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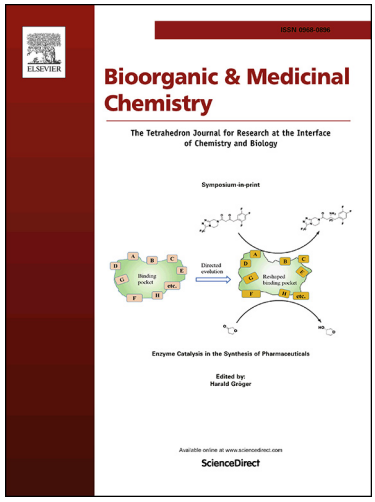

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Discovery of DS-6930, a Potent Selective PPARγ Modulator. Part II: Lead Optimization

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ABSTRACT

Attempts were made to reduce the lipophilicity of previously synthesized compound (**II**) for the avoidance of hepatotoxicity. The replacement of the left-hand side benzene with 2-pyridine resulted in the substantial loss of potency. Because poor membrane permeability was responsible for poor potency *in vitro*, the adjustment of lipophilicity was examined, which resulted in the discovery of dimethyl pyridine derivative (**I**, DS-6930). In preclinical studies, DS-6930 demonstrated high PPARγ agonist potency with robust plasma glucose reduction. DS-6930 maintained diminished PPARγ-related adverse effects upon toxicological evaluation *in vivo*, and demonstrated no hepatotoxicity. Cofactor recruitment assay showed that several cofactors, such as RIP140 and PGC1, were significantly recruited, whereas several canonical factors was not affected. This selective cofactor recruitment was caused due to the distinct binding mode of DS-6930. The calcium salt, DS-6930b, which is expected to be an effective inducer of insulin sensitization without edema, could be evaluated clinically in T2DM patients.

1. Introduction

Although eroxisome proliferator-activated receptor γ (PPARγ) agonists exhibit robust clinical pharmacological efficacy without hypoglycemic effects,[1-3] adverse effects, such as weight gain, peripheral edema, hepatotoxicity, bone fracture, carcinogenicity, and cardiovascular risks, limit their use.[4-7] If such adverse effects could be avoided, PPARγ agonists hold good anti-hyperglycemic potential for the treatment of type 2 diabetes (T2DM). A novel PPARγ modulator, DS-6930 (**I**, Figure 1) was identified with robust plasma glucose (PG) reduction as well as diminished PPARγ-related adverse effects *in vivo*. In this paper, we report the lead optimization of compound **II** (Figure 1) to identify a novel potent selective PPARγ agonist, DS-6930, with ideal preclinical characteristics.

Previously, we identified a potent PPARγ intermediate agonist **II** (Figure 1).[8] Although it possessed excellent pharmacological effects and a favorable DMPK profile with diminished PPARγ-related adverse effects, it induced hepatotoxicity. Therefore, we sought to eliminate this adverse effect and develop a clinically viable candidate. Hepatotoxicity is known as one of the most common but severe adverse effects in drug discovery. Numerous drugs have been withdrawn because of their hepatotoxic effects.[9] Hepatotoxicity may be avoided by reducing lipophilicity.[10,11] Moreover, compound **II** exhibited low solubility. Therefore, by reducing lipophilicity, both these critical issues would be addressed simultaneously. Accordingly, we directed our research towards the reduction of lipophilicity of compound **II**.

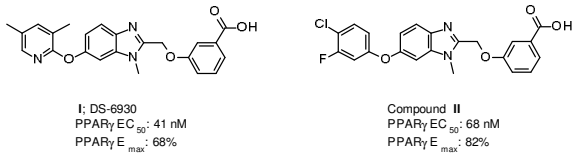
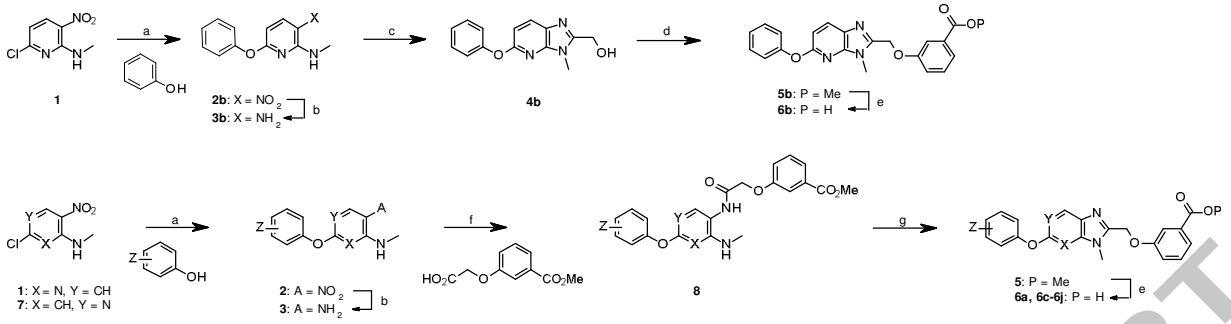


Figure 1. Structures of DS-6930 and lead compound **II** with PPARγ agonist activities in COS-7 cells.

2. RESULTS and DISCUSSION

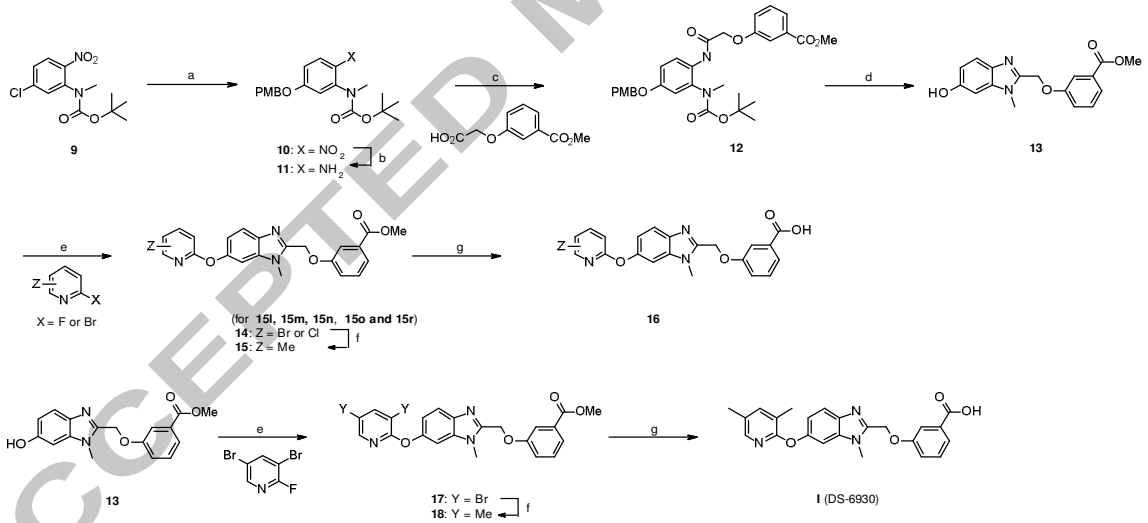
2.1. Chemical synthesis

Imidazopyridines **6** listed in Table 1 were synthesized as shown in Scheme 1. Initially, compound **6b** was synthesized from imidazo[4,5-b]pyridine carbinol **4b** as an intermediate. However, acid promoted imidazo[4,5-b]pyridine ring annulation was not possible for other amino pyridines **3** because of the weak nucleophilicity of aromatic amine. Thus, amino pyridines **3** were converted to amides **8** by reacting with [3-(methoxycarbonyl)phenoxy]acetic acid,[8] followed by the treatment of **8** with acetic acid to obtain imidazopyridines **5**. A final saponification yielded imidazopyridine derivatives **6**.



Scheme 1. Synthesis of Compounds **6**. Reagents and conditions: (a) NaH, DMF, or THF, 80 °C, 89% (**2a**), 70% (**2e**), 92% (**2f**), 33% (**2h**), 85% (**2i**), 92% (**2l**); (b) H_2, $Pd(OH)_2$ or Pd/C, THF, EtOH; or Fe, NH_4Cl, EtOH, H_2O, reflux; (c) glycolic acid, HCl, 1,4-dioxane, reflux, 80% (3 steps); (d) methyl 3-hydroxybenzoate, ADDP, PBu_3, toluene, 58%; (e) NaOH, H_2O, 1,4-dioxane, reflux, 94% (**6a**), 61% (**6b**), 71% (**6c**), 92% (**6d**), 72% (**6e**), 97% (**6f**), 85% (**6g**), 95% (**6h**), 98% (**6i**), 74% (**6j**), 94% (**6k**), 93% (**6l**), 74% (**6m**), 99% (**6n**); (f) WSC•HCl, HOBt•H_2O, CH_2Cl_2, 77% (**8a**, 2 steps), 60% (**8c**, 3 steps), 23% (**8d**, 3 steps), 79% (**8e**, 2 steps), 90% (**8f**, 2 steps), 97% (**8g**, 3 steps), 27% (**8h**, 2 steps), 97% (**8i**, 2 steps), 34% (**8k**, 3 steps), 97% (**8l**, 2 steps), 34% (**8m**, 3 steps), 77% (**8n**, 3 steps); (g) AcOH, 80 °C, 76% (**5a**), 80% (**5c**), 40% (**5d**), 76% (**5e**), 79% (**5f**), 86% (**5g**), 75% (**5h**), 68% (**5i**), 88% (**5j**, 4 steps), 39% (**5k**), 57% (**5l**), 89% (**5m**), 69% (**5n**).

2-Pyridine derivatives **16** listed in Table 2 were synthesized from versatile intermediate **13** as shown in Scheme 2. The key intermediate **13** was synthesized from chloride **9**, which was transformed in *p*-methoxy benzyl ether **10**. After reducing nitro group, acylation with phenoxyacetic acid intermediate[8] led to amide **12**. Benzimidazole ring annulation was then performed by treating amide **12** with HCl to provide compound **13**. Under this reaction condition, *p*-methoxy benzyl (PMB) ether was cleaved. The introduction of 2-pyridine ring was accomplished by reacting **13** with 2-bromo- or 2-fluoro-substituted pyridines in the presence of copper catalyst to yield **14**.[12,13] In methyl-substituted derivatives (**16l**, **16m**, **16n**, **16o** and **16r**), halogen atom (Br or Cl) was transformed to methyl group by Pd-catalyzed reaction to give compounds **15**. A final saponification of ester provided compounds **16**. DS-6930 (**I**) was prepared with a high overall yield using the same synthetic strategy as described above. The key intermediate **13** was reacted with 3,5-dibromo-2-fluoropyridine, followed by Pd-catalyzed methylation of bromide **17** to afford methyl ester **18**. A final saponification led to the formation of DS-6930. This synthetic route provided high yields of DS-6930 (over 200 g scales).



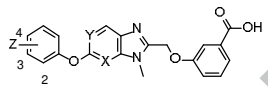
Scheme 2. Synthesis of Compounds **16** and **DS-6930**. Reagents and conditions: (a) PMBOH, NaH, DMF, 80 °C, 99%; (b) Fe, NH_4Cl, EtOH, H_2O, reflux, 99%; (c) WSC•HCl, HOBt•H_2O, CH_2Cl_2, 99%; (d) HCl, 1,4-dioxane, 60 °C, 67%; (e) CuI, 1,10-phenanthloline, Cs_2CO_3, DMF, 80 °C or Cu, Cs_2CO_3, DMF, 100 °C, microwave, 14% (**14a**), 49% (**14b**), 4.2% (**14c**), 33% (**14d**), 58% (**14e**), 18% (**14f**), 18% (**14g**), 15% (**14h**), 11% (**14i**), 4.5% (**14j**), 28% (**14k**), 11% (**14l**), 62% (**14m**), 66% (**14n**), 54% (**14o**), 53% (**14p**), 70% (**14q**), 91% (**14r**), 99% (**17**); (f) trimethylboroxine, $PdCl_2$ (diphenylphosphino)ferrocene (dppf)•CH_2Cl_2, K_2CO_3, DMF, 80 °C, 52% (**15l**), 80% (**15m**), 56% (**15n**), 60% (**15o**), 75% (**15r**), 80% (**18**); (g) NaOH, MeOH, H_2O, 48% (**16a**), 99% (**16b**), 41% (**16c**), 94% (**16d**), 67% (**16e**), 54% (**16f**), 73% (**16g**), 64% (**16h**), 98% (**16i**), 38% (**16j**), 99% (**16k**), 96% (**16l**), 50% (**16m**), 98% (**16n**), 95% (**16o**), 93% (**16p**), 94% (**16q**), 51% (**16r**), 99% (**I**).

2.2. In vitro Activity, in vitro ADME Profile

Because compound **II** already possesses carboxylic acid, the incorporation of another polar functional group is challenging. Consequently, the introduction of a nitrogen atom in each ring system was explored to reduce the lipophilicity. Initially, the nitrogen atom was introduced on the right-hand side 3-benzoic acid moiety. Picolinic, nicotinic and isonicotinic acid derivatives were synthesized with unsuccessful results (data not shown). These results led us to introduce the nitrogen atom in benzimidazole ring as shown in Table 1.

PPARγ transcriptional activities were evaluated in GAL4-PPAR-LBD reporter gene assays using COS-7 cells. The maximum transcriptional activity (E_{max}) of the test compound was defined relative to that of rosiglitazone (100%).[14] Imidazo[4,5-b]pyridine **6a** exhibited EC_{50} = 269 nM with E_{max} = 88% and showed an attenuated Log D value. Compound **6a** maintained a high stability against human liver microsomes. Consequently, several imidazo[4,5-b]pyridine derivatives were synthesized as shown in Table 1. Unsubstituted phenyl derivative **6b** showed diminished potency *in vitro*, while 4-methyl derivative **6d** exhibited 12-fold higher potency than **6b**. Because these SAR results were similar to those of benzimidazole series,[8] several promising compounds were synthesized to confirm their potencies *in vitro* (Compounds **6e**–**6j**). Imidazo[4,5-b]pyridine derivatives tend to exhibit relatively high PPARα activities, and 4-fluoro and 3-fluoro-4-methyl analogues (Compounds **6c** and **6e**) exhibited $EC_{50} < 10$ μM. On the other hand, this series of compounds caused no PPARδ transcriptional activity at 10 μM (Data not shown). Although lipophilicity was reduced with this modification, these potent compounds indicated poor aqueous solubility. Among these derivatives, compounds **6d**, **6h** and **6j** exhibited potent *in vitro* potencies as well as acceptable aqueous solubilities. As described previously,[8] the introduction of methyl group is often associated with diminished human microsomal stability; similarly, certain methyl-substituted imidazo[4,5-b]pyridine derivatives **6f**, **6g** and **6h** exhibited modest human microsomal stability. We then focused on imidazo[4,5-c]pyridines. Imidazo[4,5-c]pyridine **6k** exhibited 4.4-fold reduced *in vitro* potency compared to imidazo[4,5-b]pyridine **6a**. Although 4-methyl derivative **6l** did not exhibit significantly enhanced *in vitro* potency unlike imidazo[4,5-b]pyridine derivative **6d**, indane **6n** exhibited high potency *in vitro*. Indane **6n** exerted intermediate agonist activity (E_{max} = 55%) and possessed fair solubility as well as excellent microsomal stability. Imidazo[4,5-c]pyridine derivatives **6k**–**6n** did not show more than 50% activation of PPARα activity at 10 μM. Membrane permeability was assessed by a parallel artificial membrane permeation assay (PAMPA) because the reduction of lipophilicity is often associated with poor membrane permeability. Compounds **6c**, **6l** and **6m** might exhibit poor potency *in vitro* because of their modest permeabilities ($P_{app} < 10 \times 10^{-6}$ cm/s).

Table 1. PPAR Transcriptional Activities and *In Vitro* ADME Profiles of Compounds **6**



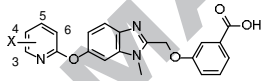
Compound	X	Y	Z	PPARγ EC_{50} (nM)[a]	PPARγ E_{max} (%)[a]	PPARα EC_{50} (nM)[b]	PPARα E_{max} (%)[b]	Log D[c]	PAMPA P_{app} (10^{-6} cm/s)[d]	Solubility (μg/mL)[e]	Human microsomal stability (%)[f]
II	CH	CH	3-F, 4-Cl	68 ± 28[i]	82 ± 4.0[i]	>10000[i]	32 ± 2.7[i]	2.7	38.5 ± 2.0[j]	0	100
6a	N	CH	3-F, 4-Cl	269	88	>10000	45	2.2	25.6	1.7	92
6b[g]	N	CH	H	550	61	NT[h]	NT[h]	1.2	NT[h]	160	100
6c	N	CH	4-F	1060	62	ND[j]	55	1.5	8.6	11	78
6d	N	CH	4-Me	45	58	>10000	38	1.7	12.6	33	NT[h]
6e	N	CH	3-F, 4-Me	50	80	ND[j]	56	2.1	14.8	5.2	96
6f	N	CH	2-Me, 4-Me	101	75	>10000	17	2.3	28.8	0.9	63
6g	N	CH	3-Me, 5-Me	41	83	>10000	19	2.3	17.4	0.5	71
6h	N	CH	3-Me, 4-Me	90	74	>10000	30	2.2	12.4	16	73
6i	N	CH		25	79	>10000	23	2.5	31.5	4.3	76
6j	N	CH		94	89	>10000	20	1.4	9.1	17	92
6k	CH	N	3-F, 4-Cl	1174	73	>10000	15	1.4	11.2	11	98
6l	CH	N	4-Me	746	80	>10000	6	1.0	6.8	360	80
6m	CH	N		335	59	>10000	4	0.6	3.6	79	100
6n	CH	N		20	55	>10000	22	1.6	16.5	70	100

[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%.[15] [c]Distribution coefficients (Log D) were measured after partition between 1-octanol and PBS (pH = 7.4). [d]PAMPA was performed at pH 7.4. Values on single experiment run in duplicate. [e]Aqueous thermodynamic solubility at pH 6.8. Values on single experiment run in

duplicate. [f]Human microsomal stability was assessed based on test compound (%) remaining after 0.5 h of incubation with human liver microsomes. [g]HCl salt. [h]Not tested. [i]Values represented as mean ± S.E.M. Values on 13 independent experiments run in octuplicate. [j]Not determined.

We then explored the introduction of nitrogen atom in the left-hand side benzene ring. Although several 3-pyridine and 4-pyridine derivatives were synthesized, only a few compounds exhibited moderate potency *in vitro* (data not shown). Thus, the derivatization was focused on 2-pyridine derivatives as shown in Table 2. Unsubstituted 2-pyridine derivative **16a** exhibited poor potency *in vitro* due to poor membrane permeability owing to its low lipophilicity ($P_{app} = 2.2 \times 10^{-6}$ cm/s; Log D, 0.4). Because lead compound **II** possessed good membrane permeability due to high lipophilicity ($P_{app} = 38.5 \times 10^{-6}$ cm/s; Log D, 2.7), lipophilic substituents were incorporated in 2-pyridine ring of **16a**. Chloro or methyl group substitution at 4- or 6- position of 2-pyridine ring was found to be optimal (Compounds **16b**–**16i**). As expected, the introduction of these substituents increased the lipophilicity that improved membrane permeability. Chloro-substituted compounds **16b**–**16e** exhibited higher membrane permeabilities than methyl derivatives **16f**–**16i** and 4-methyl derivative **16g** exhibited good potency (EC_{50} = 129 nM); therefore $P_{app} > 5.0 \times 10^{-6}$ was considered necessary. The introduction of 4-fluoro substituent did not affect *in vitro* potency unlike 4-chloro substitution (Compounds **16c** and **16j**), while 6-fluoro derivative **16k** indicated better potency than 4-fluoro analogue **16j**. Based on this SAR, one more substituent was incorporated. The introduction of methyl group at 3, 4, or 6 position in 2-pyridine ring led to the discovery of 4,6-dimethyl derivative DS-6930 (**I**). DS-6930 exhibited high potency *in vitro* with an intermediate PPARγ agonist activity (EC_{50} = 41 nM, E_{max} = 68%). DS-6930 also possessed acceptable solubility and high PPARα or PPARδ selectivity (13% PPARα activation at 10 μM and no PPARδ activation at 10 μM). Although 3,4-dimethyl derivative **16l** indicated high solubility, it exhibited poor *in vitro* potency. Because 4,6-substitution was optimal for *in vitro* potency, several 4,6-substituted compounds were synthesized. The replacement of methyl group with a fluoro group retained high potency *in vitro* (**16n** and **16o**). Although a further reduction in lipophilicity was achieved in compounds **16n** and **16o** (Log D = 1.1), both compounds were less soluble than DS-6930. To our surprise, compound **16o** exhibited a full agonist profile (E_{max} = 100%). Dichloro derivative **16p** showed fair solubility with high potency *in vitro*. The combination of fluoro and chloro groups provided promising results because compound **16q** indicated excellent potency *in vitro* with fair solubility. The *in vitro* potency was further enhanced by 4-chloro-6-methyl substitution (**16r**); however, it exhibited poor solubility. All 2-pyridyl compounds exhibited almost no PPARα activity at 10 μM. Therefore, we were successful not only in enhancing *in vitro* potency with the retention of intermediate agonist activity, but also in reducing the lipophilicity to discover 4,6-substituted-2-pyridine derivatives from lead compound **II**.

Table 2. PPAR Transcriptional Activities and *In Vitro* ADME Profiles of Compounds **16**



Compound	X	PPARγ EC_{50} (nM)[a]	PPARγ E_{max} (%)[a]	PPARα EC_{50} (nM)[b]	PPARα E_{max} (%)[b]	Log D[c]	PAMPA P_{app} (10^{-6} cm/s)[d]	Solubility (μg/mL)[e]	Human microsomal stability (%)[f]
II	3-F, 4-Cl	68 ± 28[h]	82 ± 4.0[h]	>10000[h]	32 ± 2.7[h]	2.7	38.5 ± 2.0[i]	0	100
16a	H	1132	74	>10000	1	0.4	2.2 ± 0.15[i]	62	100
16b	3-Cl	736	67	>10000	13	1.2	7.6	7.7	98
16c	4-Cl	71	66	>10000	3	1.2	16.2	17	100
16d	5-Cl	615	93	>10000	11	1.2	10.3	11	NT[g]
16e	6-Cl	200	93	>10000	6	1.1	8.1	15	99
16f	3-Me	1895	78	>10000	1	0.8	2.7	92	100
16g	4-Me	129	42	>10000	4	0.9	4.8 ± 0.75[i]	31	94
16h	5-Me	458	41	>10000	2	0.8	3.5	33	NT[g]
16i	6-Me	351	83	>10000	8	0.9	6.0 ± 1.2[i]	37	100
16j	4-F	808	87	>10000	5	0.6	4.7	79	NT[g]
16k	6-F	280	80	>10000	3	0.6	3.9	7.1	100
16l	3-Me, 4-Me	176	81	>10000	8	1.3	7.7 ± 0.65[i]	190	100
16m	3-Me, 6-Me	717	117	>10000	7	1.4	11 ± 1.8[i]	85	NT[g]
DS-6930 (**I**)	4-Me, 6-Me	41 ± 10[j]	68 ± 8.0[j]	>10000[j]	13 ± 2.0[j]	1.4	13 ± 3.4[i]	31	NT[g]
16n	4-Me, 6-F	43	74	>10000	4	1.1	5.8	9.2	100
16o	4-F, 6-Me	100	100	>10000	2	1.1	8.3	14	93

16p	4-Cl, 6-Cl	89	61	>10000	6	1.9	16.1	9.9	100
16q	4-Cl, 6-F	24	79	>10000	5	1.3	11.8	10	90
16r	4-Cl, 6-Me	21	92	>10000	7	1.8	13.7	3.9	85

[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%.[15] [c]Distribution coefficients (Log D) were measured after partition between 1-octanol and PBS (pH = 7.4). [d]PAMPA was performed at pH 7.4. Values on single experiment run in duplicate. [e]Aqueous thermodynamic solubility at pH 6.8. Values on single experiment run in duplicate. [f]Human microsomal stability was assessed based on test compound (%) remaining after 0.5 h of incubation with human liver microsomes. [g]Not tested. [h]Values represented as mean ± S.E.M. Values on 13 independent experiments run in octuplicate. [i]Values represented as mean ± S.E.M. Values on two independent experiments run in duplicate. [j]Values represented as mean ± S.E.M. Values on two independent experiments run in octuplicate.

2.3. In Vivo Efficacy in ZDF Rats

Several compounds were assessed for their abilities to reduce PG in ZDF rats at 3 mg/kg p.o. for 14 days as shown in Table 3 (n = 5). PK parameters were obtained by an additional administration of the test compounds on day 15 (Table 3). Imidazo[4,5-b]pyridines **6d**, **6i** and **6j** exhibited comparable PK profiles, despite **6i** showing diminished rat microsomal stability. Among them, **6i** and **6j** remarkably reduced PG levels in ZDF rats. In particular, compound **6i** exhibited more than 70% reduction in PG with statistical significance ($p < 0.01$), which was the maximum effect observed in this study. Imidazo[4,5-c]pyridine **6n** failed to show potent *in vivo* efficacy, despite exhibiting high *in vitro* potency as well as a PK profile comparable to those of imidazo[4,5-b]pyridines.[16,17] Similarly, 2-pyridine derivative **16c** exhibited high potency *in vitro*, but failed to show potent PG reduction due to its low plasma exposure. Because 2-pyridine derivatives DS-6930, **16p** and **16r** exhibited similar plasma concentrations with high potencies *in vitro*, these compounds demonstrated potent PG reduction in ZDF rats. Compounds **16n** and **16q** exhibited more potent *in vivo* efficacy due to their higher plasma exposures than DS-6930, **16p** and **16r**. In particular, compound **16q** reduced PG levels by 70.6% with statistical significance ($p < 0.01$). As mentioned previously,[8] this type of compounds increases the body weight of ZDF rats similar to the full agonist rosiglitazone. Body weight gain relates to *in vivo* efficacy. Accordingly, compounds DS-6930 and **16r** that exhibited potent activities *in vivo* induced body weight gain to a greater extent than the less potent compound, **6d**.

Table 3. Plasma Glucose (PG) Reduction (%) in Zucker Diabetic Fatty (ZDF) Rats After the Oral administration of the Test Compounds (3 mg/kg) 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]		
		PG reduction (%)	Body weight gain (%)	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0\text{-}24\,h}$ (h·μg/mL)
rosiglitazone	NT[d]	40.3 ± 16.2	12.6 ± 3.3*	ND[e]	ND[e]	ND[e]
6d	100	37.6 ± 17.5	6.8 ± 1.9*	0.51 ± 0.11	2.00 ±0.00	2.52 ± 0.82
6i	71	70.4 ± 1.0**	14.0 ± 1.5**	0.60 ± 0.17	2.00 ± 0.00	4.08 ± 0.86
6j	89	55.3 ± 12.1**	7.1 ± 5.7	0.63 ± 0.12	2.00 ± 0.00	3.39 ±0.78
6n	81	1.3 ± 7.3	6.3 ± 2.3	0.41 ±0.11	2.00 ± 0.00	2.41 ± 0.72
16c	100	14.8 ± 3.7*	0.20 ± 1.8	0.066 ± 0.01	4.40 ± 2.19	1.01 ± 0.08
DS-6930 (**I**)	92	57.0 ± 10.1*	17.4 ± 2.1**	0.18 ± 0.02	3.20 ± 2.68	2.49 ± 0.21
16n[f]	NT[d]	65.7 ± 9.9**	10.8 ± 2.1**	0.42 ± 0.12	2.00 ± 0.00	3.61 ± 0.64
16p	NT[d]	53.3 ± 13.4**	10.1 ± 2.8*	0.13 ± 0.04	2.40 ± 0.89	1.40 ± 0.31
16q	87	70.6 ± 2.0**	13.8 ± 1.9**	0.45 ± 0.11	2.00 ±0.00	3.91 ± 0.70
16r	81	54.1 ± 9.9**	18.5 ± 1.5**	0.12 ± 0.01	2.40 ± 0.89	1.25 ± 0.20

[a]Rat microsomal stability was 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 15. 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 14. Each value represents the mean ± S.D. [d]Not tested. [e]Not determined. [f]Sodium salt of the compound was administered.

2.4. In Vivo Pharmacological Effects of DS-6930

In vivo pharmacological effects of DS-6930 are summarized in Figure 2. DS-6930 or rosiglitazone was orally administered to male ZDF rats once daily at 0.1, 0.3, 1, or 3 mg/kg. After repeated administration for three weeks, PG levels were assessed (n = 8). DS-6930 was administered as a calcium salt. As shown in Figure 2, both compounds decreased PG levels in a dose-dependent

manner, and statistically significant ($p < 0.05$) PG reduction was observed at 1 and 3 mg/kg. In both compounds, maximum PG reduction was achieved at 1 mg/kg and higher (PG levels were around 120 mg/dL). Therefore, DS-6930 was considered to have a glucose-lowering effect comparable to rosiglitazone in this model. PK parameters were evaluated after an additional administration of these compounds after three weeks. PK parameters after administering 0.3 mg/kg of these compounds are shown in Table 5. Although the PG-lowering effects of DS-6930 and rosiglitazone were similar at 0.3 mg/kg (47 and 50% PG reduction vs vehicle control, respectively), the AUC of DS-6930 was 7.6-fold lower than that of rosiglitazone. Therefore, although DS-6930 exhibited pharmacological effects comparable to rosiglitazone at the same dose, it was significantly more potent than rosiglitazone based on the plasma levels of the two compounds. Along with its superior *in vivo* efficacy, it displayed remarkable safety. The higher *in vitro* PPARγ potency of DS-6930 supports these superior pharmacological effects.

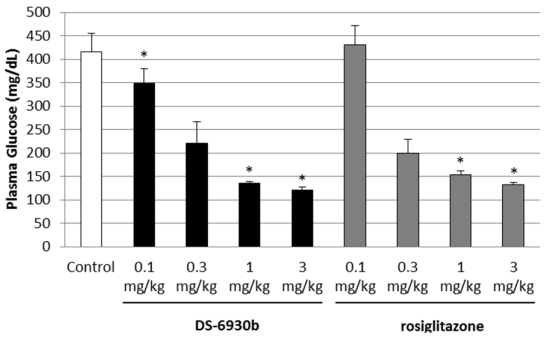


Figure 2. Pharmacological effects of DS-6930. PG levels in ZDF rats after the repeated administration of DS-6930b or rosiglitazone (0.1, 0.3, 1 and 3 mg/kg) for three weeks. DS-6930 was administered as a calcium salt. Data are represented as mean ± S.E.M. ($n = 8$). Statistical significance compared to vehicle treatment is denoted by $*p < 0.05$, $**p < 0.01$ as determined by the Student T-test.

2.5. Monkey PK Profile

The monkey PK profiles of **6j**, DS-6930, **16n** and **19q** are summarized in Table 4. The compounds were orally administered to male cynomolgus monkeys at 3 mg/kg ($n = 2$). The compounds were also administered to the same monkeys intravenously at 1 mg/kg to calculate total body clearance (*CL*), distribution volume at steady state (V_{ss}) and *F* value (%). As described previously, compound **II** exhibited exceptionally excellent PK parameters with robust monkey microsomal stability.[8] Imidazo[4,5-b]pyridine **6j** and 2-pyridine derivatives DS-6930, **16n** and **16q** showed higher *CL* and V_{ss} than compound **II** due to the relatively high basicity. Imidazo[4,5-b]pyridine **6j** showed the highest V_{ss}, whereas 2-pyridine **16n** indicated the highest *CL* in this series of compounds; nevertheless, these PK parameters were acceptable for clinical candidate selection. 2-Pyridine derivative **16n** exhibited the longest $T_{1/2}$, which is not suitable for conventional once-daily administration because of the concern of accumulation. Despite its long $T_{1/2}$, it exhibited the highest clearance in this series. Other compounds, **6j**, DS-6930 and **16q** indicated $T_{1/2}$ values suitable for once-daily dosing. Among these derivatives, DS-6930 showed the highest plasma exposure as well as an excellent bioavailability of 89%, indicating that it is the most preferred compound in this series.

Table 4. PK Parameters of the test Compounds in Cynomolgus Monkeys[a]

Compound	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)
II[e]	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
6j[d]	88	0.46 ± 0.064	1.50 ± 0.71	13.3 ± 3.3	4.91 ± 2.4	27 ± 13	2.73 ± 0.13	1.97 ± 0.23
DS-6930 (**I**)[d]	80	2.25 ± 0.72	5.00 ± 4.2	13.5 ± 0.42	23.5 ± 5.9	89 ± 15	2.06 ± 0.21	0.36 ± 0.0071
16n[d]	NT[c]	0.10 ± 0.014	4.00 ± 0.00	49.8 ± 42	1.47 ± 0.40	8.9 ± 2.4	3.07 ± 0.45	0.88 ± 0.0071
16q[d]	91	1.19 ± 0.078	3.25 ± 3.9	8.84 ± 3.3	9.94 ± 5.9	31 ± 18	1.66 ± 0.64	0.50 ± 0.31

[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 (*Vss*) and *F* value were calculated based on the data after intravenous (1 mg/kg) administration of the test compounds. Each value represents the mean ($n = 2$) or the mean ± S.D. ($n = 3$). [b]Monkey microsomal stability was assessed based on test compound (%) remaining after 0.5 h of incubation with monkey liver microsomes. [c]Not tested. [d]$n = 2$. [e]$n = 3$.

2.6. In Vitro Hepatocytotoxicity Assessment

Selected compounds were evaluated for hepatocytotoxicity *in vitro*. Hepatocytes derived from F344 rats were treated with the compounds (10, 30 and 100 μM), and mitochondrial enzyme activity was evaluated by a WST-8 assay as shown in Figure 3a. Cell viability was also evaluated at the same concentrations based on the release of LDH (Figure 3b). Lead compound **II** reduced mitochondrial enzyme activity in a concentration-dependent manner, and exhibited a 19% reduction in mitochondrial enzyme activity at 100 μM, while **II** did not affect cell viability. This series of compounds altered mitochondrial enzyme activity at high concentrations, but did not attenuate cell viability based on the LDH release assay. Owing to their reduced lipophilicities, compounds **6j**, DS-6930, **16n** and **16q** induced lower hepatotoxicity than compound **II**. Interestingly, **16n** affected mitochondrial enzyme activity more than other optimized compounds **6j**, DS-6930 and **16q**, despite being lower lipophilic (Log D: 1.1). Compound **16n** also affected cell viability at the highest concentration (Figure 3b). Although compounds **6j**, DS-6930 and **16q** reduced mitochondrial enzyme activities, no clear concentration-dependency was established. In particular, DS-6930 exhibited the lowest cell toxicity at 100 μM in both assays. The derivatization of **II** yielded compounds with reduced lipophilicity and hepatocytotoxicity. Despite the reduction of lipophilicity, the lowest lipophilic compound **16n** (Log D = 1.1) induced hepatocytotoxicity to a greater extent than relatively high lipophilic derivatives, such as **6j**, DS-6930 and **16q**, with relatively high lipophilicities (Log D = 1.3–1.4).

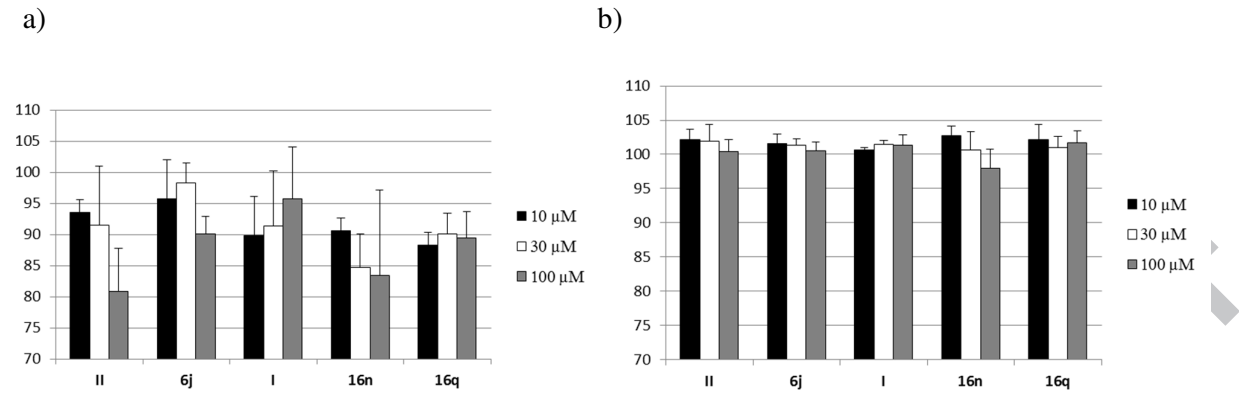
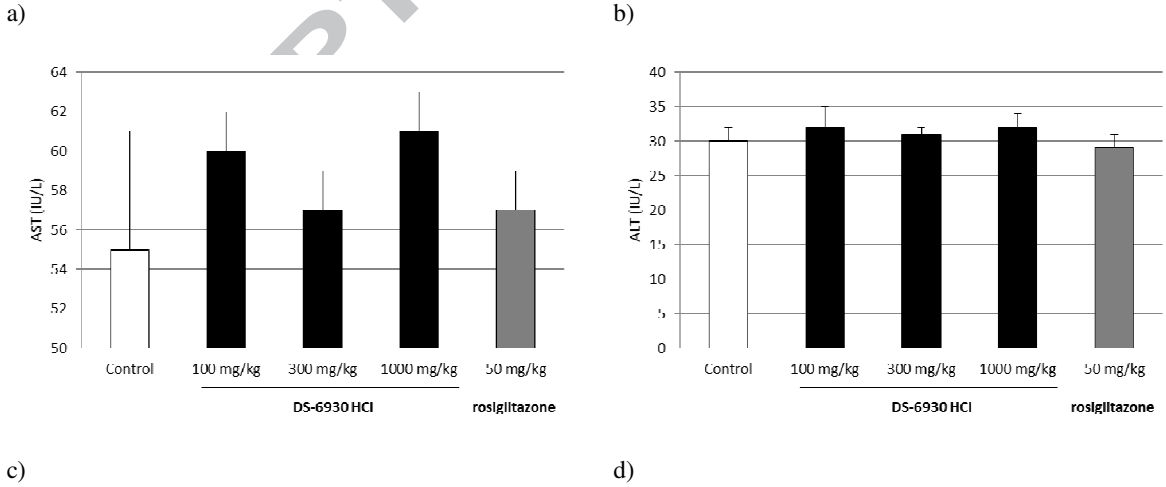


Figure 3. *In vitro* hepatocytotoxicity assessment. (a) Mitochondrial enzyme activity (WST-8 assay) after treatment with the test compounds at 10, 30 and 100 μM (n = 4). Values on single experiment run in quadruplicate. Each value represents the mean ± S.D. (b) Cell viability (LDH release) after treatment with the test compounds at 10, 30 and 100 μM (n = 4). Each value represents the mean ± S.D.

2.7. In Vivo Toxicological Profile of DS-6930

The *in vivo* toxicological profile of HCl salt of DS-6930 was assessed as shown in Figure 4.[18] Adverse effects were assessed after the oral administration of DS-6930 (100, 300 and 1000 mg/kg) to female F344 rats for four weeks (n = 5). Rosiglitazone (50 mg/kg) was evaluated as a control. TK parameters were obtained on day 28 from a satellite group of female rats as shown in Table 5 (n = 2). In this assessment, both compounds displayed dose-dependent increases in plasma exposure. Based on pharmacological studies, the therapeutically effective dosage of both compounds was found to be around 0.3 mg/kg. Based on AUC, the exposure margins of DS-6930 at 100, 300 and 1000 mg/kg were estimated as 460-, 1100-, 1300-fold higher, respectively, whereas those of rosiglitazone at 50 mg/kg was 80-fold higher. No death or clinical abnormality was observed during the administration period in any test group. As expected in the hepatocytotoxicity assessment *in vitro*, DS-6930 did not affect any liver enzyme activities *in vivo* (Figure 4a, 4b).

The administration of rosiglitazone (50 mg/kg) caused significant (p < 0.01) body weight gain (10% vs vehicle control), whereas the administration of DS-6930 increased body weight by 6.9% without statistical significance compared to vehicle control, even at 1000 mg/kg (Figure 4c). Therefore, it can be concluded that although DS-6930 causes body weight gain, it is much lower than that caused by rosiglitazone. DS-6390 induced hemodilution similar to compound **II**.[8] As shown in Figure 4d, DS-6930 was found to decrease red blood cell (RBC) count (3.8, 6.6 and 5.6% reduction at 100, 300 and 1000 mg/kg, respectively), while rosiglitazone caused remarkable reduction (13%) in RBC count, even at 50 mg/kg (p < 0.01). Similar results were observed upon hematocrit analysis (Figure 4e). Heart weight gain is thought to be associated with hemodilution,[19-21] and the administration of 50 mg/kg of rosiglitazone significantly increased heart weight (% of body weight) by 18% (p < 0.01). On the other hand, the administration of DS-6930 caused no remarkable change in relative heart weight, even at 1000 mg/kg (Figure 4f). At 50 mg/kg, rosiglitazone also affected relative weights of kidney and ovary, whereas the administration of DS-6930 caused no remarkable change at any dose (data not shown). These results clearly indicate that DS-6930 possesses an excellent safety profile.



c) d)

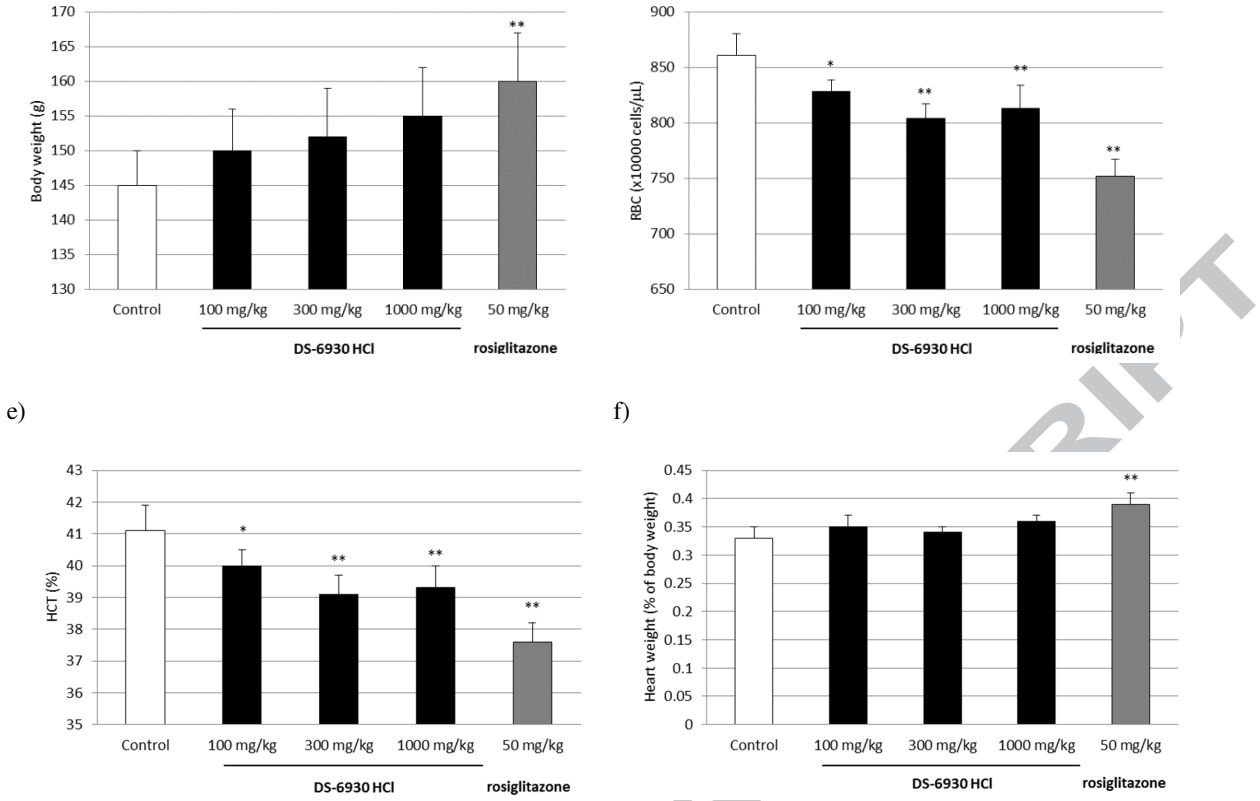


Figure 4. *In vivo* toxicological profile of DS-6930. (a) aspartate aminotransferase (AST) level, (b) alanine aminotransferase (ALT) level, (c) Body weight, (d) RBC count, (e) hematocrit analysis and (f) heart weight (% of body weight) in F344/DuCrlCrlj rats after the repeated administration of DS-6930 (100, 300 and 1000 mg/kg) or rosiglitazone (50 mg/kg) for four weeks. DS-6930 was administered as an HCl salt. Data are represented as mean ± S.D. (n = 5). Statistical significance compared to vehicle treatment is denoted by *$p < 0.05$ and **$p < 0.01$ as determined by the Student T-test.

Table 5. PK and TK Parameters of DS-6930 and Rosiglitazone in Rats[a]

Compd	DS-6930 Ca salt	DS-6930 HCl			rosiglitazone	
Dose (mg/kg/day)	0.3[a]	100[b]	300[b]	1000[b]	0.3[a]	50[b]
C_{max} (μg/mL)	0.0792 ± 0.0121	92.8 ± 17.3	206 ± 6.4	273 ± 44.5	1.04 ± 0.20	67.6 ± 5.4
T_{max} (h)	1.8 ± 0.5	0.50 ± 0.0	0.50 ± 0.0	1.0 ± 0.0	1.6 ± 0.7	1.0 ± 0.0
$AUC_{0\text{-}24h}$ (h·μg/mL)	0.861 ± 0.092	399 ± 38.9	933 ± 15.6	1080 ± 259	6.55 ± 1.25	525 ± 114

[a]PK parameters were obtained after the administration of the test compounds to ZDF rats on day 22 (n = 8). Each value represents the mean ± S.D. [b]TK parameters were obtained after the administration of the test compounds to F344 rats on day 28 (n = 2). Each value represents the mean ± S.D.

2.8. X-ray Crystal Structure of DS-6930 Bound to PPARγ-LBD

The binding mode of DS-6930 to PPARγ-LBD was determined at 1.8 Å resolution. As shown in Figure 5, it displayed the same binding mode as compound **II**.[8] DS-6930 forms hydrophobic and hydrophilic interactions with PPARγ-LBD, including two direct hydrogen bonds, two water-mediated hydrogen bonds and van der Waals contacts (Figure 5a). The benzoic acid group of DS-6930 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 DS-6930 forms a water-mediated hydrogen bond with the main-chain nitrogen of Ser342. Additional lipophilic interactions of dimethylpyridyl group in DS-6930 were also observed.

As shown in Figure 5b, DS-6930 do not directly interact with helix12. This indicates that the additional lipophilic interactions of dimethylpyridyl group with a β-sheet, helix 2' and helix 3, combined with no direct interaction with helix 12 may relate to the intermediate agonist activity of DS-6930.[8]

a) b)

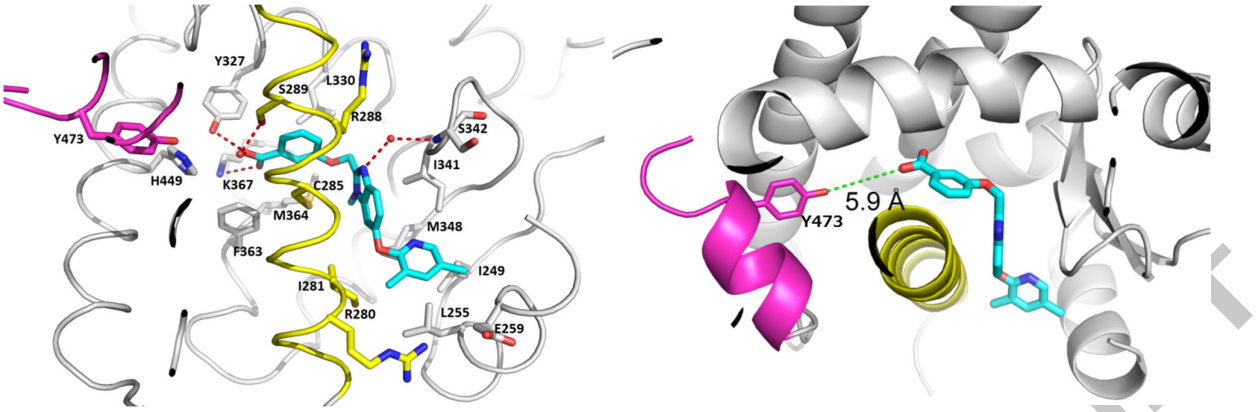


Figure 5. X-ray crystal structure of DS-6930 bound to PPARγ-LBD (PDB 5Z6S). (a) Details of the binding model of DS-6930 to PPARγ-LBD. Residues of PPARγ-LBD involved in the binding of DS-6930, residue 473 on helix 12 and DS-6930 are shown as stick models. Hydrogen bonds are marked as red dotted lines. (b) The binding mode of DS-6930 to PPARγ-LBD. DS-6930 lacks the direct interaction with Tyr473.

2.9. Cofactor Recruitment by DS-6930

Gene expression studies on DS-6930 were performed with 11 selected cofactors. Yeast 2-hybrid dose-response experiments were carried out with these 11 cofactors and AUC values for sigmoid curves ($AUC_{sigmoid}$; not shown) were calculated for analyzing the cofactor profiles (Figure 6a). DS-6930 induces the selective recruitment of cofactors similar to rosiglitazone. In particular, DS-6930 promotes the recruitment of RIP140e184b, which is an amino-terminal RIP140 domain. $AUC_{sigmoid}$ values for DS-6930 are normalized against the respective values for rosiglitazone (Figure 6b). DS-6930 did not induce the recruitment of TRAP220, CBP, SRC1 and NCoA3, unlike rosiglitazone. In contrast, it preferentially promotes the recruitment of RIP140e184b, PGC1, SHP and RAP250 constructs.

a) b)

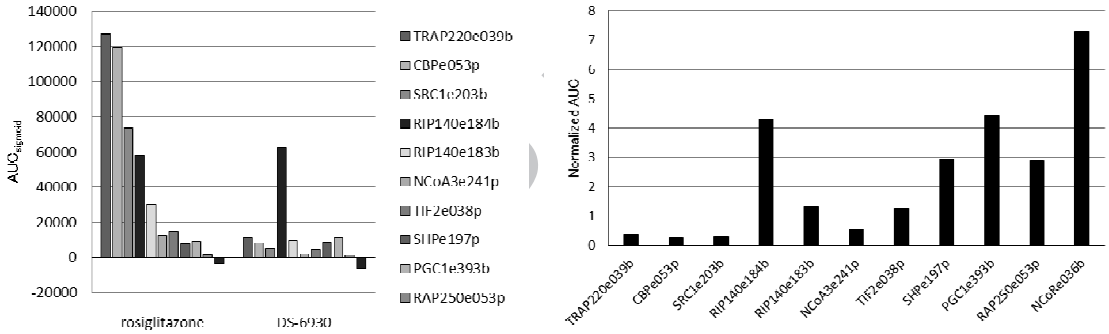


Figure 6. PPARγ cofactor profiles on the basis of AUC values. Values on single experiment run in quadruplicate (a) AUC values for sigmoid curves ($AUC_{sigmoid}$) of selected cofactors. (b) $AUC_{sigmoid}$ values normalized against the respective values for rosiglitazone ($AUC_{rosiglitazone} = 1$).

3. CONCLUSIONS

We attempted to attenuate the hepatotoxicity of compound **II** to develop a clinical candidate. Because reducing the lipophilicity was hypothesized to be the best way in order to avoid such adverse effects, the introduction of a nitrogen atom was carried out. Initially, we synthesized imidazo[4,5-b]pyridines that exerted high *in vitro* potency as well as robust *in vivo* efficacy, while imidazo[4,5-c]pyridine derivatives showed poor PG reduction, despite exhibiting high *in vitro* potencies and plasma exposures. Although unsubstituted 2-pyridine derivative showed poor potency *in vitro* due to poor membrane permeability, substituted 2-pyridines exhibited potent *in vitro* potencies as well as *in vivo* efficacies. These modifications also improved the solubility of compounds, another limitation of compound **II**. Consequently, we synthesized compounds that exerted enhanced *in vitro* potencies with the retention of intermediate agonist affinities as well as reduced lipophilicity. *In vivo* pharmacological screening, monkey PK evaluation combined with *in vitro* hepatocytotoxicity assessment led to the discovery of a potent selective PPARγ modulator, DS-6930. In preclinical studies, DS-6930 demonstrated promising pharmacological efficacy with an excellent DMPK profile as well as diminished PPARγ-related adverse effects without any signs of hepatotoxicity. Its distinct binding mode facilitates the selective recruitment of PPARγ cofactors. The calcium salt, DS-6930b was selected as a clinical candidate, which is expected to significantly induce insulin sensitization without edema in T2DM patients.

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 **2** (General Procedure A).*

NaH (12.0 mmol) was added to a solution of **1** or **7**[22] (1.88 g, 10.0 mmol) and substituted phenol (12.0 mmol) in DMF (50 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 **2**, or crude **2** was used directly for the next reaction without further purification.

*4.3. General Procedure for Reduction of Nitro Group with Iron to Prepare **3** (General Procedure B).*

A solution of **2** (18.1 mmol), iron powder (4.84 g, 90.5 mmol) and NH_4Cl (0.48 g, 9.05 mmol) in water (50 mL) and EtOH (100 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 **3**, which was used directly for the next reaction without further purification.

*4.4. General Procedure for Reduction of Nitro Group by Catalytic Hydrogenation to Prepare **3** (General Procedure C).*

A solution of **2** (38.8 mmol) and Pd/C (10%, 0.53 g) in EtOH (100 mL) was stirred under H_2 for 6 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude **3**, which was used directly for the next reaction without further purification.

*4.5. General Procedure for Amidation to Prepare **8** (General Procedure D).*

A solution of **3** (4.49 mmol), [3-(methoxycarbonyl)phenoxy]acetic acid[8] (0.94 g, 4.49 mmol), WSC•HCl (0.86 g, 4.49 mmol) and HOBt•H_2O (0.61 g, 4.49 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 **8**.

*4.6. General Procedure for Benzimidazole Ring Annulation to Prepare **5** (General Procedure E).*

A solution of **8** (3.55 mmol) in AcOH (20 mL) was stirred at 80 °C for 4 h. Water was added to the cooled mixture, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with saturated $NaHCO_3$ solution several times and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel chromatography to obtain **5**.

*4.7. General Procedure for Hydrolysis to Prepare **6** or **16** (General Procedure F).*

A solution of **5**, **14**, or **15** (5.80 mmol) and 2 M NaOH (10 mL, 10 mmol) in 1,4-dioxane (20 mL) was stirred at 80 °C for 2 h. The cooled reaction mixture was neutralized by adding 1 M HCl, and the precipitated solid was collected by filtration to obtain **6** or **16**.

*4.8. General Procedure for Copper-catalyzed Coupling Reaction to Prepare **14** (General Procedure G).*

A solution of **13** (3.12 g, 10.0 mmol), 2-fluoro or 2-bromo substituted pyridine (11.0 mmol), CuI (0.19 g, 1.00 mmol), 1,10-phenanthroline (0.18 g, 1.00 mmol) and Cs_2CO_3 (9.77 g, 30 mmol) in DMF (50 mL) was stirred under N_2 at 80 °C for 2 h. Aqueous NH_4Cl solution (10%) was added to the cooled reaction mixture, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with water and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel chromatography to obtain **14**.

*4.9. General Procedure for Alternative Copper-catalyzed Coupling Reaction to Prepare **14** (General Procedure H).*

A solution of **13** (625 mg, 2.00 mmol), 2-bromo substituted pyridine (2.40 mmol), copper (25.4 mg, 0.400 mmol) and Cs_2CO_3 (1.95 g, 6.00 mmol) in DMF (2.0 mL) was stirred at 100 °C under microwave irradiation for 20 min. Water was added to the cooled reaction mixture, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with water twice and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel chromatography to obtain **14**.

*4.10. General Procedure for Pd-Catalyzed Methylation to Prepare **15** (General Procedure I).*

A solution of **13** (625 mg, 2.00 mmol), 2-bromo substituted pyr
A solution of **14** (1.41 mmol), trimethylboroxine (50% solution in THF, 0.39 mL, 1.41 mmol), $PdCl_2$(dppf)•CH_2Cl_2 complex (120 mg, 0.140 mmol) and K_2CO_3 (390 mg, 2.82 mmol) in DMF (5.0 mL) was stirred under N_2 at 80 °C for 24 h. Water was added to the cooled reaction mixture, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with water twice and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel chromatography to obtain **15**.

*4.10.1. 6-(4-Chloro-3-fluorophenoxy)-N-methyl-3-nitropyridin-2-amine (**2a**).*

Compound **2a** was prepared according to general procedure A (yield, 89%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.90 (3H, d, J = 4.9 Hz), 6.24 (1H, d, J = 8.8 Hz), 6.97 (1H, ddd, J = 1.5, 2.4, 8.8 Hz), 7.08 (1H, dd, J = 2.4, 9.8 Hz), 7.43 (1H, t, J = 8.8 Hz), 8.45 (1H, d, J = 9.3 Hz), 8.46 (1H, br).

*4.10.2. 6-(3-Fluoro-4-methylphenoxy)-N-methyl-3-nitropyridin-2-amine (**2e**).*

Compound **2e** was prepared according to general procedure A (yield, 70%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.25 (3H, s), 2.76 (3H, d, J = 4.7 Hz), 6.30 (1H, d, J = 9.0 Hz), 7.02 (1H, dd, J = 2.4, 8.6 Hz), 7.18 (1H, dd, J = 2.0, 10.6 Hz), 7.35 (1H, t, J = 8.6 Hz), 8.44 (1H, d, J = 9.0 Hz), 8.75 (1H, br).

*4.10.3. 6-(2,4-Dimethylphenoxy)-N-methyl-3-nitropyridin-2-amine (**2f**).*

Compound **2f** was prepared according to general procedure A (yield, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s), 2.35 (3H, s), 2.90 (3H, d, J = 5.1 Hz), 6.11 (1H, d, J = 9.0 Hz), 6.95 (1H, d, J = 8.2 Hz), 7.08 (1H, d, J = 8.2 Hz), 7.07 (1H, d, J = 0.8 Hz), 7.39 (1H, d, J = 9.8 Hz), 8.45 (1H, br).

*4.10.4. 6-(3,4-Dimethylphenoxy)-N-methyl-3-nitropyridin-2-amine (**2h**).*

Compound **2h** was prepared according to general procedure A (yield, 33%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.28 (6H, s), 2.96 (3H, d, J = 4.9 Hz), 6.11 (1H, d, J = 8.8 Hz), 6.91 (1H, dd, J = 2.4, 7.8 Hz), 6.96 (1H, d, J = 2.9 Hz), 7.15 (1H, d, J = 8.3 Hz), 7.38 (1H, d, J = 8.8 Hz), 8.46 (1H, br).

*4.10.5. 6-(2,3-Dihydro-1H-inden-5-yloxy)-N-methyl-3-nitropyridin-2-amine (**2i**).*

Compound **2i** was prepared according to general procedure A (yield, 85%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.13 (2H, quint., J = 7.3 Hz), 2.93 (4H, t, J = 7.3 Hz), 2.97 (3H, d, J = 5.4 Hz), 6.11 (1H, d, J = 8.3 Hz), 6.93 (1H, dd, J = 1.5, 8.3 Hz), 7.02 (1H, s), 7.23 (1H, d, J = 7.8 Hz), 7.38 (1H, dd, J = 1.0, 9.3 Hz), 8.46 (1H, br).

*4.10.6. N-Methyl-2-(4-methylphenoxy)-5-nitropyridin-4-amine (**2l**).*

Compound **2l** was prepared according to general procedure A (yield, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, s), 2.99 (3H, d, J = 5.1 Hz), 6.10 (1H, s), 7.02 (2H, d, J = 8.2 Hz), 7.22 (2H, d, J = 8.6 Hz), 8.07 (1H, br), 8.96 (1H, s).

*4.10.7. (3-Methyl-5-phenoxy-3H-imidazo[4,5-b]pyridin-2-yl)methanol (**4b**).*

1 (20.0 g, 107 mmol) was added to a solution of NaH (60%, 5.12 g, 128 mmol) and phenol (12.1 g, 128 mmol) in THF (200 mL) at room temperature under N_2, and the mixture was stirred at 80 °C for 4 h. Water was added to the cooled reaction mixture, and the mixture was extracted with EtOAc. The organic layer was sequentially washed with 1 M KOH solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude **2b**. A solution of crude **2b** and $Pd(OH)_2$ (500 mg) in THF (50 mL) and EtOH (50 mL) was stirred under H_2 overnight. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure to obtain crude **3b**. A solution of crude **3b**, glycolic acid (24.4 g, 321 mmol) in 4 M HCl in 1,4-dioxane (150 mL) was stirred under reflux for 10 h. Saturated Na_2CO_3 solution was added to the cooled reaction mixture, and the mixture was extracted with EtOAc. The organic layer was sequentially washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The generated solid was washed with i-Pr_2O to obtain **4b** (21.8 g, 80%; 3 steps). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.67 (3H, s), 4.69 (2H, d, J = 5.0 Hz), 5.61 (1H, t, J = 5.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 7.12–7.23 (3H, m), 7.39–7.45 (2H, m), 8.06 (1H, d, J = 8.0 Hz).

*4.10.8. Methyl 3-{[5-(4-chloro-3-fluorophenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5a**).*

Compound **5a** was prepared according to general procedure E (yield, 76%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.82 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.89 (1H, d, J = 8.3 Hz), 6.93 (1H, ddd, J = 1.5, 2.4, 8.8 Hz), 7.04 (1H, dd, J = 2.9, 10.3 Hz), 7.26–7.28 (1H, m), 7.39 (2H, dt, J = 4.9, 8.3 Hz), 7.69–7.72 (2H, m), 8.06 (1H, d, J = 8.8 Hz).

*4.10.9. Methyl 3-[(3-methyl-5-phenoxy-3H-imidazo[4,5-b]pyridin-2-yl)methoxy]benzoate 2HCl (**5b**).*[23]

A solution of **4b** (380 mg, 1.50 mmol), n-Bu_3P (610 mg, 3.00 mmol), ADDP (760 mg, 3.00 mmol) and methyl 3-hydroxybenzoate (340 mg, 2.30 mmol) in toluene (30 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 (hexane/EtOAc, 1:2) to obtain the free form of **5b**. HCl in 1,4-dioxane (4.0 M, 10 mL) was added to the free form of **5b**, and the precipitated solid was collected by filtration to obtain **5b** (0.40 g, 58%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.72 (3H, s), 3.86 (3H, s), 5.54 (2H, s), 6.96 (1H, d, J = 8.6 Hz), 7.18 (1H, d, J = 7.5 Hz), 7.22 (1H, t, J = 7.3 Hz), 7.43 (2H, m), 7.45 (1H, dd, J = 7.6, 8.2 Hz), 7.61 (1H, dd, J = 1.5, 7.6 Hz), 7.66 (1H, dd, J = 1.5, 2.3 Hz), 8.18 (1H, d, J = 8.6 Hz); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_4$, 390.1454; found 390.1469.

*4.10.10. Methyl 3-{[5-(4-fluorophenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5c**).*

Compound **5c** was prepared according to general procedure E (yield, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.81 (1H, d, J = 8.6 Hz), 7.06–7.16 (4H, m), 7.25–7.28 (1H, m), 7.37 (1H, t, J = 8.2 Hz), 7.69 (1H, dt, J = 1.2, 7.8 Hz), 7.71 (1H, dd, J = 1.2, 2.7 Hz), 8.02 (1H, d, J = 8.6 Hz).

*4.10.11. Methyl 3-{[3-methyl-5-(4-methylphenoxy)-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5d**).*

Compound **5d** was prepared according to general procedure E (yield, 40%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.83 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.77 (1H, d, J = 8.6 Hz), 7.06 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.6 Hz), 7.25–7.28 (1H, m), 7.37 (1H, t, J = 7.4 Hz), 7.68–7.72 (2H, m), 8.00 (1H, d, J = 8.6 Hz).

*4.10.12. Methyl 3-{[5-(3-fluoro-4-methylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5e**).*

Compound **5e** was prepared according to general procedure E (yield, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, d, J = 1.6 Hz), 3.84 (3H, s), 3.93 (3H, s), 5.38 (2H, s), 6.83 (1H, d, J = 8.6 Hz), 6.86–6.91 (2H, m), 7.18 (1H, t, J = 8.6 Hz), 7.26–7.29 (1H, m), 7.38 (1H, t, J = 7.8 Hz), 7.69–7.72 (2H, m), 8.03 (1H, d, J = 8.6 Hz).

*4.10.13. Methyl 3-{[5-(2,4-dimethylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5f**).*

Compound **5f** was prepared according to general procedure E (yield, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.35 (3H, s), 3.83 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.84 (1H, d, J = 8.6 Hz), 6.96 (1H, d, J = 8.2 Hz), 7.03 (1H, dd, J = 1.6, 8.2 Hz), 7.09 (1H, s), 7.27 (1H, ddd, J = 0.8, 2.7, 8.2 Hz), 7.38 (1H, t, J = 7.8 Hz), 7.69 (1H, dt, J = 1.2, 7.8 Hz), 7.71 (1H, dd, J = 1.6, 2.7 Hz), 7.96 (1H, d, J = 8.6 Hz).

*4.10.14. Methyl 3-{[5-(3,5-dimethylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5g**).*

Compound **5g** was prepared according to general procedure E (yield, 86%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.32 (6H, s), 3.86 (3H, s), 3.93 (3H, s), 5.38 (2H, s), 6.71–6.81 (3H, m), 6.84 (1H, s), 7.29 (1H, dd, J = 1.0, 2.5 Hz), 7.38 (1H, t, J = 7.8 Hz), 7.67–7.71

(1H, m), 7.72 (1H, dd, *J* = 1.4, 2.5 Hz), 7.99 (1H, d, *J* = 8.6 Hz); MS (FAB) *m/z*: 418 $[M + H]^+$.

*4.10.15. Methyl 3-{[5-(3,4-dimethylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5h**).*

Compound **5h** was prepared according to general procedure E (yield, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 2.27 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.75 (1H, d, *J* = 8.6 Hz), 6.90 (1H, dd, *J* = 2.3, 7.8 Hz), 6.95 (1H, d, *J* = 2.3 Hz), 7.14 (1H, d, *J* = 8.6 Hz), 7.25–7.29 (2H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.67–7.73 (2H, m).

*4.10.16. Methyl 3-{[5-(2,3-dihydro-1H-inden-5-yloxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5i**).*

Compound **5i** was prepared according to general procedure E (yield, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.12 (2H, quint., *J* = 7.4 Hz), 2.92 (4H, t, *J* = 7.4 Hz), 3.85 (3H, s), 3.92 (3H, s), 5.38 (2H, s), 6.75 (1H, d, *J* = 8.6 Hz), 6.93 (1H, dd, *J* = 2.4, 8.2 Hz), 7.02 (1H, d, *J* = 2.4 Hz), 7.22 (1H, d, *J* = 7.8 Hz), 7.28 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.69 (1H, dt, *J* = 0.8, 7.8 Hz), 7.72 (1H, dd, *J* = 1.6, 2.7 Hz), 7.98 (1H, d, *J* = 8.6 Hz).

*4.10.17. Methyl 3-{[5-(2,3-dihydro-1-benzofuran-6-yloxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoate (**5j**).*

Compound **5j** was prepared according to general procedure E (yield, 88%, 4 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.22 (2H, t, *J* = 8.6 Hz), 3.85 (3H, s), 3.92 (3H, s), 4.64 (2H, t, *J* = 9.0 Hz), 5.38 (2H, s), 6.62–6.65 (2H, m), 6.78 (1H, d, *J* = 8.6 Hz), 7.17 (1H, d, *J* = 7.0 Hz), 7.25–7.28 (1H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.68–7.72 (2H, m), 7.99 (1H, d, *J* = 8.6 Hz); MS (FAB) *m/z*: 432 $[M + H]^+$.

*4.10.18. Methyl 3-{[6-(4-chloro-3-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoate (**5k**).*

Compound **5k** was prepared according to general procedure E (yield, 39%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.87 (1H, ddd, *J* = 1.6, 3.2, 9.0 Hz), 6.91 (1H, d, *J* = 0.8 Hz), 6.95 (1H, dd, *J* = 2.7, 10.2 Hz), 7.26–7.28 (1H, m), 7.39 (2H, q, *J* = 8.6 Hz), 7.70–7.72 (2H, m), 8.71 (1H, s).

*4.10.19. Methyl 3-{[1-methyl-6-(4-methylphenoxy)-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoate (**5l**).*

Compound **5l** was prepared according to general procedure E (yield, 57%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 3.82 (3H, s), 3.92 (3H, s), 5.39 (2H, s), 6.78 (1H, s), 7.02 (2H, d, *J* = 8.2 Hz), 7.19 (2H, d, *J* = 8.6 Hz), 7.29 (1H, dd, *J* = 1.2, 2.4 Hz), 7.39 (1H, t, *J* = 8.2 Hz), 7.69–7.74 (2H, m), 8.70 (1H, s).

*4.10.20. Methyl 3-{[6-(2,3-dihydro-1-benzofuran-6-yloxy)-1-methyl-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoate (**5m**).*

Compound **5m** was prepared according to general procedure E (yield, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.20 (2H, t, *J* = 9.0 Hz), 3.84 (3H, s), 3.93 (3H, s), 4.62 (2H, t, *J* = 8.6 Hz), 5.39 (2H, s), 6.57 (1H, d, *J* = 2.4 Hz), 6.61 (1H, dd, *J* = 2.4, 8.2 Hz), 6.81 (1H, s), 7.17 (1H, d, *J* = 7.8 Hz), 7.29 (1H, t, *J* = 2.0 Hz), 7.39 (1H, t, *J* = 8.2 Hz), 7.69–7.72 (2H, m), 8.71 (1H, d, *J* = 0.8 Hz).

*4.10.21. Methyl 3-{[6-(2,3-dihydro-1H-inden-5-yloxy)-1-methyl-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoate (**5n**).*

Compound was prepared according to general procedure E (yield, 69%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.12 (2H, quint., *J* = 7.0 Hz), 2.89-2.93 (4H, m), 3.83 (3H, s), 3.93 (3H, s), 5.39 (2H, s), 6.79 (1H, d, *J* = 0.8 Hz), 6.90 (1H, dd, *J* = 2.0, 7.8 Hz), 6.98 (1H, d, *J* = 2.0 Hz), 7.22 (1H, d, *J* = 7.8 Hz), 7.29 (1H, dd, *J* = 1.2, 2.4 Hz), 7.39 (1H, t, *J* = 8.2 Hz), 7.69–7.72 (2H, m), 8.71 (1H, d, *J* = 0.8 Hz).

*4.10.22. 3-{[5-(4-Chloro-3-fluorophenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6a**).*

Compound **6a** was prepared according to general procedure F (yield, 94%). Mp, 213–215 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.72 (3H, s), 5.49 (2H, s), 7.00 (1H, d, *J* = 8.6 Hz), 7.09 (1H, ddd, *J* = 1.6, 2.7, 9.0 Hz), 7.37 (1H, ddd, *J* = 0.8, 3.5, 8.2 Hz), 7.40 (1H, dd, *J* = 2.7, 10.6 Hz), 7.45 (1H, t, *J* = 7.8 Hz), 7.58 (1H, dt, *J* = 1.6, 7.8 Hz), 7.60–7.65 (2H, m), 8.19 (1H, d, *J* = 8.6 Hz); MS (FAB) *m/z*: 428 $[M + H]^+$; Anal. calcd for $C_{21}H_{15}ClFN_3O_4 \cdot 0.25H_2O$: C, 58.34; H, 3.61; N, 9.72; F, 4.39; Cl, 8.20; found C, 58.44; H, 3.51; N, 9.79; F, 4.56; Cl, 8.42.

*4.10.23. 3-[(3-Methyl-5-phenoxy-3H-imidazo[4,5-b]pyridin-2-yl)methoxy]benzoic acid•2HCl (**6b**).*

Compound **6b** was prepared according to general procedure F (yield, 61%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.73 (3H, s), 5.53 (2H, s), 6.96 (1H, d, *J* = 8.6 Hz), 7.18 (1H, d, *J* = 8.7 Hz), 7.22 (1H, t, *J* = 7.5 Hz), 7.38 (1H, ddd, *J* = 1.1, 2.6, 8.2 Hz), 7.42 (2H, m), 7.46 (1H, dd, *J* = 7.6, 8.2 Hz), 7.59 (1H, ddd, *J* = 1.1, 1.3, 7.6 Hz), 7.64 (1H, dd, *J* = 1.3, 2.6 Hz), 8.18 (1H, d, *J* = 8.6 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_4$, 376.1297; found 376.1295.

*4.10.24. 3-{[5-(4-Fluorophenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6c**).*

Compound **6c** was prepared according to general procedure F (yield, 71%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.69 (3H, s), 5.47 (2H, s), 6.91 (1H, d, *J* = 8.3 Hz), 7.22–7.28 (4H, m), 7.37 (1H, dd, *J* = 2.4, 8.3 Hz), 7.44 (1H, t, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 7.3 Hz), 7.62 (1H, s), 8.14 (1H, d, *J* = 8.8 Hz), 13.04 (1H, s); MS (FAB) *m/z*: 393 $[M^{+\cdot}]$; Anal. calcd for $C_{21}H_{16}FN_3O_4 \cdot 0.20H_2O$: C, 63.54; H, 4.16; N, 10.59 F, 4.79; found C, 63.61; H, 3.92; N, 10.57; F, 4.82.

*4.10.25. 3-{[3-Methyl-5-(4-methylphenoxy)-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6d**).*

Compound **6d** was prepared according to general procedure F (yield, 92%). Mp, 209–216 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.32 (3H, s), 3.70 (3H, s), 5.47 (2H, s), 6.86 (1H, d, *J* = 8.6 Hz), 7.06 (2H, d, *J* = 8.2 Hz), 7.22 (2H, d, *J* = 7.8 Hz), 7.35–7.39 (1H, m), 7.45 (1H, t, *J* = 7.8 Hz), 7.62 (1H, dd, *J* = 1.4, 2.5 Hz), 7.58 (1H, dt, *J* = 1.3, 7.5 Hz), 8.12 (1H, d, *J* = 8.6 Hz), 13.05 (1H, br); MS (FAB) *m/z*: 389 $[M^{+\cdot}]$; Anal. calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79; found C, 67.69; H, 4.71; N, 10.72.

*4.10.26. 3-{[5-(3-Fluoro-4-methylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6e**).*

Compound **6e** was prepared according to general procedure F (yield, 72%). Mp, 205–207 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.23 (3H, s), 3.70 (3H, s), 5.41 (2H, s), 6.91 (1H, d, *J* = 8.2 Hz), 6.91-.6.94 (1H, m), 7.05 (1H, dd, *J* = 2.4, 11.0 Hz), 7.15 (1H, d, *J* = 9.0 Hz), 7.28 (1H, d, *J* = 7.8 Hz), 7.32 (1H, d, *J* = 8.2 Hz), 7.51 (1H, d, *J* = 7.4 Hz), 7.57 (1H, dd, *J* = 1.2, 2.4 Hz), 8.14 (1H, d, *J* = 8.6 Hz); MS (FAB) *m/z*: 408 $[M + H]^+$; Anal. calcd for $C_{22}H_{18}FN_3O_4 \cdot 0.20H_2O$: C, 64.29; H, 4.51; N, 10.22; found C, 64.41; H, 4.31; N, 10.30.

*4.10.27. 3-{[5-(2,4-Dimethylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6f**).*

Compound **6f** was prepared according to general procedure F (yield, 97%). Mp, 209–216 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.09 (3H, s), 2.30 (3H, s), 3.67 (3H, s), 5.46 (2H, s), 6.78 (1H, d, J = 8.6 Hz), 6.97 (1H, d, J = 8.2 Hz), 7.05 (1H, dd, J = 2.0, 8.2 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.37 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, dt, J = 1.2, 7.8 Hz), 7.62 (1H, dd, J = 1.6, 2.7 Hz), 8.09 (1H, d, J = 8.6 Hz), 13.06 (1H, s); MS (FAB) *m/z*: 404 $[M + H]^+$; Anal. calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42; found C, 68.15; H, 5.20; N, 10.32.

*4.10.28. 3-{[5-(3,5-Dimethylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6g**).*

Compound **6g** was prepared according to general procedure F (yield, 85%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.27 (6H, s), 3.72 (3H, s), 5.48 (2H, s), 6.75 (2H, s), 6.84 (2H, s), 7.34–7.41 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.4 Hz), 7.63 (1H, s), 8.12 (1H, d, J = 8.6 Hz); MS (FAB) *m/z*: 404 $[M + H]^+$; Anal. calcd for C23H21N3O4•0.33H2O: C, 67.47; H, 5.33; N, 10.26; found C, 67.69; H, 5.30; N, 10.28.

*4.10.29. 3-{[5-(3,4-Dimethylphenoxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6h**).*

Compound **6h** was prepared according to general procedure F (yield, 95%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.22 (3H, s), 2.22 (3H, s), 3.71 (3H, s), 5.47 (2H, s), 6.82 (1H, d, J = 8.6 Hz), 6.88 (1H, dd, J = 2.7, 8.2 Hz), 6.96 (1H, d, J = 2.7 Hz), 7.16 (1H, d, J = 7.8 Hz), 7.37 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.56–7.59 (1H, m), 7.62–7.64 (1H, m), 8.10 (1H, d, J = 8.2 Hz), 13.03 (1H, s); MS (FAB) *m/z*: 404 $[M + H]^+$; Anal. calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42; found C, 68.07; H, 5.09; N, 10.35.

*4.10.30. 3-{[5-(2,3-Dihydro-1H-inden-5-yloxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6i**).*

Compound **6i** was prepared according to general procedure F (yield, 98%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.05 (2H, quint., J = 7.0 Hz), 2.86 (4H, t, J = 7.4 Hz), 3.71 (3H, s), 5.47 (2H, s), 6.83 (1H, d, J = 8.2 Hz), 6.92 (1H, dd, J = 2.4, 7.8 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.24 (1H, d, J = 8.2 Hz), 7.38 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, J = 7.4 Hz), 7.58 (1H, dt, J = 1.5, 7.8 Hz), 7.63 (1H, dd, J = 1.2, 2.4 Hz), 8.11 (1H, d, J = 8.2 Hz), 13.06 (1H, s); MS (FAB) *m/z*: 416 $[M + H]^+$; Anal. calcd for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11; found C, 69.34; H, 5.07; N, 10.13.

*4.10.31. 3-{[5-(2,3-Dihydro-1-benzofuran-6-yloxy)-3-methyl-3H-imidazo[4,5-b]pyridin-2-yl]methoxy}benzoic acid (**6j**).*

Compound **6j** was prepared according to general procedure F (yield, 74%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.18 (2H, t, J = 9.0 Hz), 3.72 (3H, s), 4.59 (2H, t, J = 8.6 Hz), 5.48 (2H, s), 6.58–6.60 (2H, m), 6.85 (1H, d, J = 8.6 Hz), 7.23 (1H, d, J = 8.6 Hz), 7.38 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.58 (1H, dt, J = 1.6, 7.8 Hz), 7.63 (1H, dd, J = 1.2, 2.4 Hz), 8.12 (1H, d, J = 8.6 Hz), 13.07 (1H, s); MS (FAB) *m/z*: 418 $[M + H]^+$; Anal. calcd for $C_{23}H_{19}N_3O_5$•0.20H2O: C, 65.61; H, 4.64; N, 9.98; found C, 65.77; H, 4.55; N, 9.90.

*4.10.32. 3-{[6-(4-Chloro-3-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoic acid (**6k**).*

Compound **6k** was prepared according to general procedure F (yield, 94%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.68 (3H, s), 5.53 (2H, s), 6.96 (1H, ddd, J = 1.2, 2.7, 8.6 Hz), 7.25 (1H, dd, J = 3.1, 11.0 Hz), 7.39 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.42 (1H, d, J = 0.8 Hz), 7.46 (1H, t, J = 7.4 Hz), 7.56–7.60 (2H, m), 7.64 (1H, dd, J = 1.6, 2.7 Hz), 8.61 (1H, d, J =0.8 Hz), 13.09 (1H, br); MS (FAB) *m/z*: 428 $[M + H]^+$; Anal. calcd for $C_{21}H_{15}ClFN_3O_4$•0.25H_2O: C, 58.34; H, 3.61; N, 9.72; F, 4.39; Cl, 8.20; found C, 58.53; H, 3.56; N, 9.69; F, 4.60; Cl, 8.13.

*4.10.33. 3-{[1-Methyl-6-(4-methylphenoxy)-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoic acid (**6l**).*

Compound **6l** was prepared according to general procedure F (yield, 93%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.30 (3H, s), 3.84 (3H, s), 5.51 (2H, s), 6.95 (2H, d, J = 8.6 Hz), 7.18 (2H, d, J = 8.2 Hz), 7.24 (1H, d, J = 0.8 Hz), 7.39 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 7.46 (1H, t, J = 7.8 Hz), 7.59 (1H, dt, J = 1.2, 7.4 Hz), 7.64 (1H, dd, J = 1.2, 2.4 Hz), 8.85 (1H, d, J = 1.2 Hz), 13.08 (1H, br); MS (FAB) *m/z*: 390 $[M + H]^+$; Anal. calcd for $C_{22}H_{19}N_3O_4$•0.33H_2O: C, 66.83; H, 5.01; N, 10.63; found C, 66.71; H, 5.10; N, 10.58.

*4.10.34. 3-{[6-(2,3-Dihydro-1-benzofuran-6-yloxy)-1-methyl-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoic acid (**6m**).*

Compound **6m** was prepared according to general procedure F (yield, 74%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.15 (2H, t, J = 9.0 Hz), 3.84 (3H, s), 4.57 (2H, t, J = 8.6 Hz), 5.51 (2H, s), 6.47 (1H, d, J = 2.0 Hz), 6.50 (1H, dd, J = 2.0, 7.8 Hz), 7.18 (1H, d, J = 7.8 Hz), 7.24 (1H, s), 7.38 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.46 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.4 Hz), 7.63 (1H, dd, J = 1.6, 2.4 Hz), 8.56 (1H, d, J = 0.8 Hz), 13.07 (1H, s); MS (FAB) *m/z*: 418 $[M + H]^+$; Anal. calcd for $C_{23}H_{19}N_3O_5$•0.20H_2O: C, 65.61; H, 4.64; N, 9.98; found C, 65.76; H, 4.51; N, 9.95.

*4.10.35. 3-{[6-(2,3-Dihydro-1H-inden-5-yloxy)-1-methyl-1H-imidazo[4,5-c]pyridin-2-yl]methoxy}benzoic acid (**6n**).*

Compound **6n** was prepared according to general procedure F (yield, 99%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.05 (2H, quint., J = 7.4 Hz), 2.84 (4H, t, J = 7.4 Hz), 3.84 (3H, s), 5.50 (2H, s), 6.81 (1H, dd, J = 2.4, 8.2 Hz), 6.90 (1H, d, J = 2.0 Hz), 7.20 (1H, d, J = 8.2 Hz), 7.23 (1H, d, J = 1.2 Hz), 7.39 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, J = 7.4 Hz), 7.59 (1H, dt, J = 1.6, 7.8 Hz), 7.64 (1H, dd, J = 1.6, 2.4 Hz), 8.54 (1H, d, J = 0.8 Hz), 13.06 (1H, s); MS (FAB) *m/z*: 416 $[M + H]^+$; Anal. calcd for $C_{24}H_{21}N_3O_4$•0.25H_2O: C, 68.64; H, 5.16; N, 10.01; found C, 68.71; H, 5.11; N, 9.97.

*4.10.36. Methyl 3-(2-{[6-(4-chloro-3-fluorophenoxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8a**).*

Compound **8a** was prepared according to general procedure C, followed by D (yield, 77%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.81 (3H, s), 3.94 (3H, s), 4.73 (2H, s), 6.14 (1H, d, J = 8.2 Hz), 6.93 (1H, ddd, J = 1.6, 2.7, 9.0 Hz), 7.03 (1H, dd, J = 2.0, 10.2 Hz), 7.21 (1H, ddd, J = 0.8, 2.7, 8.2 Hz), 7.35 (1H, d, J = 8.6 Hz), 7.40 (1H, d, J = 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.67 (1H, dd, J = 1.6, 2.7 Hz), 7.77 (1H, s), 7.78 (1H, dt, J = 1.2, 7.8 Hz).

*4.10.37. Methyl 3-(2-{[6-(4-fluorophenoxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8c**).*

Compound **8c** was prepared according to general procedure A, followed by procedures C and D (yield, 60%; 3 steps). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.82 (3H, s), 3.94 (3H, s), 4.72 (2H, s), 6.02 (1H, d, J = 8.3 Hz), 7.05 (2H, t, J = 8.8 Hz), 7.11–7.13 (2H, m), 7.20 (1H, dd, J = 2.9, 8.3 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.66 (1H, dd, J = 1.5, 2.4 Hz), 7.74 (1H, br), 7.77 (1H, dt, J = 1.5, 7.8 Hz).

*4.10.38. Methyl 3-(2-{[2-(methylamino)-6-(4-methylphenoxy)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8d**).*

Compound **8d** was prepared according to general procedure A, followed by procedures C and D (yield, 23%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.88 (3H, s), 3.94 (3H, s), 4.72 (2H, s), 5.96 (1H, d, J = 8.2 Hz), 7.02–7.08 (2H, m), 7.16 (2H, d, J = 8.2 Hz), 7.20 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.32 (1H, d, J = 8.2 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.66 (1H, dd, J = 1.4, 2.5 Hz), 7.73 (1H, s), 7.77 (1H, dt, J = 1.0, 1.2, 7.6 Hz); MS (FAB) *m/z*: 422 $[M + H]^+$.

*4.10.39. Methyl 3-(2-{[6-(3-fluoro-4-methylphenoxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8e**).*

Compound **8e** was prepared according to general procedure B, followed by procedure D (yield, 79%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, d, J = 2.0 Hz), 2.86 (3H, s), 3.95 (3H, s), 4.53 (1H, br), 4.73 (2H, s), 6.05 (1H, d, J = 8.2 Hz), 6.85–6.90 (2H, m), 7.15 (1H, t, J = 9.0 Hz), 7.21 (1H, ddd, J = 0.8, 2.7, 8.2 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.46 (1H, t, J = 7.8 Hz), 7.67 (1H, dd, J = 1.1, 2.4 Hz), 7.74 (1H, s), 7.78 (1H, dt, J = 1.1, 7.8 Hz).

*4.10.40. Methyl 3-(2-{[6-(2,4-dimethylphenoxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8f**).*

Compound **8f** was prepared according to general procedure C, followed by procedure D (yield, 90%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 2.33 (3H, s), 2.88 (3H, s), 3.94 (3H, s), 4.72 (2H, s), 5.80 (1H, d, J = 8.2 Hz), 6.96 (1H, t, J = 8.2 Hz), 7.00 (1H, dd, J = 2.0, 8.2 Hz), 7.05 (1H, s), 7.19 (1H, dd, J = 2.7, 8.2 Hz), 7.28 (1H, d, J = 8.2 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.66 (1H, dd, J = 1.6, 2.7 Hz), 7.74 (1H, s), 7.76 (1H, t, J = 7.8 Hz).

*4.10.41. Methyl 3-(2-{[6-(3,5-dimethylphenoxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8g**).*

Compound **8g** was prepared according to general procedure A, followed by procedures C and D (yield, 97%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.31 (6H, s), 2.89 (3H, d, J = 4.7 Hz), 3.94 (3H, s), 4.50 (1H, br), 4.72 (2H, s), 5.96 (1H, d, J = 7.8 Hz), 6.78 (2H, s), 6.81 (1H, s), 7.20 (1H, ddd, J = 1.2, 2.7, 8.6 Hz), 7.32 (1H, d, J = 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.66 (1H, dd, J = 1.6, 2.7 Hz), 7.74 (1H, br), 7.77 (1H, dt, J = 1.2, 7.8 Hz).

*4.10.42. Methyl 3-(2-{[6-(3,4-dimethylphenoxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8h**).*

Compound **8h** was prepared according to general procedure B, followed by procedure D (yield, 27%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 2.25 (3H, s), 2.89 (3H, s), 3.94 (3H, s), 4.72 (2H, s), 5.93 (1H, d, J = 8.2 Hz), 6.89 (1H, dd, J = 2.7, 8.2 Hz), 6.94 (1H, d, J = 2.3 Hz), 7.11 (1H, d, J = 7.8 Hz), 7.19 (1H, dd, J = 2.7, 8.2 Hz), 7.31 (1H, d, J = 8.2 Hz), 7.44 (1H, t, J = 8.0 Hz), 7.64–7.67 (1H, m), 7.73–7.80 (2H, m).

*4.10.43. Methyl 3-(2-{[6-(2,3-dihydro-1H-inden-5-yloxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8i**).*

Compound **8i** was prepared according to general procedure C, followed by procedure D (yield, 97%; 2 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.11 (2H, quint., J = 7.0 Hz), 2.90 (4H, q, J = 7.0 Hz), 2.91 (3H, s), 3.94 (3H, s), 4.72 (2H, s), 5.92 (1H, d, J = 8.2 Hz), 6.82 (1H, dd, J = 2.4, 8.2 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.18–7.21 (2H, m), 7.31 (1H, d, J = 8.2 Hz), 7.45 (1H, t, J = 8.2 Hz), 7.66 (1H, dd, J = 1.6, 2.7 Hz), 7.75–7.78 (2H, m).

*4.10.44. Methyl 3-(2-{[6-(2,3-dihydro-1-benzofuran-6-yloxy)-2-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8j**).*

Compound **8j** was prepared according to general procedure A, followed by procedures C and D. Crude **8j** was used for the next reaction without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.92 (3H, d, J = 5.1 Hz), 3.21 (2H, t, J = 9.4 Hz), 3.95 (3H, s), 4.53 (1H, d, J = 4.7 Hz), 4.63 (2H, t, J = 8.6 Hz), 4.73 (2H, s), 5.98 (1H, d, J = 8.2 Hz), 6.62–6.66 (2H, m), 7.15 (1H, d, J = 7.8 Hz), 7.21 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.33 (1H, d, J = 7.8 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.67 (1H, dd, J = 1.2, 2.7 Hz), 7.75 (1H, br), 7.78 (1H, dt, J = 1.2, 7.8 Hz).

*4.10.45. Methyl 3-(2-{[6-(4-chloro-3-fluorophenoxy)-4-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8k**).*

Compound **8k** was prepared according to general procedure A, followed by procedures C and D (yield, 34%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.88 (3H, d, J = 5.1 Hz), 3.94 (3H, s), 4.66 (1H, d, J = 5.1 Hz), 4.75 (2H, s), 6.18 (1H, s), 6.89 (1H, ddd, J = 1.2, 2.7, 8.6 Hz), 6.98 (1H, dd, J = 2.7, 10.2 Hz), 7.21 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.37 (1H, t, J = 8.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.67 (1H, dd, J = 1.6, 2.7 Hz), 7.75 (1H, s), 7.77 (1H, dt, J = 1.2, 7.8 Hz), 7.82 (1H, br).

*4.10.46. Methyl 3-(2-{[4-(methylamino)-6-(4-methylphenoxy)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8l**).*

Compound **8l** was prepared according to general procedure C, followed by procedure D (yield, 97%; 2 steps). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.34 (3H, s), 2.83 (3H, d, J = 4.9 Hz), 3.94 (3H, s), 4.57 (1H, d, J = 4.9 Hz), 4.73 (2H, s), 6.12 (1H, s), 7.01 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 7.8 Hz), 7.20 (1H, ddd, J = 2.0, 2.9, 8.3 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.66 (1H, dd, J = 1.5, 2.4 Hz), 7.74 (1H, s), 7.76 (1H, dt, J = 1.0, 7.8 Hz), 7.78 (1H, br).

*4.10.47. Methyl 3-(2-{[6-(2,3-dihydro-1-benzofuran-6-yloxy)-4-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8m**).*

Compound **8m** was prepared according to general procedure A, followed by procedures C and D (yield, 34%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.84 (3H, d, J = 5.1 Hz), 3.18 (2H, t, J = 8.6 Hz), 3.94 (3H, s), 4.60 (1H, br), 4.60 (2H, t, J = 8.6 Hz), 4.73 (2H, s), 6.13 (1H, s), 6.58 (1H, d, J = 2.0 Hz), 6.60 (1H, dd, J = 2.0, 8.2 Hz), 7.15 (1H, d, J = 7.8 Hz), 7.20 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.66 (1H, dd, J = 1.2, 2.7 Hz), 7.75 (1H, s), 7.75–7.77 (1H, m), 7.83 (1H, br).

*4.10.48. Methyl 3-(2-{[6-(2,3-dihydro-1H-inden-5-yloxy)-4-(methylamino)pyridin-3-yl]amino}-2-oxoethoxy)benzoate (**8n**).*

Compound **8n** was prepared according to general procedure C, followed by procedure D (yield, 77%; 3 steps). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.09 (2H, quint., J = 7.0 Hz), 2.84 (3H, d, J = 5.1 Hz), 2.90 (4H, q, J = 7.8 Hz), 3.94 (3H, s), 4.58 (1H, d, J = 5.1 Hz), 4.73 (2H, s), 6.14 (1H, s), 6.88 (1H, dd, J = 2.4, 8.2 Hz), 6.97 (1H, s), 7.19 (2H, dd, J = 2.7, 7.8 Hz), 7.74 (1H, t, J = 7.8 Hz), 7.66 (1H, dd, J = 1.7, 2.7 Hz), 7.75 (1H, s), 7.77 (1H, d, J = 6.7 Hz), 7.81 (1H, br).

*4.10.49. tert-Butyl {5-[(4-methoxybenzyl)oxy]-2-nitrophenyl}methylcarbamate (**10**).*

NaH (63%, 25.0 g, 656 mmol) was added to a solution of 4-methoxybenzyl alcohol (90.3 g, 654 mmol) and *tert*-butyl (5-chloro-2-nitrophenyl)methylcarbamate (**9**, 156 g, 544 mmol) in DMF (1.4 L) at room temperature under N_2, and the mixture was stirred at 80 °C for 4 h. Water (1.5 L) was added to the cooled reaction mixture. The precipitated solid was collected by filtration to obtain **10** (209 g, 99%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (9H, s), 3.25 (3H, s), 3.81 (3H, s), 5.04 (2H, s), 6.79–6.95 (4H, m), 7.29–7.37 (2H, m), 7.91–8.03 (1H, m).

*4.10.50. tert-Butyl {2-amino-5-[(4-methoxybenzyl)oxy]phenyl}methylcarbamate (**11**).*

A solution of **10** (209 g, 538 mmol), iron powder (150 g, 2.69 mol) and NH_4Cl (15.0 g, 280 mmol) in EtOH (1.2 L) and water (1.0 L) was stirred under reflux for 5 h. The cooled reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure, and the residue was extracted with toluene (1.0 L) twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain **11** (193 g, 99%) as a brown oil, which was used directly for the next reaction without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, br), 3.15 (3H, s), 3.49 (2H, br), 3.82 (3H, s), 4.91 (2H, s), 6.70 (1H, d, J = 8.6 Hz), 6.68–6.71 (1H, m), 6.76 (1H, dd, J = 2.4, 8.6 Hz), 6.91 (2H, d, J = 8.6 Hz), 7.34 (2H, d, J = 8.6 Hz).

*4.10.51. Methyl 3-[2-({2-[(tert-butoxycarbonyl)(methyl)amino]-4-[(4-methoxybenzyl)oxy]phenyl}amino)-2-oxoethoxy]benzoate (**12**).*

A solution of [3-(Methoxycarbonyl)phenoxy]acetic acid[8] (121 g, 577 mmol), **11** (193 g, 538 mmol), HOBt•H_2O (77.7 g, 575 mmol) and WSC•HCl (110 g, 575 mmol) in CH_2Cl_2 (1.0 L) was stirred at room temperature for 3 h under N_2. Water (1.0 L) was added to the reaction mixture, and the precipitated solid was removed by filtration. The separated organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from a solvent mixture of *i*-Pr_2O/EtOAc (20:1) to obtain **12** (296 g, 99%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, br), 3.12 (3H, s), 3.83 (3H, s), 3.93 (3H, s), 4.67 (2H, s), 4.98 (2H, s), 6.80 (1H, br), 6.93 (4H, d, J = 8.6 Hz), 7.21–7.27 (2H, m), 7.35 (2H, d, J = 8.6 Hz), 7.42 (1H, t, J = 8.2 Hz), 7.64 (1H, s), 7.75 (1H, d, J = 8.2 Hz).

*4.10.52. Methyl 3-[(6-hydroxy-1-methyl-1H-benzimidazol-2-yl)methoxy]benzoate (**13**).*

A solution of **12** (296 g, 538 mmol) in 2 M HCl in 1,4-dioxane (1.0 L) was stirred at 60 °C for 2 h. After cooling the reaction mixture, the precipitated solid was collected by filtration to obtain **13** as an HCl salt. An aqueous solution (1.0 L) of imidazole (59.0 g, 867 mmol) was added to a suspension of the HCl salt of **13** in EtOAc (1.0 L). The precipitated solid was collected by filtration to obtain **13** (113 g, 67%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.74 (3H, s), 3.85 (3H, s), 5.40 (2H, s), 6.71 (1H, dd, J = 2.4, 8.6 Hz), 6.83 (1H, d, J = 2.0 Hz), 7.40–7.43 (2H, m), 7.47 (1H, t, J = 7.4 Hz), 7.58 (1H, dt, J = 1.6, 7.8 Hz), 7.63–7.64 (1H, m), 9.36 (1H, s).

*4.10.53. Methyl 3-{[1-methyl-6-(pyridin-2-yloxy)-1H-benzimidazol-2-yl]methoxy}benzoate (**14a**).*

Compound **14a** was prepared according to general procedure G using 2-bromopyridine (yield, 14%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.94 (1H, d, J = 8.6 Hz), 6.98–7.01 (2H, m), 7.08 (1H, dd, J = 2.4, 8.6 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.31 (1H, d, J = 3.1 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.69 (1H, dt, J = 2.0, 8.2 Hz), 7.72–7.73 (1H, m), 7.78 (1H, d, J = 9.0 Hz), 8.19 (1H, ddd, J = 0.8, 2.0, 5.1 Hz).

*4.10.54. Methyl 3-({6-[(6-chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14b**).*

Compound **14b** was prepared according to general procedure G using 2-chloro-6-fluoropyridine (yield, 49%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.75 (1H, dd, J = 8.2 Hz), 7.04 (1H, dd, J = 0.8, 8.2 Hz), 7.08 (1H, dd, J = 2.4, 8.6 Hz), 7.18 (1H, d, J = 2.4 Hz), 7.30 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.38 (1H, t, J = 7.8 Hz), 7.62 (1H, t, J = 7.4 Hz), 7.69 (1H, dt, J = 1.2, 7.8 Hz), 7.73 (1H, dd, J = 1.6, 2.7 Hz), 7.78 (1H, d, J = 8.6 Hz).

*4.10.55. Methyl 3-({6-[(5-chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14c**).*

Compound **14c** was prepared according to general procedure H using 2-bromo-5-chloropyridine (yield, 4.2%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.92 (3H, s), 5.42 (2H, s), 6.91 (1H, d, J = 8.6 Hz), 7.05 (1H, dd, J = 2.4, 9.0 Hz), 7.16 (1H, d, J = 2.4 Hz), 7.29 (1H, ddd, J = 1.2, 2.7, 8.2 Hz), 7.37 (1H, t, J = 8.2 Hz), 7.66 (1H, dd, J = 2.7, 8.6 Hz), 7.69 (1H, dt, J = 1.2, 7.4 Hz), 7.72 (1H, dd, J = 1.2, 2.7 Hz), 7.79 (1H, d, J = 8.6 Hz), 8.11 (1H, d, J = 2.4 Hz).

*4.10.56. Methyl 3-({6-[(4-chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14d**).*

Compound **14d** was prepared according to general procedure G using 4-chloro-2-fluoropyridine (yield, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.95 (1H, d, J = 2.4 Hz), 7.00 (1H, dd, J = 2.0, 5.5 Hz), 7.06 (1H, dd, J = 2.4, 8.6 Hz), 7.17 (1H, d, J = 2.4 Hz), 7.29 (1H, ddd, J = 1.2, 2.7, 8.6 Hz), 7.38 (1H, t, J = 7.8 Hz), 7.69 (1H, dt, J = 1.2, 7.8 Hz), 7.72 (1H, dd, J = 1.6, 2.7 Hz), 7.79 (1H, d, J = 8.6 Hz), 8.08 (1H, d, J = 5.5 Hz).

*4.10.57. Methyl 3-({6-[(3-chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14e**).*

Compound **14e** was prepared according to general procedure G using 3-chloro-2-fluoropyridine (yield, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.98 (1H, dd, J = 4.7, 7.4 Hz), 7.10 (1H, dd, J = 2.4, 9.0 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.30 (1H, dd, J = 1.0, 8.6 Hz), 7.38 (1H, t, J = 7.8 Hz), 7.70 (1H, d, J = 7.4 Hz), 7.72–7.73 (1H, m), 7.79 (1H, dd, J = 1.6, 7.4 Hz), 7.80 (1H, d, J = 8.6 Hz), 8.02 (1H, dd, J = 1.6, 4.7 Hz).

*4.10.58. Methyl 3-({1-methyl-6-[(6-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoate (**14f**).*

Compound **14f** was prepared according to general procedure G using 2-bromo-6-methylpyridine (yield, 18%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.46 (3H, s), 3.85 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 6.56 (1H, d, J = 8.2 Hz), 6.87 (1H, d, J = 7.4 Hz), 7.08 (1H, dd, J = 2.0, 8.6 Hz), 7.16 (1H, d, J = 2.4 Hz), 7.30 (1H, dd, J = 3.1, 7.4 Hz), 7.38 (1H, t, J = 7.4 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.69 (1H, dt, J = 1.6, 9.0 Hz), 7.73 (1H, dd, J = 1.6, 3.1 Hz), 7.76 (1H, d, J = 8.6 Hz).

*4.10.59. Methyl 3-({1-methyl-6-[(5-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoate (**14g**).*

Compound **14g** was prepared according to general procedure G using 2-bromo-5-methylpyridine (yield, 18%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 3.84 (3H, s), 3.92 (3H, s), 5.41 (2H, s), 6.84 (1H, d, J = 8.6 Hz), 7.05 (1H, dd, J = 2.0, 8.6 Hz), 7.15 (1H, d, J = 2.0 Hz), 7.29 (1H, ddd, J = 0.8, 2.4, 9.0 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.51 (1H, dd, J = 3.1, 9.0 Hz), 7.68 (1H, dt, J = 1.2, 7.8 Hz), 7.72 (1H, dd, J = 1.6, 2.7 Hz), 7.76 (1H, d, J = 8.6 Hz), 8.00 (1H, dd, J = 0.8, 1.6 Hz).

*4.10.60. Methyl 3-({1-methyl-6-[(4-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoate (**14h**).*

Compound **14h** was prepared according to general procedure G using 2-bromo-4-methylpyridine (yield, 15%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 5.41 (2H,

s), 6.74 (1H, s), 6.82 (1H, d, *J* = 5.5 Hz), 7.06 (1H, dd, *J* = 2.4, 8.6 Hz), 7.15 (1H, d, *J* = 2.4 Hz), 7.30 (1H, ddd, *J* = 0.8, 2.7, 8.2 Hz), 7.37 (1H, t, *J* = 7.8 Hz), 7.68 (1H, dt, *J* = 1.2, 7.8 Hz), 7.72 (1H, dd, *J* = 1.2, 2.7 Hz), 7.77 (1H, d, *J* = 8.6 Hz), 8.04 (1H, d, *J* = 5.1 Hz).

*4.10.61. Methyl 3-({1-methyl-6-[(3-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoate (**14i**).*

Compound **14i** was prepared according to general procedure G using 2-bromo-3-methylpyridine (yield, 11%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 3.84 (3H, s), 3.92 (3H, s), 5.41 (2H, s), 6.91 (1H, dd, *J* = 4.7, 7.0 Hz), 7.05 (1H, dd, *J* = 2.4, 8.6 Hz), 7.16 (1H, d, *J* = 2.4 Hz), 7.30 (1H, ddd, *J* = 1.2, 2.4, 9.0 Hz), 7.37 (1H, t, *J* = 7.8 Hz), 7.54 (1H, ddd, *J* = 0.8, 2.0, 7.0 Hz), 7.68 (1H, dt, *J* = 1.2, 7.8 Hz), 7.72 (1H, dd, *J* = 1.6, 2.7 Hz), 7.77 (1H, d, *J* = 8.6 Hz), 7.97 (1H, dd, *J* = 2.0, 4.3 Hz).

*4.10.62. Methyl 3-({6-[(5-fluoropyridin-2-yl)oxy]-1-methyl-1*H*-benzimidazol-2-yl}methoxy)benzoate (**14j**).*

Compound **14j** was prepared according to general procedure G using 2-bromo-5-fluoropyridine (yield, 4.5%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 3.92 (3H, s), 5.42 (2H, s), 6.94 (1H, dd, *J* = 3.5, 9.0 Hz), 7.05 (1H, dd, *J* = 2.4, 9.0 Hz), 7.15 (1H, d, *J* = 2.4 Hz), 7.30 (1H, dd, *J* = 1.2, 8.2 Hz), 7.37 (1H, t, *J* = 7.8 Hz), 7.43-7.47 (1H, m), 7.69 (1H, dt, *J* = 0.8, 7.8 Hz), 7.72 (1H, t, *J* = 1.6 Hz), 7.78 (1H, d, *J* = 8.6 Hz), 8.02 (1H, d, *J* = 3.1 Hz).

*4.10.63. Methyl 3-({6-[(3-fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14k**).*

Compound **14k** was prepared according to general procedure G using 2,3-difluoropyridine (yield, 28%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.86 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 7.00 (1H, ddd, *J* = 3.1, 5.1, 8.2 Hz), 7.11 (1H, dd, *J* = 2.4, 8.6 Hz), 7.22 (1H, d, *J* = 2.4 Hz), 7.30 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.38 (1H, t, *J* = 7.2 Hz), 7.50 (1H, ddd, *J* = 1.6, 7.8, 9.8 Hz), 7.69 (1H, dt, *J* = 1.2, 7.8 Hz), 7.72 (1H, dd, *J* = 1.6, 2.4 Hz), 7.80 (1H, d, *J* = 8.6 Hz), 7.91 (1H, dd, *J* = 1.6, 5.1 Hz).

*4.10.64. Methyl 3-({6-[(5-bromo-6-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14l**).*

Compound **14l** was prepared according to general procedure G using 3-bromo-6-fluoro-2-methylpyridine (yield, 11%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.54 (3H, s), 3.86 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 6.53 (1H, d, *J* = 8.6 Hz), 7.07 (1H, dd, *J* = 2.4, 8.6 Hz), 7.15 (1H, d, *J* = 2.0 Hz), 7.31 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.39 (1H, t, *J* = 7.4 Hz), 7.69–7.73 (2H, m), 7.77 (1H, d, *J* = 8.6 Hz).

*4.10.65. Methyl 3-({6-[(3-bromo-6-chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14m**).*

Compound **14m** was prepared according to general procedure G using 3-bromo-6-chloro-2-fluoropyridine (yield, 62%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.85 (3H, s), 3.86 (3H, s), 5.50 (2H, s), 7.05 (1H, dd, *J* = 2.4, 8.6 Hz), 7.21 (1H, d, *J* = 7.8 Hz), 7.44 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.49 (1H, t, *J* = 7.4 Hz), 7.54 (1H, d, *J* = 2.4 Hz), 7.60 (1H, dt, *J* = 1.6, 9.0 Hz), 7.67 (1H, dd, *J* = 1.6, 2.4 Hz), 7.70 (1H, d, *J* = 9.0 Hz), 8.25 (1H, d, *J* = 8.2 Hz).

*4.10.66. Methyl 3-({6-[(5-bromo-3-fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14n**).*

Compound **14n** was prepared according to general procedure G using 5-bromo-2,3-difluoropyridine (yield, 66%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.93 (3H, s), 5.41 (2H, br), 7.10 (1H, br), 7.23 (1H, br), 7.31 (1H, d, *J* = 8.3 Hz), 7.38 (1H, t, *J* = 7.8 Hz), 7.67 (1H, dd, *J* = 2.0, 8.8 Hz), 7.70 (1H, d, *J* = 7.8 Hz), 7.73 (1H, s), 7.80 (1H, br), 7.96 (1H, d, *J* = 2.0 Hz).

*4.10.67. Methyl 3-({6-[(3-bromo-5-fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14o**).*

Compound **14o** was prepared according to general procedure G using 3-bromo-2,5-difluoropyridine (yield, 54%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.83 (3H, s), 3.85 (3H, s), 5.50 (2H, s), 7.00 (1H, dd, *J* = 2.4, 8.6 Hz), 7.43 (1H, ddd, *J* = 1.2, 2.4, 8.2 Hz), 7.45–7.50 (2H, m), 7.59 (1H, dt, *J* = 1.2, 7.8 Hz), 7.65–7.67 (2H, m), 8.13 (1H, d, *J* = 2.7 Hz), 8.38 (1H, dd, *J* = 2.7, 7.4 Hz).

*4.10.68. Methyl 3-({6-[(3,5-dichloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14p**).*

Compound **14p** was prepared according to general procedure G using 3,5-dichloro-2-fluoropyridine (yield, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 7.08 (1H, dd, *J* = 2.0, 8.6 Hz), 7.20 (1H, s), 7.29–7.31 (1H, m), 7.38 (1H, t, *J* = 8.2 Hz), 7.70 (1H, d, *J* = 7.4 Hz), 7.73 (1H, s), 7.80 (1H, d, *J* = 2.4 Hz), 7.82 (1H, br), 7.96 (1H, d, *J* = 2.4 Hz).

*4.10.69. Methyl 3-({6-[(5-chloro-3-fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14q**).*

Compound **14q** was prepared according to general procedure G using 5-chloro-2,3-difluoropyridine (yield, 70%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 7.09 (1H, dd, *J* = 2.4, 8.8 Hz), 7.21 (1H, d, *J* = 2.0 Hz), 7.30 (1H, ddd, *J* = 1.0, 2.4, 8.3 Hz), 7.38 (1H, t, *J* = 8.3 Hz), 7.54 (1H, dd, *J* = 2.0, 8.8 Hz), 7.70 (1H, dt, *J* = 1.0, 7.8 Hz), 7.73 (1H, dd, *J* = 1.5, 2.4 Hz), 7.80 (1H, d, *J* = 8.8 Hz), 7.88 (1H, d, *J* = 2.0 Hz).

*4.10.70. Methyl 3-({6-[(3-bromo-5-chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**14r**).*

Compound **14r** was prepared according to general procedure G using 3-bromo-5-chloro-2-fluoropyridine (yield, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83 (3H, s), 3.89 (3H, s), 5.38 (2H, s), 6.96–7.01 (1H, m), 7.09–7.11 (1H, m), 7.23–7.27 (1H, m), 7.30–7.36 (1H, m), 7.48–7.50 (1H, m), 7.62–7.66 (1H, m), 7.67–7.70 (1H, m), 7.72–7.75 (1H, m), 7.85–7.87 (1H, m).

*4.10.71. Methyl 3-({6-[(5,6-dimethylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**15l**).*

Compound **15l** was prepared according to general procedure I (yield, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, s), 2.42 (3H, s), 3.85 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 6.51 (1H, d, *J* = 8.2 Hz), 7.07 (1H, dd, *J* = 2.0, 8.6 Hz), 7.13 (1H, d, *J* = 2.0 Hz), 7.29 (1H, ddd, *J* = 1.2, 3.1, 8.6 Hz), 7.38 (1H, d, *J* = 7.8 Hz), 7.39 (1H, t, *J* = 7.8 Hz), 7.69–7.76 (3H, m).

*4.10.72. Methyl 3-({6-[(3,6-dimethylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**15m**).*

Compound **15m** was prepared according to general procedure I (yield, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 2.33 (3H, s), 3.83 (3H, s), 3.92 (3H, s), 5.40 (2H, s), 6.81 (1H, d, *J* = 7.4 Hz), 7.01 (1H, dd, *J* = 2.4, 8.6 Hz), 7.10 (1H, d, *J* = 2.0 Hz), 7.28–7.30 (1H, m), 7.37 (1H, d, *J* = 7.8 Hz), 7.44 (1H, d, *J* = 8.2 Hz), 7.68 (1H, dt, *J* = 1.6, 7.8 Hz), 7.70–7.73 (2H, m).

*4.10.73. Methyl 3-({6-[(3-fluoro-5-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**15n**).*

Compound **15n** was prepared according to general procedure I (yield, 56%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.86 (3H, s), 3.93 (3H, s), 5.42 (2H, s), 7.09 (1H, dd, *J* = 2.0, 8.8 Hz), 7.19 (1H, d, *J* = 2.0 Hz), 7.30 (1H, ddd, *J* = 1.0, 2.9, 8.3 Hz), 7.32–7.35 (1H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.69 (1H, dt, *J* = 1.5, 7.3 Hz), 7.72–7.73 (2H, m), 7.78 (1H, d, *J* = 8.8 Hz).

*4.10.74. Methyl 3-({6-[(5-fluoro-3-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**15o**).*

Compound **15o** was prepared according to general procedure I (yield, 60%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.41 (3H, s), 3.85 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 7.03 (1H, dd, *J* = 1.5, 8.8 Hz), 7.13 (1H, d, *J* = 2.0 Hz), 7.30 (1H, dd, *J* = 2.9, 8.3 Hz), 7.34 (1H, dd, *J* = 1.5, 7.3 Hz), 7.37 (1H, t, *J* = 8.3 Hz), 7.69 (1H, d, *J* = 7.3 Hz), 7.73 (1H, s), 7.77 (1H, d, *J* = 8.8 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

*4.10.75. Methyl 3-({6-[(5-chloro-3-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**15r**).*

Compound **15r** was prepared according to general procedure I (yield, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 5.38 (2H, s), 6.98–7.00 (1H, m), 7.10–7.10 (1H, m), 7.22–7.27 (1H, m), 7.31–7.37 (1H, m), 7.49–7.50 (1H, m), 7.64–7.66 (1H, m), 7.64–7.69 (1H, m), 7.74 (1H, d, J = 8.6 Hz), 7.84–7.87 (1H, m).

*4.10.76. 3-{[1-Methyl-6-(pyridin-2-yloxy)-1H-benzimidazol-2-yl]methoxy}benzoic acid (**16a**).*

Compound **16a** was prepared according to general procedure F (yield, 48%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.48 (2H, s), 6.99 (2H, t, *J* = 8.8 Hz), 7.11 (1H, dd, *J* = 5.9, 6.8 Hz), 7.39 (1H, d, *J* = 8.3 Hz), 7.43 (1H, s), 7.45 (1H, t, *J* = 7.3 Hz), 7.58 (1H, d, *J* = 7.8 Hz), 7.64 (1H, s), 7.66 (1H, d, *J* = 8.8 Hz), 7.83 (1H, t, *J* = 6.4 Hz), 8.14 (1H, d, *J* = 6.4 Hz), 13.02 (1H, br); MS (FAB) *m/z*: 376 $[M + H]^+$; Anal. calcd for $C_{21}H_{17}N_3O_4 \bullet 0.67H_2O$: C, 65.11; H, 4.77; N, 10.85; found C, 65.26; H, 4.47; N, 10.71.

*4.10.77. 3-({6-[(6-Chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16b**).*

Compound **16b** was prepared according to general procedure F (yield, 99%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.85 (3H, s), 5.49 (2H, s), 6.98 (1H, d, *J* = 7.4 Hz), 7.03 (1H, dd, *J* = 2.0, 8.6 Hz), 7.23 (1H, d, *J* = 7.4 Hz), 7.40 (1H, ddd, *J* = 1.2, 2.7, 8.6 Hz), 7.46 (1H, t, *J* = 7.8 Hz), 7.51 (1H, d, *J* = 2.0 Hz), 7.58 (1H, dt, *J* = 1.2, 7.4 Hz), 7.65 (1H, dd, *J* = 1.2, 2.7 Hz), 7.70 (1H, d, *J* = 9.0 Hz), 7.89 (1H, t, *J* = 7.8 Hz), 13.07 (1H, br); Anal. calcd for $C_{21}H_{16}ClN_3O_4 \bullet 0.50H_2O$: C, 60.22; H, 4.09; N, 10.03; Cl, 8.46; found C, 60.26; H, 3.91; N, 10.02; Cl, 8.67.

*4.10.78. 3-({6-[(5-Chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16c**).*

Compound **16c** was prepared according to general procedure F (yield, 41%). Mp, 251–253 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.48 (2H, s), 7.01 (1H, dd, *J* = 2.0, 8.6 Hz), 7.08 (1H, d, *J* = 8.2 Hz), 7.39 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.43–7.47 (2H, m), 7.58 (1H, dt, *J* = 1.2, 7.4 Hz), 7.64 (1H, dd, *J* = 1.6, 2.7 Hz), 7.67 (1H, d, *J* = 8.6 Hz), 7.95 (1H, dd, *J* = 2.7, 9.0 Hz), 8.19 (1H, d, *J* = 2.7 Hz), 13.03 (1H, br); Anal. calcd for $C_{21}H_{16}ClN_3O_4 \bullet 0.20H_2O$: C, 61.01; H, 4.00; N, 10.16; Cl, 8.58; found C, 61.22; H, 3.82; N, 10.16; Cl, 8.78.

*4.10.79. 3-({6-[(4-Chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16d**).*

Compound **16d** was prepared according to general procedure F (yield, 94%). Mp, 246–252 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.84 (3H, s), 5.49 (2H, s), 7.02 (1H, dd, *J* = 2.4, 8.6 Hz), 7.20 (1H, d, *J* = 1.6 Hz), 7.26 (1H, dd, *J* = 1.6, 5.5 Hz), 7.39 (1H, ddd, *J* = 0.8, 2.4, 7.8 Hz), 7.45 (1H, t, *J* = 7.4 Hz), 7.47 (1H, s), 7.58 (1H, dt, *J* = 1.2, 7.4 Hz), 7.64 (1H, dd, *J* = 1.2, 2.4 Hz), 7.68 (1H, d, *J* = 9.0 Hz), 8.12 (1H, d, *J* = 5.5 Hz), 13.05 (1H, br); Anal. calcd for $C_{21}H_{16}ClN_3O_4$: C, 61.54; H, 3.94; N, 10.25; Cl, 8.65; found C, 61.44; H, 3.92; N, 9.97; Cl, 8.24.

*4.10.80. 3-({6-[(3-Chloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16e**).*

Compound **16e** was prepared according to general procedure F (yield, 67%). Mp, 264–266 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.49 (2H, s), 7.01 (1H, dd, *J* = 2.4, 9.0 Hz), 7.15 (1H, dd, *J* = 5.1, 7.8 Hz), 7.37–7.40 (1H, m), 7.45 (1H, t, *J* = 7.4 Hz), 7.49 (1H, d, *J* = 2.4 Hz), 7.57 (1H, d, *J* = 7.8 Hz), 7.63–7.64 (1H, m), 7.67 (1H, d, *J* = 8.6 Hz), 8.03 (1H, dd, *J* = 2.0, 5.1 Hz), 8.06 (1H, dd, *J* = 1.6, 7.8 Hz), 13.06 (1H, br); Anal. calcd for $C_{21}H_{16}ClN_3O_4$: C, 61.54; H, 3.94; N, 10.25; Cl, 8.65; found C, 61.40; H, 3.86; N, 10.17; Cl, 8.61.

*4.10.81. 3-({1-Methyl-6-[(6-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16f**).*

Compound **16f** was prepared according to general procedure F (yield, 54%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.30 (3H, s), 3.83 (3H, s), 5.48 (2H, s), 6.72 (1H, d, *J* = 7.8 Hz), 6.96–6.98 (2H, m), 7.38–7.41 (2H, m), 7.46 (1H, t, *J* = 7.8 Hz), 7.58 (1H, dd, *J* = 1.0, 7.3 Hz), 7.65 (1H, s), 7.66 (1H, d, *J* = 8.3 Hz), 7.70 (1H, t, *J* = 7.8 Hz), 13.03 (1H, br); MS (FAB) *m/z*: 390 $[M + H]^+$; Anal. calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79; found C, 67.58; H, 4.82; N, 10.67.

*4.10.82. 3-({1-Methyl-6-[(5-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16g**).*

Compound **16g** was prepared according to general procedure F (yield, 73%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.24 (3H, s), 3.82 (3H, s), 5.48 (2H, s), 6.91 (1H, d, *J* = 8.3 Hz), 6.96 (1H, dd, *J* = 2.0, 8.3 Hz), 7.38–7.40 (2H, m), 7.45 (1H, t, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 7.3 Hz), 7.63–7.67 (3H, m), 7.95 (1H, s), 13.02 (1H, br); MS (FAB) *m/z*: 390 $[M + H]^+$; Anal. calcd for $C_{22}H_{19}N_3O_4 \bullet 0.25H_2O$: C, 67.08; H, 4.99; N, 10.67; found C, 67.26; H, 4.87; N, 10.45.

4.10.83. 3-({1-Methyl-6-[(4-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoic acid (16h).

Compound **16h** was prepared according to general procedure F (yield, 64%). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.31 (3H, s), 3.83 (3H, s), 5.48 (2H, s), 6.81 (1H, s), 6.95 (1H, d, *J* = 6.4 Hz), 6.97 (1H, dd, *J* = 2.0, 8.8 Hz), 7.38–7.40 (2H, m), 7.45 (1H, t, *J* = 7.3 Hz), 7.58 (1H, d, *J* = 7.3 Hz), 7.64–7.66 (2H, m), 7.99 (1H, d, *J* = 5.4 Hz), 13.03 (1H, br); MS (FAB) *m/z*: 390 $[M + H]^+$; Anal. calcd for $C_{21}H_{16}ClN_3O_4 \bullet 0.25H_2O$: C, 67.08; H, 4.99; N, 10.67; found C, 67.33; H, 4.93; N, 10.40.

*4.10.84. 3-({1-Methyl-6-[(3-methylpyridin-2-yl)oxy]-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16i**).*

Compound **16i** was prepared according to general procedure F (yield, 98%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.35 (3H, s), 3.83 (3H, s), 5.48 (2H, s), 6.97 (1H, ddd, *J* = 0.8, 2.4, 8.6 Hz), 7.02 (1H, dd, *J* = 5.1, 7.4 Hz), 7.38–7.41 (2H, m), 7.45 (1H, t, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 7.4 Hz), 7.63–7.65 (2H, m), 7.71 (1H, ddd, *J* = 0.8, 2.0, 7.4 Hz), 7.89 (1H, dd, *J* = 2.0, 4.7 Hz), 13.06 (1H, br); MS

(FAB) *m/z*: 390 $[M + H]^+$; Anal. calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79; found C, 67.86; H, 5.10; N, 10.42.

*4.10.85. 3-({6-[(5-Fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16j**).*

Compound **16j** was prepared according to general procedure F (yield, 38%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.48 (2H, s), 6.99 (1H, dd, *J* = 2.4, 8.6 Hz), 7.09 (1H, dd, *J* = 3.5, 9.0 Hz), 7.37–7.40 (1H, m), 7.43–7.43 (1H, m), 7.45 (1H, t, *J* = 7.4 Hz), 7.58 (1H, dd, *J* = 1.2, 7.4 Hz), 7.64 (1H, dd, *J* = 1.2, 2.0 Hz), 7.65 (1H, t, *J* = 8.6 Hz), 7.78–7.83 (1H, m), 8.13 (1H, d, *J* = 3.1 Hz), 13.02 (1H, br); Anal. calcd for $C_{21}H_{16}ClN_3O_4$•0.20H_2O: C, 61.01; H, 4.00; N, 10.16; Cl, 8.58; found C, 61.22; H, 3.82; N, 10.16; Cl, 8.78.

*4.10.86. 3-({6-[(3-Fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16k**).*

Compound **16k** was prepared according to general procedure F (yield, 99%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.84 (3H, s), 5.49 (2H, s), 7.04 (1H, dd, *J* = 2.4, 9.0 Hz), 7.18 (1H, ddd, *J* = 3.1, 4.7, 8.2 Hz), 7.39 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, *J* = 7.4 Hz), 7.50 (1H, d, *J* = 2.4 Hz), 7.58 (1H, dt, *J* = 1.2, 7.4 Hz), 7.64 (1H, dd, *J* = 1.2, 1.6 Hz), 7.67 (1H, d, *J* = 8.6 Hz), 7.87 (1H, ddd, *J* = 1.2, 7.8, 10.6 Hz), 7.91 (1H, dd, *J* = 1.2, 5.1 Hz), 13.05 (1H, br); Anal. calcd for $C_{21}H_{16}FN_3O_4$: C, 64.12; H, 4.10; N, 10.68; found C, 63.95; H, 4.12; N, 10.49.

*4.10.87. 3-({6-[(5,6-Dimethylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16l**).*

Compound **16l** was prepared according to general procedure F (yield, 96%). Mp, 234–241 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.19 (3H, s), 2.25 (3H, s), 3.82 (3H, s), 5.47 (2H, s), 6.66 (1H, d, *J* = 7.8 Hz), 6.94 (1H, dd, *J* = 2.4, 8.6 Hz), 7.37 (1H, d, *J* = 2.0 Hz), 7.38 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.45 (1H, t, *J* = 7.4 Hz), 7.54 (1H, d, *J* = 8.2 Hz), 7.58 (1H, dt, *J* = 1.6, 6.3 Hz), 7.63–7.65 (2H, m), 13.03 (1H, br); Anal. calcd for $C_{23}H_{21}N_3O_4$•0.33H_2O: C, 67.47; H, 5.33; N, 10.26; found C, 67.40; H, 5.26; N, 10.27.

*4.10.88. 3-({6-[(3,6-Dimethylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16m**).*

Compound **16m** was prepared according to general procedure F (yield, 50%). Mp, 215–220 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.19 (3H, s), 2.28 (3H, s), 3.82 (3H, s), 5.47 (2H, s), 6.88 (1H, d, *J* = 7.0 Hz), 6.93 (1H, dd, *J* = 2.4, 8.6 Hz), 7.35 (1H, d, *J* = 2.4 Hz), 7.37–7.39 (1H, m), 7.45 (1H, t, *J* = 7.8 Hz), 7.57–7.65 (4H, m), 13.04 (1H, br); Anal. calcd for $C_{23}H_{21}N_3O_4$•0.20H_2O: C, 67.87; H, 5.30; N, 10.32; found C, 68.14; H, 5.17; N, 10.32.

*4.10.89. 3-({6-[(3-Fluoro-5-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16n**).*

Compound **16n** was prepared according to general procedure F (yield, 98%). Mp, 266–268 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 2.27 (3H, s), 3.82 (3H, s), 5.47 (2H, s), 7.00 (1H, dd, *J* = 2.4, 8.8 Hz), 7.38 (1H, dd, *J* = 1.5, 7.8 Hz), 7.42 (1H, d, *J* = 2.4 Hz), 7.44 (1H, t, *J* = 8.3 Hz), 7.56 (1H, dt, *J* = 1.5, 7.3 Hz), 7.63–7.65 (2H, m), 7.73 (1H, dd, *J* = 1.5, 11.2 Hz), 7.75 (1H, s), 13.01 (1H, br); Anal. calcd for $C_{22}H_{18}FN_3O_4$•0.20H_2O: C, 64.29; H, 4.51; N, 10.22; found C, 64.28; H, 4.41; N, 10.20.

*4.10.90. 3-({6-[(5-Fluoro-3-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16o**).*

Compound **16o** was prepared according to general procedure F (yield, 95%). Mp, 255–264 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.35 (3H, s), 3.81 (3H, s), 5.47 (2H, s), 6.95 (1H, dd, *J* = 2.4, 8.6 Hz), 7.36–7.38 (2H, m), 7.44 (1H, t, *J* = 7.4 Hz), 7.57 (1H, d, *J* = 7.4 Hz), 7.62–7.64 (2H, m), 7.75 (1H, dd, *J* = 2.7, 8.6 Hz), 7.89 (1H, dd, *J* = 0.8, 2.7 Hz), 13.04 (1H, br); Anal. calcd for $C_{22}H_{18}FN_3O_4$•0.50H_2O: C, 63.46; H, 4.60; N, 10.09; found C, 63.74; H, 4.26; N, 10.26.

*4.10.91. 3-({6-[(3,5-Dichloropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16p**).*

Compound **16p** was prepared according to general procedure F (yield, 93%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.49 (2H, s), 7.04 (1H, dd, *J* = 2.4, 9.0 Hz), 7.39 (1H, dd, *J* = 2.4, 8.2 Hz), 7.45 (1H, t, *J* = 7.8 Hz), 7.51 (1H, d, *J* = 2.4 Hz), 7.57 (1H, d, *J* = 7.4 Hz), 7.64 (1H, s), 7.68 (1H, d, *J* = 9.0 Hz), 8.12 (1H, dd, *J* = 0.8, 2.4 Hz), 8.36 (1H, d, *J* = 2.4 Hz), 13.04 (1H, br); Anal. calcd for $C_{21}H_{15}Cl_2N_3O_4$•0.25H_2O: C, 56.20; H, 3.48; N, 9.36; found C, 56.20; H, 3.30; N, 9.53.

*4.10.92. 3-({6-[(5-Chloro-3-fluoropyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16q**).*

Compound **16q** was prepared according to general procedure F (yield, 94%). Mp, 245–262 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 5.49 (2H, s), 7.06 (1H, ddd, *J* = 1.2, 2.4, 8.6 Hz), 7.37–7.40 (1H, m), 7.45 (1H, t, *J* = 7.4 Hz), 7.52 (1H, d, *J* = 2.4 Hz), 7.58 (1H, dd, *J* = 1.6, 7.8 Hz), 7.64 (1H, t, *J* = 1.2 Hz), 7.68 (1H, d, *J* = 8.6 Hz), 8.02 (1H, dd, *J* = 1.2, 2.4 Hz), 8.23 (1H, ddd, *J* = 1.2, 2.0, 9.8 Hz), 13.06 (1H, s); Anal. calcd for $C_{21}H_{15}ClFN_3O_4$: C, 58.96; H, 3.53; N, 9.82; found C, 58.73; H, 3.40; N, 9.74.

*4.10.93. 3-({6-[(5-Chloro-3-methylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**16r**).*

Compound **16r** was prepared according to general procedure F (yield, 51%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.32 (3H, s), 3.79 (3H, s), 5.45 (2H, s), 6.94 (1H, dd, *J* = 2.2. 8.8 Hz), 7.37–7.41 (3H, m), 7.53–7.55 (1H, m), 7.60–7.62 (2H, m), 7.83–7.85 (1H, m), 7.89–7.92 (1H, m), 13.01 (1H, s); MS (FAB) *m/z*: 424 $[M + H]^+$; Anal. calcd for $C_{22}H_{18}ClN_3O_4$: C, 58.96; H, 3.53; N, 9.82; found C, 58.73; H, 3.40; N, 9.74.

*4.10.94. Methyl 3-({6-[(3,5-dibromopyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**17**).*

A solution of **13** (275 g, 881 mmol), 3,5-dibromo-2-fluoropyridine (247 g, 969 mmol), CuI (16.8 g, 88.2 mmol), 1,10-phenanthroline (15.9 g, 88.2 mmol) and Cs_2CO_3 (861 g, 2.64 mol) in DMF (4.0 L) was stirred at 80 °C for 24 h under N_2. Aqueous NH_4Cl solution (10%, 5.0 L) was added to the cooled reaction mixture, and the precipitated solid was collected. The solid was dissolved in CH_2Cl_2 (17.0 L). The organic layer was washed with water (2.0 L) and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel chromatography (Chromatorex NH; CH_2Cl_2) to obtain **17** (476 g, 99%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.83 (3H, s), 3.85 (3H, s), 5.50 (2H, s), 7.02 (1H, dd, *J* = 2.4, 8.6 Hz), 7.43 (1H, ddd, *J* = 1.2, 2.7, 8.2 Hz), 7.46–7.50 (2H, m), 7.59 (1H, dt, *J* = 1.6, 7.4 Hz), 7.66–7.68 (2H, m), 8.20 (1H, d, J = 2.0 Hz), 8.52 (1H, d, J = 2.4 Hz).

*4.10.95. Methyl 3-({6-[(3,5-dimethylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoate (**18**).*

A solution of **17** (238 g, 435 mmol), trimethylboroxine (50% solution in THF, 500 mL, 1.77 mol), $PdCl_2$(dppf)•CH_2Cl_2 complex

(35.0 g, 43.5 mmol) and K_2CO_3 (241 g, 1.74 mol) in DMF (4.5 L) was stirred at 80 °C for 17 h under N_2. Water (20 L) was added to the cooled reaction mixture, and the mixture was extracted with EtOAc (17.0 L). The organic layer was washed with brine (3.0 L) and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue was purified by silica gel chromatography (EtOAc) to obtain **18** (145 g, 80%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 2.36 (3H, s), 3.84 (3H, s), 3.93 (3H, s), 5.41 (2H, s), 7.02 (1H, dd, J = 2.0, 8.6 Hz), 7.12 (1H, d, J = 2.0 Hz), 7.28–7.31 (1H, m), 7.35–7.39 (2H, m), 7.69 (1H, dt, J = 1.2, 7.4 Hz), 7.72–7.79 (3H, m).

*4.10.96. 3-({6-[(3,5-Dimethylpyridin-2-yl)oxy]-1-methyl-1H-benzimidazol-2-yl}methoxy)benzoic acid (**I**, DS-6930).*

A solution of **18** (296 g, 709 mmol) and 1 M NaOH (1.8 L) in MeOH (3.5 L) was stirred at 80 °C for 2 h. The reaction mixture was neutralized by adding 1 M HCl at 0 °C, and the precipitated solid was collected by filtration to obtain **I** (281 g, 99%) as a white solid. Mp, 243–247 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.20 (3H, s), 2.30 (3H, s), 3.81 (3H, s), 5.47 (2H, s), 6.92 (1H, dd, J = 2.4, 8.6 Hz), 7.32 (1H, d, J = 2.4 Hz), 7.36 (1H, dd, J = 1.6, 7.4 Hz), 7.44 (1H, t, J = 7.4 Hz), 7.54–7.63 (4H, m), 7.72 (1H, s), 13.04 (1H, br); Anal. calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42; Cl, 0.00; Na, 0.00; found C, 68.29; H, 5.17; N, 10.41; Cl, 0.00; Na,0.00.

4.11. Measurement of PPAR 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[15] 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 DS-6930, which are from two independent experiments run in octuplicate.

4.12. 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).

4.13. 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.

4.14. Parallel Artificial Membrane Permeation Assay (PAMPA).

DMSO solution of the test compounds (10 mM) was diluted with buffer (consisting of PRISMA HT (pION) and DMSO) to obtain donor solutions (pH 7.4) with concentration of 5 μM. GIT-0 lipid solution (pION) was applied onto acceptor plate filters (Stirwell PAMPA Sandwich, pION). And the donor solutions of pH 7.4 were added to the donor plate, and the acceptor sink buffer (pION) to the acceptor plate, respectively. The donor plate was placed on the top of the acceptor plate and incubated at 25 °C for 4 hours. The donor and acceptor solutions were collected, and the concentrations of each compound were determined by LC-MS/MS. The apparent permeability coefficient (P_{app}, 10^{-6} cm/sec) was calculated by PAMPA Evolution DP (pION) from the area ratio and incubation time to the internal standard. Data represent single experiment run in duplicate unless otherwise noted.

4.15. 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

4.16. In Vivo Pharmacological Effects of DS-6930.

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 ZDF rats were purchased from Charles River Laboratories Japan,

Inc. and acclimatized for one week. Before the study, the PG level was measured, and individuals having a PG level of about 240 mg/dL or more were selected. The test compound was orally administered to ZDF rats once daily for 21 days ($n = 8$). Water was administered orally to the control group. Body weight was measured and blood was collected from the tail vein to measure the PG level.

4.17. 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).

4.18. In Vitro hepatotoxicity Evaluation.

Rat primary cultured hepatocytes were harvested from male F344/DuCrlCrlj rats (> 8 weeks age) and maintained with sandwich culture between extracellular matrix layers. Test compounds were dissolved with DMSO, diluted with medium to be 0.5% as final DMSO concentration, and exposed for 24 hrs. Cytotoxicity was evaluated with LDH leakage assay and water-soluble tetrazolium based assay (WST-8 assay). Data represent single experiment run in quadruplicate.

4.19. 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. Six-week-old female F344/DuCrlCrlj SPF 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.

4.20. Yeast 2-Hybrid (Y2H) Assay.

Two expression plasmids were used allowing expression of distinct hybrid proteins. The fusion protein expressed from pGBT9 (Clontech)-based vector expressing the NR or cofactor C-terminally fused to the DNA BD of the GAL4 transcription factor is referred to as BAIT. The fusion protein espressed from pGAD424 (Clontech)-based vector expressing the NR or cofactor C-terminally fused to the transcriptional activation domain of the GAL4 transcription factor is referred to as PREY. The BAIT expression plasmids were transformed into yeast strain AH109a (Clontech), and the PREY expression plasmids into strain Y187alpha (Clontech) using a standard lithium acetate/PEG/heatshock procedure. Yeast strains were mated by mixing equal volumes of the haploid yeast strains in selective medium supplemented with 0.5 volumes of rich YPDA medium. Cells were incubated for 5-7 h at 28 °C. After mating, a small aliquot of the yeast cell suspension was transferred into the medium selective for diploid cells and grown to saturation. The cells were diluted in the medium selective for interacting clones.

Serial dilutions of the test compounds and the control solution (0.25% DMSO) were added into the individual wells of 96-well plates. The plate was incubated for 24 or 48 h in an incubator at 28 °C and fluorescence was measured upon excitation at 355 nm wavelength and emission at 460 nm wavelength (Perkin Elmer VictorTMX4 instrument). Data represent single experiment run in quadruplicate.

4.21. Protein Crystallography Method.

Histidine-tagged human PPARγ-LBD was expressed and purified as described previously.[24] 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 DS-6930 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,[25] and converted to structure factors using the CCP4 software suite.[26] The structure of PPARγ-LBD derived from the structure 3V9T.pdb[27] was used as an initial model. Several rounds of manual rebuilding with O[28] followed by refinement with CNX[29] (Accerlys) were carried out. A Ramachandran plot for the final model was calculated with RAMPAGE.[30] 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 5Z6S.

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7. Notes

The authors declare no competing financial interest.

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Graphical Abstract

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Discovery of DS-6930, a Potent Selective PPARγ Modulator. Part II: Lead Optimization

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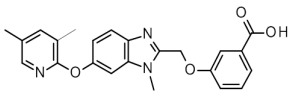

DS-6930
PPARγ EC_{50}: 41 nM
PPARγ E_{max}: 68%