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3-(2-Aminocarbonylphenyl)propanoic acid analogs as potent and selective EP3 receptor antagonists. Part 2: Optimization of the side chains to improve in vitro and in vivo potencies

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ABSTRACT

A series of 3-[2-{[(3-methyl-1-phenylbutyl)amino]carbonyl}-4-(phenoxymethyl)phenyl]propanoic acid analogs were synthesized and evaluated for their in vitro potency. In most cases, introduction of one or two substituents into the two phenyl moieties resulted in the tendency of an increase or retention of in vitro activities. Several compounds, which showed excellent subtype selectivity, were evaluated for their inhibitory effect against PGE_2-induced uterine contraction in pregnant rats, which is thought to be mediated by the EP3 receptor subtype. The structure–activity relationships (SARs) are also discussed.

1. Introduction

Prostaglandin E_2 (PGE_2), which plays important roles in numerous physiological actions, has been known as the most widely distributed prostanoid in the living body. It has been demonstrated that these various biological actions are mediated by the four receptor subtypes, namely EP1, EP2, EP3, and EP4.[1] Since a large number of studies using EP1-4 knockout mice have made significant contributions toward understanding their accessibility as new therapeutic targets, the discovery of subtype selective ligands has renewed interest for medicinal chemists in the field. In addition, clinical trials for several selective ligands including ONO-8539 (ONO, EP1 antagonist),[2] ONO-8815 (ONO, EP2 agonist),[3] CP-533536 (Pfizer, EP2 agonist),[4] DG-041 (de CODE, EP3 antagonist),[5] ONO-4819 (ONO, EP4 agonist),[6] RQ-00000007 (RaQualia, EP4 antagonist),[7] and BGC20-1531 (BTG, EP4 antagonist)[8] have also been reported. Among them, the EP3 antagonist, DG-041, has been clinically tested for the treatment of peripheral occupied arterial disease (PAOD).

In our previous paper,[9] we reported the discovery of 3-(2-aminocarbonyl-4-phenoxymethylphenyl)propanoic acid analogs **1** and **2** (Table 1) as new chemical leads of a potent and selective EP3 antagonist. Compound **2** showed significantly more potent antagonist activity relative to **1**, while **2** showed nearly equipotent activity relative to **1** in its in vivo evaluation. This inconsistency between in vitro and in vivo data was considered to be mainly due to the pharmacokinetic profiles of **1** ($F = 31\%$) and **2** ($F = 3.9\%$). In this paper, we report the further optimization of **1** to improve its in vitro and in vivo potencies as a potent and selective EP3 antagonist.

2. Chemistry

Synthesis of test compounds listed in Tables 2 and 3 is outlined in Schemes 1–8.

A series of 1-phenyl-3-methylbutylamines were synthesized as described in Schemes 1–4. Amines **59a–h** were synthesized as shown in Scheme 1. Reaction of *t*-butyl magnesium chloride (**53**) with gaseous sulfur dioxide provided sulfinic acid **54**. Reaction of **54** with thionyl chloride followed by the addition of aqueous ammonia afforded sulfinamide **55**.[10] Dehydrative condensation of **55** with benzaldehydes **56a–h** afforded sulfinimines **57a–h**, respectively. Nucleophilic addition reaction of 2-methylpropenylmagnesium chloride to **57a–h** afforded the corresponding sulfinamides **58a–h**, respectively. Catalytic hydrogenation of **58a–h** followed by acidic deprotection resulted in **59a–h** as their respective hydrochlorides.

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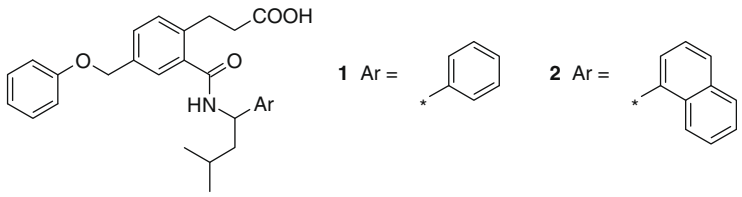
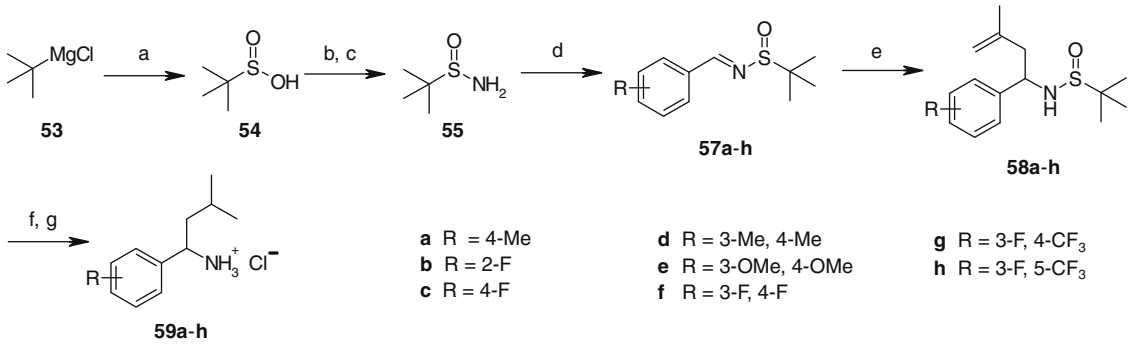
Table 1
Activity and pharmacokinetic profiles of **1** and **2**

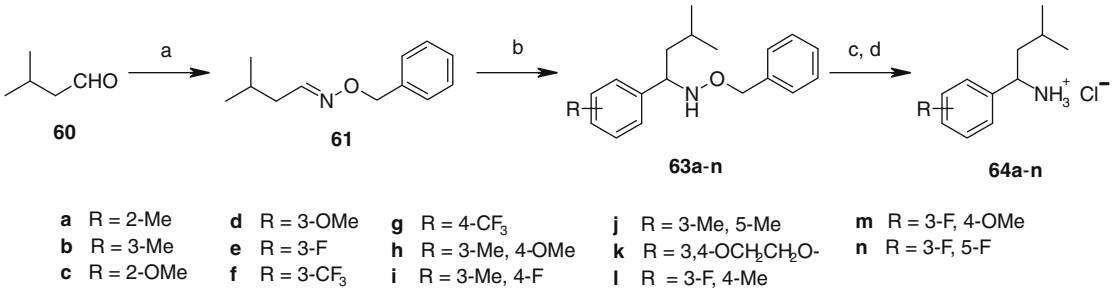


Compound	In vitro EP3 activity[a]		In vivo efficacy[c]	PK profiles in rats		
	Binding K_i (nM)	Function IC_{50}[b] (nM)	%inh. (3 mg/kg id)	CL_{tot} (mL/min/kg)	C_{max} (μg/mL) at 10 mg/kg po	F (%)
1	0.70	68	71%	15.3	2.66	31
2	0.34	2.0	83%	16.0	0.28	3.9

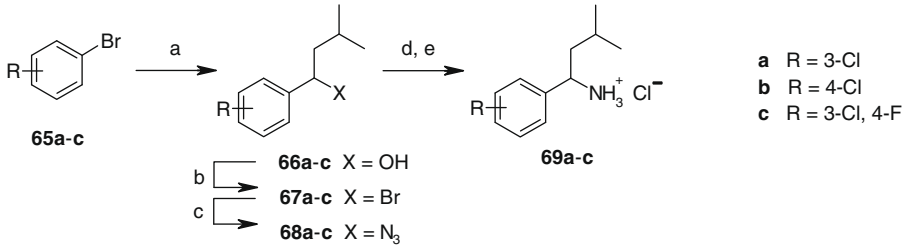
[a] Mouse EP3 receptor was used.
[b] EP3 antagonist activity was evaluated in the presence of 1% BSA.
[c] In vivo efficacy was evaluated as % inhibition against the PGE_2-induced uterine contraction in pregnant rats.



Scheme 1. Synthesis of **59a–h**. Reagents: (a) SO_2, Et_2O; (b) $SOCl_2$, CH_2Cl_2; (c) NH_3aq, THF; (d) benzaldehydes **56a–h**, PPTS, $MgSO_4$, CH_2Cl_2; (e) 2-methylpropenylmagnesium chloride, THF; (f) H_2, PtO_2, MeOH; (g) HCl–dioxane, MeOH.

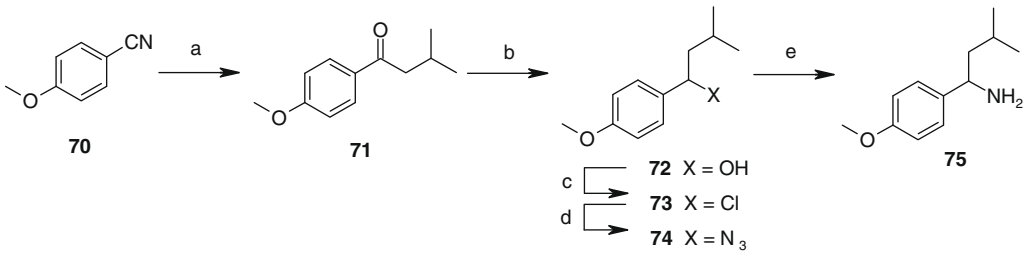


Scheme 2. Synthesis of **64a–n**. Reagents: (a) *O*-benzylhydroxylamine hydrochloride, $MgSO_4$, CH_2Cl_2; (b) aryl bromides **62a–n**, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF; (c) H_2, Pd–C, MeOH; (d) HCl–dioxane, EtOAc.

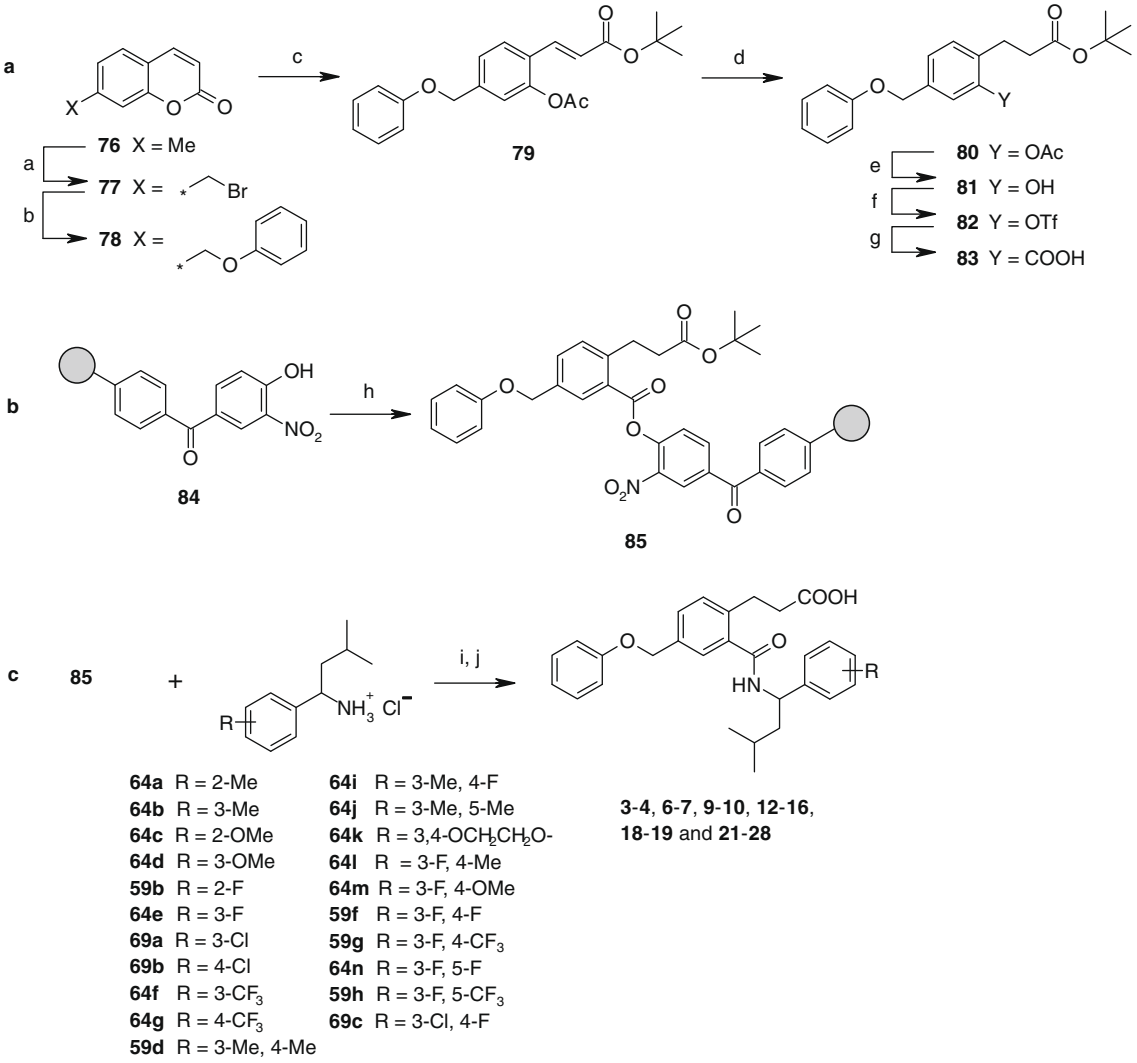


Scheme 3. Synthesis of **69a–c**. Reagents: (a) *n*-BuLi, isovaleraldehyde (**60**), THF; (b) PBr_3, CH_2Cl_2; (c) NaN_3, DMF; (d) Ph_3P, THF, H_2O; (e) HCl–dioxane.

Synthesis of amines **64a–n** is described in Scheme 2. A common intermediate **61** was prepared by a dehydrative condensation of isovaleraldehyde (**60**) with *O*-benzylhydroxylamine hydrochloride in the presence of magnesium sulfate. Lithiation of aryl bromides



Scheme 4. Synthesis of **75**. Reagents: (a) isobutylmagnesium chloride, THF then HClaq; (b) $NaBH_4$, MeOH; (c) MsCl, LiCl, Et_3N, THF; (d) NaN_3, DMF; (e) Ph_3P, THF, H_2O.

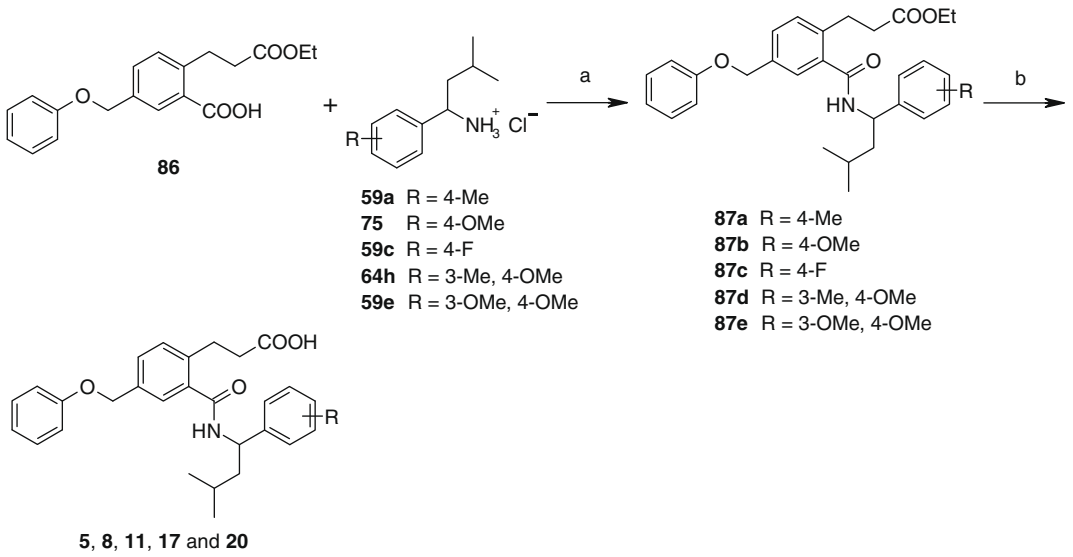


Scheme 5. Synthesis of **3**–**4**, **6**–**7**, **9**–**10**, **12**–**16**, **18**–**19**, and **21**–**28**. Reagents: (a) NBS, AIBN, CCl_4; (b) phenol, NaH, DMF; (c) *t*-BuOK, THF then AcCl; (d) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, THF, MeOH; (e) K_2CO_3, MeOH; (f) Tf_2O, pyridine, CH_2Cl_2; (g) CO, $Pd(OAc)_2$, DPPF, KOAc, DMF; (h) **83**, EDC·HCl, DMAP, $ClCH_2CH_2Cl$; (i) *i*-Pr_2NEt, $ClCH_2CH_2Cl$; (j) TFA, anisole, CH_2Cl_2.

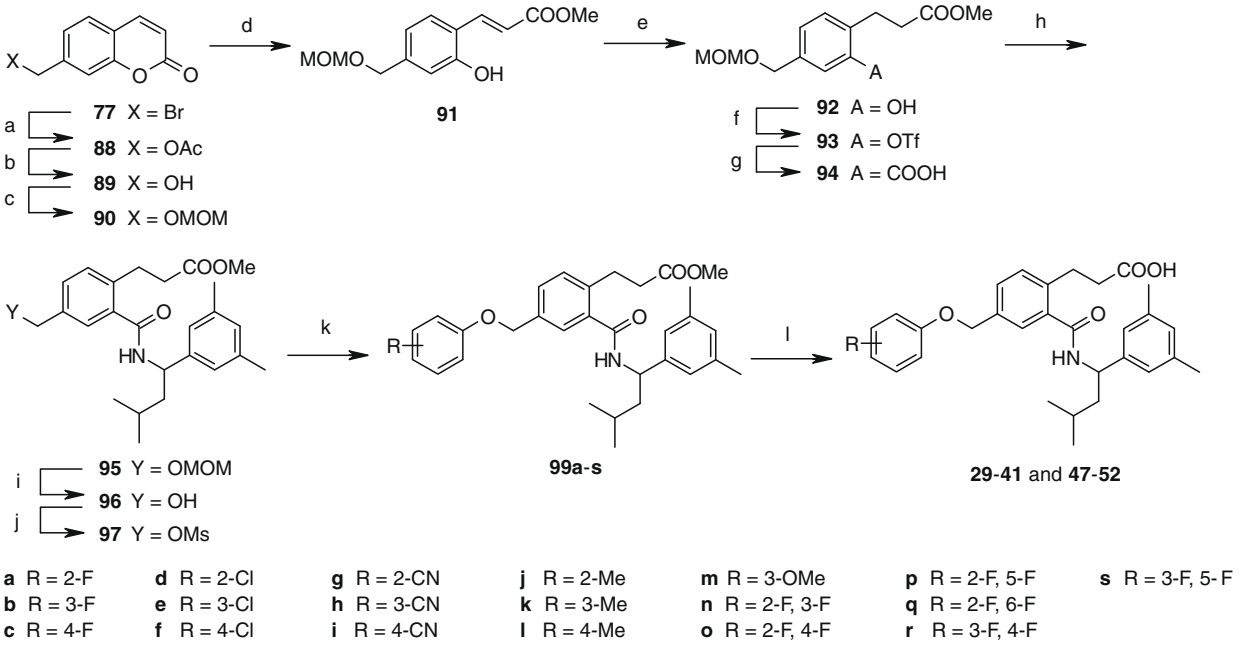
62a–**n** followed by the addition of **61** in the presence of boron trifluoride etherate afforded **63a**–**n**, respectively.[11] Catalytic hydrogenation of **63a**–**n** followed by treatment with hydrogen chloride afforded **64a**–**n** as their respective hydrochlorides.

Synthesis of amines **69a**–**c** is outlined in Scheme 3. Lithiation of aryl bromides **65a**–**c** followed by the addition of isovaleraldehyde (**60**) afforded **66a**–**c**, bromination of which with phosphoric tribromide provided **67a**–**c**. Substitution reaction of **67a**–**c** with sodium azide afforded **68a**–**c**. Reduction of the azides **68a**–**c** with triphenylphosphine followed by the treatment with hydrogen chloride produced amines **69a**–**c**, as their respective hydrochlorides.

Amine **75** was synthesized from 4-methoxybenzonitrile (**70**), as shown in Scheme 4. Nucleophilic addition reaction of isobutylmagnesium chloride to **70** followed by the acidic treatment afforded ketone **71**. Sodium borohydride reduction of **71** provided **72**. Reaction of **72** with methanesulfonyl chloride in the presence of lithium chloride and triethylamine afforded **73**, substitution reaction of which with sodium azide provided **74**. Reduction of **74** with triphenylphosphine resulted in **75**.



Scheme 6. Synthesis of **5**, **8**, **11**, **17**, and **20**. Reagents: (a) EDC·HCl, HOBt, *N*-methylmorpholine, DMF; (b) NaOHaq, THF, MeOH.

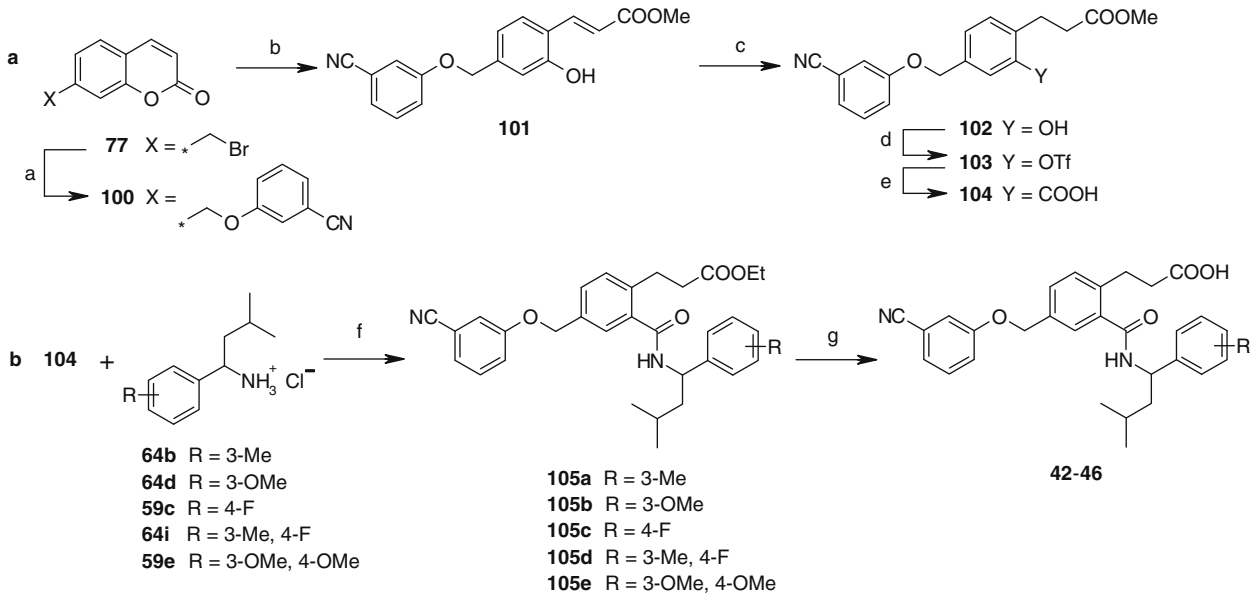


Scheme 7. Synthesis of **29**–**41** and **47**–**52**. Reagents: (a) KOAc, DMF; (b) NaOHaq, THF, MeOH; (c) MOMCl, *i*-Pr_2NEt, dichloroethane; (d) NaOMe, THF, MeOH; (e) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, THF, MeOH; (f) Tf_2O, pyridine, CH_2Cl_2; (g) CO, $Pd(OAc)_2$, DPPF, KOAc, DMF; (h) **64j**, EDC·HCl, HOBt, *N*-methylmorpholine, DMF; (i) HCl–dioxane, MeOH; (j) MsCl, Et_3N, THF; (k) phenols **98a**–**s**, NaH, DMF; (l) NaOHaq, THF, MeOH.

As shown in Scheme 5a–c, compounds **3**–**4**, **6**–**7**, **9**–**10**, **12**–**16**, **18**–**19**, and **21**–**28** were synthesized using a polymer-supported activated ester **85** as a key intermediate. Synthesis of the carboxylic acid **83** is described in Scheme 5a. Bromination of 7-methylcoumarin (**76**) with *N*-bromosuccinimide in the presence of azobisisobutyronitrile in carbon tetrachloride afforded **77**. Substitution reaction of the bromide **77** with sodium phenoxide provided **78**. Ring-opening reaction of **78** with *t*-butoxide followed by the treatment of the formed phenoxide with acetyl chloride afforded **79**. 1,4-Reduction of the unsaturated ester **79** with sodium borohydride in the presence of nickel chloride provided saturated ester **80**,[12] methanolysis of which provided **81**. Trifluoromethanesulfonylation of the phenol **81** afforded **82**, which was converted to the carboxylic acid **83** by the palladium-catalyzed insertion reaction of carbon monoxide. Dehydrative condensation of the nitrophenol resin **84**[13] with **83** afforded the nitrophenol ester resin **85** as shown in Scheme 5b. Aminolysis of **85** with amines **64a**–**d**, **59b**, **64e**, **69a**–**b**, **64f**–**g**, **59d**, **64i**–**m**, **59f**–**g**, **64n**, **59h**, and **69c** followed by acidic deprotection afforded analogs **3**–**4**, **6**–**7**, **9**–**10**, **12**–**16**, **18**–**19**, and **21**–**28**, respectively, as shown in Scheme 5c.

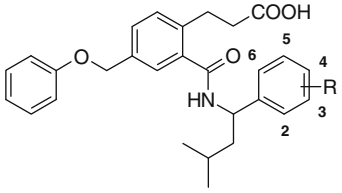
As shown in Scheme 6, several analogs such as **5**, **8**, **11**, **17**, and **20** were derived from the previously reported carboxylic acid **86**.[9] Condensation reaction of **86** with amines **59a**, **75**, **59c**, **64h**, and **59e** afforded **87a**–**e**, respectively, alkaline hydrolysis of which afforded the corresponding carboxylic acids **5**, **8**, **11**, **17**, and **20**, respectively.

Synthesis of **29**–**41** and **47**–**52** is described in Scheme 7. Substitution reaction of the bromide **77** with potassium acetate afforded



Scheme 8. Synthesis of **42–46**. Reagents: (a) 3-cyanophenol, NaH, DMF; (b) NaOMe, THF, MeOH; (c) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, THF, MeOH; (d) Tf_2O, pyridine, CH_2Cl_2; (e) CO, $Pd(OAc)_2$, DPPF, KOAc, DMF; (f) EDC·HCl, HOBt, *N*-methylmorpholine, DMF; (g) NaOHaq, THF, MeOH.

Table 2
Effect of the substituent on the benzene ring of the carboxyamide side chain on activity profiles



Compound	R	In vitro EP3 activity[a]	
		Binding K_i (nM)	Function IC_{50}[b] (nM)
1	H	0.70	68
3	2-Me	0.94	230
4	3-Me	0.30	37
5	4-Me	0.63	51
6	2-OMe	1.2	190
7	3-OMe	0.13	21
8	4-OMe	0.36	59
9	2-F	1.4	130
10	3-F	0.20	40
11	4-F	0.93	20
12	3-Cl	0.18	35
13	4-Cl	0.28	51
14	3-CF_3	0.39	39
15	4-CF_3	0.76	32
16	3-Me, 4-Me	0.17	16
17	3-Me, 4-OMe	0.16	11
18	3-Me, 4-F	0.16	18
19	3-Me, 5-Me	0.19	17
20	3-OMe, 4-OMe	0.50	24
21	3,4-(–OCH_2CH_2O–)	0.44	19
22	3-F, 4-Me	0.20	67
23	3-F, 4-OMe	0.14	42
24	3-F, 4-F	0.40	47
25	3-F, 4-CF_3	0.70	53
26	3-F, 5-F	0.30	19
27	3-F, 5-CF_3	0.45	15
28	3-Cl, 4-F	0.26	25

[a] Mouse EP3 receptor was used.
[b] EP3 antagonist activity was evaluated in the presence of 1% BSA.

88, alkaline hydrolysis of which provided **89**. Protection of the formed hydroxy group of **89** as a methoxymethyl ether afforded **90**, ring-opening reaction of which resulted in methyl acrylate **91**. Sodium borohydride reduction of **91** in the presence of nickel chloride afforded saturated ester **92**,[12] which was converted to the carboxylic acid **94** in the same manner as described for **83**. Condensation of **94** and 1-(3,5-dimethylphenyl)-3-methylbutylamine hydrochloride (**64j**) afforded carboxyamide **95**, acidic deprotection of which provided benzyl alcohol **96**. Methanesulfonylation of **96** gave **97**, substitution reaction of which with sodium phenoxides derived from the commercially available phenols **98a–s** afforded the corresponding phenoxyethers **99a–s**, respectively. Alkaline hydrolysis of **99a–s** produced the corresponding carboxylic acids **29–41** and **47–52**, respectively.

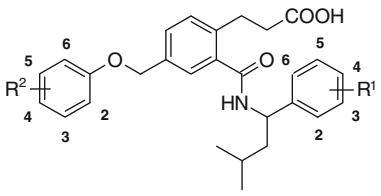
4-(3-Cyanophenoxymethylphenyl)propanoic acid analogs **42–46** were synthesized as shown in Scheme 8. Substitution reaction of the bromide **77** with sodium 3-cyanophenoxide resulted in **100**, which was converted to carboxylic acid **104** by the same procedures as described above. Condensation reaction of **104** with 3-methyl-1-phenylbutylamines **64b**, **64d**, **59c**, **64i**, and **59e** gave carboxyamides **105a–e**, respectively, alkaline hydrolysis of which produced the corresponding carboxylic acids **42–46**, respectively.

3. Results and discussion

Test compounds listed in Tables 2 and 3 were biologically evaluated for their inhibition of the specific binding of a radiolabeled ligand, [^{3}H]PGE_2 to membrane fractions prepared from cells stably expressing mouse EP1, EP2, EP3α, or EP4 receptor. The EP3 receptor antagonist activity was determined by a Ca^{2+} assay using mouse EP3α receptors expressed on CHO cells in the presence of 1% bovine serum albumin (BSA).

In our previous paper,[9] we reported the discovery of 3-(2-aminocarbonyl-4-phenoxymethylphenyl)propanoic acids **1** and **2** as new chemical leads for a selective EP3 receptor antagonist. Among them, *N*-benzylcarboxyamide analog **1** was selected as a new chemical lead for further optimization because of its superior PK profiles relative to **2**. To optimize the benzene ring of the carboxyamide side chain of **1**, polymer-supported activated ester was used

Table 3
Effect of the substituent on the benzene ring of the phenoxymethyl side chain on activity profiless



Compound	R^1	R^2	In vitro EP3 activity[a]	
			Binding K_i (nM)	Function IC_{50}[b] (nM)
19	3-Me, 5-Me	H	0.19	17
29	3-Me, 5-Me	2-F	0.10	13
30	3-Me, 5-Me	3-F	0.13	15
31	3-Me, 5-Me	4-F	0.25	5.4
32	3-Me, 5-Me	2-Cl	0.090	8.3
33	3-Me, 5-Me	3-Cl	0.21	3.8
34	3-Me, 5-Me	4-Cl	0.62	30
35	3-Me, 5-Me	2-CN	0.35	9.4
36	3-Me, 5-Me	3-CN	0.12	3.9
37	3-Me, 5-Me	4-CN	0.46	16
38	3-Me, 5-Me	2-Me	0.17	3.9
39	3-Me, 5-Me	3-Me	0.11	4.2
40	3-Me, 5-Me	4-Me	0.67	16
41	3-Me, 5-Me	3-OMe	0.27	3.2
42	3-Me	3-CN	0.20	6.6
43	3-OMe	3-CN	0.13	3.2
44	4-F	3-CN	0.17	7.1
45	3-Me, 4-F	3-CN	0.20	2.8
46	3-OMe, 4-OMe	3-CN	0.67	3.7
47	3-Me, 5-Me	2-F, 3-F	0.15	3.6
48	3-Me, 5-Me	2-F, 4-F	0.19	6.0
49	3-Me, 5-Me	2-F, 5-F	0.10	7.0
50	3-Me, 5-Me	2-F, 6-F	1.3	59
51	3-Me, 5-Me	3-F, 4-F	0.34	5.7
52	3-Me, 5-Me	3-F, 5-F	0.19	10

[a] Mouse EP3 receptor was used.
[b] EP3 antagonist activity was evaluated in the presence of 1% BSA.

Table 4
In vivo efficacy of **18**, **19**, **30**, **36**, **38**, and **49**

Compound	In vivo efficacy (%inh., id)[a]		
	0.1 mg/kg (%)	0.3 mg/kg (%)	1 mg/kg (%)
18	NT[b]	31	73
19	NT[b]	28	73
30	NT[b]	66	84
36	NT[b]	55	95
38	NT[b]	62	83
49	48	93	98

[a] In vivo efficacy was evaluated as %inhibition against the PGE_2-induced uterine contraction in pregnant rats.
[b] Not tested.

as an intermediate. Further chemical modification of the benzene ring of the 4-phenoxymethyl moiety was also easily carried out because of the readily available substituted phenols.

Effect of the substituent on the benzene ring of the carboxyamide side chain was investigated as shown in Table 2. Introduction of a methyl group into the benzene ring afforded **3**–**5**. Among them, 3-methylphenyl analog **4** was more potent than **3** and **5**. Methoxyphenyl analogs **6**–**8** and fluorophenyl analogs **9**–**11** were also synthesized and evaluated for their binding affinity and antagonist activity. Again 3-substituted phenyl analogs **7** and **10** were more potent in terms of their binding affinity than others in each of the series, although the antagonist activity did not always follow the same trend as the binding affinity as exemplified by **11**. Evaluation of the binding affinity (K_i values) was carried out in the absence of BSA, while the evaluation of the antagonist activity (IC_{50} values) was carried out in the presence of 1% BSA to estimate more exact in vivo potency. Compound **10** was functionally 200-fold weaker than its K_i value in the presence of 1% BSA, while compound **11** was functionally only 21-fold weaker than its K_i value. The same tendency was also observed in **1** and **2**, as shown in Table 1. We estimate that these relationships between the K_i values and the IC_{50} values are mainly due to the different potencies of their protein-binding characteristic resulting from the structural features such as basicity and acidity, lipophilicity and hydrophilicity, and three-dimensional structure. Presumed protein binding in an in vivo evaluation has been known as one of the important factors to give an influence on the in vivo efficacy of a drug. For such a reason, the antagonist activity was assessed in the presence of BSA. Unfortunately, 2-substituted phenyl analogs **3**, **6**, and **9** did not show a significant improvement in either binding affinity or antagonist activity relative to others in each of the series. This may be the result of an unfavorable steric interaction between the introduced substituent at the 2-position and an adjacent isobutyl group. Based on the above-described information, chlorophenyl analogs **12**–**13** and trifluoromethylphenyl analogs **14**–**15** were synthesized. 3-Chlorophenyl analog **12** was more potent than 4-chlorophenyl analog **13**. 3-Trifluoromethylphenyl analog **14** was equipotent to 4-trifluoromethylphenyl analog **15** in terms of its EP3 antagonist activities.

Introduction of two substituents into the benzene ring of the carboxyamide side chain was also carried out to afford **16**–**28**. Among them, 3,4-dimethylphenyl analog **16**, 4-methoxy-3-methylphenyl analog **17**, 4-fluoro-3-methylphenyl analog **18**, 3,5-dimethylphenyl analog **19**, 3,4-ethylenedioxyphenyl analog **21**, 3,5-difluorophenyl analog **26**, and 3-fluoro-5-trifluoromethylphenyl analog **27** exhibited equivalent or more potent antagonist activities relative to any other mono-substituent analogs including **7** and **11** regardless of their binding affinity.

Using some of the optimized *N*-benzylcarboxyamide analogs such as **4**, **7**, **11**, and **18**–**20**, further chemical modification of their phenoxymethyl side chain was carried out as described in Table 3. Replacement of the phenoxy moiety of **19** with 2-fluorophenoxy, 3-fluorophenoxy, or 4-fluorophenoxy afforded **29**–**31**, all with equipotent binding affinity. The 4-fluorophenoxy analog **31** was more potent in terms of antagonist activity than **29** and **30**. Further optimization of the substituents provided chlorophenoxy analogs **32**–**34**, cyanophenoxy analogs **35**–**37**, and methylphenoxy analogs **38**–**40**. Among them, 3-chlorophenyl analog **33**, 3-cyanophenyl analog **36**, and 2-methyl analog **38** showed improved antagonist activity with an IC_{50} value of 3.8, 3.9, and 3.9 nM, respectively. However, 4-substituted phenyl analogs **34**, **37**, and **40** tended to exhibit reduced potency in terms of both the binding affinity and the antagonist activity relative to the others. 3-Methoxyphenyl analog **41** had equipotent binding affinity and more potent antagonist activity relative to **19**. Because of the lower *c* log *P* value of 3-cyanophenoxy analog **36** relative to that of **19**, replacement of the phenoxy moiety of **4**, **7**, **11**, **18**, and **20** with a 3-cyanophenoxy moiety afforded **42**–**46**, respectively, with retention of the potent binding affinity. All these substitutions produced compounds with 2.8–6.6-fold more potent antagonist activities relative to their unsubstituted analogs. Further efforts to explore the optimum substituents of the phenoxy moiety resulted in a series of difluorophenoxy analogs **47**–**52** because substitution of the phenoxy moiety with electron-withdrawing fluorine atoms was considered to be effective on the predicted oxidative metabolism. All analogs except **50** exhibited more potent antagonist activities relative to **19**. 2,6-Difluorophenoxy analog **50** showed a significant reduction in both binding affinity and antagonist activity. This significant

Table 5
Pharmacokinetic profiles of **30** and **49** in rats

Compound	Route	Dose	AUC (μg h/mL)	$t_{1/2}$ (h)	CL_{tot} (mL/min/kg)	V_{ss} (L/kg)	C_{max} (μg/mL)	F (%)
30	iv	1.2	0.44	1.5	45.2	1.32		
	po	13	1.09	1.9			0.39	23
49	iv	1.2	0.47	2.1	44.5	1.43		
	po	11	0.85	5.4			0.52	19

reduction in potency for **50** may indicate a deleterious effect of the 2,6-disubstituted phenoxy moiety on the activity profile.

Compounds **18**, **19**, **30**, **36**, **38**, and **49**, all of which showed relatively potent binding affinity and/or antagonist activity, were selected for in vivo evaluation. After intraduodenal dosing, they were evaluated for their inhibitory effect against the PGE_2-induced uterine contraction in pregnant rats, which is thought to be mediated by the EP3 receptor subtype.[14] These results are summarized in Table 4. Compounds **18** and **19**, which had nearly equipotent in vitro activities, showed nearly equipotent in vivo efficacy at dosages of 0.3 mg/kg and 1 mg/kg. Their in vivo potencies were threefold more potent than that of **1**, which was the original lead compound. Compound **30**, which showed nearly equipotent in vitro activity to **18** and **19**, exhibited an increased in vivo efficacy relative to **18** and **19** at dosages of 0.3 mg/kg and 1 mg/kg. Compounds **36** and **38** also showed more potent in vivo efficacy than **18** and **19** at similar dosages. Although compound **49** showed slightly reduced potency in terms of antagonist activity relative to **36** and **38**, it was found to exhibit the most potent in vivo efficacy (48% inhibition at 0.1 mg/kg, 93% inhibition at 0.3 mg/kg, and 98% inhibition at 1 mg/kg) in a dose-dependent manner among the tested compounds. Among the compounds tested for the in vivo efficacy, 3-fluorophenoxy analog **30** and 2,5-difluorophenoxy analog **49** were evaluated for their pharmacokinetic profiles in rats as shown in Table 5. Total clearance (CL_{tot}) of **30** and **49** was larger than that of **1** and **2**, while the bioavailability (F) of **30** and **49** was lower than that of **1** and higher than that of **2**. The maximum concentration (C_{max}) of **49** was lower than that of **1** and slightly higher than that of **2**, while the maximum concentration (C_{max}) of **30** was close to that of **2**. Thus, these two analogs showed improved PK profiles in the maximum concentration (C_{max}) and bioavailability (F) relative to **2**, with potent EP3 antagonist activity. This was the plausible reason for their increased in vivo efficacy.

The binding profiles of **18**, **19**, **30**, **36**, **38**, and **49** for EP1-4 receptor subtypes were also evaluated as shown in Table 6. None had appreciable binding affinity for EP1 and EP2 receptors with K_is >10,000 nM, while they had moderate binding affinity for the EP4 receptor and sub-nanomolar binding affinity for the EP3 receptor. Thus, these compounds were potent and selective EP3 antagonists with in vivo efficacy.

Table 6
Subtype selectivity of **18**, **19**, **30**, **36**, **38**, and **49**

Compound	Binding affinity K_i[a] (nM)			
	EP1	EP2	EP3	EP4
18	>10,000	>10,000	0.16	630
19	>10,000	>10,000	0.19	780
30	>10,000	>10,000	0.13	190
36	>10,000	>10,000	0.12	77
38	>10,000	>10,000	0.17	1200
49	>10,000	>10,000	0.10	230

[a] Mouse EP1-4 receptors were used.

4. Conclusion

Using 3-(2-aminocarbonylphenyl)propanoic acid analog **1** as a scaffold, further optimization was carried out to improve in vitro and in vivo potencies. Chemical modification was focused on the two phenyl moieties of **1**. In most cases, introduction of one or two substituents into the benzene ring of the carboxyamide side chain resulted in the tendency to increase the in vitro activity relative to the unsubstituted phenyl analog **1**. An *ortho*-substitution, which is illustrated by compounds **3**, **6**, and **9**, did not improve the potency of the EP3 binding affinity and antagonist activity. Further chemical modification of another phenyl moiety of **4**, **7**, **11**, and **18**–**20** was carried out. Most of the compounds listed in Table 3 had improved antagonist activity relative to those of their corresponding unsubstituted phenoxymethyl analogs. Several compounds were evaluated for their inhibitory effect against the PGE_2-induced uterine contraction in pregnant rats. Among them, compound **49** possessing excellent subtype selectivity exhibited the most potent in vivo efficacy among the tested compounds with a 10-fold higher potency relative to **1**. Further investigation involving the synthesis of optically active forms and evaluation of their activity profiles will be disclosed elsewhere.

5. Experimental

5.1. Chemistry

5.1.1. General procedures

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra (^{1}H NMR) were taken on a Varian Mercury 300 spectrometer, Varian GEMINI-200, or VXR-200s spectrometer using deuterated chloroform ($CDCl_3$), deuterated dimethylsulfoxide (DMSO-d_6), or deuterated methanol (CD_3OD) as the solvent. Fast atom bombardment mass spectra (FAB-MS, HRMS) and electron ionization (EI) were obtained on a JEOL JMS-DX303HF spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a HITACHI MI200H spectrometer. Infrared spectra (IR) were measured in a Perkin–Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyses were uncorrected. Column chromatography was carried out on silica gel [Merck Silica Gel 60 (0.063–0.200 mm), Wako gel C-200, or Fuji Silysia FL60D]. Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, Silica Gel 60 F254). The following abbreviations for solvents and reagents are used; *t*-butylmethylether (TBME), diethylether (Et_2O), *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethanol (EtOH), ethyl acetate (EtOAc), methanol (MeOH), tetrahydrofuran (THF), azobisisobutylonitrile (AIBN), 1,1′-bis-(diphenylphosphino)ferrocene (DPPF), *N*-bromosuccinimide (NBS), diisopropylethylamime (DIPEA), *N*,*N*-dimethyl-4-aminopyridine (DMAP), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole (HOBt), methanesulfonyl chloride (MsCl), pyridinium *p*-toluenesulfonate (PPTS),

triethylamine (TEA), and trifluoromethanesulfonic anhydride (Tf_2O).

5.1.2. 2-Methylpropane-2-sulfinic acid (54)

A solution of *t*-butylmagnesium chloride (**53**) (2 M in Et_2O, 100 mL, 0.200 mol) in Et_2O (100 mL) was cooled with ice-bath and then sulfur dioxide gas was bubbled into the solution for 2 h below 10 °C. Excess sulfur dioxide gas was removed under reduced pressure and then aqueous NH_4Cl was added. The resultant white precipitate was removed by filtration and the filtrate was saturated with NaCl and then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield **54** (9.90 g, 41%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (br s, 1H), 1.18 (s, 9H).

5.1.3. 2-Methylpropane-2-sulfinamide (55)

To a stirred solution of **54** (5.00 g, 41.4 mmol) in CH_2Cl_2 (50 mL) was added dropwise thionyl chloride (6.20 mL, 82.8 mmol) at 0 °C under argon atmosphere. After being stirred for 20 min, the reaction mixture was diluted with toluene (150 mL) and then evaporated to approximately one-fourth volume. The resultant solution was diluted with THF (100 mL) and was then added dropwise to aqueous NH_3 (28%, 200 mL) in THF (200 mL) at 0 °C. After being stirred for 15 min, the reaction mixture was saturated with NaCl and then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield **55** (3.20 g, 64% in two steps) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (br s, 2H), 1.18 (s, 9H).

5.1.4. 3-Methyl-1-(4-methylphenyl)butan-1-amine hydrochloride (59a)

A solution of **55** (500 mg, 4.10 mmol), **56a** (1.48 g, 12.4 mmol), PPTS (52 mg, 0.205 mmol), and $MgSO_4$ (2.50 g, 20.5 mmol) in dichloroethane (6 mL) was stirred for 12 h at room temperature under argon atmosphere. The reaction mixture was filtrated and the filtrate was concentrated in vacuo to afford **57a**, which was used for the next step without purification. To a stirred solution of **57a** in CH_2Cl_2 (15 mL) was added dropwise 2-methylpropenyl magnesium chloride (0.5 M in Et_2O, 35 mL, 17.5 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min, the reaction was quenched with water and then the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was passed through a short-pass column chromatography to remove less polar impurities. The resultant residue was diluted with MeOH (5 mL) and then PtO_2 (300 mg) was added. The suspension was stirred for 12 h under hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The resultant residue was diluted with MeOH (4 mL) and then 4 M HCl in dioxane (4 mL) was added at room temperature. After being stirred for 1 h, the reaction mixture was concentrated in vacuo. The resultant residue was washed with EtOAc–hexane to afford **59a** (135 mg, 13% from **55**) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (br s, 3H), 7.47 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 4.27 (m, 1H), 2.40 (s, 3H), 1.88–1.76 (m, 2H), 1.35 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H).

5.1.5. 1-(2-Fluorophenyl)-3-methylbutan-1-amine hydrochloride (59b)

The titled compound was synthesized in the same manner as described for **59a** using **56b** instead of **56a** as a brown powder. Yield 55% from **55**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.55–7.42 (m, 2H), 7.35–7.17 (m, 2H), 4.62 (dd, J = 9.9, 6.0 Hz, 1H), 2.03–1.89 (m, 1H), 1.87–1.75 (m, 1H), 1.49–1.33 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

5.1.6. 1-(4-Fluorophenyl)-3-methylbutan-1-amine hydrochloride (59c)

The titled compound was synthesized in the same manner as described for **59a** using **56c** instead of **56a** as a white powder. Yield 50% from **55**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.54–7.45 (m, 2H), 7.26–7.16 (m, 2H), 4.34 (dd, J = 9.9, 5.7 Hz, 1H), 1.98–1.87 (m, 1H), 1.84–1.72 (m, 1H), 1.47–1.30 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H).

5.1.7. 1-(3,4-Dimethylphenyl)-3-methylbutan-1-amine hydrochloride (59d)

The titled compound was synthesized in the same manner as described for **59a** using **56d** instead of **56a** as a white powder. Yield 43% from **55**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.23–7.08 (m, 3H), 4.21 (dd, J = 10, 5.7 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 1.97–1.83 (m, 1H), 1.78–1.67 (m, 1H), 1.47–1.29 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H).

5.1.8. 1-(3,4-Dimethoxyphenyl)-3-methylbutan-1-amine hydrochloride (59e)

The titled compound was synthesized in the same manner as described for **59a** using **56e** instead of **56a** as a brown powder. Yield 57% from **55**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.06–6.97 (m, 3H), 4.26 (dd, J = 10, 5.6 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 1.98–1.86 (m, 1H), 1.80–1.68 (m, 1H), 1.49–1.33 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H).

5.1.9. 1-(3,4-Difluorophenyl)-3-methylbutan-1-amine hydrochloride (59f)

The titled compound was synthesized in the same manner as described for **59a** using **56f** instead of **56a** as a gray powder. Yield 53% from **55**; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (br s, 3H), 7.74–7.62 (m, 1H), 7.59–7.47 (m, 1H), 7.43–7.32 (m, 1H), 4.30 (t, J = 7.5 Hz, 1H), 1.82–1.64 (m, 2H), 1.37–1.18 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H).

5.1.10. 1-[3-Fluoro-4-(trifluoromethyl)phenyl]-3-methylbutan-1-amine hydrochloride (59g)

The titled compound was synthesized in the same manner as described for **59a** using **56g** instead of **56a** as a white powder. Yield 19% from **55**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.59 (dd, J = 8.4, 7.8 Hz, 1H), 7.41 (dd, J= 10, 2.0 Hz, 1H), 7.33–7.27 (m, 1H), 4.38 (dd, J = 9.8, 6.2 Hz, 1H), 1.97–1.72 (m, 2H), 1.48–1.32 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

5.1.11. 1-[3-Fluoro-5-(trifluoromethyl)phenyl]-3-methylbutan-1-amine hydrochloride (59h)

The titled compound was synthesized in the same manner as described for **59a** using **56h** instead of **56a** as a white powder. Yield 31% from **55**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.67 (s, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 4.50 (dd, J = 9.3, 6.5 Hz, 1H), 1.97–1.75 (m, 2H), 1.50–1.32 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H).

5.1.12. 3-Methylbutanal *O*-benzyloxime (61)

A solution of **60** (20.0 g, 0.232 mol) and *O*-benzylhydroxylamine hydrochloride (37.1 g, 0.232 mol) in pyridine (500 mL) was stirred for 2 h at 80 °C under argon atmosphere. The reaction mixture was concentrated in vacuo and then diluted with EtOAc. The solution was washed with 1 M HCl, water and brine, dried over $MgSO_4$ and concentration in vacuo to yield **61** (44.3 g, quant., *E,Z* mixture) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 6.9 Hz, 0.58H), 7.39–7.24 (m, 5H), 6.72 (d, J = 6.9 Hz, 0.42H), 5.10 (s, 0.84H), 5.07 (s, 1.16H), 2.28 (m, 1H), 2.05 (m, 1H), 1.82 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H).

5.1.13. 3-Methyl-1-(2-methylphenyl)butan-1-amine hydrochloride (64a)

To a stirred solution of **62a** (2.14 g, 12.5 mmol) in THF (30 mL) was added dropwise *n*-BuLi (1.59 M in hexane, 7.90 mL, 12.5 mmol) at −70 °C under argon atmosphere and then the mixture was stirred for 1.5 h at −70 °C. To the resultant mixture were added dropwise **61** (800 mg, 4.18 mmol) in toluene (30 mL) and successively $BF_3{\cdot}OEt_2$ 1.59 mL (12.5 mmol) at −70 °C. After being stirred for 2 h at −70 °C, the reaction was quenched with water and then the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was diluted with MeOH (20 mL) and then Pd/C (10% wet, 100 mg) was added. The suspension was stirred for 12 h under hydrogen atmosphere. The Pd/C was removed by filtration through a pad of Celite and the filtrate was concentrated in vacuo. The resultant residue was dissolved in EtOAc (20 mL) and then treated with 4 M HCl in dioxane (10 mL). After concentration in vacuo, the resultant solid was washed with EtOAc to yield **64a** (107 mg, 12% from **61**) as a white powder. ^{1}H NMR (300 MHz, CD_3OD) δ 7.46–7.26 (m, 4H), 4.60 (dd, J = 8.6, 6.8 Hz, 1H), 2.43 (s, 3H), 1.96–1.75 (m, 2H), 1.56–1.41 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H).

5.1.14. 3-Methyl-1-(3-methylphenyl)butan-1-amine hydrochloride (64b)

The titled compound was synthesized in the same manner as described for **64a** using **62b** instead of **62a** as a white powder. Yield 27% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.34 (t, J = 7.8 Hz, 1H), 7.28–7.18 (m, 3H), 4.26 (dd, J = 10, 5.7 Hz, 1H), 3.03 (s, 3H), 1.96–1.86 (m, 1H), 1.81–1.69 (m, 1H), 1.50–1.30 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

5.1.15. 1-(2-Methoxyphenyl)-3-methylbutan-1-amine hydrochloride (64c)

The titled compound was synthesized in the same manner as described for **64a** using **62c** instead of **62a** as a beige powder. Yield 27% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.44–7.29 (m, 2H), 7.10 (d, J = 8.1 Hz, 1H), 7.02 (m, 1H), 4.57 (dd, J = 9.8, 5.9 Hz, 1H), 3.91 (s, 3H), 2.05–1.92 (m, 1H), 1.81–1.68 (m, 1H), 1.49–1.32 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

5.1.16. 1-(3-Methoxyphenyl)-3-methylbutan-1-amine hydrochloride (64d)

The titled compound was synthesized in the same manner as described for **64a** using **62d** instead of **62a** as a white powder. Yield 21% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.37 (d, J = 8.3 Hz, 1H), 7.03–6.95 (m, 3H), 4.27 (dd, J = 9.9, 5.7 Hz, 1H), 3.82 (s, 3H), 1.96–1.83 (m, 1H), 1.81–1.68 (m, 1H), 1.50–1.33 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

5.1.17. 1-(3-Fluorophenyl)-3-methylbutan-1-amine hydrochloride (64e)

The titled compound was synthesized in the same manner as described for **64a** using **62e** instead of **62a** as a white powder. Yield 26% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.53–7.43 (m, 1H), 7.32–7.12 (m, 3H), 4.35 (dd, J = 9.6, 5.7 Hz, 1H), 1.97–1.72 (m, 2H), 1.48–1.32 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H).

5.1.18. 3-Methyl-1-[3-(trifluoromethyl)phenyl]butan-1-amine hydrochloride (64f)

The titled compound was synthesized in the same manner as described for **64a** using **62f** instead of **62a** as a white powder. Yield 54% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.83–7.63 (m, 4H), 4.46 (dd, J = 9.7, 6.2 Hz, 1H), 1.98–1.77 (m, 2H), 1.47–1.30 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

5.1.19. 3-Methyl-1-[4-(trifluoromethyl)phenyl]butan-1-amine hydrochloride (64g)

The titled compound was synthesized in the same manner as described for **64a** using **62g** instead of **62a** as a white powder. Yield 57% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.78 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 4.44 (dd, J = 9.9, 6.0 Hz, 1H), 1.98–1.76 (m, 2H), 1.47–1.31 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

5.1.20. 1-(4-Methoxy-3-methylphenyl)-3-methylbutan-1-amine hydrochloride (64h)

The titled compound was synthesized in the same manner as described for **64a** using **62h** instead of **62a** as a beige powder. Yield 46% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.27–7.16 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 4.20 (dd, J = 10, 5.4 Hz, 1H), 3.84 (s, 3H), 2.21 (s, 3H), 1.96–1.83 (m, 1H), 1.78–1.64 (m, 1H),1.48–1.29 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

5.1.21. 1-(4-Fluoro-3-methylphenyl)-3-methylbutan-1-amine hydrochloride (64i)

The titled compound was synthesized in the same manner as described for **64a** using **62i** instead of **62a** as a white powder. Yield 32% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.35–7.25 (m, 2H), 7.11 (t, J = 9.0 Hz, 1H), 4.29 (dd, J = 10, 5.9 Hz, 1H), 2.30 (d, J = 2.1 Hz, 3H), 1.97–1.83 (m, 1H), 1.81–1.71 (m, 1H), 1.46–1.29 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H).

5.1.22. 1-(3,5-Dimethylphenyl)-3-methylbutan-1-amine hydrochloride (64j)

The titled compound was synthesized in the same manner as described for **64a** using **62j** instead of **62a** as a white powder. Yield 41% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.06 (s, 1H), 7.04 (s, 2H), 4.20 (dd, J = 9.9, 5.9 Hz, 1H), 2.33 (s, 6H), 1.96–1.83 (m, 1H), 1.80–1.69 (m, 1H), 1.47–1.32 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

5.1.23. 1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-methylbutan-1-amine hydrochloride (64k)

The titled compound was synthesized in the same manner as described for **64a** using **62k** instead of **62a** as a yellow powder. Yield 18% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 6.96–6.87 (m, 3H), 4.26 (s, 4H), 4.18 (dd, J = 9.9, 5.1 Hz, 1H), 1.94–1.81 (m, 1H), 1.76–1.64 (m, 1H), 1.47–1.30 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H).

5.1.24. 1-(3-Fluoro-4-methylphenyl)-3-methylbutan-1-amine hydrochloride (64l)

The titled compound was synthesized in the same manner as described for **64a** using **62l** instead of **62a** as a white powder. Yield 39% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.33 (t, J = 7.7 Hz, 1H), 7.20–7.11 (m, 2H), 4.29 (dd, J = 10, 5.9 Hz, 1H), 2.28 (s, 3H), 1.95–1.83 (m, 1H), 1.81–1.69 (m, 1H), 1.48–1.31 (m, 1H), 0.96 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H).

5.1.25. 1-(3-Fluoro-4-methoxyphenyl)-3-methylbutan-1-amine hydrochloride (64m)

The titled compound was synthesized in the same manner as described for **64a** using **62m** instead of **62a** as a brown powder. Yield 31% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.28–7.11 (m, 3H), 4.27 (dd, J = 9.9, 5.7 Hz, 1H), 3.89 (s, 3H), 1.96–1.83 (m, 1H), 1.78–1.67 (m, 1H), 1.47–1.30 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

5.1.26. 1-(3,5-Difluorophenyl)-3-methylbutan-1-amine hydrochloride (64n)

The titled compound was synthesized in the same manner as described for **64a** using **62n** instead of **62a** as a white powder.

Yield 10% from **61**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.19–7.01 (m, 3H), 4.38 (dd, J = 9.5, 6.2 Hz, 1H), 1.95–1.72 (m, 2H), 1.50–1.32 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H).

5.1.27. 1-(3-Chlorophenyl)-3-methylbutan-1-amine hydrochloride (69a)

To a stirred solution of **65a** (500 mg, 2.61 mmol) in THF (10 mL) was added dropwise *n*-BuLi (1.59 M in hexane, 1.81 mL, 2.87 mmol) at −70 °C under argon atmosphere and then the mixture was stirred for 1 h at −70 °C. To the resultant mixture was added dropwise isovaleraldehyde (**60**) (0.225 mL, 3.03 mmol) at −70 °C. After being stirred for 2 h at −70 °C, the reaction was quenched with water and then the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was diluted with CH_2Cl_2 (7 mL) and then PBr_3 (0.272 mL, 2.87 mmol) was added at −25 °C under argon atmosphere. After being stirred for 1 h at −15 °C, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in DMF (6 mL) and then NaN_3 (190 mg, 2.87 mmol) was added. After being stirred for 2 h at 50 °C under argon atmosphere, the reaction mixture was diluted with Et_2O, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in THF (9 mL) and water (1 mL), and then Ph_3P (1.37 g, 5.22 mmol) was added under argon atmosphere. After being stirred for 24 h, the reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in MeOH (1 mL) and then 4 M HCl in dioxane (2 mL) was added. After concentration in vacuo, the resultant solid was washed with EtOAc to yield **69a** (77 mg, 13% from **65a**) as a white powder. ^{1}H NMR (300 MHz, CD_3OD) δ 7.53–7.34 (m, 4H), 4.33 (dd, J = 9.6, 6.0 Hz, 1H), 1.96–1.71 (m, 2H), 1.47–1.32 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

5.1.28. 1-(4-Chlorophenyl)-3-methylbutan-1-amine hydrochloride (69b)

The titled compound was synthesized in the same manner as described for **69a** using **65b** instead of **65a** as a white powder. Yield 75% from **65b**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.52–7.37 (m, 4H), 4.33 (dd, J = 9.6, 6.0 Hz, 1H), 1.96–1.83 (m, 1H), 1.81–1.70 (m, 1H), 1.47–1.30 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H).

5.1.29. 1-(3-Chloro-4-fluorophenyl)-3-methylbutan-1-amine hydrochloride (69c)

The titled compound was synthesized in the same manner as described for **69a** using **65c** instead of **65a** as a white powder. Yield 50% from **65c**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.64 (dd, J = 6.8, 2.3 Hz, 1H), 7.49–7.41 (m, 1H), 7.35 (t, J = 8.7 Hz, 1H), 4.35 (dd, J = 9.8, 6.2 Hz, 1H), 1.97–1.72 (m, 2H), 1.49–1.32 (m, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H).

5.1.30. 1-(4-Methoxyphenyl)-3-methylbutan-1-one (71)

To a stirred solution of **70** (1.00 g, 7.51 mmol) in THF (20 mL) was added dropwise *i*-butylmagnesium chloride (1 M in THF, 9.01 mL, 9.01 mmol) at 0 °C under argon atmosphere. After being stirred for 7 h at room temperature, the reaction was quenched with 1 M HCl at 0 °C and then the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to yield **71** (730 mg, 51%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.78 (d, J = 6.9 Hz, 2H), 2.28 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H).

5.1.31. 1-(4-Methoxyphenyl)-3-methylbutan-1-amine (75)

To a stirred solution of **71** (380 mg, 1.98 mmol) in MeOH (10 mL) was added $NaBH_4$ (112 mg, 2.97 mmol) at 0 °C under argon atmosphere. After being stirred for 2 h, the reaction was quenched with water and then the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in CH_2Cl_2 (3 mL) and then TEA (1.29 mL, 9.18 mmol) and LiCl (485 mg, 11.5 mmol) were added. To the stirred solution was added MsCl (0.355 mL, 4.59 mmol) at 0 °C under argon atmosphere. After being stirred for 14 h at room temperature, the reaction mixture was diluted with EtOAc and then washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in DMF (2 mL) and then NaN_3 (179 mg, 2.74 mmol) was added. After being stirred for 3 h at room temperature under argon atmosphere, water was added and then the resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in EtOH (3 mL) and then Pd/C (10%, wet, 45 mg) was added. The resultant suspension was stirred for 1 h at room temperature under hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 99:1–90:10) to yield **75** (74 mg, 19% in four steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.92 (t, J = 6.9 Hz, 1H), 3.80 (s, 3H), 2.15 (br s, 2H), 1.78–1.44 (m, 3H), 0.91 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).

5.1.32. 7-(Bromomethyl)-2*H*-chromen-2-one (77)

A solution of **76** (35.0 g, 0.220 mol), NBS (38.8 g, 0.220 mol), and AIBN (360 mg, 2.20 mmol) in CCl_4 (1000 mL) was refluxed for 1 h. To the reaction mixture were added NBS (4.00 g, 25.1 mmol)) and AIBN (50 mg, 0.306 mmol) at room temperature and then the reaction mixture was refluxed for additionally 1 h. After concentration in vacuo, the resultant residue was diluted with water and then stirred for 1 h. The resultant precipitate was collected by filtration and dried under reduced pressure to yield **77**, which was used for the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.6 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.35 (m, 1H), 7.32 (m, 1H), 6.44 (d, J = 9.6 Hz, 1H), 4.52 (s, 2H).

5.1.33. 7-(Phenoxymethyl)-2*H*-chromen-2-one (78)

To a stirred suspension of NaH (63.1% in oil, 8.30 g, 0.220 mol) in DMF (200 mL) were successively added dropwise phenol (20.5 g, 0.220 mol) in DMF (100 mL) and **77** in DMF (500 mL) at 0 °C under argon atmosphere. After being stirred for 12 h at room temperature, the reaction was quenched with aqueous NH_4Cl at 0 °C and then the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was recrystallized with EtOAc–hexane to yield **78** (45.0 g, 77% in two steps) as a pale yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.6 Hz, 1H), 7.52–7.25 (m, 5H), 7.04–6.93 (m, 3H), 6.42 (d, J = 9.6 Hz, 1H), 5.16 (s, 2H).

5.1.34. *tert*-Butyl (2*E*)-3-[2-(acetyloxy)-4-(phenoxymethyl)phenyl]acrylate (79)

To a stirred solution of **78** (28.4 g, 0.111 mol) in THF (330 mL) was added *t*-BuOK (37.3 g, 0.333 mol) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h at 45 °C and then acetyl chloride (23.6 mL, 0.333 mol) was added dropwise at 0 °C. After being stirred for 30 min at 0 °C, the reaction was quenched with water and then the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield **79**, which was used for the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.64 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 16 Hz, 1H), 7.34–7.15 (m, 4H), 7.02–6.92 (m, 3H), 6.39 (d, J = 16 Hz, 1H), 5.07 (s, 2H), 2.37 (s, 3H), 1.53 (s, 9H).

5.1.35. *tert*-Butyl 3-[2-hydroxy-4-(phenoxymethyl)phenyl]propanoate (81)

To a stirred solution of **79** and $NiCl_2{\cdot}6H_2O$ (26.4 g, 0.111 mol) in THF (250 mL) and MeOH (100 mL) was added $NaBH_4$ (16.8 g, 0.455 mol) in several portions for 30 min at 0 °C under argon atmosphere. After being stirred for 15 min at 0 °C, the reaction mixture was diluted with EtOAc and water, and then filtered through a pad of Celite. The filtrate was separated and the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in MeOH (50 mL) and the solution was added dropwise to a stirred solution of K_2CO_3 (18.4 g, 0.133 mol) in MeOH (150 mL) at 0 °C under argon atmosphere. After being stirred for 15 min at room temperature, the reaction mixture was diluted with EtOAc and then filtered through a pad of Celite. The filtrate was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **81**, which was used for the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.32–7.22 (m, 2H), 7.07 (d, J = 7.8 Hz, 1H), 7.00–6.90 (m, 5H), 4.98 (s, 2H), 2.88–2.81 (m, 2H), 2.66–2.60 (m, 2H), 1.42 (s, 9H).

5.1.36. 2-(3-*tert*-Butoxy-3-oxopropyl)-5-(phenoxymethyl)benzoic acid (83)

To a stirred solution of **81** and pyridine (13.5 mL, 0.167 mol) in CH_2Cl_2 (150 mL) was added dropwise Tf_2O (22.4 mL, 0.133 mol) at 0 °C under argon atmosphere. After being stirred for 10 min at 0 °C, the reaction was quenched with water and then the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **82**, which was used for the next step without purification. A suspension of **82**, potassium acetate (54.5 g, 0.555 mol), DPPF (6.15 g, 11.1 mmol), and $Pd(OAc)_2$ (1.24 g, 5.55 mmol) was stirred for 5 h at 75 °C under carbon monooxide atmosphere. The reaction mixture was diluted with EtOAc and water, and then filtered through a pad of Celite. The filtrate was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2 to 1:1) to yield **83** (17.0 g, 43% from **78**) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 1.8 Hz, 1H), 7.56 (dd, J = 7.8, 1.8 Hz, 1H), 7.39–7.25 (m, 3H), 7.02–6.94 (m, 3H), 5.08 (s, 2H), 3.29 (t, J = 7.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.41 (s, 9H).

5.1.37. Nitrophenol ester resin (85)

Nitrophenol resin **84** (1.80 mmol/g, 9.10 g, 16.4 mmol) was suspended in dichloroethane (110 mL). To the suspension were successively added **83** (7.00 g, 19.7 mmol), DMAP (2.40 g, 19.7 mmol), and EDC·HCl (3.77 g, 19.7 mmol) and the suspension was agitated for 20 h at 60 °C. After cooling to room temperature, the resin was collected by filtration and washed with CH_2Cl_2. Drying under reduced pressure afforded the nitrophenol ester resin **85** (14.5 g, 0.729 mmol/g) as a yellow resin. IR (KBr) 3434, 3026, 2925, 1945, 1751, 1720, 1655, 1609, 1534, 1492, 1450, 1347, 1127, 1075, 1018, 976, 751, 684, 608, 537 cm^{-1}.

5.1.38. 3-[2-({[3-Methyl-1-(2-methylphenyl)butyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (3)

The nitrophenol ester resin **85** (0.729 mmol/g, 300 mg, 0.219 mmol) was suspended in dichloroethane (5 mL). To the suspension were successively added DIPEA (73 μL, 0.420 mmol) and **64a** (53 mg, 0.250 mmol), and the suspension was agitated for 20 h at 70 °C. After cooling to room temperature, the resultant mixture was filtrated and the resin was washed with CH_2Cl_2 (3 mL × 4). The filtrate and washings were combined and concentrated in vacuo. After purification by a short-passed column chromatography on silica gel (EtOAc), the resultant residue was dissolved in CH_2Cl_2 (0.5 mL). To the stirred solution were successively added anisole (0.250 mL) and trifluoroacetic acid (3 mL) at room temperature. After being stirred for 12 h at room temperature, the reaction mixture was concentrated in vacuo. The resultant residue was recrystallized from EtOAc and hexane to yield **3** (58 mg, 58% in two steps) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.38–7.13 (m, 7H), 7.05–6.91 (m, 3H), 6.32 (d, J = 8.0 Hz, 1H), 5.60–5.41 (m, 1H), 5.03 (s, 2H), 3.10–2.97 (m, 2H), 2.75 (t, J = 7.6 Hz, 2H), 2.49 (s, 3H), 1.88–1.57 (m, 3H), 1.03 (d, J = 6.2 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H); MS (APCI, Neg.) m/e 458 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{34}NO_4$: 460.2488; found: 460.2497.

5.1.39. 3-[2-({[3-Methyl-1-(3-methylphenyl)butyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (4)

The titled compound was synthesized in the same manner as described for **3** using **64b** instead of **64a** as a white powder. Yield 56% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.39 (m, 2H), 7.36–7.20 (m, 4H), 7.20–7.05 (m, 3H), 7.03–6.93 (m, 3H), 6.33 (d, J = 8.5 Hz, 1H), 5.28–5.13 (m, 1H), 5.03 (s, 2H), 3.11–2.96 (m, 2H), 2.73 (t, J = 7.7 Hz, 2H), 2.36 (s, 3H), 1.90–1.49 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 458 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{34}NO_4$: 460.2488; found: 460.2498.

5.1.40. 3-[2-({[1-(2-Methoxyphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (6)

The titled compound was synthesized in the same manner as described for **3** using **64c** instead of **64a** as a white powder. Yield 68% in two steps; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.73 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 7.8, 1.8 Hz, 1H), 7.37–7.24 (m, 5H), 7.24–7.14 (m, 1H), 7.05–6.82 (m, 5H), 5.51–5.36 (m, 1H), 5.10 (s, 2H), 3.82 (s, 3H), 3.01–2.75 (m, 2H), 2.49–2.39 (m, 2H), 1.82–1.50 (m, 2H), 1.44–1.28 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); MS (FAB, Pos.) m/e 476 $(M+H)^+$; HRMS (Pos.) calcd for $C_{29}H_{34}NO_5$: 476.2437; found: 476.2438.

5.1.41. 3-[2-({[1-(3-Methoxyphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (7)

The titled compound was synthesized in the same manner as described for **3** using **64d** instead of **64a** as a white powder. Yield 68% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.40 (m, 2H), 7.36–7.22 (m, 4H), 7.06–6.88 (m, 5H), 6.86–6.76 (m, 1H), 6.38 (d, J = 8.5 Hz, 1H), 5.29–5.14 (m, 1H), 5.03 (s, 2H), 3.81 (s, 3H), 3.10–2.97 (m, 2H), 2.75 (t, J = 7.6 Hz, 2H), 1.86–1.50 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 474 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{34}NO_5$: 476.2437; found: 476.2436.

5.1.42. 3-[2-({[1-(2-Fluorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (9)

The titled compound was synthesized in the same manner as described for **3** using **59b** instead of **64a** as a white powder. Yield 18% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.41 (m, 2H), 7.38–7.21 (m, 5H), 7.17–6.93 (m, 5H), 6.57 (d, J = 8.7 Hz, 1H), 5.44–5.32 (m, 1H), 5.03 (s, 2H), 3.09–2.96 (m, 2H), 2.78–2.66 (m, 2H), 1.89–1.51 (m, 3H), 0.99 (d, J = 6.6 Hz, 6H); MS (APCI, Neg.) m/e 462 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{31}FNO_4$: 464.2237; found: 464.2242.

5.1.43. 3-[2-({[1-(3-Fluorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (10)

The titled compound was synthesized in the same manner as described for **3** using **64e** instead of **64a** as a white powder. Yield

73% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.40 (m, 2H), 7.37–7.27 (m, 4H), 7.15 (d, J = 8.0 Hz, 1H), 7.09–6.86 (m, 5H), 6.46 (d, J = 8.2 Hz, 1H), 5.27–5.17 (m, 1H), 5.04 (s, 2H), 3.02 (t, J = 6.9 Hz, 2H), 2.82–2.69 (m, 2H), 1.87–1.53 (m, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); MS (APCI, Neg.) m/e 462 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{31}FNO_4$: 464.2237; found: 464.2237.

5.1.44. 3-[2-({[1-(3-Chlorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (12)

The titled compound was synthesized in the same manner as described for **3** using **69a** instead of **64a** as a white powder. Yield 68% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.39 (m, 2H), 7.38–7.19 (m, 7H), 7.05–6.92 (m, 3H), 6.47 (d, J = 8.2 Hz, 1H), 5.26–5.13 (m, 1H), 5.04 (s, 2H), 3.08–2.95 (m, 2H), 2.82–2.69 (m, 2H), 1.89–1.50 (m, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); MS (APCI, Neg.) m/e 478 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{31}ClNO_4$: 480.1942; found: 480.1943.

5.1.45. 3-[2-({[1-(4-Chlorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (13)

The titled compound was synthesized in the same manner as described for **3** using **69b** instead of **64a** as a white powder. Yield 68% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.37–7.27 (m, 7H), 7.05–6.92 (m, 3H), 6.43 (d, J = 8.2 Hz, 1H), 5.28–5.13 (m, 1H), 5.03 (s, 2H), 3.01 (t, J = 6.7 Hz, 2H), 2.81–2.66 (m, 2H), 1.87–1.49 (m, 3H), 0.98 (d, J = 6.6 Hz, 6H); MS (APCI, Neg.) m/e 478 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{31}ClNO_4$: 480.1942; found: 480.1935.

5.1.46. 3-[2-[({3-Methyl-1-[3-(trifluoromethyl)phenyl]butyl}amino)carbonyl]-4-(phenoxymethyl)phenyl]propanoic acid (14)

The titled compound was synthesized in the same manner as described for **3** using **64f** instead of **64a** as a white powder. Yield 56% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.40 (m, 6H), 7.37–7.27 (m, 3H), 7.06–6.92 (m, 3H), 6.60 (d, J = 8.0 Hz, 1H), 5.36–5.21 (m, 1H), 5.04 (s, 2H), 3.06–2.94 (m, 2H), 2.81–2.67 (m, 2H), 1.93–1.55 (m, 3H), 1.01 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H); MS (APCI, Neg.) m/e 512 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{31}F_3NO_4$: 514.2205; found: 514.2211.

5.1.47. 3-[2-[({3-Methyl-1-[4-(trifluoromethyl)phenyl]butyl}amino)carbonyl]-4-(phenoxymethyl)phenyl]propanoic acid (15)

The titled compound was synthesized in the same manner as described for **3** using **64g** instead of **64a** as an off-white powder. Yield 30% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.51–7.40 (m, 4H), 7.35–7.25 (m, 3H), 7.02–6.93 (m, 3H), 6.54 (d, J = 8.1 Hz, 1H), 5.26 (m, 1H), 5.03 (s, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.76–2.68 (m, 2H), 1.84–1.55 (m, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); IR (KBr) 3294, 2959, 1711, 1638, 1532, 1496, 1327, 1245, 1165, 1122, 1068, 1017, 752, 689 cm^{-1}; MS (APCI, Neg.) m/e 512 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{31}F_3NO_4$: 514.2205; found: 514.2210.

5.1.48. 3-[2-({[1-(3,4-Dimethylphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (16)

The titled compound was synthesized in the same manner as described for **3** using **59d** instead of **64a** as a white powder. Yield 36% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.35–7.27 (m, 3H), 7.17–7.06 (m, 3H), 7.03–6.92 (m, 3H), 6.30 (d, J = 8.8 Hz, 1H), 5.25–5.13 (m, 1H), 5.02 (s, 2H), 3.11–2.97 (m, 2H), 2.75 (t, J = 7.3 Hz, 2H), 2.26 (s, 3H), 2.25 (s, 3H), 1.88–1.50 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 472 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{36}NO_4$: 474.2644; found: 474.2647.

5.1.49. 3-[2-({[1-(4-Fluoro-3-methylphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (18)

The titled compound was synthesized in the same manner as described for **3** using **64i** instead of **64a** as a white powder. Yield 61% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2H), 7.35–7.27 (m, 3H), 7.22–7.08 (m, 2H), 7.06–6.92 (m, 4H), 6.35 (d, J = 8.5 Hz, 1H), 5.26–5.10 (m, 1H), 5.03 (s, 2H), 3.10–2.94 (m, 2H), 2.81–2.67 (m, 2H), 2.27 (d, J = 1.9 Hz, 3H), 1.90–1.50 (m, 3H), 0.98 (d, J = 6.6 Hz, 6H); MS (APCI, Neg.) m/e 476 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{33}FNO_4$: 478.2394; found: 478.2396.

5.1.50. 3-[2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (19)

The titled compound was synthesized in the same manner as described for **3** using **64j** instead of **64a** as a white powder. Yield 71% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.35–7.23 (m, 3H), 7.02–6.87 (m, 6H), 6.30 (d, J = 8.4 Hz, 1H), 5.16 (m, 1H), 5.02 (s, 2H), 3.11–2.94 (m, 2H), 2.71 (t, J = 7.7 Hz, 2H), 2.30 (s, 6H), 1.84–1.52 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); IR (KBr) 3295, 1700, 1637, 1602, 1528, 1301, 1240, 1172, 1036, 847, 820, 755, 691 cm^{-1}; MS (APCI, Neg.) m/e 472 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{36}NO_4$: 474.2644; found: 474.2642.

5.1.51. 3-[2-({[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (21)

The titled compound was synthesized in the same manner as described for **3** using **64k** instead of **64a** as a white powder. Yield 26% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.36–7.24 (m, 3H), 7.06–6.92 (m, 3H), 6.91–6.80 (m, 3H), 6.29 (d, J = 8.5 Hz, 1H), 5.21–5.06 (m, 1H), 5.02 (s, 2H), 4.24 (s, 4H), 3.04 (t, J = 7.1 Hz, 2H), 2.74 (t, J = 7.1 Hz, 2H), 1.86–1.47 (m, 3H), 0.97 (t, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 502 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}NO_6$: 504.2386; found: 504.2390.

5.1.52. 3-[2-({[1-(3-Fluoro-4-methylphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (22)

The titled compound was synthesized in the same manner as described for **3** using **64l** instead of **64a** as a white powder. Yield 67% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.35–7.25 (m, 3H), 7.16 (t, J = 8.0 Hz, 1H), 7.09–6.92 (m, 5H), 6.39 (d, J = 8.5 Hz, 1H), 5.27–5.11 (m, 1H), 5.03 (s, 2H), 3.03 (t, J = 6.9 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 2.25 (d, J = 1.7 Hz, 3H), 1.86–1.50 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 476 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{33}FNO_4$: 478.2394; found: 478.2393.

5.1.53. 3-[2-({[1-(3-Fluoro-4-methoxyphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (23)

The titled compound was synthesized in the same manner as described for **3** using **64m** instead of **64a** as a pale pink powder. Yield 27% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2H), 7.36–7.27 (m, 3H), 7.16–7.04 (m, 2H), 7.03–6.89 (m, 4H), 6.40 (d, J = 8.2 Hz, 1H), 5.23–5.10 (m, 1H), 5.03 (s, 2H), 3.88 (s, 3H), 3.02 (t, J = 6.9 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 1.90–1.48 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 492 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{33}FNO_5$: 494.2343; found: 494.2334.

5.1.54. 3-[2-({[1-(3,4-Difluorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (24)

The titled compound was synthesized in the same manner as described for **3** using **59f** instead of **64a** as a white powder. Yield 22% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.34–7.24 (m, 3H), 7.22–7.07 (m, 3H), 7.02–6.92 (m, 3H), 6.50

(d, J = 8.1 Hz, 1H), 5.23–5.11 (m, 1H), 5.03 (s, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.78–2.69 (m, 2H), 1.82–1.55 (m, 3H), 0.98 (d, J = 6.0 Hz, 6H); MS (APCI, Neg.) m/e 480 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{30}F_2NO_4$: 482.2143; found: 482.2146.

5.1.55. 3-[2-[({1-[3-Fluoro-4-(trifluoromethyl)phenyl]-3-methylbutyl}amino)carbonyl]-4-(phenoxymethyl)phenyl]propanoic acid (25)

The titled compound was synthesized in the same manner as described for **3** using **59g** instead of **64a** as a white powder. Yield 34% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, J = 7.5 Hz, 1H), 7.47–7.41 (m, 2H), 7.37–7.16 (m, 5H), 7.03–6.92 (m, 3H), 6.64 (d, J = 7.5 Hz, 1H), 5.28–5.17 (m, 1H), 5.04 (s, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.80–2.70 (m, 2H), 1.83–1.52 (m, 3H), 1.00 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H); MS (APCI, Neg.) m/e 530 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{30}F_4NO_4$: 532.2111; found: 532.2114.

5.1.56. 3-[2-({[1-(3,5-Difluorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (26)

The titled compound was synthesized in the same manner as described for **3** using **64n** instead of **64a** as a white powder. Yield 46% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2H), 7.35–7.24 (m, 3H), 7.02–6.94 (m, 3H), 6.94–6.84 (m, 2H), 6.76–6.66 (m, 1H), 6.54 (d, J = 8.4 Hz, 1H), 5.23–5.13 (m, 1H), 5.04 (s, 2H), 3.02 (t, J = 7.2 Hz, 2H), 2.80–2.70 (m, 2H), 1.80–1.40 (m, 3H), 0.99 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 6.0 Hz, 3H); IR (KBr) 3286, 2958, 1708, 1639, 1599, 1531, 1496, 1454, 1317, 1246, 1171, 1119, 1054, 991, 911, 851, 751, 689 cm^{-1}; MS (APCI, Neg.) m/e 480 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{30}F_2NO_4$: 482.2143; found: 482.2143.

5.1.57. 3-[2-[({1-[3-Fluoro-5-(trifluoromethyl)phenyl]-3-methylbutyl}amino)carbonyl]-4-(phenoxymethyl)phenyl]propanoic acid (27)

The titled compound was synthesized in the same manner as described for **3** using **59h** instead of **64a** as a white powder. Yield 29% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.39 (m, 3H), 7.37–7.17 (m, 5H), 7.05–6.92 (m, 3H), 6.68 (d, J = 8.0 Hz, 1H), 5.31–5.18 (m, 1H), 5.04 (s, 2H), 3.06–2.94 (m, 2H), 2.82–2.67 (m, 2H), 1.88–1.54 (m, 3H), 1.01 (d, J = 5.8 Hz, 3H), 0.99 (d, J = 5.8 Hz, 3H); MS (APCI, Neg.) m/e 530 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{30}F_4NO_4$: 532.2111; found: 532.2120.

5.1.58. 3-[2-({[1-(3-Chloro-4-fluorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (28)

The titled compound was synthesized in the same manner as described for **3** using **69c** instead of **64a** as a white powder. Yield 54% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.37 (m, 3H), 7.36–7.20 (m, 4H), 7.11 (t, J = 8.7 Hz, 1H), 7.03–6.93 (m, 3H), 6.50 (d, J = 8.0 Hz, 1H), 5.23–5.11 (m, 1H), 5.04 (s, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.81–2.69 (m, 2H), 1.90–1.48 (m, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H); MS (APCI, Neg.) m/e 496 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{30}ClFNO_4$: 498.1847; found: 498.1848.

5.1.59. 3-[2-({[3-Methyl-1-(4-methylphenyl)butyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (5)

A solution of **86** (200 mg, 0.612 mmol), **59a** (144 mg, 0.673 mmol), *N*-methylmorpholine (67 μL, 0.612 mmol), EDC·HCl (141 mg, 0.735 mmol), and HOBt (165 mg, 1.22 mmol) in DMF (2 mL) was stirred for 12 h at room temperature under argon atmosphere. The reaction was quenched with 1 M HCl and then the reaction mixture was extracted with TBME. The organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **87a**, which was used for the next step without purification. The obtained **87a** was dissolved in THF (1 mL) and MeOH (1 mL) and then 2 M NaOH (1 mL) was added. After being stirred for 12 h at room temperature, the reaction mixture was acidified with 1 M HCl and then extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was triturated with EtOAc–hexane to yield **5** (210 mg, 75% in two steps) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.12 (m, 9H), 7.02–6.92 (m, 3H), 6.33 (d, J = 8.4 Hz, 1H), 5.20 (m, 1H), 5.02 (s, 2H), 3.07–2.95 (m, 2H), 2.78–2.69 (m, 2H), 2.34 (s, 3H), 1.88–1.44 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); IR (KBr) 3293, 2954, 1707, 1637, 1599, 1533, 1496, 1435, 1368, 1302, 1234, 1172, 1140, 1104, 1078, 1032, 1015, 903, 814, 754 cm^{-1}; MS (APCI, Neg.) m/e 458 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{34}NO_4$: 460.2488; found: 460.2497.

5.1.60. 3-[2-({[1-(4-Methoxyphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (8)

The titled compound was synthesized in the same manner as described for **5** using **75** instead of **59a** as a white powder. Yield 63% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.34–7.23 (m, 5H), 7.03–6.93 (m, 3H), 6.88 (d, J = 8.7 Hz, 2H), 6.33 (d, J = 8.1 Hz, 1H), 5.19 (m, 1H), 5.02 (s, 2H), 3.80 (s, 3H), 3.01 (dt, J = 3.0, 7.2 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 1.85–1.65 (m, 2H), 1.63 (m, 1H), 0.97 (d, J = 6.6 Hz, 6H); IR (KBr) 3303, 2958, 1701, 1632, 1516, 1308, 1252, 1213, 1032, 831, 752, 691 cm^{-1}; MS (APCI, Neg.) m/e 474 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{34}NO_5$: 476.2437; found: 476.2437.

5.1.61. 3-[2-({[1-(4-Fluorophenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (11)

The titled compound was synthesized in the same manner as described for **5** using **59c** instead of **59a** as a white powder. Yield 76% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.24 (m, 7H), 7.08–6.93 (m, 5H), 6.40 (d, J = 8.4 Hz, 1H), 5.21 (m, 1H), 5.02 (s, 2H), 3.05–2.95 (m, 2H), 2.76–2.67 (m, 2H), 1.86–1.51 (m, 3H), 0.98 (d, J = 6.6 Hz, 6H); IR (KBr) 3292, 2956, 1709, 1638, 1600, 1510, 1467, 1368, 1302, 1231, 1160, 1096, 1079, 1033, 1015, 904, 836, 817 cm^{-1}; MS (APCI, Neg.) m/e 462 $(M-H)^-$; HRMS (Pos.) calcd for $C_{28}H_{31}FNO_4$: 464.2237; found: 464.2239.

5.1.62. 3-[2-({[1-(4-Methoxy-3-methylphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (17)

The titled compound was synthesized in the same manner as described for **5** using **64h** instead of **59a** as a white powder. Yield 57% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.36 (m, 2H), 7.36–7.26 (m, 3H), 7.20–7.09 (m, 2H), 7.04–6.91 (m, 3H), 6.79 (d, J = 8.2 Hz, 1H), 6.27 (d, J = 8.8 Hz, 1H), 5.26–5.09 (m, 1H), 5.02 (s, 2H), 3.82 (s, 3H), 3.10–2.96 (m, 2H), 2.73 (t, J = 7.4 Hz, 2H), 2.22 (s, 3H), 1.92–1.46 (m, 3H), 0.98 (d, J = 6.6 Hz, 6H); MS (APCI, Neg.) m/e 488 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{36}NO_5$: 490.2593; found: 490.2590.

5.1.63. 3-[2-({[1-(3,4-Dimethoxyphenyl)-3-methylbutyl]amino}carbonyl)-4-(phenoxymethyl)phenyl]propanoic acid (20)

The titled compound was synthesized in the same manner as described for **5** using **59e** instead of **59a** as a white powder. Yield 76% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.38 (m, 2H), 7.37–7.25 (m, 3H), 7.07–6.78 (m, 6H), 6.32 (d, J = 8.5 Hz, 1H), 5.29–5.13 (m, 1H), 5.02 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.11–2.96 (m, 2H), 2.74 (t, J = 7.3 Hz, 2H), 1.90–1.47 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 504 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{36}NO_6$: 506.2543; found: 506.2544.

5.1.64. 7-[(Methoxymethoxy)methyl]-2*H*-chromen-2-one (90)

Compound **77** was prepared from **76** (64.5 g, 0.403 mol) according to the aforementioned procedure and used without purification. To a stirred solution of **77** in DMF (800 mL) was added potassium acetate (40.0 g, 0.410 mol) at room temperature under argon atmosphere. After being stirred for 1 h at 50 °C, the reaction mixture was poured into cold water and then extracted with EtOAc The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in THF (500 mL) and MeOH (500 mL) and then 5 M NaOH (200 mL) was added. After being stirred for 1 h at room temperature, the reaction mixture was neutralized with 5 M HCl, evaporated to approximately one-third volume, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was dissolved in dichloroethane (250 mL) and DIPEA (85.0 mL, 0.490 mol) was added. To the stirred solution was added dropwise methoxymethyl chloride (34.0 mL, 0.450 mol) at 0 °C under argon atmosphere. After being stirred for 4.5 h at 50 °C, the reaction mixture was poured into cold water and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4–1:2) to yield **90** (67.4 g, 76% in four steps) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.35 (s, 1H), 7.29–7.24 (m, 1H), 6.41 (d, J = 9.6 Hz, 1H), 4.74 (s, 2H), 4.68 (s, 2H), 3.43 (s, 3H).

5.1.65. Methyl (2*E*)-3-{2-hydroxy-4-[(methoxymethoxy)methyl]phenyl}acrylate (91)

To a stirred suspension of NaH (60% in oil, 34.5 g, 0.900 mol) in THF (800 mL) was added dropwise MeOH (50.0 mL, 1.22 mol) at room temperature under argon atmosphere and then the reaction mixture was stirred for 1 h at 50 °C. To the resultant suspension was added dropwise **90** (67.0 g, 0.300 mol) in THF (400 mL) at room temperature. After being stirred for 1 h at 60 °C, the reaction was quenched with aqueous NH_4Cl and successively 2 M HCl at 0 °C and then the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield **91** which was used for the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 16 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 6.92 (m, 1H), 6.84 (s, 1H), 6.57 (d, J = 16 Hz, 1H), 5.64 (s, 1H), 4.71 (s, 2H), 4.56 (s, 2H), 3.81 (s, 3H), 3.42 (s, 3H).

5.1.66. Methyl 3-{2-hydroxy-4-[(methoxymethoxy)methyl]-phenyl}propanoate (92)

To a stirred solution of **91** and $NiCl_2{\cdot}6H_2O$ (53.5 g, 0.225 mol) in THF (560 mL) and MeOH (140 mL) was added $NaBH_4$ (34.0 g, 0.900 mol) in several portions at 0 °C under argon atmosphere and then the reaction mixture was stirred for 1 h at room temperature. To the reaction mixture were added $NiCl_2{\cdot}6H_2O$ (26.8 g, 0.113 mol) and successively $NaBH_4$ (17.0 g, 0.450 mol) at room temperature and the reaction mixture was stirred for additionally 30 min at room temperature. The resultant mixture was diluted with TBME and then filtered through a pad of Celite. The filtrate was evaporated to approximately half volume and then poured into EtOAc and water. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3–1:2) to yield **92** (52.5 g, 80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–7.03 (m, 2H), 6.91–6.83 (m, 2H), 4.69 (s, 2H), 4.51 (s, 2H), 3.68 (s, 3H), 3.41 (s, 3H), 2.93–2.86 (m, 2H), 2.74–2.67 (m, 2H).

5.1.67. 5-[(Methoxymethoxy)methyl]-2-(3-methoxy-3-oxopropyl)benzoic acid (94)

The titled compound was synthesized in the same manner as described for **83** using **92** instead of **81** as a white powder. Yield 82% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 1.5 Hz, 1H), 7.49 (dd, J = 8.1, 1.5 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 4.72 (s, 2H), 4.61 (s, 2H), 3.67 (s, 3H), 3.43 (s, 3H), 3.33 (t, J = 7.8 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H).

5.1.68. Methyl 3-{2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]-amino}carbonyl)-4-[(methoxymethoxy)methyl]phenyl} propanoate (95)

A solution of **94** (6.00 g, 21.3 mmol), **64g** (6.34 g, 27.8 mmol), *N*-methylmorpholine (3.34 mL, 30.8 mmol), EDC·HCl (5.82 g, 30.4 mmol), and HOBt (4.65 g, 30.4 mmol) in DMF (50 mL) was stirred for 12 h at room temperature under argon atmosphere. The reaction was quenched with water and then the reaction mixture was extracted with TBME. The organic layer was washed with 0.5 M HCl, aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **95**, which was used for the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 3H), 6.96 (s, 2H), 6.90 (s, 1H), 6.54 (d, J = 8.7 Hz, 1H), 5.16 (m, 1H), 4.70 (s, 2H), 4.54 (s, 2H), 3.62 (s, 3H), 3.40 (s, 3H), 3.02–2.97 (m, 2H), 2.68–2.62 (m, 2H), 2.31 (s, 6H), 1.83–1.55 (m, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H).

5.1.69. Methyl 3-{2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]-amino}carbonyl)-4-(hydroxymethyl)phenyl} propanoate (96)

To a stirred solution of **95** in MeOH (60 mL) was added 4 M HCl in dioxane (30 mL) at room temperature and the reaction mixture was stirred for 2 h at room temperature. After concentration in vacuo, the resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to yield **96** (7.66 g, 87% in two steps) as a beige powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.20 (d, J = 7.8 Hz, 1H), 6.97 (s, 2H), 6.90 (s, 1H), 6.56 (d, J = 8.7 Hz, 1H), 5.17 (m, 1H), 4.64 (s, 2H), 3.62 (s, 3H), 3.02–2.97 (m, 2H), 2.69–2.63 (m, 2H), 2.31 (s, 6H), 1.85–1.55 (m, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.3 Hz, 3H).

5.1.70. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}-carbonyl)-4-[(2-fluorophenoxy)methyl]phenyl}propanoic acid (29)

To a stirred solution of **96** (300 mg, 0.729 mmol) and TEA (153 μL, 1.09 mmol) in THF (3 mL) was added MsCl (68 μL, 0.875 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min at 0 °C, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **97**, which was used for the next step without purification. To a stirred solution of **98a** (98 mg, 0.875 mmol) in DMF (1 mL) was added NaH (60% in oil, 29 mg, 0.801 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred for 30 min at room temperature. To the reaction mixture was added **97** in DMF (1 mL) at 0 °C. After being stirred for 12 h at room temperature, the reaction was quenched with aqueous NH_4Cl and then the reaction mixture was extracted with TBME. The organic layer was washed with 0.5 M NaOH, water and brine, and dried over $MgSO_4$. Concentration in vacuo afforded **99a** which was used for the next step without purification. To a stirred solution of **99a** in THF (2 mL) and MeOH (2 mL) was added 2 M NaOH (2 mL) at room temperature. After being stirred for 12 h at room temperature, the reaction mixture was diluted with water and then extracted with TBME. The aqueous layer was acidified with 1 M HCl and then extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue was recrystallized with EtOAc–hexane to yield **29** (193 mg, 54% in three steps) as a white powder. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.46–7.38 (m, 2H), 7.28 (d, J = 7.8 Hz, 1H), 7.14–6.88 (m, 7H), 6.31 (d, J = 7.8 Hz, 1H), 5.15 (m, 1H), 5.09 (s, 2H), 3.12–2.95 (m, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.31 (s, 6H), 1.85–1.55 (m, 3H), 0.98 (d, J = 5.7 Hz, 6H); MS (APCI, Neg.) m/e 490 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{35}FNO_4$: 492.2550; found: 492.2546.

5.1.71. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}-carbonyl)-4-[(3-fluorophenoxy)methyl]phenyl}propanoic acid (30)

The titled compound was synthesized in the same manner as described for **29** using **98b** instead of **98a** as a white powder. Yield 80% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.35 (m, 2H), 7.30–7.21 (m, 2H), 6.95 (s, 2H), 6.91 (s, 1H), 6.75–6.64 (m, 3H), 6.31 (d, J = 8.2 Hz, 1 H), 5.16 (m, 1H), 5.00 (s, 2H), 3.11–2.95 (m, 2H), 2.80–2.65 (m, 2H), 2.31 (s, 6H), 1.85–1.55 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 490 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{35}FNO_4$: 492.2550; found: 492.2548.

5.1.72. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}-carbonyl)-4-[(4-fluorophenoxy)methyl]phenyl}propanoic acid (31)

The titled compound was synthesized in the same manner as described for **29** using **98c** instead of **98a** as a white powder. Yield 74% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.30–7.26 (m, 1H), 7.02–6.85 (m, 7H), 6.30 (d, J = 8.1 Hz, 1H), 5.20–5.11 (m, 1H), 4.98 (s, 2H), 3.10–2.95 (m, 2H), 2.73 (t, J = 6.9 Hz, 2H), 2.30 (s, 6H), 1.85–1.50 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 490 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{35}FNO_4$: 492.2550; found: 492.2552.

5.1.73. 3-[4-[(2-Chlorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (32)

The titled compound was synthesized in the same manner as described for **29** using **98d** instead of **98a** as a white powder. Yield 57% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.46–7.37 (m, 2H), 7.31–7.17 (m, 2H), 7.00–6.87 (m, 5H), 6.30 (d, J = 8.4 Hz, 1H), 5.22–5.12 (m, 1H), 5.11 (s, 2H), 3.13–2.96 (m, 2H), 2.73 (t, J = 7.7 Hz, 2H), 2.31 (s, 6H), 1.86–1.54 (m, 3H), 0.98 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 6.3 Hz, 3H); MS (APCI, Neg.) m/e 506 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{35}ClNO_4$: 508.2255; found: 508.2255.

5.1.74. 3-[4-[(3-Chlorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (33)

The titled compound was synthesized in the same manner as described for **29** using **98e** instead of **98a** as a white powder. Yield 44% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.37 (m, 2H), 7.32–7.17 (m, 2H), 7.00–6.81 (m, 6H), 6.29 (d, J = 8.7 Hz, 1H), 5.17 (m, 1H), 5.00 (s, 2H), 3.09–2.97 (m, 2H), 2.73 (t, J = 7.1 Hz, 2H), 2.31 (s, 6H), 1.87–1.52 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 506 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{35}ClNO_4$: 508.2255; found: 508.2254.

5.1.75. 3-[4-[(4-Chlorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (34)

The titled compound was synthesized in the same manner as described for **29** using **98f** instead of **98a** as a white powder. Yield 23% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.35 (m, 2H), 7.34–7.19 (m, 3H), 6.95 (s, 2H), 6.93–6.81 (m, 3H), 6.29 (d, J = 8.5 Hz, 1H), 5.26–5.09 (m, 1H), 4.99 (s, 2H), 3.12–2.95 (m, 2H), 2.74 (t, J = 7.4 Hz, 2H), 2.31 (s, 6H), 1.92–1.47 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 506 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{35}ClNO_4$: 508.2255; found: 508.2253.

5.1.76. 3-[4-[(2-Cyanophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (35)

The titled compound was synthesized in the same manner as described for **29** using **98g** instead of **98a** as a white powder. Yield 65% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.49 (m, 2H), 7.43–7.27 (m, 3H), 7.09–6.87 (m, 5H), 6.55 (d, J = 8.7 Hz, 1H), 5.23–5.07 (m, 3H), 3.03 (t, J = 7.0 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H), 2.30 (s, 6H), 1.88–1.52 (m, 3H), 0.98 (d, J = 6.0 Hz, 6H); MS (APCI, Neg.) m/e 497 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{35}N_2O_4$: 499.2597; found: 499.2588.

5.1.77. 3-[4-[(3-Cyanophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (36)

The titled compound was synthesized in the same manner as described for **29** using **98h** instead of **98a** as a white powder. Yield 67% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.06 (m, 7H), 6.95 (s, 2H), 6.90 (s, 1H), 6.42 (d, J = 7.5 Hz, 1H), 5.16 (m, 1H), 5.00 (s, 2H), 3.10–2.92 (m, 2H), 2.78–2.62 (m, 2H), 2.29 (s, 6H), 1.86–1.48 (m, 3H), 0.97 (d, J = 6.3 Hz, 6H); IR (KBr) 3282, 2230, 1711, 1637, 1606, 1532, 1291, 1262, 1168, 1042, 848, 788, 681 cm^{-1}; MS (APCI, Neg.) m/e 497 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{35}N_2O_4$: 499.2597; found: 499.2599.

5.1.78. 3-[4-[(4-Cyanophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (37)

The titled compound was synthesized in the same manner as described for **29** using **98i** instead of **98a** as a white powder. Yield 76% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 9.0 Hz, 2H), 7.43–7.26 (m, 3H), 6.99 (d, J = 9.0 Hz, 2H), 6.95 (s, 2H), 6.90 (s, 1H), 6.38 (d, J = 8.4 Hz, 1H), 5.23–5.11 (m, 1H), 5.05 (s, 2H), 3.10–2.96 (m, 2H), 2.82–2.63 (m, 2H), 2.30 (s, 6H), 1.84–1.52 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 497 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{35}N_2O_4$: 499.2597; found: 499.2600.

5.1.79. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}-carbonyl)-4-[(2-methylphenoxy)methyl]phenyl}propanoic acid (38)

The titled compound was synthesized in the same manner as described for **29** using **98j** instead of **98a** as a white powder. Yield 33% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.39 (m, 2H), 7.31–7.22 (m, 1H), 7.20–7.11 (m, 2H), 6.95 (s, 2H), 6.93–6.82 (m, 3H), 6.26 (d, J = 8.4 Hz, 1H), 5.22–5.12 (m, 1H), 5.04 (s, 2H), 3.14–2.99 (m, 2H), 2.78–2.67 (m, 2H), 2.31 (s, 6H), 2.27 (s, 3H), 1.85–1.52 (m, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); IR (KBr) 3305, 1719, 1637, 1603, 1527, 1246, 1122, 1061, 848, 818 cm^{-1}; MS (APCI, Neg.) m/e 486 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{38}NO_4$: 488.2801; found: 488.2798.

5.1.80. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}-carbonyl)-4-[(3-methylphenoxy)methyl]phenyl}propanoic acid (39)

The titled compound was synthesized in the same manner as described for **29** using **98k** instead of **98a** as a white powder. Yield 47% in three steps; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.36 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 8.1 Hz, 1H), 6.95 (s, 2H), 6.90 (s, 1H), 6.85–6.72 (m, 3H), 6.29 (d, J = 9.0 Hz, 1H), 5.24–5.11 (m, 1H), 4.99 (s, 2H), 3.11–2.93 (m, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.33 (s, 3H), 2.30 (s, 6H), 1.85–1.52 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 486 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{38}NO_4$: 488.2801; found: 488.2803.

5.1.81. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}carbonyl)-4-[(4-methylphenoxy)methyl]phenyl}propanoic acid (40)

The titled compound was synthesized in the same manner as described for **29** using **98l** instead of **98a** as a white powder. Yield 56% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.94 (s, 2H), 6.90 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.29 (d, J = 8.4 Hz, 1H), 5.22–5.10 (m, 1H), 4.99 (s, 2H), 3.11–2.93 (m, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.31 (s, 6H), 2.29 (s, 3H), 1.86–1.52 (m, 3H), 0.98 (d, J = 6.0 Hz, 6H); MS (APCI, Neg.) m/e 486 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{38}NO_4$: 488.2801; found: 488.2800.

5.1.82. 3-{2-({[1-(3,5-Dimethylphenyl)-3-methylbutyl]amino}carbonyl)-4-[(3-methoxyphenoxy)methyl]phenyl}propanoic acid (41)

The titled compound was synthesized in the same manner as described for **29** using **98m** instead of **98a** as a white powder. Yield 77% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.38 (m, 2H), 7.32–7.12 (m, 2H), 6.95 (s, 2H), 6.90 (s, 1H), 6.60–6.49 (m, 3H), 6.28 (d, J = 8.1 Hz, 1H), 5.24–5.11 (m, 1H), 5.00 (s, 2H), 3.78 (s, 3H), 3.09–2.96 (m, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.31 (s, 6H), 1.87–1.52 (m, 3H), 0.98 (d, J = 6.0 Hz, 6H); MS (APCI, Neg.) m/e 502 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{38}NO_5$: 504.2750; found: 504.2750.

5.1.83. 3-[4-[(2,3-Difluorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (47)

The titled compound was synthesized in the same manner as described for **29** using **98n** instead of **98a** as a white powder. Yield 50% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.02–6.89 (m, 4H), 6.85–6.73 (m, 2H), 6.32 (d, J = 8.7 Hz, 1H), 5.17 (m, 1H), 5.10 (s, 2H), 3.07–2.95 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.31 (s, 6H), 1.86–1.53 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 508 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}F_2NO_4$: 510.2456; found: 510.2459.

5.1.84. 3-[4-[(2,4-Difluorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (48)

The titled compound was synthesized in the same manner as described for **29** using **98o** instead of **98a** as a white powder. Yield 18% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.37 (m, 2H), 7.27 (d, J = 8.4 Hz, 1H), 6.98–6.72 (m, 6H), 6.31 (d, J = 8.7 Hz, 1H), 5.22–5.08 (m, 1H), 5.04 (s, 2H), 3.11–2.94 (m, 2H), 2.71 (t, J = 7.8 Hz, 2H), 2.31 (s, 6H), 1.86–1.52 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 508 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}F_2NO_4$: 510.2456; found: 510.2457.

5.1.85. 3-[4-[(2,5-Difluorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (49)

The titled compound was synthesized in the same manner as described for **29** using **98p** instead of **98a** as a white powder. Yield 66% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.03 (m, 1H), 6.96 (s, 2H), 6.90 (s, 1H), 6.73 (m, 1H), 6.62 (m, 1H), 6.35 (d, J = 8.5 Hz, 1H), 5.17 (m, 1H), 5.05 (s, 2H), 3.11–2.93 (m, 2H), 2.81–2.62 (m, 2H), 2.31 (s, 6H), 1.84–1.52 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); IR (KBr) 3293, 3018, 2957, 2871, 1712, 1636, 1607, 1514, 1284, 1205, 1156, 1100, 834 cm^{-1}; MS (APCI, Neg.) m/e 508 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}F_2NO_4$: 510.2456; found: 510.2457.

5.1.86. 3-[4-[(2,6-Difluorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (50)

The titled compound was synthesized in the same manner as described for **29** using **98q** instead of **98a** as a white powder. Yield 16% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.32–7.21 (m, 2H), 7.07–6.82 (m, 5H), 6.25 (d, J = 8.8 Hz, 1H), 5.26–5.08 (m, 3H), 3.13–2.97 (m, 2H), 2.72 (t, J = 7.3 Hz, 2H), 2.32 (s, 6H), 1.94–1.50 (m, 3H), 1.00 (d, J = 6.0 Hz, 6H); MS (APCI, Neg.) m/e 508 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}F_2NO_4$: 510.2456; found: 510.2460.

5.1.87. 3-[4-[(3,4-Difluorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (51)

The titled compound was synthesized in the same manner as described for **29** using **98r** instead of **98a** as a white powder. Yield 20% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (m, 3H), 7.12–7.02 (m, 1H), 6.95 (s, 2H), 6.91 (s, 1H), 6.82–6.73 (m, 1H), 6.69–6.59 (m, 1H), 6.34 (d, J = 9.0 Hz, 1H), 5.23–5.12 (m, 1H), 4.95 (s, 2H), 3.11–2.93 (m, 2H), 2.72 (t, J = 7.5 Hz, 2H), 2.30 (s, 6H), 1.85–1.54 (m, 3H), 0.98 (d, J = 6.0 Hz, 6H); MS (APCI, Neg.) m/e 508 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}F_2NO_4$: 510.2456; found: 510.2454.

5.1.88. 3-[4-[(3,5-Difluorophenoxy)methyl]-2-({[1-(3,5-dimethylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (52)

The titled compound was synthesized in the same manner as described for **29** using **98s** instead of **98a** as a white powder. Yield 47% in three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2H), 7.30 (d, J = 7.5 Hz, 1H), 6.95 (s, 2H), 6.91 (s, 1H), 6.54–6.40 (m, 3H), 6.32 (d, J = 8.7 Hz, 1H), 5.17 (m, 1H), 4.97 (s, 2H), 3.12–2.94 (m, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.31 (s, 6H), 1.87–1.52 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); MS (APCI, Neg.) m/e 508 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{34}F_2NO_4$: 510.2456; found: 510.2454.

5.1.89. 3-[(2-Oxo-2*H*-chromen-7-yl)methoxy]benzonitrile (100)

The titled compound was synthesized in the same manner as described for **78** using 3-cyanophenol instead of phenol as a white powder. Yield 83% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 9.6 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.45–7.20 (m, 6H), 6.45 (d, J = 9.6 Hz, 1H), 5.19 (s, 2H).

5.1.90. Methyl (2*E*)-3-{4-[(3-cyanophenoxy)methyl]-2-hydroxyphenyl}acrylate (101)

The titled compound was synthesized in the same manner as described for **91** using **100** instead of **90** as a white powder. Yield 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 16 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.42–7.12 (m, 4H), 6.96 (d, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.60 (d, J = 16 Hz, 1H), 5.05 (s, 2H), 3.82 (s, 3H).

5.1.91. Methyl 3-{4-[(3-cyanophenoxy)methyl]-2-hydroxyphenyl}propanoate (102)

The titled compound was synthesized in the same manner as described for **92** using **101** instead of **91** as a colorless oil. Yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–6.85 (m, 7H), 5.01 (s, 2H), 3.70 (s, 3H), 2.91 (t, J = 6.3 Hz, 2H), 2.73 (t, J = 6.3 Hz, 2H).

5.1.92. 5-[(3-Cyanophenoxy)methyl]-2-(3-methoxy-3-oxopropyl)benzoic acid (104)

The titled compound was synthesized in the same manner as described for **83** using **102** instead of **81** as a brown solid. Yield 82% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42–7.20 (m, 6H), 5.09 (s, 2H), 3.67 (s, 3H), 3.33 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H).

5.1.93. 3-[4-[(3-Cyanophenoxy)methyl]-2-({[3-methyl-1-(3-methylphenyl)butyl]amino}carbonyl)phenyl]propanoic acid (42)

The titled compound was synthesized in the same manner as described for **5** using **104** and **64b** instead of **86** and **59a** as a white powder. Yield 61% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.06 (m, 11H), 6.40 (d, J = 8.7 Hz, 1H), 5.26–5.16 (m, 1H), 5.04 (s, 2H), 3.13–2.97 (m, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.35 (s, 3H), 1.85–1.58 (m, 3H), 0.99 (d, J = 6.3 Hz, 6H); IR (KBr) 3277, 2956, 2230, 1709, 1638, 1534, 1491, 1290, 1262, 1156, 1023, 787, 681 cm^{-1}; MS (APCI, Neg.) m/e 483 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{33}N_2O_4$: 485.2440; found: 485.2437.

5.1.94. 3-[4-[(3-Cyanophenoxy)methyl]-2-({[1-(3-methoxyphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (43)

The titled compound was synthesized in the same manner as described for **5** using **104** and **64d** instead of **86** and **59a** as a white powder. Yield 55% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.15 (m, 8H), 6.95 (d, J = 7.8 Hz, 1H), 6.91 (m, 1H), 6.81 (dd, J = 8.4, 2.7 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 5.22 (m, 1H), 5.03 (s, 2H), 3.81 (s, 3H), 3.02 (t, J = 7.2 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 1.83–1.58 (m, 3H), 0.98 (d, J = 6.3 Hz, 6H); IR (KBr) 3278, 2957, 2229, 1704, 1639, 1579, 1535, 1490, 1433, 1290, 1263, 1161, 1046, 818, 783, 680 cm^{-1}; MS (APCI, Neg.) m/e 499 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{33}N_2O_5$: 501.2389; found: 501.2393.

5.1.95. 3-[4-[(3-Cyanophenoxy)methyl]-2-({[1-(4-fluorophenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (44)

The titled compound was synthesized in the same manner as described for **5** using **104** and **59c** instead of **86** and **59a** as a white powder. Yield 61% in two steps; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.26 (br s, 1H), 7.57–7.26 (m, 9H), 7.18–7.06 (m, 2H), 5.13 (s, 2H), 5.09–4.97 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.80–1.52 (m, 2H), 1.48–1.37 (m, 1H), 0.91 (t, J = 6.2 Hz, 3H), 0.89 (t, J = 6.2 Hz, 3H); MS (APCI, Neg.) m/e 489 $(M-H)^-$; HRMS (Pos.) calcd for $C_{29}H_{30}FN_2O_4$: 489.2190; found: 489.2194.

5.1.96. 3-[4-[(3-Cyanophenoxy)methyl]-2-({[1-(4-fluoro-3-methylphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (45)

The titled compound was synthesized in the same manner as described for **5** using **104** and **64i** instead of **86** and **59a** as a white powder. Yield 57% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.35 (m, 3H), 7.31–7.25 (m, 2H), 7.21–7.11 (m, 4H), 6.96 (t, J = 8.7 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 5.17 (m, 1H), 5.03 (s, 2H), 3.06–2.95 (m, 2H), 2.76–2.64 (m, 2H), 2.26 (d, J = 1.5 Hz, 3H), 1.81–1.53 (m, 3H), 0.97 (d, J = 6.6 Hz, 6H); IR (KBr) 3284, 2957, 2231, 1710, 1637, 1598, 1578, 1534, 1503, 1432, 1328, 1291, 1262, 1211, 1157, 1025, 942, 826, 788, 758, 681 cm^{-1}; MS (APCI, Neg.) m/e 501 $(M-H)^-$; HRMS (Pos.) calcd for $C_{30}H_{32}FN_2O_4$: 503.2346; found: 503.2342.

5.1.97. 3-[4-[(3-Cyanophenoxy)methyl]-2-({[1-(3,4-dimethoxyphenyl)-3-methylbutyl]amino}carbonyl)phenyl]propanoic acid (46)

The titled compound was synthesized in the same manner as described for **5** using **104** and **59e** instead of **86** and **59a** as a white powder. Yield 72% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.34 (m, 3H), 7.32–7.24 (m, 2H), 7.20–7.14 (m, 2H), 6.94–6.88 (m, 2H), 6.84 (d, J = 8.7 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.20 (m, 1H), 5.02 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.01 (t, J = 8.1 Hz, 2H), 2.73 (t, J = 8.1 Hz, 2H), 1.90–1.50 (m, 3H), 0.99 (d, J = 6.6 Hz, 6H); IR (KBr) 3299, 2956, 2230, 1734, 1635, 1596, 1519, 1464, 1368, 1327, 1261, 1144, 1025, 789, 681 cm^{-1}; MS (APCI, Neg.) m/e 529 $(M-H)^-$; HRMS (Pos.) calcd for $C_{31}H_{35}N_2O_6$: 531.2495; found: 531.2497.

5.2. Pharmacology

5.2.1. mEP1-4 receptor binding assay

Competitive binding studies were conducted using radiolabeled ligands and membrane fractions prepared from Chinese hamster ovary (CHO) cells stably expressing the prostanoid receptors mEP1-4. Membranes from CHO cells expressing prostanoid receptors were incubated with radiolabeled ligand (2.5 nM [^{3}H]PGE_2) and test compounds at various concentrations in assay buffer (10 mM KH_2PO_4–KOH buffer containing 1 mM EDTA, 10 mM $MgCl_2$, and 0.1 mM NaCl, pH 6.0). Incubation was carried out at 25 °C for 60 min except for mEP1 which was incubated for 20 min. Incubation was terminated by filtration through a Whatman GF/B filter. The filter was subsequently washed with ice-cold buffer (10 mM KH_2PO_4–KOH buffer containing 0.1 mM NaCl, pH 6.0), and the radioactivity on the filter was measured in 6 mL of liquid scintillation (ACSII) mixture with a liquid scintillation counter. Nonspecific binding was achieved by adding excess amounts of unlabeled PGE_2 in assay buffer. The half maximal inhibitory concentration of specific binding (IC_{50} value) was estimated from the regression curve. The K_i value (M) was calculated according to the following equation:

$$K_i = IC_{50}/(1 + [L]/K_d)$$

where [L] is the concentration of radiolabeled ligand, and K_d is the dissociation constant of radiolabeled ligand for the prostanoid receptor of interest.

5.2.2. mEP3 receptor antagonist activity

To confirm that test compounds antagonized the mEP3 receptor and to estimate the extent of antagonism for the mEP3 receptor, a functional assay was performed by measuring PGE_2-stimulated increases in intracellular Ca^{2+}. The cells expressing mEP3α receptor were seeded at 1×10^4 cells/well in 96 well plates and cultured for two days with 10% FBS (fetal bovine serum)/minimum essential medium Eagle alpha modification (αMEM) in an incubator (37 °C, 5% CO_2). The cells in each well were rinsed with phosphate buffer (PBS(−)), and load buffer (10% FBS/αMEM containing 5 μM of Fura 2/AM, 20 μM of indomethacin, and 2.5 mM of probenecid) was added. After incubation for 1 h, the cells in each well were rinsed with assay buffer (Hank's balanced salt solution (HBSS) containing 1% (w/v) BSA, 2 μM of indomethacin, 2.5 mM of probenecid, and 10 mM of HEPES–NaOH) twice. Then 90 μL of assay buffer was added to each well and the cells were incubated in the dark at room temperature for 1 h. After the addition of a solution containing test compound (30 μL) and PGE_2 (30 μL), which were prepared with assay buffer, the intracellular calcium concentration was measured with a fluorescence drug screening system (FDSS-3000, Hamamatsu Photonics). The fluorescence intensities emitted at 500 nm using excitation wavelengths of 340 nm and 380 nm were measured. The percent inhibition from the increase in the intracellular Ca^{2+} concentration induced by PGE_2 (10 nM) was calculated relative to the maximum Ca^{2+} concentration that occurred in the absence of the test compound (100%). This was then used to estimate the IC_{50} value.

5.2.3. Inhibitory effect of test compounds on the PGE_2-induced uterine contraction in pregnant rats

Fed pregnant rats were anesthetized with urethane (1.5 g/5 mL/kg sc) and fixed in the dorsal position. A midline incision was made in the lower abdomen and a small incision was made near the cervical area of the right or left uterine horn, and a

balloon catheter (Okamoto Medical Industry, for rats) was inserted between the uterine wall and the amnion. After suturing the abdominal incision, the intraballoon pressure was loaded to approximately 10 mm Hg. Uterine motility was recorded on a recticoder (WR3320 or WR3701, GRAPHTEC) via a pressure transducer (Life Kit DX-360, Nihon Kohden Corp.) and a strain pressure amplifier (AP-601G, Nihon Kohden Corp.). After spontaneous uterine motility was kept at a stable level, a test compound (5 mL/kg in 0.5% methylcellulose (MC)) or vehicle (0.5% MC) was intraduodenally administrated. After 30 min, an increased uterine contraction was elicited by an intravenous administration of PGE_2 (30 μg/kg). Subtraction of the area under the uterus pressure–time curve (AUC) for 10 min before PGE_2 administration from the AUC for 10 min after PGE_2 administration was determined to be the increased uterine contraction (=ΔS). The inhibitory effect of a test compound (% inhibition) was calculated according to the following equation:

$$\text{Inhibitory effect (\% inhibition)} = [\Delta S\ (\text{vehicle}) - \Delta S\ (\text{test compound})]/\Delta S\ (\text{vehicle}) * 100$$

where ΔS (test compound) is an increased uterine contraction of administration of a test compound and ΔS (vehicle) is an increased uterine contraction of administration of vehicle.

References and notes

1. (a) Coleman, R. A.; Grix, S. P.; Head, S. A.; Louttit, J. B.; Mallett, A.; Sheldrick, R. L. G. *Prostaglandins* **1994**, *47*, 151; (b) Negishi, M.; Sugimoto, Y.; Ichikawa, A. J. *Lipid Mediat. Cell Signal.* **1995**, *12*, 379.
2. Sorbera, L. A.; Bozzo, J.; Rosa, E.; Dulsat, C. *Drugs Future* **2008**, *33*, 455.
3. Breyer, M. D.; Hebert, R. L.; Breyer, R. M. *Curr. Opin. Invest. Drugs* **2003**, *4*, 1343.
4. Cameron, K. O.; Lefker, B. A.; Ke, H. Z.; Li, M.; Zawistoski, M. P.; Tjoa, C. M.; Wright, A. S.; DeNinno, S. L.; Paralkar, V. M.; Owen, T. A.; Yu, L.; Thompson, D. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2075.
5. Singh, J.; Zeller, W.; Zhou, N.; Hategen, G.; Mishra, R.; Polozov, A.; Yu, P.; Onua, E.; Zhang, J.; Zembower, D.; Kiselyov, A.; Ramirez, J. L.; Sigthorsson, G.; Bjornsson, J. M.; Thorsteinsdottir, M.; Andresson, T.; Bjarnadottir, M.; Magnusson, O.; Fabre, J. E.; Stefansson, K.; Gurney, M. E. *ACS Chem. Biol.* **2009**, *4*, 115.
6. Ohta, C.; Kuwabe, S.; Shiraishi, T.; Shinohara, I.; Araki, H.; Sakuyama, S.; Makihara, T.; Kawanaka, Y.; Ohuchida, S.; Seko, T. *J. Org. Chem.* **2009**, *74*, 8298.
7. RaQualia Phrma Inc. Home Page. http://www.raqualia.co.jp/.
8. Just, S.; Arndt, K.; Weiser, T.; Doods, H. *Drug Discovery Today Dis. Mech.* **2006**, *3*, 327.
9. Asada, M.; Obitsu, T.; Nagase, T.; Tanaka, M.; Yamaura, Y.; Takizawa, H.; Yoshikawa, K.; Sato, K.; Narita, M.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2010**, *18*, 80.
10. Backes, B. J.; Dragoli, D. R.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 5472.
11. Rodriques, K. E.; Basha, A.; Summers, J. B.; Broocks, D. W. *Tetrahedron Lett.* **1988**, *29*, 3455.
12. Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.
13. Cohen, B. J.; Karoly-Hafeli, H.; Patchornik, A. *J. Org. Chem.* **1984**, *49*, 922.
14. (a) Senior, J.; Marshall, K.; Sangha, R.; Baxter, G. S.; Clayton, J. K. *Br. J. Pharmacol.* **1991**, *102*, 747; (b) Goureau, O.; Tanfin, Z.; Marc, S.; Harbon, S. *Am. J. Physiol.* **1992**, *263*, C257.