2H, s), 4.67 (2H, d, J = 5.9 Hz), 5.53 (1H, t, J = 5.9 Hz), 6.57 (2H, s), 6.78 (1H, dd, J = 2.4, 8.6 Hz), 7.02 (1H, d, J = 2.0 Hz), 7.49 (1H, d, J = 8.6 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{20}N_3O_2$, 298.1556; found 298.1558.

*4.8.2. tert-Butyl (4-{[2-(hydroxymethyl)-1-methyl-1H-benzimidazol-6-yl]oxy}-2,6-dimethylphenyl)carbamate (**5**).*

A solution of **4** (13.0 g, 43.7 mmol) and BOC_2O (19.0 g, 87.0 mmol) in *i*-PrOH (150 mL) was stirred for 16 h. Water was added to the cooled mixture, and the mixture was extracted with EtOAc several times. Combined organic layers were successively washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/MeOH, 90:10). The resulting form was crystallized from EtOAc and hexane to obtain

5 (4.50 g, 26%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (9H, s), 2.21 (6H, s), 3.75 (3H, s), 4.89 (2H, s), 6.67 (2H, s), 6.93 (1H, d, *J* = 2.0 Hz), 6.96 (1H, dd, *J* = 2.0, 9.0 Hz), 7.63 (1H, d, *J* = 9.0 Hz).

*4.8.3. Ethyl 2-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•2HCl (**7h**).*

Compound **7h** was prepared according to general procedure C (yield, 67%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.20 (3H, t, *J* = 7.2 Hz), 2.33 (6H, s), 3.94 (3H, s), 4.23 (2H, q, *J* = 7.2 Hz), 5.64 (2H, s), 6.79 (2H, s), 7.11 (1H, d, *J* = 8.8 Hz), 7.13 (1H, dd, *J* = 7.3, 7.8 Hz), 7.45 (1H, d, *J* = 8.4 Hz), 7.55 (1H, s), 7.60 (1H, ddd, *J* = 1.4, 7.3, 8.4 Hz), 7.72 (1H, dd, *J* = 1.4, 7.8 Hz), 7.77 (1H, d, *J* = 8.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_4$, 446.2080; found 446.2100.

*4.8.4. Methyl 3-{[6-(4-amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•2HCl (**7i**).*

Compound **7i** was prepared according to general procedure C (yield, 63%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.25 (6H, s), 3.87 (3H, s), 3.87 (3H, s), 5.60 (2H, s), 6.74 (2H, s), 7.03 (1H, d, *J* = 8.8 Hz), 7.41 (1H, s), 7.45 (1H, d, J = 8.3 Hz), 7.52 (1H, dd, *J* = 7.8, 8.3 Hz), 7.63 (1H, d, *J* = 7.8 Hz), 7.69 (1H, s), 7.72 (1H, d, *J* = 8. 8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_4$, 432.1923; found 432.1904.

*4.8.5. Ethyl 4-{[6-(4-amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•2HCl (**7j**).*

Compound **7j** was prepared according to general procedure C (yield, 67%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, *J* = 7.0 Hz), 2.12 (6H, s), 3.90 (3H, s), 4.29 (2H, q, *J* = 7.0 Hz), 5.66 (2H, s), 6.71 (2H, s), 7.10 (1H, d, *J* = 8.8 Hz), 7.29 (2H, d, *J* = 8.8 Hz), 7.51 (1H, s), 7.75 (1H, d, *J* = 8.8 Hz), 7.98 (2H, d, *J* = 8.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_4$, 446.2080; found 446.2080.

*4.8.6. 2,6-Dimethyl-4-{[1-methyl-2-(phenoxymethyl)-1H-benzimidazol-6-yl]oxy}aniline•2 HCl (**8a**).*

Compound **8a** was prepared according to general procedure C (yield, 53%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.28 (6H, s), 3.88 (3H, s), 5.56 (2H, s), 6.74 (2H, s), 6.99 (1H, t, *J* = 7.0 Hz), 7.08-7.14 (3H, m), 7.32 (2H, t, *J* = 8.0 Hz), 7.52 (1H, d, *J* = 2.0 Hz), 7.73 (1H, d, *J* = 8.6 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{24}N_3O_2$, 374.1869; found 374.1860.

*4.8.7. 1-(2-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}phenyl)ethanone•2 HCl (**8b**).*

Compound **8b** was prepared according to general procedure C (yield, 53%, 2 steps). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.23 (6H, s), 2.57 (3H, s), 3.84 (3H, s), 5.47 (2H, s), 6.71 (2H, s), 6.98 (1H, d, *J* = 2.4 Hz), 7.02–7.07 (2H, m), 7.33 (1H, d, *J* = 8.2 Hz), 7.46–7.50 (1H, m), 7.70 (1H, dd, *J* = 1.6, 7.4 Hz), 7.72 (1H, d, *J* = 8.6 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$, 416.1974; found 416.1945.

*4.8.8. 1-(3-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}phenyl)ethanone•2 HCl (**8c**).*

Compound **8c** was prepared according to general procedure C (yield, 87%, 2 steps). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.32 (6H, s), 2.61 (3H, s), 3.93 (3H, s), 5.68 (2H, s), 6.79 (2H, s), 7.14 (1H, dd, *J* = 2.4, 8.8 Hz), 7.46 (1H, dd, *J* = 2.9, 8.3 Hz), 7.53 (1H, d, *J* = 7.8 Hz), 7.55 (1H, s), 7.67 (1H, d, *J* = 7.8 Hz), 7.70 (1H, s), 7.78 (1H, d, *J* = 8.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$, 416.1974; found 416.1951.

*4.8.9. 1-(4-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}phenyl)ethanone•2 HCl (**8d**).*

Compound **8d** was prepared according to general procedure C (yield, 92%, 2 steps). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.33 (6H, s), 2.54 (3H, s), 3.93 (3H, s), 5.71 (2H, s), 6.80 (2H, s), 7.15 (1H, dd, *J* = 2.0, 8.8 Hz), 7.30 (2H, dd, *J* = 7.3, 7.8 Hz), 7.57 (1H, d, *J* = 1.5 Hz), 7.79 (1H, d, *J* = 8.8 Hz), 8.00 (2H, d, *J* = 8.8 Hz) ; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$, 416.1974; found 416.1982; Anal. calcd for $C_{24}H_{22}N_4O_2$•2HCl•0.40H_2O: C, 60.23; H, 5.22; N, 11.71; Cl, 14.82; found C, 60.31; H, 5.04; N, 11.65; Cl, 14.64.

*4.8.10. 2-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzonitrile•2HCl (**8e**).*

Compound **8e** was prepared according to general procedure C (yield, 68%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.33 (6H, s), 3.93 (3H, s), 5.73 (2H, s), 6.80 (2H, s), 7.06 (1H, dd, *J* = 2.0, 9.0 Hz), 7.19 (1H, t, *J* = 7.4 Hz), 7.50 (1H, d, *J* = 2.0 Hz), 7.55 (1H, d, *J* = 8.6 Hz), 7.71–7.76 (2H, m), 7.80 (1H, dd, *J* = 1.6, 7.4 Hz) ; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_4O_2$, 399.1821; found 399.1850.

*4.8.11. 3-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzonitrile•2HCl (**8f**).*

Compound **8f** was prepared according to general procedure C (yield, 83%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.31 (6H, s), 3.89 (3H, s), 5.65 (2H, s), 6.78 (2H, s), 7.10 (1H, dd, *J* = 1.6, 8.6 Hz), 7.51–7.53 (3H, m), 7.56–7.60 (1H, m), 7.71 (1H, s), 7.76 (1H, d, *J* = 9.0 Hz) ; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_4O_2$, 399.1821; found 399.1847.

*4.8.12. 4-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzonitrile•2HCl (**8g**).*

Compound **8g** was prepared according to general procedure C (yield, 92%, 2 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.32 (6H, s), 3.89 (3H, s), 5.68 (2H, s), 6.78 (2H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.36 (2H, d, *J* = 8.6 Hz), 7.51 (1H, s), 7.76 (1H, d, *J* = 8.6 Hz), 7.87 (2H, d, *J* = 9.0 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_4O_2$, 399.1821; found 399.1841.

*4.8.13. 2-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•2HCl (**8h**).*

Compound **8h** was prepared according to general procedure E (yield, 66%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.30 (6H, s), 3.92 (3H, s), 5.62 (2H, s), 6.87 (2H, s), 7.10 (1H, m), 7.11 (1H, m), 7.43 (1H, d, *J* = 8.3 Hz), 7.55 (1H, m), 7.58 (1H, s), 7.69 (1H, dd, *J* = 1.4, 7.6 Hz), 7.75 (1H, d, *J* = 8. 8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_3O_4$, 418.1767; found 418.1742.

*4.8.14. 3-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•2HCl (**8i**).*

Compound **8i** was prepared according to general procedure E (yield, 61%). Mp, 235–239 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.30 (6H, s), 3.91 (3H, s), 5.65 (2H, s), 6.78 (2H, s), 7.11 (1H, dd, *J* = 2. 0, 8.8 Hz), 7.43 (1H, d, *J* = 7.8 Hz), 7.49 (1H, dd, *J* = 7.8, 7.8 Hz), 7.51 (1H, d, *J* = 2.0 Hz), 7.63 (1H, d, *J* = 7.8 Hz), 7.76 (1H, d, *J* = 8.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_3O_4$, 418.1767; found 418.1802.

*4.8.15. 4-{[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•2HCl (**8j**).*

Compound **8j** was prepared according to general procedure E (yield, 77%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.30 (6H, s), 3.89 (3H, s), 5.64 (2H, s), 6.77 (2H, s), 7.08 (1H, d, *J* = 8. 8 Hz), 7.25 (2H, d, *J* = 8.8 Hz), 7.49 (1H, s), 7.75 (1H, d, *J* = 8.8 Hz), 7.95 (2H, d, *J* = 8. 8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{23}N_3O_4$, 418.1767; found 418.1752.

*4.8.16. tert-Butyl [5-(4-fluorophenoxy)-2-nitrophenyl]methylcarbamate (**9d**).*

Compound **9d** was prepared according to general procedure A (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s), 1.50 (3H, s), 3.26 (3H, s), 6.81 (1H, dd, *J* = 2.7, 9.0 Hz), 6.85 (1H, br), 7.07–7.17 (4H, m), 7.93–7.97 (1H, m).

*4.8.17. tert-Butyl methyl[5-(4-methylphenoxy)-2-nitrophenyl]carbamate (**9g**).*

Compound **9g** was prepared according to general procedure A (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, s), 1.49 (3H, br), 2.39 (3H, s), 3.24 (3H, s), 6.80–6.82 (2H, m), 6.99 (2H, d, *J* = 8.2 Hz), 7.23 (2H, d, *J* = 7.8 Hz), 7.92 (1H, dd, *J* = 1.6, 8.6 Hz).

*4.8.18. tert-Butyl [5-(3-chlorophenoxy)-2-nitrophenyl]methylcarbamate (**9h**).*

Compound **9h** was prepared according to general procedure A, (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s), 1.50 (3H, s), 3.27 (3H, s), 6.87 (1H, dd, *J* = 2.7, 8.6 Hz), 6.89 (1H, br), 7.01 (1H, d, *J* = 8.1 Hz), 7.12 (1H, t, *J* = 2.0 Hz), 7.24–7.26 (1H, m), 7.38 (1H, t, *J* = 8.2 Hz), 7.96 (1H, d, *J* = 9.0 Hz).

*4.8.19. tert-Butyl [5-(4-chlorophenoxy)-2-nitrophenyl]methylcarbamate (**9i**).*

Compound **9i** was prepared according to general procedure A (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, s), 1.49 (3H, br), 2.39 (3H, s), 3.24 (3H, s), 6.80–6.82 (2H, m), 6.99 (2H, d, *J* = 8.2 Hz), 7.23 (2H, d, *J* = 7.8 Hz), 7.92 (1H, dd, *J* = 1.6, 8.6 Hz).

*4.8.20. tert-Butyl methyl{2-nitro-5-[3-(trifluoromethoxy)phenoxy]phenyl}carbamate (**9n**).*

Compound **9n** was prepared according to general procedure A (yield, 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s), 1.50 (3H, s), 3.27 (3H, s), 6.89–6.91 (2H, m), 6.99 (1H, s.), 7.05 (1H, d, *J* = 8.6 Hz), 7.13 (1H, d, *J* = 7.8 Hz), 7.47 (1H, t, *J* = 8.2 Hz), 7.97 (1H, d, *J* = 8.6 Hz).

*4.8.21. tert-Butyl [2-amino-5-(2,5-difluorophenoxy)phenyl]methylcarbamate (**9r**).*

Compound **9r** was prepared according to general procedure A (yield, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, s), 1.50 (3H, br), 3.28 (3H, s), 6.81–7.07 (4H, m), 7.17–7.26 (1H, m), 7.96 (1 H, d, *J* = 9.0 Hz).

*4.8.22. tert-Butyl [5-(3-fluoro-5-methylphenoxy)-2-nitrophenyl]methylcarbamate (**9ab**).*

Compound **9ab** was prepared according to general procedure A (yield, 69%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s), 1.51 (3H, s), 2.38 (3H, s), 3.27 (3H, s), 6.63 (1H, dt, *J* = 2.4, 9.4 Hz), 6.71 (1H, s), 6.80 (1H, d, *J* = 8.6 Hz), 6.86–6.88 (2H, m), 7.95 (1H, d, *J* = 8.2 Hz).

*4.8.23. tert-Butyl [5-(4-chloro-3-fluorophenoxy)-2-nitrophenyl]methylcarbamate (**9ac**).*

Compound **9ac** was prepared according to general procedure A (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (9H, s), 3.26 (3H, s), 6.85–6.92 (4H, m), 7.43 (1H, t, *J* = 8. 6 Hz), 7.93 (1H, t, *J* = 8. 6 Hz).

*4.8.24. tert-Butyl [5-(3-chloro-5-fluorophenoxy)-2-nitrophenyl]methylcarbamate (**9ad**).*

Compound **9ad** was prepared according to general procedure A (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (6H, s), 1.51 (3H, s), 3.28 (3H, s), 6.74 (1H, dt, *J* = 2.4, 9.0 Hz), 6.90–6.93 (3H, m), 7.00 (1H, d, *J* = 7.8 Hz), 7.98 (1H, d, *J* = 8.6 Hz).

*4.8.25. tert-Butyl [5-(3-chloro-4-fluorophenoxy)-2-nitrophenyl]methylcarbamate (**9ae**).*

Compound **9ae** was prepared according to general procedure A (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (9H, s), 3.26 (3H, s), 6.79–6.85 (2H, m), 6.95–6.97 (1H, m), 7.15–7.18 (2H, m), 7.91–7.93 (1H, m).

*4.8.26. tert-Butyl [5-(2,3-dihydro-1-benzofuran-5-yloxy)-2-nitrophenyl]methylcarbamate (**9af**).*

Compound **9af** was prepared according to general procedure A (yield, 27%) ^{1}H-NMR (500 MHz, $CDCl_3$) δ1.32 (6H, s), 1.50 (3H, s), 3.24–3.27 (2H, m), 3.25 (3H, s), 4.64 (2H, t, *J* = 8.8 Hz), 6.77–63.83 (4H, m), 6.96 (1H, s), 7.91 (1H, d, *J* = 9.3 Hz).

*4.8.27. (1-Methyl-6-phenoxy-1H-benzimidazol-2-yl)methanol (**11a**).*

Compound **11a** was prepared according to general procedure A, followed by procedure B (yield, 73%; 3 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.77 (3H, s), 4.70 (2H, s), 6.90 (1H, dt, *J* = 2.0, 8.6 Hz), 6.96 (2H, d, *J* = 7.8 Hz), 7.08 (1H, t, *J* = 7.4 Hz), 7.29 (1H, s), 7.36 (2H, t, *J* = 8.6 Hz), 7.60 (1H, dd, *J* = 1.6 Hz).

*4.8.28. [6-(2-Fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11b**).*

Compound **11b** was prepared according to general procedure A, followed by procedure B (yield, 72%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.74 (3H, s), 4.88 (2H, s), 6.91 (1H, d, *J* = 2.4 Hz), 6.98 (1H, dd, *J* = 2.4, 9.0 Hz), 7.00–7.03 (1H, m), 7.09 (1H, d, *J* = 2.7 Hz), 7.11 (1H, d, *J* = 3.1 Hz), 7.17–7.22 (1H, m), 7.63 (1H, d, *J* = 9.0 Hz).

*4.8.29. [6-(3-Fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11c**).*

Compound **11c** was prepared according to general procedure A, followed by procedure B (yield, 80%; 3 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.80 (3H, s), 4.71 (2H, d, *J* = 5.5 Hz), 5.59 (1H, t, *J* = 5.5 Hz), 6.75–6.82 (2H, m), 6.87–6.97 (2H, m), 7.33–7.42 (2H, m), 7.62 (1H, d, *J* = 8. 6 Hz).

*4.8.30. [6-(4-Fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11d**).*

Compound **11d** was prepared according to general procedure B (yield, 29%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (3H, s), 4.89 (2H, s), 6.90 (1H, d, *J* = 2.0 Hz), 6.94–7.05 (5H, m), 7.64 (1H, d, *J* = 8.6 Hz).

*4.8.31. [1-Methyl-6-(2-methylphenoxy)-1H-benzimidazol-2-yl]methanol (**11e**).*

Compound **11e** was prepared according to general procedure A, followed by procedure B (yield, 72%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 3.73 (3H, s), 4.86 (2H, s), 6.80 (1H, d, J = 2.0 Hz), 6.83–6.87 (1H, m), 6.91 (1H, dd, *J* = 2.0, 8.6 Hz), 7.03–7.08 (1H, m), 7.12–7.18 (1H, m), 7.24–7.29 (1H, m), 7.59 (1H, d, *J* = 8.6 Hz).

*4.8.32. [1-Methyl-6-(3-methylphenoxy)-1H-benzimidazol-2-yl]methanol (**11f**).*

Compound **11f** was prepared according to general procedure A, followed by procedure B (yield, 63%; 3 steps). ^{1}H-NMR (400

MHz, $CDCl_3$) δ 2.32 (3H, s), 3.75 (3H, s), 4.90 (2H, s), 6.80 (2H, s), 6.90 (1H, d, *J* = 7.4 Hz), 6.94–7.02 (2H, m), 7.21 (1H, t, *J* = 7.8 Hz), 7.65 (1H, d, *J* = 8.6 Hz).

*4.8.33. [1-Methyl-6-(4-methylphenoxy)-1H-benzimidazol-2-yl]methanol (**11g**).*

Compound **11g** was prepared according to general procedure B (yield, 89%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 3.74 (3H, s), 4.86 (2H, s), 6.87–6.92 (3H, m), 6.95 (1H, dd, *J* = 2.3, 8.6 Hz), 7.14 (2H, d, *J* = 7.8 Hz), 7.59 (1H, d, *J* = 8.6 Hz).

*4.8.34. [6-(3-Chlorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11h**).*

Compound **11h** was prepared according to general procedure B (yield, 20%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 4.91 (2H, s), 6.88 (1H, d, *J* = 8.6 Hz), 6.95 (1H, s), 6.98–7.01 (2H, m), 7.05 (1H, d, *J* = 8.2 Hz), 7.24 (1H, d, *J* = 8.2 Hz), 7.69 (1H, d, *J* = 9.4 Hz).

*4.8.35. [6-(4-Chlorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11i**).*

Compound **11i** was prepared according to general procedure B (yield, 78%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.76 (3H, s), 4.90 (2H, s), 6.86-7.02 (4H, m), 7.26-7.30 (2H, m), 7.65 (1H, d, *J* = 9.2 Hz).

*4.8.36. [6-(2-Methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11j**).*

Compound **11j** was prepared according to general procedure A, followed by procedure B (yield, 61%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.73 (3H, s), 3.87 (3H, s), 4.88 (2H, s), 6.91–6.95 (3H, m), 6.97 (1H, dd, *J* = 2.0, 8.6 Hz), 7.03 (1H, dd, *J* = 1.6, 8.6 Hz), 7.10–7.15 (1H, m), 7.63 (1H, d, *J* = 8.2 Hz).

*4.8.37. [6-(3-Methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11k**).*

Compound **11k** was prepared according to general procedure A, followed by procedure B (yield, 89%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.76 (3H, s), 3.77 (3H, s), 4.08 (2H, s), 6.54–6.57 (2H, m), 6.64 (1H, ddd, *J* = 1.2, 2.4, 8.2 Hz), 6.96 (1H, d, *J* = 2.0 Hz), 6.99 (1H, dd, *J* = 2.0, 8.6 Hz), 7.21 (1H, t, *J* = 8.6 Hz), 7.63 (1H, dd, *J* = 0.8, 8.6 Hz).

*4.8.38. [6-(4-Methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11l**).*

Compound **11l** was prepared according to general procedure A, followed by procedure B (yield, 87%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.73 (3H, s), 3.81 (3H, s), 4.85 (2H, s), 5.23 (1H, br), 6.81 (1H, d, *J* = 2.4 Hz), 6.89 (2H, d, *J* = 9.0 Hz), 6.88–6.98 (1H, m), 6.98 (2H, d, *J* = 9.0 Hz), 7.57 (1H, d, *J* = 9.0 Hz).

*4.8.39. [6-(3-Ethoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11m**).*

Compound **11m** was prepared according to general procedure A, followed by procedure B (yield, 75%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, *J* = 7.0 Hz), 3.75 (3H, s), 3.99 (2H, q, *J* = 7.0 Hz), 4.90 (2H, s), 6.53–6.58 (2H, m), 6.83 (1H, ddd, *J* = 0.8, 2.4, 8.2 Hz), 6.99–7.02 (2H, m), 7.20 (1H, t, *J* = 8.2 Hz), 7.66 (1H, d, *J* = 8.2 Hz).

*4.8.40. {1-Methyl-6-[3-(trifluoromethoxy)phenoxy]-1H-benzimidazol-2-yl}methanol (**11n**).*

Compound **11n** was prepared according to general procedure B (yield, 91%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 4.91 (2H, s), 6.85 (1H, s), 6.89 (1H, dd, *J* = 2.4, 8.6 Hz), 6.92–6.95 (1H, m), 6.98–7.01 (2H, m), 7.32 (1H, t, *J* = 8.2 Hz), 7.67 (1H, d, *J* = 9.0 Hz).

*4.8.41. {1-Methyl-6-[3-(trifluoromethyl)phenoxy]-1H-benzimidazol-2-yl}methanol (**11o**).*

Compound **11o** was prepared according to general procedure A, followed by procedure B (yield, 57%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.93 (2H, s), 6.97–7.04 (2H, m), 7.09–7.18 (1H, m), 7.21 (1H, s), 7.33 (1H, d, *J* = 8.6 Hz), 7.43 (1H, t, *J* = 7.8 Hz), 7.71 (1H, d, *J* = 8.2 Hz).

*4.8.42. [6-(2,3-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11p**).*

Compound **11p** was prepared according to general procedure A, followed by procedure B (yield, 75%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 4.90 (2H, s), 6.73 (1H, t, *J* = 8.2 Hz), 6.90–7.02 (4H, m), 7.66 (1H, d, *J* = 8.6 Hz).

*4.8.43. [6-(2,4-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11q**).*

Compound **11q** was prepared according to general procedure A, followed by procedure B (yield, 76%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.74 (3H, s), 4.58 (1H, br), 4.87 (2H, s), 6.79–6.90 (2H, m), 6.90–7.07 (3H, m), 7.61 (1H, d, *J* = 8.6 Hz).

*4.8.44. [6-(2,5-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11r**).*

Compound **11r** was prepared according to general procedure B (yield, 83%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 4.91 (2H, s), 6.60–6.71 (1H, m), 6.71–6.82 (1H, m), 6.97–7.06 (2 H, m), 7.09–7.21 (1H, m), 7.68 (1H, d, *J* = 9.0 Hz).

*4.8.45. [6-(2,6-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11s**).*

Compound **11s** was prepared according to general procedure A, followed by procedure B (yield, 60%; 3 steps). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.73 (3H, s), 4.88 (2H, s), 6.88 (1H, d, *J* = 2.4 Hz), 6.95 (1H, dd, *J* = 2.0, 8.8 Hz), 7.03 (2H, t, *J* = 7.8 Hz), 7.14–7.20 (1H, m), 7.62 (1H, d, *J* = 8.8 Hz).

*4.8.46. [6-(3,4-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11t**).*

Compound **11t** was prepared according to general procedure A, followed by procedure B (yield, 88%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.90 (2H, s), 6.68–6.73 (1H, m), 6.78–6.83 (1H, m), 6.95 (1H, s), 6.95–6.98 (1H, m), 7.11 (1H, q, *J* = 9.4 Hz), 7.67 (1H, dd, *J* = 1.2, 8.2 Hz).

*4.8.47. [6-(3,5-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11u**).*

Compound **11u** was prepared according to general procedure A, followed by procedure B (yield, 69%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 4.92 (2H, s), 6.42–6.55 (3H, m), 7.00 (1H, dd, *J* = 2.4, 8.6 Hz), 7.04 (1H, d, *J* = 2.4 Hz), 7.71 (1H, d, *J* = 8.6 Hz).

*4.8.48. [6-(4-Fluoro-2-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11v**).*

Compound **11v** was prepared according to general procedure A, followed by procedure B (yield, 86%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ2.25 (3H, s), 3.73 (3H, s), 4.86 (2H, s), 6.73 (1H, d, *J* = 2.3 Hz), 6.84–6.90 (3H, m), 6.96–7.00 (1H, m), 7.59 (1H, d, *J* = 8.6 Hz).

*4.8.49. [6-(5-Fluoro-2-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11w**).*

Compound **11w** was prepared according to general procedure A, followed by procedure B (yield, 85%; 3 steps). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.26 (3H, s), 3.77 (3H, s), 4.88 (2H, s), 6.50 (1H, dd, *J* = 2.4, 10.3 Hz), 6.73 (1H, dt, *J* = 2.4, 8.3 Hz), 6.87 (1H, d, *J* = 2.4 Hz), 6.93 (1H, dd, *J* = 2.4, 8.8 Hz), 7.16–7.20 (1H, m), 7.63 (1H, d, *J* = 8.8 Hz).

*4.8.50. [6-(2-Fluoro-4-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11x**).*

Compound **11x** was prepared according to general procedure A, followed by procedure B (yield, 87%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 3.72 (3H, s), 4.60 (1H, br), 4.86 (2H, s), 6.85 (1H, d, J = 2.0 Hz), 6.86–6.96 (3H, m), 7.01 (1H, dd, J = 1.6, 11.4 Hz), 7.60 (1H, d, J = 8.26 Hz).

*4.8.51. [6-(2-Fluoro-5-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11y**).*

Compound **11y** was prepared according to general procedure A, followed by procedure B (yield, 70%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 3.75 (3H, s), 4.89 (2H, s), 6.78–6.84 (1H, m), 6.85–6.91 (1H, m), 6.92 (1H, d, J = 2.4 Hz), 6.98 (1H, dd, J = 2.2, 8.8 Hz), 7.07 (1H, dd, J = 8.6, 10. 6 Hz), 7.64 (1H, d, J = 9.0 Hz).

*4.8.52. [6-(3-Fluoro-4-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11z**).*

Compound **11z** was prepared according to general procedure A, followed by procedure B (yield, 83%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, d, J = 2.0 Hz), 3.76 (3H, s), 4.90 (2H, s), 6.63–6.72 (2H, m), 6.92–7.01 (2H, m), 7.11 (1H, t, J = 9.0 Hz), 7.65 (1H, d, J = 8.6 Hz).

*4.8.53. [6-(4-Fluoro-3-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11aa**).*

Compound **11aa** was prepared according to general procedure A, followed by procedure B (yield, 77%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, d, J = 2.0 Hz), 3.78 (3H, s), 4.05 (1H, br), 4.91 (2H, s), 6.75–6.81 (1H, m), 6.83 (2H, dd, J = 2.9, 6.1 Hz), 6.87 (1H, d, J = 2.0 Hz), 6.96 (2H, d, J = 8.6 Hz), 7.60 (1H, d, J = 8.6 Hz).

*4.8.54. [6-(3-Fluoro-5-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11ab**).*

Compound **11ab** was prepared according to general procedure B (yield, 58% 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.78 (3H, s), 4.92 (2H, s), 6.49 (1H, dt, J = 2.0, 10.2 Hz), 6.58 (1H, s), 6.61 (1H, d, J = 11.0 Hz), 6.99–7.01 (2H, m), 7.69 (1H, d, J = 9.4 Hz).

*4.8.55. [6-(4-Chloro-3-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11ac**).*

Compound **11ac** was prepared according to general procedure B (yield, 57%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.88 (2H, s), 6.69 (1H, dd, J = 3.9, 10.1 Hz), 6.73 (1H, dd, J = 3.2, 10.1 Hz), 6.93–6.95 (2H, m), 7.28 (1H, t, J = 8.7 Hz), 7.05 (1H, d, J = 8.7 Hz).

*4.8.56. [6-(3-Chloro-5-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11ad**).*

Compound **11ad** was prepared according to general procedure B (yield, 49%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 4.91 (2H, s), 6.58 (1H, dt, J = 2.4, 10.2 Hz), 6.98–7.02 (2H, m), 7.23 (1H, dd, J = 2.0, 9.4 Hz), 7.32 (1H, d, J = 2.0 Hz), 7.70 (1H, d, J = 8.6 Hz).

*4.8.57. [6-(3-Chloro-4-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methanol (**11ae**).*

Compound **11ae** was prepared according to general procedure B (yield, 45%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.89 (2H, s), 6.85–7.00 (4H, m), 7.09 (1H, t, J = 8. 6 Hz), 7.05 (1H, d, J = 8.8 Hz).

*4.8.58. Methyl 3-[(1-methyl-6-phenoxy-1H-benzimidazol-2-yl)methoxy]benzoate•HCl (**12a**).*[39]

Compound **12a** was prepared according to general procedure D (yield, 66%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.88 (3H, s), 3.93 (3H, s), 5.69 (2H, s), 7.02 (2H, d, J = 8.7 Hz), 7.12 (1H, dd, J = 2.2, 8.8 Hz), 7.15 (1H, t, J = 7. 5 Hz), 7.41 (2H, dd, J = 7.5, 8.7 Hz), 7.48 (1H, ddd, J = 1.3, 2.6, 8.2 Hz), 7.54 (1H, dd, J = 7.5, 8.2 Hz), 7.59 (1H, d, J = 2.2 Hz), 7.66 (1H, ddd, J = 1.3, 1.5, 7.5 Hz), 7.72 (1H, dd, J = 1.5, 2.6 Hz), 7.80 (1H, d, J = 8.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{21}N_2O_4$, 389.1501; found 389.1518.

*4.8.59. Methyl 3-{[6-(2-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12b**).*

Compound **12b** was prepared according to general procedure D (yield, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.96 (1H, s), 7.00–7.05 (2H, m), 7.07–7.13 (2H, m), 7.20 (1H, t, J = 9.5 Hz), 7.29 (1H, d, J = 7.3 Hz), 7.37 (1H, t, J = 7.3 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.70–7.74 (2H, m).

*4.8.60. Methyl 3-{[6-(3-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12c**).*

Compound **12c** was prepared according to general procedure D (yield, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 6.89 (1H, dt, J = 2.4, 10.2 Hz), 6.76–6.80 (2H, m), 7.02–7.04 (2H, m), 7.23–7.31 (2H, m), 7.38 (1H, t, J = 7.4 Hz), 7.69 (1H, dt, J = 1.2, 7.4 Hz), 7.73 (1H, dd, J = 1.2, 2.4 Hz), 7.74–7.77 (1H, m); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{20}FN_2O_4$, 407.1407; found 407.1396.

*4.8.61. Methyl 3-{[6-(4-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12d**).*

Compound **12d** was prepared according to general procedure D (yield, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.82 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.94–7.05 (5H, m), 7.29 (1H, br), 7.38 (1H, t, J = 7.8 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.71–7.74 (2H, m).

*4.8.62. Methyl 3-{[1-methyl-6-(2-methylphenoxy)-1H-benzimidazol-2-yl]methoxy}benzoate (**12e**).*

Compound **12e** was prepared according to general procedure D (yield, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 3.79 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.84 (1H, d, J = 2.3 Hz), 6.88 (1H, d, J = 8.2 Hz), 6.97 (1 H, dd, J = 2.3, 9.0 Hz), 7.04–7.10 (1H, m), 7.13–7.19 (1H, m), 7.25–7.32 (2H, m), 7.37 (1H, t, J = 7.8 Hz), 7.66–7.73 (3H, m).

*4.8.63. Methyl 3-{[1-methyl-6-(3-methylphenoxy)-1H-benzimidazol-2-yl]methoxy}benzoate (**12f**).*

Compound **12f** was prepared according to general procedure D (yield, 85%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (3H, br), 3.92 (3H, s), 5.39 (2H, s), 6.78–6.83 (2H, m), 6.91 (1H, d, J = 7.8 Hz), 6.97–7.04 (2H, m), 7.21 (1H, t, J = 8.0 Hz), 7.27–7.32 (1H, m), 7.38 (1H, t, J = 7.8 Hz), 7.69 (1H, td, J = 1.2, 1.4, 7.6 Hz), 7.71–7.75 (2H, m).

*4.8.64. Methyl 3-{[1-methyl-6-(4-methylphenoxy)-1H-benzimidazol-2-yl]methoxy}benzoate (**12g**).*

Compound **12g** was prepared according to general procedure D (yield, 83%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.34 (3H, s), 3.80 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.89–6.97 (3H, m), 7.01 (1H, dd, J = 2.4, 8.8 Hz), 7.14 (2H, d, J = 8.3 Hz), 7.27–7.31 (1H, m), 7.37 (1H, t, J = 8.1 Hz), 7.66–7.74 (3H, m).

*4.8.65. Methyl 3-{[6-(3-Chlorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12h**).*

Compound **12h** was prepared according to general procedure D (yield, 97%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 6.89 (1H, ddd, J = 0.8, 3.1, 8.2 Hz), 6.97 (1H, t, J = 2.0 Hz), 7.01–7.07 (3H, m), 7.24 (1H, d, J = 8.2 Hz), 7.29–7.32 (1H, m), 7.39 (1H, t, J = 7.8 Hz), 7.70 (1H, dt, J = 1.1, 7.4 Hz), 7.73–7.74 (1H, m), 7.77 (1H, d, J = 9.4 Hz).

*4.8.66. Methyl 3-{[6-(4-Chlorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12i**).*

Compound **12i** was prepared according to general procedure D (yield, 44%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.82 (3H, s), 3.93 (3H, s), 5.40 (2H, s), 6.91-7.02 (4H, m), 7.24-7.31 (3H, m), 7.38 (1H, t, *J* = 7.9 Hz), 7.68-7.76 (3H, m).

*4.8.67. Methyl 3-{[6-(2-methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12j**).*

Compound **12j** was prepared according to general procedure D (yield, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.87 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.89–6.96 (3H, m), 7.00 (1H, dd, *J* = 2.4, 8.6 Hz), 7.03 (1H, dd, *J* = 1.2, 7.8 Hz), 7.13 (1 H, ddd, *J* = 1.4, 7.0, 8.2 Hz), 7.29 (1 H, ddd, *J* = 0.8, 2.4, 8.2 Hz), 7.37 (1 H, t, *J* = 7.8 Hz), 7.68 (1 H, dt, *J* = 1.5, 7.8 Hz), 7.69 (1 H, d, *J* = 8.6 Hz), 7.72 (1 H, dd, *J* = 1.6, 2.7 Hz).

*4.8.68. Methyl 3-{[6-(3-methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12k**).*

Compound **12k** was prepared according to general procedure D (yield, 65%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 3.89 (3H, s), 5.57 (2H, s), 6.55–6.58 (2H, m), 6.61–6.69 (1H, m), 7.00–7.07 (2H, m), 7.19–7.25 (2H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.84 (1H, d, *J* = 8.6 Hz), 7.78 (1H, d, *J* = 7.4 Hz), 8.03 (1H, s).

*4.8.69. Methyl 3-{[6-(4-methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12l**).*

Compound **12l** was prepared according to general procedure D (yield, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.81 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.88–6.91 (3H, m), 6.97–7.01 (3H, m), 7.27–7.31 (1H, m), 7.37 (1H, t, *J* = 7.8 Hz), 7.66–7.73 (3H, m).

*4.8.70. Methyl 3-{[6-(3-ethoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12m**).*

Compound **12m** was prepared according to general procedure D (yield, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, *J* = 7.0 Hz), 3.82 (3H, s), 3.93 (3H, s), 3.99 (2H, q, *J* = 7.0 Hz), 5.40 (2H, s), 6.54–6.58 (2H, m), 6.63 (1H, dd, *J* = 2.4, 8.2 Hz), 7.01–7.05 (2H, m), 7.21 (1H, t, *J* = 8.2 Hz), 7.30 (1H, ddd, *J* = 0.8, 2.4, 5.9 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.69 (1H, d, *J* = 7.8 Hz), 7.72–7.74 (2H, m).

*4.8.71. Methyl 3-({1-methyl-6-[3-(trifluoromethoxy)phenoxy]-1H-benzimidazol-2-yl}methoxy)benzoate (**12n**).*

Compound **12n** was prepared according to general procedure D (yield, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.86 (1H, s), 6.91 (1H, dd, *J* = 2.4, 7.4 Hz), 6.93–6.96 (1H, m), 7.02–7.06 (2H, m), 7.29–7.34 (2H, m), 7.39 (1H, t, *J* = 7.4 Hz), 7.69–7.74 (2H, m), 7.77 (1H, d, *J* = 8.2 Hz).

*4.8.72. Methyl 3-({1-methyl-6-[3-(trifluoromethyl)phenoxy]-1H-benzimidazol-2-yl}methoxy)benzoate (**12o**).*

Compound **12o** was prepared according to general procedure D (yield, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 7.01–7.06 (2H, m), 7.15 (1H, dd, *J* = 2.4, 8.2 Hz), 7.23 (1H, s), 7.28–7.45 (4H, m), 7.69 (1H, dt, *J* = 1.2, 7.8 Hz), 7.73 (1H, dd, *J* = 1.6, 2.7 Hz), 7.77 (1H, dd, *J* = 0.8, 9.0 Hz).

*4.8.73. Methyl 3-{[6-(2,3-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12p**).*

Compound **12p** was prepared according to general procedure D (yield, 78%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s), 3.93 (3H, s), 5.40 (2H, s), 6.75 (1H, dt, *J* = 2.0, 6.85 Hz), 6.91–7.04 (4H, m), 7.30 (1H, dd, *J* = 2.4, 8.3 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.69 (1H, d, *J* = 7.8 Hz), 7.73 (1H, dd, *J* = 1.5, 2.9 Hz), 7.74 (1H, d, *J* = 8.3 Hz).

*4.8.74. Methyl 3-{[6-(2,4-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12q**).*

Compound **12q** was prepared according to general procedure D (yield, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.81–6.88 (1H, m), 6.90 (1H, d, *J* = 2.4 Hz), 6.94–7.07 (3H, m), 7.29 (1H, d, *J* = 1.6 Hz), 7.37 (1H, t, *J* = 8.2 Hz), 7.66–7.76 (3H, m).

*4.8.75. Methyl 3-{[6-(2,5-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12r**).*

Compound **12r** was prepared according to general procedure D (yield, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (3 H, s), 3.92 (3 H, s), 5.40 (2 H, s), 6.65–6.71 (1 H, m), 6.73–6.80 (1 H, m), 7.01–7.05 (2 H, m), 7.11–7.18 (1 H, m), 7.29 (1 H, dd, *J* = 2.7, 8.2 Hz), 7.38 (1 H, t, *J* = 8.0 Hz), 7.67–7.77 (3 H, m).

*4.8.76. Methyl 3-{[6-(2,6-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12s**).*

Compound **12s** was prepared according to general procedure D (yield, 60%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.89 (1H, d, *J* = 2.4 Hz), 6.98 (1H, dd, *J* = 2.4, 8.6 Hz), 7.01–7.07 (2H, m), 7.14–7.21 (1H, m), 7.28 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.37 (1H, t, *J* = 7.8 Hz), 7.66–7.71 (3H, m); MS (FAB) *m/z*: 425 $[M + H]^+$.

*4.8.77. Methyl 3-{[6-(3,4-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12t**).*

Compound **12t** was prepared according to general procedure D (yield, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.77–6.85 (2H, m), 6.92–7.00 (3H, m), 7.29 (1H, ddd, *J* = 0.8, 2.4, 8.2 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.67–7.73 (3H, m).

*4.8.78. Methyl 3-{[6-(3,5-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12u**).*

Compound **12u** was prepared according to general procedure D (yield, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 3.92 (3H, s), 3.93 (9H, s), 5.41 (2H, s), 6.44–6.55 (2H, m), 7.03 (1H, dd, *J* = 2.2, 8.8 Hz), 7.07 (1H, d, *J* = 2.4 Hz), 7.27–7.33 (2H, m), 7.39 (1H, t, *J* = 7.8 Hz), 7.67–7.71 (1H, m), 7.73 (1H, dd, *J* = 1.4, 2.5 Hz), 7.78 (1H, d, *J* = 8.6 Hz).

*4.8.79. Methyl 3-{[6-(4-fluoro-2-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12v**).*

Compound **12v** was prepared according to general procedure D (yield, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 3.79 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.77 (1H, d, *J* = 2.3 Hz), 6.84–7.02 (4H, m), 7.25–7.33 (1H, m), 7.37 (1H, t, *J* = 8.0 Hz), 7.66–7.74 (3H, m).

*4.8.80. Methyl 3-{[6-(5-fluoro-2-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12w**).*

Compound **12w** was prepared according to general procedure D (yield, 65%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 3.82 (3H, s), 3.92 (3H, s), 5.40 (2H, s), 6.53 (1H, dd, *J* = 2.7, 9.8 Hz), 6.74 (1H, dt, *J* = 2.7, 8.2 Hz), 6.91 (1H, d, *J* = 2.0 Hz), 6.98 (1H, dd, *J* = 2.0, 8.6 Hz), 7.17–7.22 (1H, m), 7.27–7.32 (1H, m), 7.38 (1H, t, *J* = 8.2 Hz), 7.67–7.76 (3H, m).

*4.8.81. Methyl 3-{[6-(2-fluoro-4-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12x**).*

Compound **12x** was prepared according to general procedure D (yield, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 3.80 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.88–7.04 (5H, m), 7.29 (1H, s), 7.37 (1H, t, *J* = 8.0 Hz), 7.65–7.75 (3H, m).

*4.8.82. Methyl 3-{[6-(2-fluoro-5-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12y**).*

Compound **12y** was prepared according to general procedure D (yield, 49%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 3.82 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.82 (1H, s), 6.86–6.92 (1H, m), 6.95 (1H, d, *J* = 2.4 Hz), 7.01 (1H, dd, *J* = 2.4, 9.0 Hz), 7.07 (1H, dd, *J* = 8.2, 10.6 Hz), 7.28–7.31 (1H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.67–7.73 (3H, m).

*4.8.83. Methyl 3-{[6-(3-fluoro-4-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12z**).*

Compound **12z** was prepared according to the general procedure D (yield, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, d, *J* = 1.6 Hz), 3.82 (3H, s), 3.92 (3H, s), 5.40 (2H, s), 6.66–6.71 (2H, m), 6.98–7.04 (2H, m), 7.11 (1H, t, J = 9.0 Hz), 7.27–7.32 (1H, m), 7.38 (1H, t, *J* = 8.0 Hz), 7.67–7.70 (1H, m), 7.71–7.75 (2H, m).

*4.8.84. Methyl 3-{[6-(4-fluoro-3-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12aa**).*

Compound **12aa** was prepared according to general procedure D (yield, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, d, *J* = 2.0 Hz), 3.81 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.76–6.86 (2H, m), 6.92–7.00 (3H, m), 7.27–7.31 (1H, m), 7.38 (1H, t, *J* = 8.0 Hz), 7.71 (3H, d, *J* = 8.6 Hz).

*4.8.85. Methyl 3-{[6-(3-fluoro-5-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12ab**).*

Compound **12ab** was prepared according to general procedure D (yield, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 3.84 (3H, s), 3.93 (3H, s), 5.40 (2H, s), 6.49 (1H, dt, *J* = 2.4, 10.2 Hz), 6.58 (1H, s), 6.60 (1H, d, *J* = 10.6 Hz), 7.00–7.03 (2H, m), 7.28–7.31 (1H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.68 (1H, dt, *J* = 1.6, 8.6 Hz), 7.72–7.76 (2H, m).

*4.8.86. Methyl 3-{[6-(4-chloro-3-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12ac**).*

Compound **12ac** was prepared according to general procedure D (yield, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 6.74 (1H, ddd, *J* = 1.2, 2.8, 9.0 Hz), 6.78 (1H, dd, *J* = 2.7, 10.2 Hz), 7.00–7.03 (2H, m), 7.28–7.33 (2H, m), 7.38 (1H, t, *J* = 7.4 Hz), 7.69 (1H, dt, *J* = 1.6, 7.4 Hz), 7.73 (1H, dd, *J* = 1.6, 2.7 Hz), 7.77 (1H, d, *J* = 8.2 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{19}ClFN_2O_4$, 441.1017; found 441.1071.

*4.8.87. Methyl 3-{[6-(3-chloro-5-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate (**12ad**).*

Compound **12ad** was prepared according to general procedure D (yield, 32%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.59 (1H, dt, *J* = 2.4, 9.8 Hz), 6.75 (1H, s) 6.80 (1H, dt, *J* = 2.4, 7.8 Hz), 7.03 (1H, dd, *J* = 2.0, 8.6 Hz), 7.07 (1H, d, *J* = 2.4 Hz), 7.31 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.39 (1H, t, *J* = 7.8 Hz), 7.70 (1H, dd, *J* = 1.2, 7.8 Hz), 7.74 (1H, s), 7.79 (1H, d, *J* = 8.6 Hz).

*4.8.88. Methyl 3-{[6-(3-chloro-4-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•HCl (**12ae**).*[39]

Compound **12ae** was prepared according to general procedure D (yield, 67%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.87 (3H, s), 3.92 (3H, s), 5.66 (2H, s), 7.06 (1H, ddd, *J* = 3.0, 3.9, 9.1 Hz), 7.19 (1H, dd, *J* = 2.2, 8.9 Hz), 7.28 (1H, dd, *J* = 3.0, 6.3 Hz), 7.46 (1H, dd, *J* = 8.9, 9.1 Hz), 7.47 (1H, ddd, *J* = 1.1, 2.2, 8.2 Hz), 7.53 (1H, dd, *J* = 7.6, 8.2 Hz), 7.59 (1H, d, *J* = 2.2 Hz), 7.65 (1H, ddd, *J* = 1.1, 1.5, 7.6 Hz), 7.71 (1H, dd, *J* = 1.5, 2.2 Hz), 7.79 (1H, d, *J* = 8.9 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{19}ClFN_2O_4$, 441.1017; found 441.1018.

*4.8.89. Methyl 3-{[6-(2,3-dihydro-1-benzofuran-5-yloxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•HCl (**12af**).*

Compound **12af** was prepared according to general procedure G (yield, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.25 (2H, t, *J* = 8.6 Hz), 3.93 (3H, s), 4.00 (3H, s), 4.64 (2H, t, *J* = 8.6 Hz), 5.88 (2H, s), 6.80–6.85 (2H, m), 6.93 (2H, d, *J* = 2.0 Hz), 7.24–7.27 (1H, m), 7.42–7.50 (2H, m), 7.68 (1H, d, *J* = 2.4 Hz), 7.73 (1H, dt, *J* = 1.6, 7.0 Hz), 7.91 (1H, d, *J* = 9.0 Hz).

*4.8.90. Methyl 3-{[6-(2,3-dihydro-1-benzofuran-6-yloxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•HCl (**12ag**).*

Compound **12ag** was prepared according to general procedure G (yield, 47%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.15 (2H, t, *J* = 8.8 Hz), 3.88 (3H, s), 3.93 (3H, s), 4.57 (2H, t, *J* = 8.8 Hz), 5.69 (2H, s), 6.47 (2H, s), 7.16 (1H, d, *J* = 8.8 Hz), 7.21 (1H, d, *J* = 7.8 Hz), 7.47–7.56 (3H, m), 7.66 (1H, d, *J* = 8.3 Hz), 7.72 (1H, s), 7.78 (1H, d, *J* = 9.3 Hz).

*4.8.91. Methyl 3-{[6-(1-benzofuran-6-yloxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoate•HCl (**12ah**).*

Compound **12ah** was prepared according to the general procedure G (yield, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (3H, s), 4.00 (3H, s), 5.89 (2H, s), 6.82 (1H, dd, *J* = 0.8, 2.0 Hz), 7.02 (1H, dd, *J* = 2.0, 8.6 Hz), 7.03 (1H, d, *J* = 2.4 Hz), 7.24 (1H, d, *J* = 1.2 Hz), 7.32 (1H, dd, *J* = 2.4, 9.0 Hz), 7.42–7.49 (2H, m), 7.63 (1H, d, *J* = 8.6 Hz), 7.68 (2H, d, *J* = 2.0 Hz), 7.74 (1H, dt, *J* = 1.6, 7.0 Hz), 7.94 (1H, d, *J* = 9.4 Hz).

*4.8.92. 3-[(1-Methyl-6-phenoxy-1H-benzimidazol-2-yl)methoxy]benzoic acid•HCl (**13a**).*

Compound **13a** was prepared according to general procedure E (yield, 70%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.95 (3H, s), 5.72 (2H, s), 7.04 (2H, d, *J* = 8. 8 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 7.21 (1H, dd, *J* = 2.4, 8.8 Hz), 7.41 (2H, dd, *J* = 7.5, 8.8 Hz), 7.46 (1H, ddd, *J* = 1.1, 2.6, 8.2 Hz), 7.50 (1H, dd, *J* = 7.5, 8.2 Hz), 7.62 (1H, d, *J* = 2.2 Hz), 7.64 (1H, ddd, *J* = 1.1, 1.5, 7.5 Hz), 7.71 (1H, dd, *J* = 1.5, 2.6 Hz), 7.82 (1H, d, *J* = 8. 8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_4$, 375.1345; found 375.1344.

*4.8.93. 3-{[6-(2-Fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13b**).*

Compound **13b** was prepared according to general procedure E (yield, 68%). Mp, 205–212 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.81 (3H, s), 5.47 (2H, s), 6.94 (1H, dd, *J* = 2.5, 8.8 Hz), 7.04–7.09 (1H, m), 7.18 (2H, ddd, *J* = 3.1, 3.3, 6.1 Hz), 7.30 (1H, d, *J* = 2.4 Hz), 7.35–7.42 (2H, m), 7.45 (1H, t, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 7.4 Hz), 7.66 (1H, d, *J* = 8.6 Hz), 7.63 (1H, s), 13.03 (1H, br); MS (FAB) *m/z*: 393 $[M + H]^+$; Anal. calcd for $C_{24}H_{22}N_2O_5$•0.14H_2O: C, 66.91; H, 4.41; N, 7.09; F, 4.81; found C, 66.86; H, 4.48; N, 7.08; F, 4.80.

*4.8.94. 3-{[6-(3-Fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13c**).*

Compound **13c** was prepared according to general procedure E (yield, 93%). Mp, 236–237 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.48 (2H, s), 6.77–6.84 (2H, m), 6.92 (1H, ddt, J = 0.8, 2.4, 8.2 Hz), 6.99 (1H, dd, J = 2.4, 8.6 Hz), 7.35–7.41 (2H, m), 7.42 (1H, d, J = 2.0 Hz), 7.46 (1H, t, J = 7.8 Hz), 7.58 (1H, dt, J = 1.2, 7.4 Hz), 7.64 (1H, dd, J = 1.6, 2.7 Hz), 7.70 (1H, d, J = 8.6 Hz), 13.05 (1H, br); HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{22}H_{18}FN_2O_4$, 393.1251; found 393.1223; Anal. calcd for $C_{22}H_{17}FN_2O_4$: C, 67.34; H, 4.37; N, 7.14; F, 4.84; found C, 67.41; H, 4.33; N, 7.13; F, 5.03.

*4.8.95. 3-{[6-(4-Fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13d**).*

Compound **13d** was prepared according to general procedure E (yield, 37%). Mp, 250–254 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.81 (3H, s), 5.46 (2H, s), 6.93 (1H, dd, J = 2.4, 8.8 Hz), 7.01–7.04 (2H, m), 7.19 (2H, t, J = 8.8 Hz), 7.30 (1H, d, J = 2.4 Hz), 7.37–7.39 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 7.57 (2H, d, J = 7.8 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.63 (1H, s), 13.03 (1H, br); MS (FAB) m/z: 393 [M + H]$^+$; Anal. calcd for $C_{22}H_{17}FN_2O_4$•0.20H_2O: C, 66.73; H, 4.43; N, 7.07; F, 4.80; found C, 66.75; H, 4.55; N, 7.06; F, 4.91.

*4.8.96. 3-{[1-Methyl-6-(2-methylphenoxy)-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13e**).*

Compound **13e** was prepared according to general procedure E (yield, 98%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.25 (3H, s), 3.79 (3H, s), 5.45 (2H, s), 6.81 (1H, d, J = 7.8 Hz), 6.86 (1H, dd, J = 2.4, 8.8 Hz), 7.06 (1H, t, J = 7.3 Hz), 7.14–7.21 (2H, m), 7.32 (1H, d, J = 7.3 Hz), 7.36–7.41 (1H, m), 7.45 (1H, t, J = 8.1 Hz), 7.57 (1H, d, J = 7.3 Hz), 7.63 (2H, d, J = 8.3 Hz), 13.03 (1H, s); MS (FAB) m/z: 389 [M + H]$^+$; Anal. calcd for $C_{23}H_{20}N_2O_4$•0.20H_2O: C, 70.47; H, 5.25; N, 7.15; found C, 70.44; H, 5.12; N, 7.16.

*4.8.97. 3-{[1-Methyl-6-(3-methylphenoxy)-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13f**).*

Compound **13f** was prepared according to general procedure E (yield, 60%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.27 (3H, s), 3.81 (3H, s), 5.47 (2H, s), 6.74–6.83 (2H, m), 6.87–6.97 (2H, m), 7.32 (1H, d, J = 2.4 Hz), 7.36–7.41 (1H, m), 7.45 (1H, t, J = 8.0 Hz), 7.58 (1H, dt, J = 1.2, 1.4, 7.6 Hz), 7.62–7.68 (2H, m); MS (FAB) m/z: 389 [M + H]$^+$; Anal. calcd for $C_{23}H_{20}N_2O_4$•0.33H_2O: C, 70.04; H, 5.28; N, 7.10; found C, 69.99; H, 5.16; N, 7.15.

*4.8.98. 3-{[1-Methyl-6-(4-methylphenoxy)-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13g**).*

Compound **13g** was prepared according to general procedure E (yield, 68%). Mp > 300 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.28 (3H, s), 3.80 (3H, s), 5.46 (2H, s), 6.87–6.94 (3H, m), 7.17 (2H, d, J = 9.0 Hz), 7.26 (1H, d, J = 2.3 Hz), 7.36–7.41 (1H, m), 7.45 (1H, t, J = 8.0 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.62–7.67 (2H, m), 13.05 (1H, s); MS (FAB) *m/z*: 389 [M + H]$^+$; Anal. calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21; found C, 71.17; H, 5.09; N, 7.29.

*4.8.99. 3-{[6-(3-Chlorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•0.83HCl (**13h**).*

Compound **13h** was prepared according to general procedure E (yield, 84%). Mp, 218–222 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.91 (3H, s), 5.62 (2H, s), 6.98 (1H, dd, J = 3.1, 9.0 Hz), 7.04 (1H, t, J = 2.0 Hz), 7.17 (1H, dd, J = 2.4, 9.0 Hz), 7.18–7.20 (1H, m), 7.40 (1H, d, J = 8.2 Hz), 7.42–7.44 (1H, m), 7.49 (1H, t, J = 7.8 Hz), 7.61 (1H, s), 7.62 (1H, d, J = 7.4 Hz), 7.69 (1H, s), 7.79 (1H, d, J = 9.0 Hz); MS (FAB) *m/z*: 409 [M + H]$^+$; Anal. calcd for $C_{22}H_{17}ClN_2O_4$•0.83HCl: C, 60.16; H, 4.09; N, 6.38; Cl, 14.80; found C, 60.13; H, 3.98; N, 6.49; Cl, 14.96.

*4.8.100. 3-{[6-(4-Chlorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13i**).*

Compound **13i** was prepared according to general procedure E (yield, 89%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.78 (3H, s), 5.44 (2H, s), 6.91-6.98 (3H, m), 7.33-7.37 (4H, m), 7.42 (1H, t, J = 7.8 Hz), 7.54 (1H, dt, J = 1.3, 7.7 Hz), 7.60-7.61 (1H, m), 7.65 (1H, d, J = 8.2 Hz), 13.04 (1H, br); Anal. calcd for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85; Cl, 8.67; found C, 64.54; H, 4.20; N, 6.84; Cl, 8.90.

*4.8.101. 3-{[6-(2-Methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•0.13HCl (**13j**).*

Compound **13j** was prepared according to general procedure E (yield, 89%). Mp, 193–196 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.76 (3H, s), 3.77 (3H, s), 5.44 (2H, s), 6.81 (1H, dd, J = 2.4, 8.6 Hz), 6.91–6.97 (2H, m), 7.09 (1H, d, J = 2.4 Hz), 7.15–7.17 (2H, m), 7.38 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.44 (1H, t, J = 7.4 Hz), 7.57 (1H, dt, J = 1.2, 7.4 Hz), 7.59 (1H, d, J = 8.6 Hz), 7.63 (1H, dd, J = 1.6, 2.7 Hz), 13.04 (1H, br); MS (FAB) *m/z*: 405 [M + H]$^+$; Anal. calcd for $C_{23}H_{20}N_2O_5$•0.13HCl: C, 67.55; H, 4.96; N, 6.85; Cl, 1.08; found C, 67.76; H, 4.90; N, 6.92; Cl, 1.08.

*4.8.102. 3-{[6-(3-Methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13k**).*

Compound **13k** was prepared according to general procedure E (yield, 89%). Mp, 210–214 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 3.89 (3H, s), 5.57 (2H, s), 6.55–6.58 (2H, m), 6.61–6.69 (1H, m), 7.00–7.07 (2H, m), 7.19–7.25 (2H, m), 7.38 (1H, t, J = 7.8 Hz), 7.84 (1H, d, J = 8.6 Hz), 7.78 (1H, d, J = 7.4 Hz), 8.03 (1H, s); MS (FAB) m/z: 405 [M + H]$^+$; Anal. calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93; found C, 68.04; H, 4.97; N, 6.91.

*4.8.103. 3-{[6-(4-Methoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13l**).*

Compound **13l** was prepared according to general procedure E (yield, 86%). Mp, 208–211 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.81 (3H, s), 5.36 (2H, br), 6.87–6.93 (3H, m) 6.98 (3H, d, J = 8.3 Hz), 7.20–7.29 (1H, m), 7.36 (1H, s), 7.65–7.76 (3H, m); MS (FAB) *m/z*: 405 [M + H]$^+$; Anal. calcd for $C_{23}H_{20}N_2O_5$•1.5H_2O: C, 64.03; H, 5.37; N, 6.49; found C, 63.96; H, 5.30; N, 6.52.

*4.8.104. 3-{[6-(3-Ethoxyphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13m**).*

Compound **13m** was prepared according to general procedure E (yield, 86%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 6.7 Hz), 3.82 (3H, s), 3.98 (2H, q, J = 7.0 Hz), 5.47 (2H, s), 6.48–6.52 (2H, m), 6.66 (1H, ddd, J = 1.2, 2.4, 8.2 Hz), 6.95 (1H, dd, J = 2.4, 8.6 Hz), 7.23 (1H, dt, J = 0.8, 7.4 Hz), 7.34 (1H, d, J = 2.4 Hz), 7.38 (1H, ddd, J = 1.2, 2.4, 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, dt, J = 1.2, 7.4 Hz), 7.64 (1H, dd, J = 1.6, 2.4 Hz), 7.67 (1H, d, J = 8.6 Hz), 13.03 (1H, br); MS (FAB) *m/z*: 419 [M + H]$^+$.

*4.8.105. 3-({1-Methyl-6-[3-(trifluoromethoxy)phenoxy]-1H-benzimidazol-2-yl}methoxy)benzoic acid (**13n**).*

Compound **13n** was prepared according to general procedure E (yield, 81%). Mp, 221–227 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.48 (2H, s), 6.95–6.97 (2H, m), 7.00 (1H, dd, J = 2.4, 8.6 Hz), 7.07–7.09 (1H, m), 7.36–7.39 (1H, m), 7.43–7.49 (3H, m), 7.58 (1H, dt, J = 1.2, 7.8 Hz), 7.64 (1H, dd, J = 1.2, 2.4 Hz), 7.71 (1H, d, J = 8.2 Hz), 13.08 (1H, br); MS (FAB) *m/z*: 459 [M + H]$^+$; Anal. calcd for $C_{23}H_{17}F_3N_2O_5$: C, 60.26; H, 3.74; N, 6.11; found C, 60.00; H, 3.70; N, 6.23.

*4.8.106. 3-({1-Methyl-6-[3-(trifluoromethyl)phenoxy]-1H-benzimidazol-2-yl}methoxy)benzoic acid•0.1HCl (**13o**).*

Compound **13o** was prepared according to general procedure E (yield, 89%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.84 (3H, s), 5.48 (2H, s), 7.02 (1H, dd, J = 2.4, 9.0 Hz), 7.23–7.27 (2H, m), 7.33–7.48 (4H, m), 7.57–7.61 (2H, m), 7.64 (1H, s), 7.72 (1H, d, J = 8.6 Hz); MS (FAB) *m/z*: 443 [M + H]$^+$; Anal. calcd for $C_{23}H_{17}F_3N_2O_4$•0.10HCl: C, 61.93; H, 3.86; F, 12.78; N, 6.28; Cl, 0.79; found C, 61.78; H, 3.85; F, 12.55; N, 6.37; Cl, 0.83.

*4.8.107. 3-{[6-(2,3-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13p**).*

Compound **13p** was prepared according to general procedure E (yield, 86%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.82 (3H, s), 5.47 (2H, s), 6.84 (1H, tt, J = 2.0, 7.0 Hz), 7.01 (1H, dd, J = 2.0, 8.6 Hz), 7.13–7.24 (2H, m), 7.36–7.41 (2H, m), 7.45 (1H, t, J = 7.4 Hz), 7.57 (1H, dt, J = 1.6, 7.8 Hz), 7.63 (1H, dd, J = 1.6, 2.7 Hz), 7.68 (1H, d, J = 8.6 Hz), 13.00 (1H, br); MS (FAB) *m/z*: 411 [M + H]$^+$; Anal. calcd for $C_{22}H_{16}F_2N_2O_4$•0.17H_2O: C, 63.92; H, 3.98; F, 9.19; N, 6.78; found C, 63.88; H, 3.80; F, 9.11; N, 6.90.

*4.8.108. 3-{[6-(2,4-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13q**).*

Compound **13q** was prepared according to general procedure E (yield, 48%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.80 (3H, s), 5.45 (2H, s), 6.93 (1H, dd, J = 2.5, 8.8 Hz), 7.05–7.12 (1H, m), 7.19 (1H, dt, J = 5.9, 9.2 Hz), 7.25 (1H, d, J = 2.4 Hz), 7.32–7.37 (1H, m), 7.43 (1H, t, J = 7.82 Hz), 7.44–7.51 (1H, m), 7.54–7.59 (1H, m), 7.62 (1H, dd, J = 1.4, 2.5 Hz), 7.64 (1H, d, J = 8.6 Hz); MS (FAB) *m/z*: 411 [M + H]$^+$; Anal. calcd for $C_{22}H_{16}F_2N_2O_4$•0.50H_2O: C, 63.01; H, 4.09; F, 9.06; N, 6.68; found C, 63.13; H, 3.86; F, 9.20; N, 6.70.

*4.8.109. 3-{[6-(2,5-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13r**).*

Compound **13r** was prepared according to general procedure E (yield, 91%). Mp, 224–227 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.47 (2H, s), 6.88–6.95 (1H, m), 6.98–7.05 (2H, m), 7.38 (2H, s), 7.41–7.48 (2H, m), 7.58 (1H, d, J = 7.3 Hz), 7.63 (1H, s), 7.68 (1H, d, J = 8.8 Hz), 13.03 (1H, br); MS (FAB) *m/z*: 411 [M + H]$^+$; Anal. calcd for $C_{22}H_{16}F_2N_2O_4$•0.25H_2O: C, 63.69; H, 4.01; F, 9.16; N, 6.75; found C, 63.84; H, 4.05; F, 9.22; N, 6.83.

*4.8.110. 3-{[6-(2,6-difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13s**).*

Compound **13s** was prepared according to general procedure E (yield, 85%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.79 (3H, s), 5.43 (2H, s), 6.89 (1H, dd, J = 2.4, 8.6 Hz), 7.17 (1H, d, J = 2.4 Hz), 7.29–7.42 (5H, m), 7.55 (1H, dt, J = 1.6, 7.8 Hz), 7.60–7.62 (2H, m); MS (FAB) *m/z*: 411 [M + H]$^+$.

*4.8.111. 3-{[6-(3,4-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•0.1HCl (**13t**).*

Compound **13t** was prepared according to general procedure E (yield, 82%). Mp, 256–260 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.82 (3H, s), 5.47 (2H, s), 6.77–6.84 (1H, m), 6.97 (1H, dd, J = 2.4, 8.6 Hz), 7.10–7.18 (1H, m), 7.35–7.48 (4H, m), 7.55–7.70 (3H, m); MS (FAB) *m/z*: 411 [M + H]$^+$; Anal. calcd for $C_{22}H_{16}F_2N_2O_4$•0.10HCl: C, 67.37; H, 4.69; F, 4.63; N, 6.83; Cl, 0.86; found C, 67.24; H, 4.70; F, 4.56; N, 7.00; Cl, 0.64.

*4.8.112. 3-{[6-(3,5-Difluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13u**).*

Compound **13u** was prepared according to general procedure E (yield, 76%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.85 (3H, s), 5.47 (2H, s), 6.69 (2H, dd, J = 2.2, 8.8 Hz), 6.95 (1H, tt, J = 2.2, 9.3 Hz), 7.02 (1H, dd, J = 2.4, 8.6 Hz), 7.30–7.36 (1H, m), 7.42 (1H, t, J = 7.8 Hz), 7.48 (1H, d, J = 2.4 Hz), 7.57 (1H, d, J = 7.4 Hz), 7.63 (1H, dd, J = 1.6, 2.4 Hz), 7.72 (1H, d, J = 8.6 Hz); MS (FAB) *m/z*: 411 [M + H]$^+$; Anal. calcd for $C_{22}H_{16}F_2N_2O_4$•H_2O: C, 61.68; H, 4.24; F, 8.87; N, 6.54; found C, 61.58; H, 3.95; F, 9.06; N, 6.51.

*4.8.113. 3-{[6-(4-Fluoro-2-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13v**).*

Compound **13v** was prepared according to general procedure E (yield, 89%). Mp, 217–218 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.22 (3H, s), 3.78 (3H, s), 5.45 (2H, s), 6.82–6.91 (2H, m), 6.98–7.05 (1H, m), 7.12 (1H, d, J = 2.3 Hz), 7.20 (1H, dd, J = 3.1, 9.4 Hz), 7.35–7.40 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 7.55–7.59 (1H, m), 7.60–7.65 (2H, m), 13.03 (1H, s); MS (FAB) *m/z*: 407 [M + H]$^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$•0.20H_2O: C, 67.38; H, 4.77; N, 6.83; found C, 67.44; H, 4.47; F, 4.75; N, 6.90.

*4.8.114. 3-{[6-(5-Fluoro-2-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13w**).*

Compound **13w** was prepared according to general procedure E (yield, 93%). Mp, 208–213 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.24 (3H, s), 3.82 (3H, s), 5.47 (2H, s), 6.57 (1H, dd, J = 2.5, 10.4 Hz), 6.85–6.95 (2H, m), 7.29 (1H, d, J = 2.3 Hz), 7.31–7.41 (2H, m), 7.46 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.63–7.66 (1H, m), 7.67 (1H, d, J = 8.6 Hz), 13.04 (1H, s); MS (FAB) *m/z*: 407 [M + H]$^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$•0.50H_2O: C, 66.50; H, 4.85; N, 6.74; found C, 66.87; H, 5.16; N, 6.59.

*4.8.115. 3-{[6-(2-Fluoro-4-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13x**).*

Compound **13x** was prepared according to general procedure E (yield, 48%). Mp, 230–235 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.31 (3H, s), 3.79 (3H, s), 5.45 (2H, s), 6.90 (1H, dd, J = 2.4, 9.0 Hz), 6.99–7.02 (2H, m), 7.21 (1H, t, J = 6.7 Hz), 7.21 (1H, s), 7.35–7.40 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 7.55–7.59 (1 H, m), 7.63 (1H, d, J = 8.6 Hz), 7.63 (1H, dd, J = 1.6, 2.4 Hz), 13.03 (1H, br), MS (FAB) *m/z*: 407 [M + H]$^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$•0.20H_2O: C, 67.38; H, 4.77; F, 4.63; N, 6.83; found C, 67.46; H, 4.72; F, 4.75; N, 6.89.

*4.8.116. 3-{[6-(2-Fluoro-5-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13y**).*

Compound **13y** was prepared according to general procedure E (yield, 95%). Mp, 227–233 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.23 (3H, s), 3.81 (3H, s), 5.46 (2H, s), 6.87 (1H, s), 6.93 (1H, dd, J = 2.4, 9.0 Hz), 6.94–6.99 (1H, m), 7.22–7.31 (2H, m), 7.39 (1H, s), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.4 Hz), 7.62–7.68 (2H, m); MS (FAB) *m/z*: 407 [M + H]$^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$•0.20H_2O: C, 67.38; H, 4.77; F, 4.63; N, 6.83; found C, 67.43; H, 4.71; F, 4.80; N, 6.87.

*4.8.117. 3-{[6-(3-Fluoro-4-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13z**).*

Compound **13z** was prepared according to general procedure E (yield, 94%). Mp, 220–223 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.18 (3H, s), 3.82 (3H, s), 5.47 (2H, s), 6.72 (6H, dd, J = 2.4, 8.6 Hz), 6.80 (6H, dd, J = 2.5, 11.1 Hz), 6.95 (6H, dd, J = 2.4, 8.6 Hz), 7.25 (6H, t, J = 8.6 Hz), 7.35–7.40 (2H, m), 7.36 (1H, d, J = 2.4 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.67 (1H, d, J = 8.6 Hz), 7.63–7.69 (1H, m), 13.08 (1H, br); MS (FAB) *m/z*: 407 [M + H]$^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$: C, 67.97; H, 4.71; F, 4.67; N, 6.89; found C, 67.58; H, 4.63; F, 4.67; N, 6.91.

*4.8.118. 3-{[6-(4-Fluoro-3-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•0.1HCl (**13aa**).*

Compound **13aa** was prepared according to general procedure E (yield, 81%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.20 (3H, s), 3.81 (3H, s), 5.46 (2H, s), 6.80–6.87 (1 H, m), 6.89–6.95 (2H, m), 7.12 (1H, t, J = 9.0 Hz), 7.28 (1H, d, J = 2.0 Hz), 7.36–7.41 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 7.57 (1H, d, J = 7.8 Hz), 7.62–7.67 (2H, m), 13.03 (1H, br); MS (FAB) *m/z*: 407 $[M + H]^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$•0.10HCl: C, 67.37; H, 4.69; F, 4.63; N, 6.83; Cl, 0.86; found C, 67.24; H, 4.70; F, 4.56; N, 7.00; Cl, 0.64.

*4.8.119. 3-{[6-(3-Fluoro-5-methylphenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13ab**).*

Compound **13ab** was prepared according to general procedure E (yield, 73%). Mp, 224–226 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.25 (3H, s), 3.83 (3H, s), 5.47 (2H, s), 6.58–6.60 (2H, m), 6.75 (1H, d, J = 10.6 Hz), 6.96 (1H, dd, J = 2.4, 8.6 Hz), 7.37–7.39 (2H, m), 7.45 (1H, t, J = 7.4 Hz), 7.57 (1H, dt, J = 1.2, 7.8 Hz), 7.64 (1H, dd, J = 1.2, 2.4 Hz), 7.68 (1H, d, J = 8.6 Hz), 13.03 (1H, s); MS (FAB) *m/z*: 407 $[M + H]^+$; Anal. calcd for $C_{23}H_{19}FN_2O_4$: C, 67.97; H, 4.71; N, 6.89; found C, 68.13; H, 4.57; N, 6.95.

*4.8.120. 3-{[6-(4-Chloro-3-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13ac**).*

Compound **13ac** was prepared according to general procedure E (yield, 72%). Mp, 234–236 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.84 (3H, s), 5.48 (2H, s), 6.83 (1H, ddd, J = 1.2, 2.7, 9.0 Hz), 7.01 (1H, dd, J = 2.4, 8.6 Hz), 7.10 (1H, dd, J = 2.7, 10.6 Hz), 7.39 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.44–7.48 (2H, m), 7.54 (1H, t, J = 9.0 Hz), 7.58 (1H, dt, J = 1.6, 7.8 Hz), 7.64 (1H, dd, J = 1.6, 2.4 Hz), 7.71 (1H, d, J = 9.0 Hz), 13.05 (1H, br); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{17}ClFN_2O_4$, 427.0861; found 427.0853; Anal. calcd for $C_{22}H_{16}ClFN_2O_4$: C, 61.91; H, 3.78; N, 6.56; Cl, 8.31; found C, 61.72; H, 3.70; N, 6.63; Cl, 8.54.

*4.8.121. 3-{[6-(3-Chloro-5-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13ad**).*

Compound **13ad** was prepared according to general procedure E (yield, 86%). Mp, 209–213 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.84 (3H, s), 5.48 (2H, s), 6.83–6.86 (2H, m), 7.02 (1H, dd, J = 2.4, 9.0 Hz), 7.15 (1H, dt, J = 2.0, 8.6 Hz), 7.39 (1H, ddd, J = 1.2, 2.4, 8.2 Hz), 7.45 (1H, t, J = 7.4 Hz), 7.49 (1H, d, J = 2.4 Hz), 7.58 (1H, dt, J = 1.2, 7.4 Hz), 7.65 (1H, dd, J = 1.2, 2.4 Hz), 7.72 (1H, d, J = 8.6 Hz), 13.04 (1H, s); MS (FAB) *m/z*: 427 $[M + H]^+$; Anal. calcd for $C_{22}H_{16}ClFN_2O_4$•0.2H_2O: C, 61.39; H, 3.84; N, 6.51; Cl, 8.24; found C, 61.56; H, 3.76; N, 6.53; Cl, 8.53.

*4.8.122. 3-{[6-(3-Chloro-4-fluorophenoxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid•0.13HCl (**13ae**).*

Compound **13ae** was prepared according to general procedure E (yield, 70%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.94 (3H, s), 5.69 (2H, s), 7.07 (1H, ddd, J = 3.0, 3.9, 9.1 Hz), 7.22 (1H, dd, J = 2.2, 8.9 Hz), 7.29 (1H, dd, J = 3.0, 6.2 Hz), 7.44 (1H, ddd, J = 1.1, 2.7, 8.2 Hz), 7.46 (1H, dd, J = 9.1, 9.1 Hz), 7.50 (1H, dd, J = 7.6, 8.2 Hz), 7.63 (1H, d, J = 2.2 Hz), 7.64 (1H, ddd, J = 1.1, 1.3, 7.6 Hz), 7.70 (1H, dd, J = 1.3, 2.7 Hz), 7.82 (1H, d, J = 8. 9 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{17}ClFN_2O_4$, 427.0861; found 427.0854; Anal. calcd for $C_{22}H_{16}ClFN_2O_4$•0.13HCl: C, 61.25; H, 3.77; N, 6.49; Cl, 9.25; F, 4.40; found C, 61.40; H, 3.76; N, 6.52; Cl, 8.95; F, 4.86.

*4.8.123. 3-{[6-(2,3-Dihydro-1-benzofuran-5-yloxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid 0.17 HCl (**13af**).*

Compound **13af** was prepared according to general procedure E (yield, 63%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.16 (2H, t, J = 8.6 Hz), 3.79 (3H, s), 4.52 (2H, t, J = 8.6 Hz), 5.45 (2H, s), 6.73–6.78 (2H, m), 6.88 (1H, dd, J = 2.7, 9.0 Hz), 6.93 (1H, dd, J = 0.8, 2.4 Hz), 7.18 (1H, d, J = 2.4 Hz), 7.38 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, J = 7.4 Hz), 7.57 (1H, dt, J = 1.2, 9.0 Hz), 7.61 (1H, d, J = 8.6 Hz), 7.63 (1H, dd, J = 1.6, 2.7 Hz), 13.06 (1H, br); MS (FAB) *m/z*: 417 $[M + H]^+$; Anal. calcd for $C_{24}H_{20}N_2O_5$•0.17HCl•1.25H_2O: C, 64.77; H, 5.13; N, 6.29; Cl, 1.33; found C, 64.91; H, 4.71; N, 6.23; Cl, 1.26.

*4.8.124. 3-{[6-(2,3-Dihydro-1-benzofuran-6-yloxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13ag**).*

Compound **13ag** was prepared according to general procedure E (yield, 74%). Mp, 213–217 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.13 (2H, t, J = 8.4 Hz), 3.81 (3H, s), 4.55 (2H, t, J = 8.6 Hz), 5.46 (2H, s), 6.39–6.44 (2H, m), 6.91 (1H, dd, J = 2.4, 8.6 Hz), 7.16 (1H, d, J = 7.8 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.36–7.40 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, dt, J = 1.2, 1.4, 7.6 Hz), 7.62–7.66 (2H, m), 13.04 (1H, br); MS (FAB) *m/z*: 417 $[M + H]^+$; Anal. calcd for $C_{24}H_{20}N_2O_5$•0.33H_2O: C, 68.24; H, 4.93; N, 6.63; found C, 68.34; H, 4.84; N, 6.79.

*4.8.125. 3-{[6-(1-Benzofuran-6-yloxy)-1-methyl-1H-benzimidazol-2-yl]methoxy}benzoic acid (**13ah**).*

Compound **13ah** was prepared according to general procedure E (yield, 98%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.81 (3H, s), 5.47 (2H, s), 6.95 (1H, dd, J = 0.8, 2.4 Hz), 6.97 (1H, dd, J = 2.4, 4.3 Hz), 6.99 (1H, dd, J = 20, 3.9 Hz), 7.22 (1H, d, J = 2.7 Hz), 7.33 (1H, d, J = 2.4 Hz), 7.37–7.40 (1H, m), 7.45 (1H, t, J = 7.4 Hz), 7.58 (1H, dt, J = 1.2, 7.4 Hz), 7.62–7.68 (3H, m), 7.95 (1H, d, J = 2.4 Hz), 13.05 (1H, br); MS (FAB) *m/z*: 415 $[M + H]^+$; Anal. calcd for $C_{24}H_{18}N_2O_5$•0.20H_2O: C, 68.96; H, 4.44; N, 6.70; found C, 69.18; H, 4.32; N, 6.61.

*4.8.126. [3-(Methoxycarbonyl)phenoxy]acetic acid (**14**).*

A solution of *tert*-butyl bromoacetate (506 g, 2.59 mol), methyl 3-hydroxybenzoate (395 g, 2.60 mol) and K_2CO_3 (789 g, 5.71 mol) in DMF (2.0 L) was stirred at room temperature for 2 h under N_2. The reaction mixture was concentrated and water (1.0 L) was added, followed by extraction with EtOAc (2.0 L). The organic layer was washed with water (1.0 L) twice, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude *tert*-butyl [3-(methoxycarbonyl)phenoxy]acetate as a colorless oil. A solution of crude *tert*-butyl [3-(methoxycarbonyl)phenoxy]acetate in TFA (1.0 kg), anisole (100 mL) and CH_2Cl_2 (1.0 L) was stirred at room temperature for 48 h under N_2. The reaction mixture was concentrated, and the residue was crystallized from *i*-Pr_2O to obtain **14** (467 g, 86%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (3H, s), 4.76 (2H, s), 7.17 (1H, dd, J = 2.4, 8.2 Hz), 7.39 (1H, t, J = 7.8 Hz), 7.57–7.58 (1H, m), 7.72 (1H, d, J = 7.4 Hz).

*4.8.127. Methyl 3-[2-({2-[(tert-butoxycarbonyl)(methyl)amino]-4-(2,3-dihydro-1-benzofuran-5-yloxy)phenyl}amino)-2-oxoethoxy]benzoate (**15af**).*

Compound **15af** was prepared according to general procedure F (yield, 86%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, br), 3.10 (3H, br), 3.21 (2H, t, J = 8.6 Hz), 3.93 (3H, s), 4.60 (2H, t, J = 8.6 Hz), 4.67 (2H, s), 6.73–6.87 (4H, m), 6.90 (1H, d, J = 2.0 Hz), 7.20 (1H, dd, J = 2.4, 7.8 Hz), 7.26–7.27 (1H, m), 7.41 (1H, t, J = 7.8 Hz), 7.63 (1H, s), 7.74 (1H, d, J = 7.4 Hz).

*4.8.128. Methyl 3-[2-({2-[(tert-butoxycarbonyl)(methyl)amino]-4-(2,3-dihydro-1-benzofuran-6-yloxy)phenyl}amino)-2-oxoethoxy]benzoate (**15ag**).*

Compound **15ag** was prepared according to general procedure F Yield: 94% (3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, br), 3.11 (3H, br), 3.19 (2H, t, *J* = 8.6 Hz), 3.93 (3H, s), 4.62 (2H, t, *J* = 8.6 Hz), 4.68 (2H, s), 6.48–6.50 (3H, m), 6.86 (1H, br), 6.94 (1H, d, *J* = 3.9 Hz), 7.12 (1H, d, *J* = 7.4 Hz), 7.21 (1H, dd, *J* = 2.0, 7.8 Hz), 7.42 (1H, t, *J* = 8.2 Hz), 7.64 (1H, s), 7.75 (1H, d, J = 7.8 Hz).

*4.8.129. Methyl 3-[2-({4-(1-benzofuran-6-yloxy)-2-[(tert-butoxycarbonyl)(methyl)amino]phenyl}amino)-2-oxoethoxy]benzoate (**15ah**).*

Compound **15ah** was prepared according to general procedure F (yield, 93%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.42 (9H, br), 3.11 (3H, br), 3.93 (3H, s), 4.68 (2H, s), 6.76 (1H, d, *J* = 0.8, 2.0 Hz), 6.88 (1H, br), 6.95 (1H, br), 6.99 (1H, dd, *J* = 2.0, 8.6 Hz), 7.17 (1H, s), 7.21 (1H, dd, *J* = 2.0, 8.6 Hz), 7.42 (1H, t, *J* = 7.8 Hz), 7.54 (1H, d, J = 8.6 Hz) , 3.19 (2H, t, *J* = 8.6 Hz), 7.62 (1H, d, *J* = 2.0 Hz), 7.64 (1H, br), 7.75 (1H, dt, *J* = 1.2, 7.8 Hz).

4.9. Measurement of PPARγ Transcriptional Activity.

GAL4-human PPARγ chimera receptor expression vector, pM-h PPARγ, expressed the LBD of PPARγ as a fusion protein with the DNA-DB of yeast transcription factor GAL4. The pG5luc vector (included in CheckMate Mammalian Two-Hybrid System, Promega Corporation), which contains five tandem repeats of a GAL4-binding DNA sequence upstream of minimal TATA to facilitate the detection of firefly luciferase activity induced by a GAL4-h PPARγ fusion protein, was used as a GAL4-dependent reporter vector. Dulbecco's Modified Eagle Medium (DMEM, Invitrogen Corporation) containing 10% (v/v) heat-inactivated fetal bovine serum (FBS, Invitrogen Corporation) was prepared as a culture medium. The COS-7 cells were cultured in the culture medium at 37 °C with 5% CO_2 (5% CO_2, 95% air). The COS-7 cells were cultured to the confluent in 75-cm^2 culture flasks. Cells were transfected with 4.8 μg of the pM-h PPARγ and 19.2 μg of pG5luc using Lipofectamine 2000 (Invitrogen Corporation) in Opti-MEM I reduced serum medium (Opti-MEM I, Invitrogen Corporation) according to the manufacturer's instruction. After the transfection, the COS-7 cells were harvested and re-seeded in 96-well white plates and cultured for about 24 h in a CO_2 incubator. The pM-h PPARα expression vector was used for the GAL4-h PPARα-LBD reporter gene assay.

The serial dilutions of the test compounds (1, 3, 10, 30, 100, 300, 1000, 3000, 10000 nM) and the control solution (0.1% DMSO) were added into the individual wells in the 96-well plates, and the cells were further incubated for about 24 h in a CO_2 incubator. A luciferase assay was performed using a Picagene LT 2.0 Luminescence Reagent (TOYO INK, Co., Ltd.) according to the manufacturer's instruction. The light intensity in each well was measured using a Multimode Microplate Reader (Analyst GT, Molecular Devices, Inc.). Rosiglitazone and 2-(4-tert-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid[32] were used as positive references for the PPARγ and PPARα, respectively. The maximum transcriptional activity of the test compound alone was defined as the maximum efficacy (E_{max}, %). The concentration of the test compound indicating a half value of E_{max} was defined as the EC_{50} value. Values of each parameter were determined by nonlinear curve fitting using GraphPad Prism 4.0 (GraphPad Software Inc.). Data represent single experiment run in octuplicate, except for **13ac**, which are from thirteen independent experiments run in octuplicate.

4.10. Measurement of Log D.

Equal amounts of PBS and 1-octanol were shaken and left overnight. The upper layer (1-octanol) and lower layer (PBS) were collected individually. Each test compound was dissolved in 1-octanol or PBS (200 mM). The same amount of either PBS or 1-octanol was added and the mixture was shaken vigorously for 30 min at room temperature followed by centrifugation at 2100g for 5 min at room temperature. Then, both phases were separated and assayed by HPLC and LC-MS. Log D7.4 was calculated by the following equation:

Log D7.4 = log (peak area of compound in 1-octanol/peak area of compound in PBS).

4.11. Solubility Assay.

After lyophilization of 10 mM DMSO solution of the test compounds, aqueous neutral solution (pH 6.8) was added, stirred, and allowed to stand at room temperature for at least 4 hours. After allowing to filter by suction through Uni Filter (Uni Filter), the concentration of the filtrate was measured by HPLC-UV methodologies. Data represent single experiment run in duplicate.

4.12. Hypoglycemic effect in KK mice.

All experimental procedures were performed in accordance with the in-house guidelines of the Institutional Animal Care and Use Committee of Daiichi Sankyo Co., Ltd. Six-week-old male KK mice were purchased from CLEA Japan, Inc. and then were fed until 14 to 15 weeks old to develop diabetes. Before the study, the each PG level was measured by Glucoloader GXT (A&T Corp.), and individuals having a PG level of about 350 mg/dL or more were selected. The test compound was administered to mice with a diet admixture containing 0.03% of the test compound for 3 days (*n* = 3). A separate group in which the mice were fed only with diet was a control group. The body weight was measured and blood was collected from the tail vein to measure the PG level. The glucose lowering rate was determined by the following formula.

PG reduction (%) = [(PG level (Control group) - PG level (Compound-administered group))/ PG level (Control group)] x 100

The plasma concentration of the test compound was measured from the same blood sample on day 3 (*n* = 3).

4.13. Hypoglycemic effect in ZDF rats.

All experimental procedures were performed in accordance with the in-house guideline of the Institutional Animal Care and Use Committee of Daiichi Sankyo Co., Ltd. Six-week-old male Zucker diabetic fatty rats were purchased from Charles River Japan, Inc. and then were fed until 8 weeks old. Before the study, the each PG level was measured by Glucoloader GXT (A&T Corp.), and individuals having a PG level of about 300 mg/dL or more were selected. The test compound (0.5%methylcellulose) was orally administered to ZDF rats once daily for 14 days (*n* = 5). The body weight was measured and blood was collected from the tail vein to measure the PG level. The glucose lowering rate was determined by the following formula.

PG reduction (%) = [(PG level (Control group) - PG level (Compound-administered group))/ PG level (Control group)] x 100

4.14. Monkey Pharmacokinetic Study.

All experimental procedures were performed in accordance with the in-house guideline of the Institutional Animal Care and Use Committee of Daiichi Sankyo Co., Ltd. For the determination of test compound exposures in male cynomolgus monkeys, blood samples were taken at several time points postdose. The plasma was separated from blood by centrifugation, and stored at −70 °C until use for measurement of plasma concentration. The determination of the plasma concentration of the compound was performed by LC-MS/MS method using API 4000QTRAP (Applied Biosystems/MDS SCIEX). PK parameters were calculated using a non-compartmental analysis techniques by the computer software WinNonlin Professional version 4.0.1. (Pharsight Corporation).

4.15. In Vivo Toxicological Evaluation.

All experimental procedures were performed in accordance with the in-house guideline of the Institutional Animal Care and Use Committee of Daiichi Sankyo Co., Ltd. Seven-week-old female Wistar–Imamichi rats were purchased from Charles River Japan, Inc. and then were housed for one week. Rats (n = 5) were orally dosed once daily by gavage with vehicle or test compounds at indicated doses in 0.5% methylcellulose for 28 days. Animals were euthanized on the next day of the last dose, and the indicated tissues and organs were collected for organ weight assessment and histopathological examination. Blood samples were exsanguinated via the abdominal aorta and assayed for serum chemistry.

4.16. Protein Crystallography Method.

Histidine-tagged human PPARγ-LBD was expressed and purified as described previously.[20] A synthetic peptide with a sequence derived from PGC-1 (QEAEEPSLLKKLLLAPANT) was purchased from Sigma-Aldrich. Before crystallization, PPARγ-LBD was concentrated to 22 mg/mL and mixed with **13ac** and PGC-1 in a molar ratio of 1:4:4. Crystals were obtained by the hanging drop vapor diffusion technique with a reservoir solution of 24% (w/v) PEG4000, 200 mM NaSCN and 100 mM Tris-HCl (pH 8.5). Prior to data collection, crystals were transiently soaked in the reservoir solution containing additional 8% (v/v) PEG400 as a cryoprotectant. X-ray diffraction data were collected using an X-ray generator FR-E with detector R-AXIS IV (RIGAKU). The diffraction data were integrated, scaled using HKL2000,[40] and converted to structure factors using the CCP4 software suite.[41] The structure of PPARγ-LBD derived from the structure 3V9T.pdb[19] was used as an initial model. Several rounds of manual rebuilding with O[42] followed by refinement with CNX[43] (Accerlys) were carried out. A Ramachandran plot for the final model was calculated with RAMPAGE.[44] Figures were created with PyMOL (v.1.7; Schrödinger).Authors will release the atomic coordinates and experimental data upon article publication. Coordinates are available from PDB using accession code 5Z5S.

5. AUTHOR INFORMATION

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7. Notes

The authors declare no competing financial interest.

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Discovery of DS-6930, a Potent Selective PPARγ Modulator. Part I: Lead Identification

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