Bioorganic & Medicinal Chemistry 17 (2009) 6567–6582

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery of a series of acrylic acids and their derivatives as chemical leads for selective EP3 receptor antagonists

Masaki Asada *, Tetsuo Obitsu, Toshihiko Nagase, Isamu Sugimoto, Yoshiyuki Yamaura, Kazutoyo Sato, Masami Narita, Shuichi Ohuchida, Hisao Nakai, Masaaki Toda

Minase Research Institute, Ono Pharmaceutical Co., Ltd, Shimamoto, Mishima, Osaka 618-8585, Japan

ARTICLE INFO

Article history:
Received 3 July 2009
Revised 31 July 2009
Accepted 1 August 2009
Available online 8 August 2009

Keywords:
Prostaglandin
EP3 receptor
Antagonist
Pyrazole

ABSTRACT

A series of acrylic acids and their structurally related compounds were evaluated for their binding affinity to four EP receptor subtypes (EP1-4). Starting from the initial hit **3**, which was discovered in our in-house library, compounds **4** and **5** were identified as new chemical leads as candidates for further optimization towards a selective EP3 receptor antagonist. The identification process of these compounds and their pharmacokinetic profiles are presented.

1. Introduction

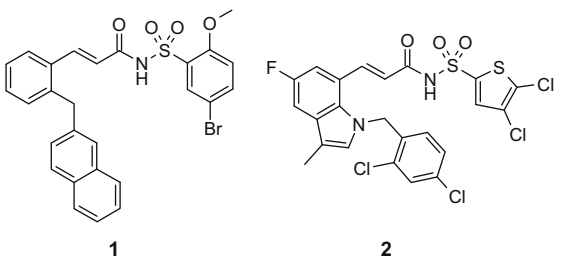
Prostanoids, which include prostaglandins (PGs) and thromboxanes (TXs), are the oxidative metabolites of arachidonic acid by cyclooxygenase. They play important roles in a multitude of significant physiological processes. During the last several decades, a large number of structural analogs of PGs were designed, synthesized and evaluated as potential drugs. Some of these drug candidates have been launched as clinically useful drugs although they still show non-selective receptor affinity during recent reassessments.

Coleman et al. proposed the existence of receptors specific for PGF, PGE, PGD, PGI and TX that were named FP, EP, DP, IP and TP receptors, respectively.[1] They further classified the EP receptor into four subtypes (EP1, EP2, EP3 and EP4), all of which respond to PGE_2 in different ways. It is well known that PGE_2 is the most widely produced prostaglandin in the body and exhibits versatile physiological responses through its interaction with four receptor subtypes. Characterization of these receptors at the molecular level has resulted in renewed interest in this field. The EP3 receptor has been detected in many organs including the brain, kidney, uterus and gastrointestinal tract. Recent studies utilizing KO mice, in which the EP3 receptor subtype is specifically knocked out, suggest that the EP3 receptor plays key roles in regulating hyperalgesia,[2] pyrexia,[3] uterine contraction,[4] gastric acid secretion,[5] platelet aggregation[6] and thrombosis.[7] Thus, a selective EP3 receptor antagonist is expected to be a new therapeutic agent to treat pyrexia, pain, threatened abortion and peripheral occupied arterial disease (PAOD).

During our research, two EP3 selective antagonists **1** and **2** (Fig. 1) were reported by Merck[8] and de CODE,[9] respectively. Of these, compound **2** (DG-041) has been clinically evaluated for the treatment of PAOD by the de CODE. Herein we report on our discovery process of new chemical leads **4** and **5** as selective EP3 receptor antagonists starting from a newly identified hit **3** from our in-house library as shown in Scheme 1.

2. Chemistry

Synthesis of test compounds listed in Tables 1–4 is outlined in Schemes 2–8.

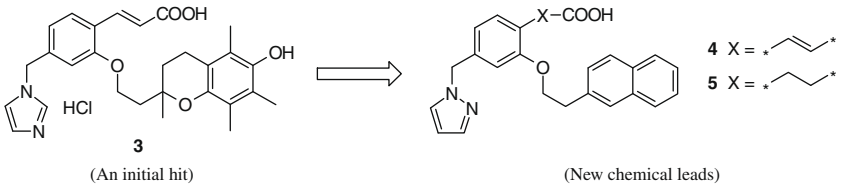


1 2

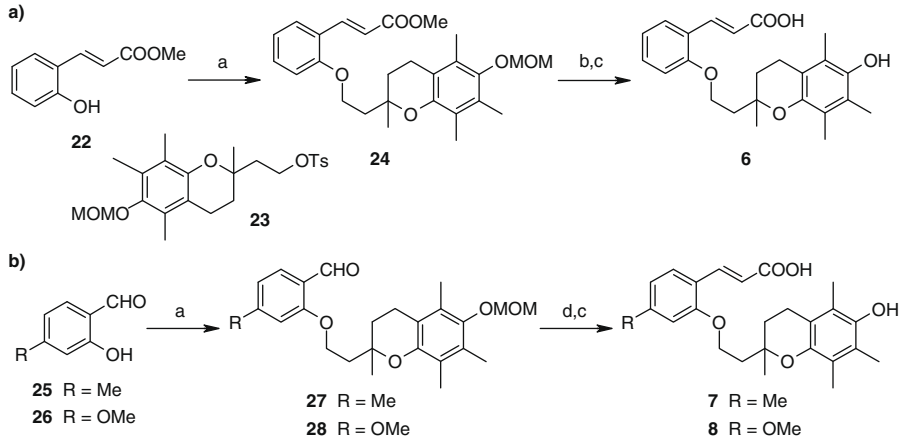
Figure 1. Reported EP3 receptor antagonists.

* Corresponding author. Tel.: +81 75 961 1151; fax: +81 75 962 9314.
E-mail address: m.asada@ono.co.jp (M. Asada).

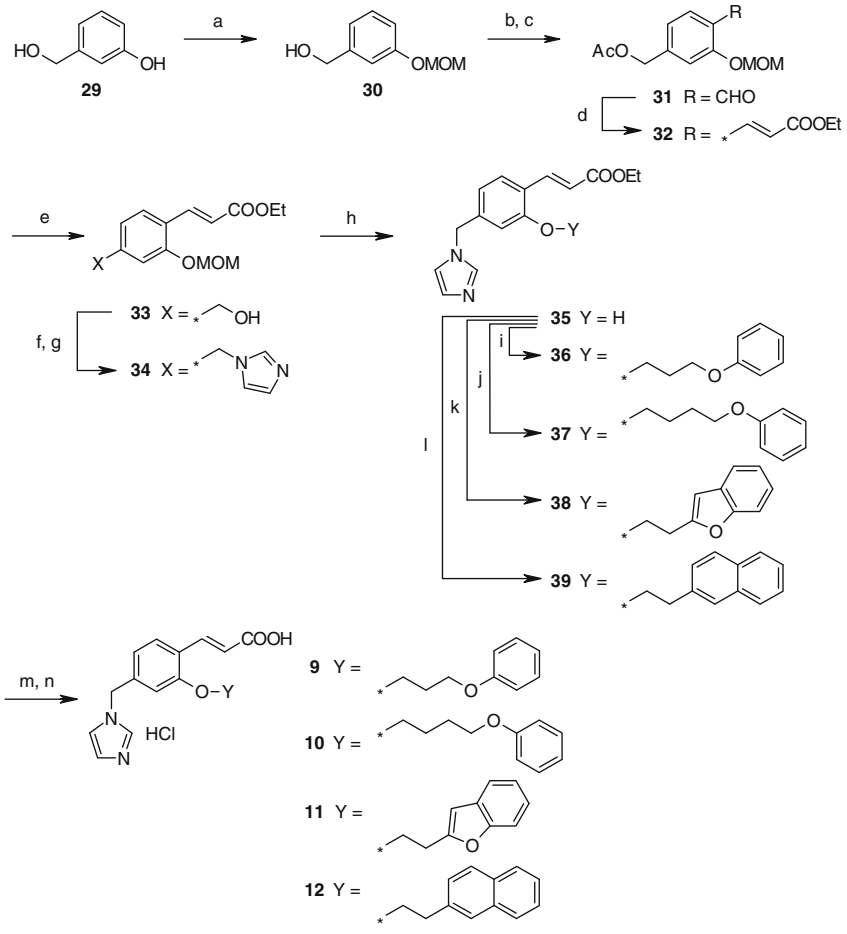
0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.08.007



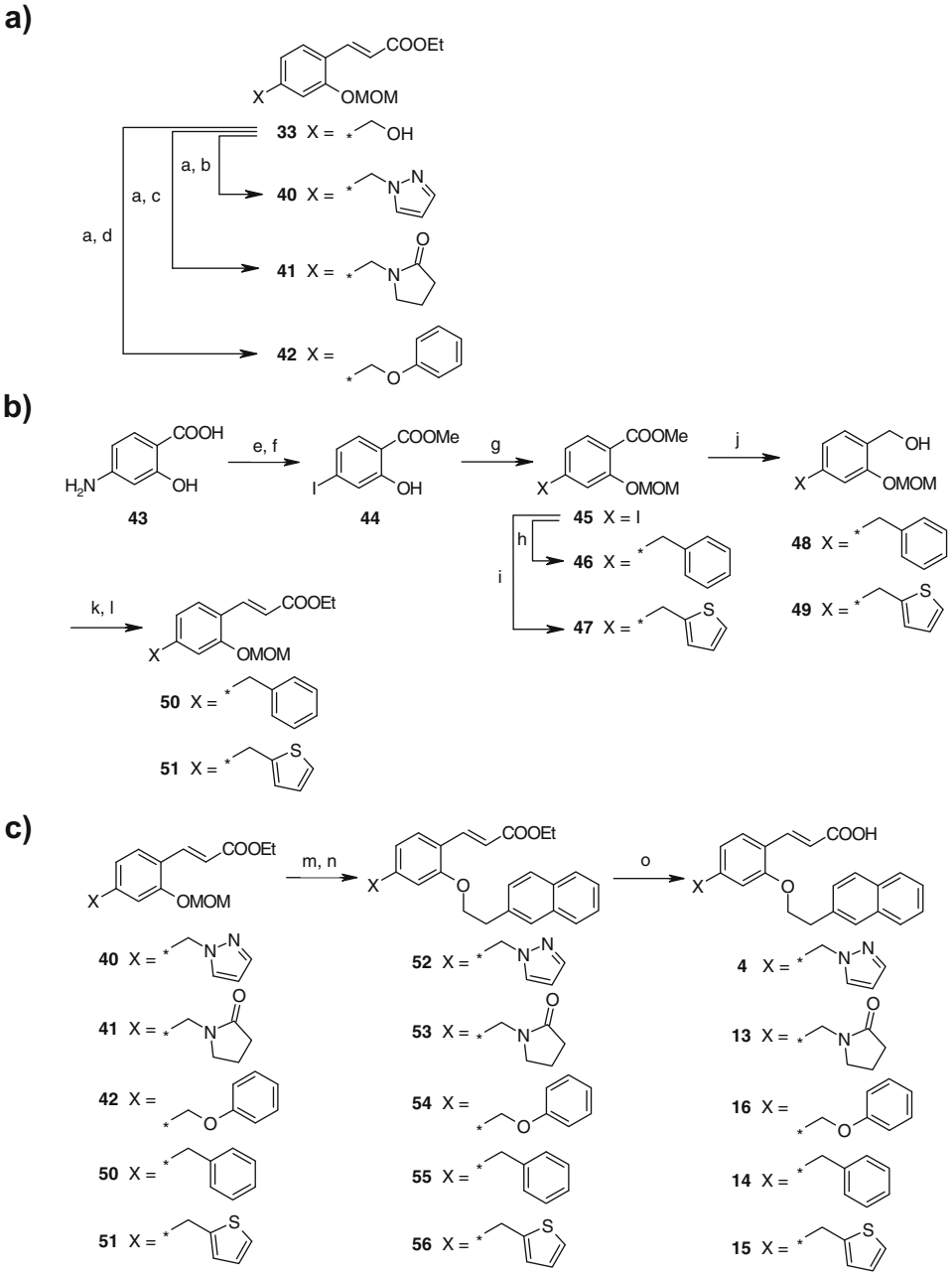
Scheme 1. Discovery of new chemical leads as selective EP3 antagonists.



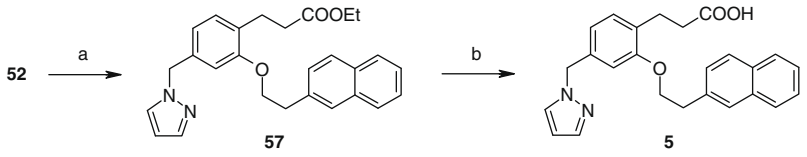
Scheme 2. Synthesis of **6–8**. Reagents: (a) **23**, NaH, DMF; (b) NaOHaq, THF, MeOH; (c) HCl–dioxane; (d) malonic acid, piperidine, pyridine.



Scheme 3. Synthesis of **9–12**. Reagents: (a) MOMCl, NaH, DMF; (b) *n*-BuLi, *t*-BuLi, TMEDA, Et_2O then *N*-formylpiperidine; (c) Ac_2O, pyridine; (d) ethyl diethylphosphonoacetate, NaH, THF; (e) NaOEt, EtOH; (f) MsCl, Et_3N, THF; (g) imidazole, toluene; (h) HCl–dioxane, EtOH; (i) 3-phenoxypropyl bromide, NaH, DMF; (j) 4-phenoxybutyl bromide, NaH, DMF; (k) 2-(benzofuran-2-yl)ethanol, DEAD, Ph_3P, THF; (l) 2-(naphthalen-2-yl)ethanol, DEAD, Ph_3P, THF; (m) NaOHaq, THF, MeOH; (n) HCl–dioxane.

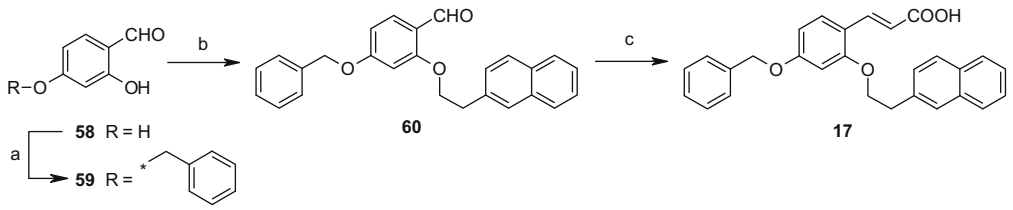


Scheme 4. Synthesis of **4 and 13–16**. Reagents: (a) MsCl, Et_3N, THF; (b) pyrazole, NaH, DMF; (c) 2-pyrrolidone, NaH, DMF; (d) phenol, NaH, DMF; (e) $NaNO_2$aq, H_2SO_4aq then KIaq; (f) concd H_2SO_4, MeOH; (g) MOMCl, NaH, DMF; (h) benzylzinc bromide, $Pd_2(dba)_3$, DPPF, THF; (i) 2-thienylmethylzinc bromide, $Pd_2(dba)_3$, DPPF, THF; (j) $LiAlH_4$, THF; (k) SO_3–pyridine, DMSO, Et_3N, CH_2Cl_2; (l) ethyl diethylphosphonoacetate, NaH, THF; (m) HCl–dioxane, EtOH; (n) 2-(naphthalen-2-yl)ethanol, ADDP, Ph_3P, THF; (o) NaOHaq, THF, MeOH.

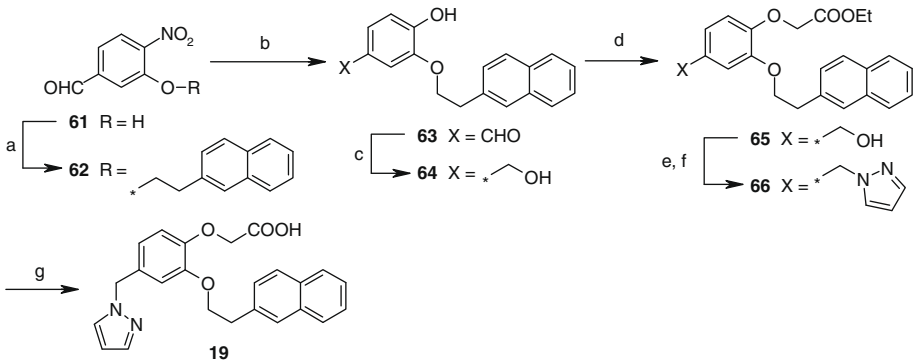


Scheme 5. Synthesis of **5**. Reagents: (a) $NaBH_4$, $NiCl_2$–$6H_2O$, THF, EtOH; (b) NaOHaq, THF, MeOH.

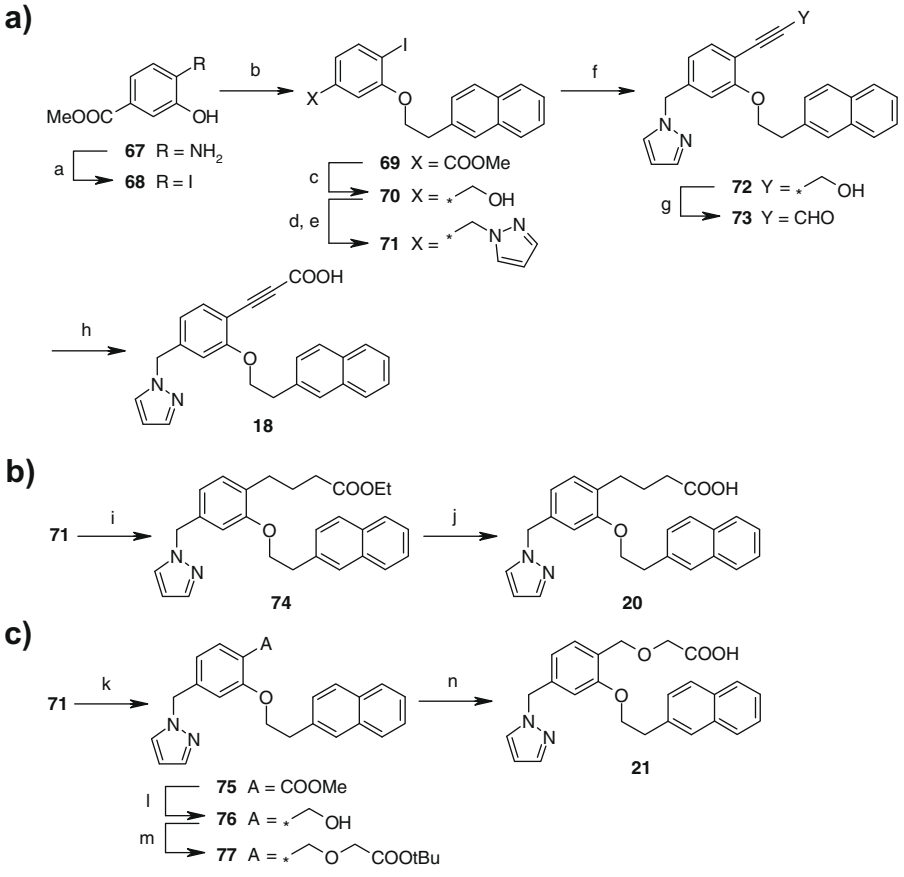
Compounds **6** and **7–8** possessing the 6-hydroxy-2,5,7,8-tetramethylchromane moiety were synthesized as shown in Scheme 2a and b, respectively. O-Alkylation of **22** with **23**[10] in the presence of sodium hydride afforded **24**. Alkaline hydrolysis of **24** followed by acidic deprotection of the methoxymethyl (MOM) group provided **6**. O-Alkylation of compounds **25** and **26** in the presence of sodium hydride afforded **27** and **28**, respectively. Perkin reaction of the aldehydes **27** and **28** with malonic acid in the



Scheme 6. Synthesis of **17**. Reagents: (a) benzyl chloride, $NaHCO_3$, KI, CH_3CN; (b) 2-(naphthalen-2-yl)ethanol, ADDP, Ph_3P, THF; (c) malonic acid, piperidine, pyridine.



Scheme 7. Synthesis of **19**. Reagents: (a) 2-(naphthalen-2-yl)ethanol, ADDP, Ph_3P, THF; (b) benzaldoxime, *t*-BuOK, DMSO; (c) $NaBH_4$, EtOH, (d) ethyl bromoacetate, NaH, DMF; (e) PBr_3, CH_2Cl_2; (f) pyrazole, NaH, DMF; (g) NaOHaq, THF, MeOH.



Scheme 8. Synthesis of **18** and **20–21**. Reagents: (a) $NaNO_2$aq, concd HCl then KIaq; (b) 2-(naphthalen-2-yl)ethanol, ADDP, Ph_3P, THF; (c) DIBAL-H, CH_2Cl_2, (d) MsCl, Et_3N, THF; (e) pyrazole, NaH, DMF; (f) propargyl alcohol, CuI, $PdCl_2(Ph_3P)_2$, tetrabutylammonium iodide, Et_3N, DMF; (g) Dess–Martin periodinate, CH_2Cl_2; (h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O; (i) 4-ethoxy-4-oxobutylzinc bromide, $PdCl_2$(dppf), THF; (j) NaOHaq, THF, MeOH; (k) CO, $Pd(OAc)_2$, DPPF, Et_3N, DMF, MeOH; (l) $LiAlH_4$, THF; (m) *t*-butyl bromoacetate, tetrabutylammonium hydrogen sulfate, NaOHaq, toluene; (n) TFA, anisole, CH_2Cl_2.

presence of piperidine in pyridine followed by deprotection under acidic conditions resulted in the corresponding acrylic acid derivatives **7** and **8**, respectively.

Synthesis of **9–12** is shown in Scheme 3. O-Alkylation of the phenolic hydroxyl group of 3-hydroxybenzyl alcohol (**29**) with chloromethyl methyl ether in the presence of sodium hydride afforded **30**. 4-Formyl-3-(methoxymethoxy)benzylacetate (**31**) was prepared from **30** by the following sequential reactions: (1) lithiation of the benzylic hydroxyl group with *n*-butyl lithium, (2) *ortho*-lithiation with *t*-butyl lithium, (3) formylation with *N*-formylpiperidine, and (4) acetylation with acetic anhydride in pyridine. Horner–Emmons olefination of **31** with ethyl diethylphosophonoacetate in the presence of sodium hydride provided the unsaturated ester **32**. Deprotection of the *O*-acetate of **32** with sodium ethoxide in ethanol afforded **33**. Methanesulfonylation of **33** followed by the reaction with imidazole in toluene resulted in **34**, acidic deprotection of which afforded **35**. O-Alkylation of **35** with 3-phenoxypropyl bromide and 4-phenoxybutyl bromide in the presence of sodium hydride afforded **36** and **37**, respectively. Mitsunobu reaction of **35** with 2-(benzofuran-2-yl)ethanol and 2-(naphthalen-2-yl)ethanol provided **38** and **39**, respectively. Alkaline hydrolysis of **36–39** followed by treatment with hydrogen chloride produced **9–12**, respectively.

Synthesis of **4** and **13–16** is outlined in Scheme 4a–c. As shown in Scheme 4a, ethyl acrylates **40–42** were prepared from **33** by methanesulfonylation followed by substitution reactions with pyrazole, 2-pyrrolidone and phenol in the presence of sodium hydride. As shown in Scheme 4b, ethyl acrylates **50** and **51** were synthesized from 4-amino-2-hydroxy benzoic acid (**43**). Treatment of **43** with sodium nitrite followed by the addition of potassium iodide and then esterification with methanol afforded **44**. Protection of the phenolic hydroxyl group of **44** as a MOM ether gave a protected iodide **45**. A palladium-catalyzed coupling reaction of **45** with benzylzinc bromide and 2-thienylmethylzinc bromide afforded **46** and **47**, respectively. Reduction of **46** and **47** produced the corresponding benzyl alcohols **48** and **49**, respectively. The oxidation reaction of **48** and **49** with sulfur trioxide-pyridine in dimethyl sulfoxide-triethylamine followed by Horner–Emmons olefination afforded ethyl acrylates **50** and **51**, respectively. As shown in Scheme 4c, acidic deprotection of the MOM ether of **40–42**, **50** and **51** followed by Mitsunobu reaction with 2-(naphthalen-2-yl)ethanol afforded **52–56**, alkaline hydrolysis of which afforded **4**, **13**, **16**, **14** and **15**, respectively.

The phenyl propanoic acid derivative **5** was prepared from **52** as described in Scheme 5. Reduction of the acrylate **52** with sodium borohydride in the presence of nickel chloride afforded **57**, alkaline hydrolysis of which produced **5**.

Synthesis of **17** is described in Scheme 6. Regioselective O-benzylation of 2,4-dihydroxybenzaldehyde (**58**) afforded **59**,[11] O-Alkylation of **59** with 2-(naphthalen-2-yl)ethanol under the Mitsunobu reaction condition provided **60**. Perkin reaction of **60** with malonic acid in the presence of piperidine in pyridine produced **17**.

Phenoxyacetic acid analog **19** was prepared from 3-hydroxy-4-nitrobenzaldehyde (**61**) as shown in Scheme 7. O-Alkylation of **61** with 2-(naphthalen-2-yl)ethanol under the Mitsunobu reaction condition afforded **62**, the nitro group of which was converted to a hydroxyl group with benzaldoxime in the presence of potassium *t*-butoxide to afford **63**.[12] Reduction of the aldehyde **63** gave **64**, selective O-alkylation of which with ethyl bromoacetate in the presence of sodium hydride afforded **65**. Bromination of **65** followed by the treatment with pyrazole gave **66**, alkaline hydrolysis of which provided **19**.

Synthesis of **18** and **20–21** is described in Scheme 8a–c, respectively. Methyl 4-amino-3-hydroxybenzoate (**67**) was converted to an iodide **68** by the conventional method as shown in Scheme 8a. O-Alkylation of **68** with 2-(naphthalen-2-yl)ethanol under the Mitsunobu reaction condition afforded **69**, which was reduced with diisobutylaluminum hydride to afford **70**. Methanesulfonylation of **70** followed by the treatment with pyrazole provided **71**. Sonogashira reaction of **71** with propargyl alcohol afforded **72**, oxidation reaction of which provided an aldehyde **73**. Further oxidation of **73** afforded the corresponding carboxylic acid **18**. Synthesis of **20** is shown in Scheme 8b. A palladium-catalyzed cross coupling reaction of **71** and an alkyl zinc reagent afforded **74**, alkaline hydrolysis of which provided **20**. Compound **21** was prepared from **71** as shown in Scheme 8c. A palladium-catalyzed insertion reaction of carbon monoxide into **71** in the presence of methanol afforded **75**, which was reduced with lithium aluminum hydride to provide **76**. O-Alkylation of the hydroxymethyl residue of **76** with *t*-butyl bromoacetate under phase transfer conditions[13] afforded **77**, which was converted to **21** by a deprotection reaction with trifluoroacetic acid-anisole.

3. Results and discussion

Test compounds listed in Tables 1–4 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 each mouse EP1, EP2, EP3α and EP4 receptors. The EP3 receptor antagonist activity was determined by a Ca^{2+} assay using mouse EP3α receptor expressed on CHO cells in the presence of 0.1% bovine serum albumin (BSA).

In the course of our screening program of a selective EP3 receptor antagonist, 2-alkoxy-4-(imidazol-1-yl)methylphenylacrylic acid **3**, which was structurally distinct from previously reported ones (Fig. 1) and exhibited moderate binding affinity for the EP3 receptor with good subtype selectivity, was identified as an initial hit compound. As depicted in Figure 2, the initial hit compound **3** was believed to have a structural analogy to PGs regarding the acidic part, which corresponds to the α-chain and the lipophilic part, which corresponds to the ω-chain. Furthermore, PGEs are regarded as a series of compounds possessing 2,3,4-trisubstituted cyclopentanone as a core template while **3** is regarded as a compound possessing 1,2,4-trisubstituted benzene as a core template. Based on historical evidence, chemical modification of the α- and

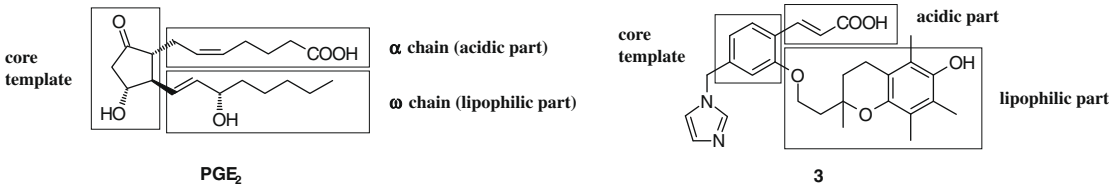


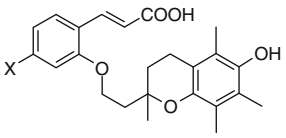
Figure 2. Structural analogy of PGE$_2$ and **3**.

ω-chains of PGs has been shown to be crucial for receptor affinity and/or subtype selectivity. Given this information, optimization of the acidic and lipophilic part of **3** including another substituent, the imidazol-1-ylmethyl part, was considered to be a promising approach for increasing the receptor affinity and subtype selectivity.

First, our focus was on the optimization of the imidazol-1-ylmethyl moiety as described in Table 1. Replacement of the imidazol-1-ylmethyl moiety of **3** with smaller groups such as hydrogen, methyl and methoxy groups afforded **6**, **7** and **8**, respectively with a gradual decrease in the binding affinity. Compounds **6** and **7** still retained subtype selectivity while **8** showed EP4 selectivity with a loss of EP3 receptor affinity. Thus, the basic imidazol-1-ylmethyl moiety was found to be required for **3** to have potent EP3 receptor affinity and/or subtype selectivity.

Second, optimization of the 2-alkoxy moiety of **3** was carried out as shown in Table 2. Replacement of the 6-hydroxy-2,5,7,8-tetramethylchroman-2-ylethyl moiety of **3** with 3-phenoxypropyl and 4-phenoxybutyl afforded **9** and **10**, respectively corresponding to 4.4-fold less potent and 3.5-fold less potent binding affinities. Replacement of the 6-hydroxy-2,5,7,8-tetramethylchroman-2-ylethyl moiety of **3** with the more π-electron rich benzofuran-2-ylethyl and naphtalen-2-ylethyl moiety afforded **11** and **12**, respectively with an increase in the receptor affinity. The naphtha-

Table 1
Activity profiles of the initial hit **3** and its derivatives



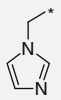
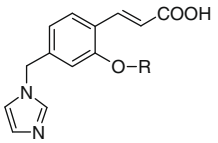
Compound	X	Binding K_i (nM)				Antagonist activity IC_{50} (nM)
		EP1	EP2	EP3	EP4	EP3
3		>10,000	>10,000	63	>10,000	600
6	H	>10,000	1200	530	2600	4800
7	Me	>10,000	5700	940	2200	3100
8	OMe	>10,000	6800	>10,000	920	>10,000

Table 2
Effect of the alkoxy moiety on activity profiles



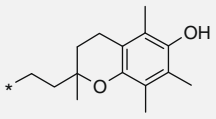
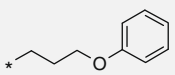
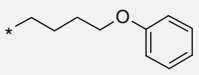
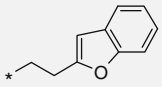
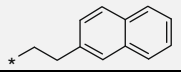
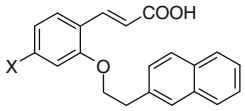
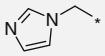
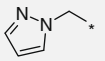
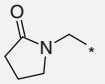
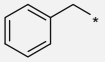
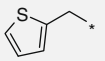
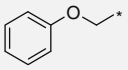
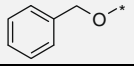
Compound	R	Binding K_i (nM)				Antagonist activity IC_{50} (nM)
		EP1	EP2	EP3	EP4	EP3
3		>10,000	>10,000	63	>10,000	600
9		>10,000	>10,000	280	>10,000	3000
10		>10,000	>10,000	220	>10,000	3500
11		>10,000	>10,000	44	4300	330
12		>10,000	>10,000	16	2200	50

Table 3
Effect of the imidazol-1-ylmethyl side chain on activity profiles



Compound	X	Binding K_i (nM)				Antagonist activity IC_{50} (nM)
		EP1	EP2	EP3	EP4	EP3
12		>10,000	>10,000	16	2200	50
4		2900	3300	12	670	73
13		6400	5900	110	2300	580
14		>10,000	>10,000	130	2100	400
15		>10,000	2100	150	2200	150
16		>10,000	9200	130	2600	140
17		>10,000	1200	850	>10,000	1500

len-2-ylethyl analogue **12** exhibited 3.9-fold more potency in binding affinity and 12-fold more potency in antagonist activity relative to **3** while retaining subtype selectivity. Thus, the lipophilic π-electron rich moieties such as benzofuran-2-ylethyl and naphthalene-2-ylethyl moieties were found to be required for the increase in potency.

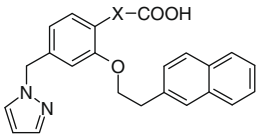
As shown in Table 3, further optimization of the imidazol-1-ylmethyl moiety of **12** was continued. Replacement of the imidazol-1-ylmethyl moiety of **12** with the less basic pyrazol-1-ylmethyl moiety afforded **4** with retention of the activities and subtype selectivity. Replacement of the imidazol-1-ylmethyl moiety of **12** with pyrrolidon-1-ylmethyl, benzyl, thiophen-2-ylmethyl and phenoxymethyl moieties provided **13–16**, respectively with nearly 10-fold less potent binding affinity and significantly less potent antagonist activity. A marked decrease in the activities was observed in the corresponding benzyloxy analogue **17**. As described above, the imidazol-1-ylmethyl analogue **12** and the pyrazol-1-ylmethyl analogue **4** clearly showed stronger EP3 receptor affinity, antagonist activity and better subtype selectivity than the other analogues **13–17**.

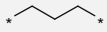
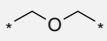
Further optimization of the acidic chain of **4**, which is one of the most optimized structure, was carried out as shown in Table 4. Saturation of the acrylic acid moiety provided phenylpropanoic acid analogue **5** with nearly equipotent binding affinity and increased antagonist activity. The corresponding phenylbutanoic acid analogue **20** showed slightly decreased binding affinity and decreased antagonist activity. Unexpectedly this remarkable decrease in the antagonist activity of **20** compared with its potent binding affinity was estimated to be due to increased protein binding resulting from its increased lipophilicity. Replacement of the trans-double bond of the acrylic acid moiety of **4** with a linear triple bond afforded the phenylpropynoic acid analogue **18** with 8.3-fold less potent binding affinity and 16-fold less potent antagonist activity. Replacement of the acrylic acid moiety of **4** with an oxyacetic acid moiety and a methyleneoxyacetic acid moiety afforded **19** and **21**, respectively with decreased activities. The larger decrease in binding affinity of the oxygen-containing analogues **19** and **21** relative to the others **4–5**, **18** and **20** was considered to be due to the hydrophilic ether oxygen, which is unfavorable for these analogues to interact with the receptor.

The newly identified chemical leads **4–5** and **12** were investigated for their profiles to inhibit major cytochrome P450 (CYP) isozymes, 1A2, 2C9, 2C19, 2D6 and 3A4. Data are summarized in Table 5. For compound **12**, the IC_{50} values were below 1 μM for 1A2, 2C9, 2C19, 3A4 and 4.4 μM for 2D6. These inhibitory activities for all the isozymes were predicted based on the fact that its partial structure possesses an imidazol-1-ylmethyl moiety, whereas **4** and **5**, in which the imidazol-1-ylmethyl moiety is replaced with the pyrazol-1-ylmethyl moiety, showed significantly weaker inhibitory activities for these five isozymes.

Compounds **4** and **5** were also investigated for their pharmacokinetic profiles in both in vitro and in vivo tests as shown in Table 6. The remaining percentage (% remaining) of intact **4** and **5** after in vitro incubation with human liver microsomes (HLM) and rat liver microsomes (RLM) for 15 min at 37 °C were 100% and 72–73%, respectively. They were found to be metabolically more stable in HLM relative to RLM based on the above data. The pharmacokinetics of **4** and **5** were evaluated via oral administration to rats at 10 mg/kg as shown in Table 6. While the C_{max} value and the AUC value of **4** was 0.943 μg/mL and 1.36 μg h/mL, the C_{max} value and the AUC value of **5** was 8.32 μg/mL and 22.9 μg h/mL. The values of **5** were found to be more than 8 times higher than those of **4**.

Table 4
Effect of the linker between COOH and the core benzene ring on activity profiles



Compound	X	Binding K_i (nM)				Antagonist activity IC_{50} (nM)
		EP1	EP2	EP3	EP4	EP3
4		2900	3300	12	670	73
5		7100	2800	12	1100	22
18		>10,000	>10,000	99	2900	1200
19		>10,000	>10,000	260	>10,000	2600
20		4000	1800	39	1400	460
21		>10,000	1300	210	>10,000	540

A more detailed pharmacokinetic study (Table 7) indicated that **5** showed low clearance (CL_{tot} 2.77 mL/min/kg) and good oral bioavailability (*F* 53%).

4. Conclusion

In conclusion, compounds **4** and **5** possessing a pyrazol-1-ylmethyl moiety were identified as new chemical leads for a selective EP3 receptor antagonist starting from the initial hit compound **3**. By replacing the imidazol-1-ylmethyl moiety of **12** with the pyrazol-1-ylmethyl moiety, **4** and **5** were found to have a significant reduction in CYP inhibition. Pharmacokinetic studies demonstrated that **5** showed improved pharmacokinetic profiles relative to **4**. Further optimization of **4** and **5** to improve their potency and subtype selectivity will be reported in due course.

Table 5
CYP inhibitory activities of **12**, **4** and **5**

Compd	CYP inhibition IC_{50} (μM)				
	1A2	2C9	2C19	2D6	3A4
12	<1	<1	<1	4.4	<1
4	>30	12.8	30.0	>30	>30
5	>30	30.0	>30	>30	>30

Table 6
In vitro metabolic stability and pharmacokinetic parameters of oral administration of **4** and **5**

Compd	In vitro stability (% remaining)		Pharmacokinetic parameters in rat at 10 mg/kg po	
	HLM	RLM	C_{max} (μg/mL)	AUC_{0-4h}
4	100	72	0.943	1.36
5	100	73	8.32	22.9

Compounds **4** and **5** were administered as the sodium salt.

Table 7
Pharmacokinetic parameters of **5**

$t_{1/2}$ (h)	CL_{tot} (mL/min/kg)	V_{ss} (mL/kg)	*F* (%)
2.93	2.77	538	53

Compound **5** was administered as the sodium salt at 10 mg/kg iv and 10 mg/kg po.

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; tetrahydrofuran (THF), diethylether (Et_2O), dimethylsulfoxide (DMSO), ethyl acetate (EtOAc), dimethylformamide (DMF), methanol (MeOH), ethanol (EtOH), *t*-butylalcohol (*t*-BuOH), acetic acid (AcOH), triethylamine (TEA), diethyl azodicarboxylate (DEAD), 1,1′-(azodicarbonyl)dipiperidine (ADDP) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF).

5.1.2. Methyl (2*E*)-3-{2-[2-(6-methoxymethoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]phenyl} acrylate (24)

To a stirred solution of **22** (160 mg, 0.900 mmol) in DMF (2 mL) was added NaH (62.7% in oil, 46 mg, 1.20 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min, a solution of **23** (538 mg, 1.20 mmol) in DMF (2 mL) was added. After being stirred for 1 h at 90 °C, the reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane/, 1/7) to yield **24** (375 mg, 95%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, J = 16 Hz, 1H), 7.50 (dd, J = 7.5, 1.7 Hz, 1H), 7.31 (m, 1H), 7.00–6.86 (m, 2H), 6.51 (d, J = 16 Hz, 1H), 4.86 (s, 2H), 4.37–4.15 (m, 2H), 3.80 (s, 3H), 3.62 (s, 3H), 2.65 (t, J = 6.8 Hz, 2H), 2.32–1.79 (m, 4H), 2.19 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.36 (s, 3H).

5.1.3. (2*E*)-3-{2-[2-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]phenyl}acrylic acid (6)

To a stirred solution of **24** (356 mg, 0.783 mmol) in THF (3 mL) and MeOH (2 mL) was added 2 M NaOH (1 mL). After being stirred for 4 h at room temperature, the reaction mixture was neutralized with 1 M HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was diluted with dioxane (1 mL) and then treated with 4 M HCl in dioxane (1 mL). After being stirred for 30 min, the solvent was removed by evaporation to yield **6** (229 mg, 74% in two steps) as a beige powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 16 Hz, 1H), 7.53 (dd, J = 7.7, 1.7 Hz, 1H), 7.34 (m, 1H), 7.01–6.88 (m, 2H), 6.52 (d, J = 16 Hz, 1H), 4.36–4.18 (m, 2H), 2.68 (t, J = 6.9 Hz, 2H), 2.32–2.03 (m, 2H), 2.16 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.02–1.82 (m, 2H), 1.37 (s, 3H); IR (KBr) 3441, 2932, 1686, 1626, 1598, 1493, 1457, 1418, 1307, 1241, 1167, 1109, 1086, 1021, 988, 929, 873, 752 cm^{-1}; MS (APCI, Neg.) *m/e* 395 (M−H)$^-$; HRMS (Neg.) calcd for $C_{24}H_{27}O_5$: 395.1858; found: 395.1856.

5.1.4. 2-{2-[6-(Methoxymethoxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl]ethoxy}-4-methylbenzaldehyde (27)

The titled compound was synthesized in the same manner as described for **24** using **25** instead of **22** as a pale yellow oil. Yield 64%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.37 (d, J = 0.6 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.76 (s, 1H), 4.86 (s, 2H), 4.40–4.19 (m, 2H), 3.62 (s, 3H), 2.65 (m, 2H), 2.37 (s, 3H), 2.29–2.06 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.97–1.84 (m, 2H), 1.36 (s, 3H).

5.1.5. (2*E*)-3-{2-[2-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]-4-methylphenyl}acrylic acid (7)

A solution of **27** (225 mg, 0.545 mmol), malonic acid (99 mg, 0.954 mmol), piperidine (0.100 mL) in pyridine (2 mL) was stirred for 1 h at 100 °C. The reaction mixture was diluted with water and 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 dioxane (1 mL) and then 4 M HCl in dioxane (1 mL) was added. After concentration in vacuo to remove the solvent, the resultant residue was recrystallized from MeOH–$CHCl_3$ to yield **7** (98 mg, 45% in two steps) as an off-white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.19 (br s, 1H), 7.78 (d, J = 16 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 6.87 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.43 (d, J = 16 Hz, 1H), 4.26 (m, 1H), 4.16 (m, 1H), 2.58–2.53 (m, 2H), 2.28 (s, 3H), 2.10–1.96 (m, 2H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.92–1.74 (m, 2H), 1.28 (s, 3H); IR (KBr) 3471, 3200, 2932, 1690, 1627, 1456, 1378, 1315, 1292, 1251, 1157, 1086, 1029, 989, 966, 932, 813, 662 cm^{-1}; MS (APCI, Neg.) *m/e* 409 (M−H)$^-$; HRMS (Neg.) calcd for $C_{25}H_{29}O_5$: 409.2015; found: 409.2032.

5.1.6. 4-Methoxy-2-{2-[6-(methoxymethoxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl]ethoxy}benzaldehyde (28)

The titled compound was synthesized in the same manner as described for **24** using **26** instead of **22** as a colorless oil. Yield 86%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.80 (dd, J = 8.8, 1.0 Hz, 1H), 6.58 (m, 1H), 6.54 (m, 1H), 4.86 (s, 2H), 4.35–4.25 (m, 2H), 3.85 (s, 3H), 3.61 (s, 3H), 2.70–2.58 (m, 2H), 2.32–2.02 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 1.98–1.82 (m, 2H), 1.36 (s, 3H).

5.1.7. (2*E*)-3-{2-[2-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]-4-methoxyphenyl}acrylic acid (8)

The titled compound was synthesized in the same manner as described for **7** using **28** instead of **27** as a white powder. Yield 40% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 16 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 6.50 (dd, J = 8.4, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 4.33–4.13 (m, 2H), 3.82 (s, 3H), 2.75–2.60 (m, 2H), 2.30–2.05 (m, 2H), 2.16 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.00–1.80 (m, 2H), 1.36 (s, 3H); IR (KBr) 1685, 1603, 1265, 1212, 1162, 1119, 833 cm^{-1}; MS (APCI, Neg.) *m/e* 425 (M−H)$^-$; HRMS (Neg.) calcd for $C_{25}H_{29}O_6$: 425.1964; found: 425.1969.

5.1.8. 3-(Methoxymethoxy)benzylalcohol (30)

To a stirred solution of NaH (62.7% in oil, 6.78 g, 0.177 mol) in DMF (100 mL) was added **29** (20.0 g, 0.161 mol) in DMF (150 mL) at 0 °C under argon atmosphere. After being stirred for 15 min, chloromethyl methyl ether (14.7 mL, 0.193 mol) in DMF (10 mL) was added dropwise. After being stirred for 15 min at ambient temperature, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, and dried over $MgSO_4$. Concentration in vacuo provided **30** (22.4 g, 77%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (t, J = 7.9 Hz, 1H), 7.09–6.92 (m, 3H), 5.19 (s, 2H), 4.67 (s, 2H), 3.48 (s, 3H).

5.1.9. 4-Formyl-3-(methoxymethoxy)benzyl acetate (31)

To a stirred solution of **30** (21.2 g, 0.126 mol), *N,N,N′,N′*-tetramethylethylene diamine (TMEDA) (41.8 mL, 0.277 mol) in Et_2O (350 mL),were added dropwise *n*-butylithium (1.53 M in hexane, 82.4 mL, 0.126 mol) and *t*-butyllithium (1.51 M, in pentane, 100 mL, 0.151 mol) below −70 °C under argon atmosphere. The reaction mixture was allowed to warm to −40 °C over 1 h and stirred for an additional 15 min at −40 °C. To this mixture was added *N*-formylpiperidine (28 mL, 0.252 mol) in Et_2O (30 mL) at −65 °C. The resultant mixture was allowed to warm to room temperature over 2 h, quenched with aqueous NH_4Cl and then extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography on silica gel (EtOAc/hexane, 1/2–3/1) provided a yellow oil including *N*-formylpiperidine, which was treated with acetic anhydride (100 mL) in pyridine (100 mL) at 0 °C. After being stirred for 20 min, the reaction mixture was quenched with water and 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, 1/4) to yield **31** (11.9 g, 40% in two steps) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.47 (d, J = 0.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 7.06 (m, 1H), 5.32 (s, 2H), 5.12 (s, 2H), 3.54 (s, 3H), 2.15 (s, 3H).

5.1.10. Ethyl (2*E*)-3-[4-[(acetyloxy)methyl]-2-(methoxymethoxy)phenyl]acrylate (32)

To a stirred solution of ethyl diethylphosphonoacetate (5.50 g, 24.6 mmol) in THF (80 mL) was added NaH (62.7% in oil, 942 mg,

24.6 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min at room temperature, **31** (4.50 g, 18.9 mmol) in THF (50 mL) was slowly added. The resultant mixture was stirred for 1 h at room temperature, quenched with water and 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, 1/3–1/1) to yield **32** (5.11 g, 88%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, J = 16 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 16 Hz, 1H), 5.27 (s, 2H), 5.08 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.51 (s, 3H), 2.12 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

5.1.11. Ethyl (2*E*)-3-[4-(hydroxymethyl)-2-(methoxymethoxy)phenyl]acrylate (33)

To a stirred solution of **32** (750 mg, 2.43 mmol) in EtOH (8 mL) was added sodium ethoxide (330 mg, 4.86 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min at room temperature, the reaction mixture was poured into ice-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 purified by column chromatography on silica gel (EtOAc/hexane, 2/3–1/1) to yield **33** (562 mg, 87%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, J = 16 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.17 (m, 1H), 7.00 (m, 1H), 6.49 (d, J = 16 Hz, 1H), 5.27 (s, 2H), 4.70 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.50 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

5.1.12. Ethyl (2*E*)-3-[4-(1*H*-imidazol-1-ylmethyl)-2-(methoxymethoxy)phenyl]acrylate (34)

To a stirred solution of **33** (558 mg, 2.09 mmol) and TEA (0.350 mL, 2.51 mmol) in THF (7 mL) was added methanesulfonyl chloride (0.180 mL, 2.31 mmol) at 0 °C under argon atmosphere. After being stirred for 20 min, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was treated with imidazole (770 mg, 11.3 mmol) in toluene (3 mL) under argon atmosphere. After being stirred for 3 h at 80 °C, the reaction mixture was quenched with aqueous $NaHCO_3$ and 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 ($CHCl_3$/MeOH, 80/1) to yield **34** (617 mg, 86% in two steps) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, J = 16 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.11 (m, 1H), 7.04–6.88 (m, 2H), 6.75 (m, 1H), 6.48 (d, J = 16 Hz, 1H), 5.22 (s, 2H), 5.11 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.49 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

5.1.13. Ethyl (2*E*)-3-[2-hydroxy-4-(1*H*-imidazol-1-ylmethyl)phenyl]acrylate (35)

To a stirred solution of **34** (615 mg, 1.94 mmol) in EtOH (4 mL) was added 4 M HCl in dioxane (2 mL). After being stirred for 2 h, the reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$. Concentration in vacuo provided **35** (434 mg, 82%) as a white powder. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, J = 16 Hz, 1H), 7.54 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 16 Hz, 1H), 6.36 (s, 1H), 5.12 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.78 (s, 1H), 1.32 (t, J = 7.2 Hz, 3H).

5.1.14. Ethyl (2*E*)-3-[4-(1*H*-imidazol-1-ylmethyl)-2-(3-phenoxypropoxy)phenyl]acrylate (36)

To a stirred solution of **35** (153 mg, 0.562 mmol) in DMF (1.5 mL) was added NaH (62.7% in oil, 26 mg, 0.674 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min, a solution of 3-phenoxypropyl bromide (181 mg, 0.843 mmol) in DMF (1 mL) was added. After being stirred for 1.5 h at 90 °C, the reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 25/1) to yield **36** (164 mg, 72%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, J = 16 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.35–7.21 (m, 2H), 7.11 (s, 1H), 7.00–6.85 (m, 4H), 6.77–6.63 (m, 2H), 6.50 (d, J = 16 Hz, 1H), 5.08 (s, 2H), 4.33–4.09 (m, 6H), 2.39–2.23 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H).

5.1.15. (2*E*)-3-[4-(1*H*-Imidazol-1-ylmethyl)-2-(3-phenoxypropoxy)phenyl]acrylic acid hydrochloride (9)

To a solution of **36** (158 mg, 0.389 mmol) in THF (1.5 mL) and MeOH (1 mL) was added 2 M NaOH (0.5 mL). After being stirred for 3 h at 50 °C, the reaction mixture was neutralized with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was triturated with MeOH–THF–Et_2O. The obtained powder was treated with 4 M HCl in dioxane (2 mL) to afforded **9** (80 mg, 50% in two steps) as a pale yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (m, 1H), 7.80 (d, J = 16 Hz, 1H), 7.79 (m, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.67 (m, 1H), 7.32–7.22 (m, 3H), 7.04–6.88 (m, 4H), 6.55 (d, J = 16 Hz, 1H), 5.41 (s, 2H), 4.24 (t, J = 6.2 Hz, 2H), 4.15 (t, J = 6.1 Hz, 2H), 2.24 (m, 2H); IR (KCl) 3423, 3035, 1688, 1629, 1601, 1568, 1438, 1322, 1296, 1271, 1242, 1206, 1175, 1064, 990, 764, 727, 697 cm^{-1}; MS (APCI, Neg.) *m/e* 377 $(M-H)^-$; HRMS (Pos.) calcd for $C_{22}H_{23}N_2O_4$: 379.1658; found: 379.1658.

5.1.16. Ethyl (2*E*)-3-[4-(1*H*-imidazol-1-ylmethyl)-2-(4-phenoxybutoxy)phenyl]acrylate (37)

The titled compound was synthesized in the same manner as described for **36** using 4-phenoxybutyl bromide instead of 3-phenoxypropyl bromide as a yellow solid. Yield 92% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J = 16 Hz, 1H), 7.55 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.35–7.21 (m, 2H), 6.99–6.86 (m, 5H), 6.80–6.60 (m, 2H), 6.52 (d, J = 16 Hz, 1H), 4.69 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.13 (t, J = 5.9 Hz, 2H), 4.05 (t, J = 5.8 Hz, 2H), 2.17–1.90 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H).

5.1.17. (2*E*)-3-[4-(1*H*-Imidazol-1-ylmethyl)-2-(4-phenoxybutoxy)phenyl]acrylic acid hydrochloride (10)

The titled compound was synthesized in the same manner as described for **9** as a pale yellow powder. Yield 42% in two steps; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (m, 1H), 7.81 (m, 1H), 7.80 (d, J = 16 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.67 (m, 1H), 7.32–7.21 (m, 3H), 7.04–6.86 (m, 4H), 6.57 (d, J = 16 Hz, 1H), 5.41 (s, 2H), 4.15 (t, J = 5.7 Hz, 2H), 4.03 (t, J = 6.0 Hz, 2H), 2.02–1.81 (m, 4H); IR (KCl) 3423, 3035, 1688, 1629, 1601, 1568, 1438, 1322, 1296, 1271, 1242, 1206, 1175, 1064, 990, 764, 727, 697 cm^{-1}; MS (APCI, Neg.) *m/e* 391 $(M-H)^-$; HRMS (Pos.) calcd for $C_{23}H_{25}N_2O_4$: 393.1814; found: 393.1800.

5.1.18. (2*E*)-3-[2-[2-(1-Benzofuran-2-yl)ethoxy]-4-(1*H*-imidazol-1-ylmethyl)phenyl]acrylic acid hydrochloride (11)

To a stirred solution of **35** (145 mg, 0.532 mmol), 2-(benzofuran-2-yl)ethanol (104 mg, 0.638 mmol), Ph_3P (209 mg, 0.936 mmol) in THF (2 mL) was added DEAD (1.6 M in toluene, 126 μL, 0.936 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel ($CHCl_3$/MeOH, 100/1) to yield **38** which was hydrolyzed with 2 M NaOH (0.5 mL) in THF (1.5 mL) and MeOH (1 mL). After being stirred for 2 h at 50 °C,

the reaction mixture was neutralized with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. After purification by column chromatography on silica gel ($CHCl_3$/MeOH, 100/1–9/1), the obtained residue was treated with 4 M HCl in dioxane (2 mL) to yield **11** (53 mg, 23% in three steps) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.84–7.65 (m, 4H), 7.58–7.47 (m, 2H), 7.31 (s, 1H), 7.27–7.15 (m, 2H), 7.00 (d, J = 8.1 Hz, 1H), 6.73 (s, 1H), 6.57 (d, J = 16 Hz, 1H), 5.41 (s, 2H), 4.41 (t, J = 6.3 Hz, 2H), 3.34 (t, J = 6.3 Hz, 2H); IR (KCl) 3423, 3037, 2823, 1686, 1611, 1576, 1455, 1435, 1302, 1269, 1173, 1118, 1085, 1032, 992, 751, 660, 635 cm^{-1}; MS (APCI, Neg.) *m/e* 387 (M−H)$^-$; HRMS (Pos.) calcd for $C_{23}H_{21}N_2O_4$: 389.1501; found: 389.1503.

5.1.19. (2*E*)-3-{4-(1*H*-Imidazol-1-ylmethyl)-2-[2-(2-naphthyl)ethoxy]phenyl}acrylic acid hydrochloride (12)

The titled compound was synthesized in the same manner as described for **11** using 2-(naphthalen-2-yl)ethanol instead of 2-(benzofuran-2-yl)ethanol as a white powder. Yield 38% in three steps; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28 (m, 1H), 7.92–7.77 (m, 6H), 7.72–7.64 (m, 2H), 7.56–7.42 (m, 3H), 7.27 (s, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 16 Hz, 1H), 5.39 (s, 2H), 4.35 (t, J = 6.6 Hz, 2H), 3.27 (t, J = 6.6 Hz, 2H); IR (KCl) 3041, 2825, 1685, 1608, 1576, 1504, 1435, 1391, 1366, 1271, 1172, 1118, 1086, 1024, 987, 847, 808, 746, 660, 636 cm^{-1}; MS (APCI, Neg.) *m/e* 397 (M−H)$^-$; HRMS (Pos.) calcd for $C_{25}H_{23}N_2O_3$: 399.1709; found: 399.1699.

5.1.20. Ethyl (2*E*)-3-[2-(methoxymethoxy)-4-(1*H*-pyrazol-1-ylmethyl)phenyl]acrylate (40)

To a stirred solution of **33** (360 mg, 1.34 mmol) and TEA (0.280 mL, 2.01 mmol) in THF (7 mL) was added methanesulfonyl chloride (0.130 mL, 1.61 mmol) at 0 °C under argon atmosphere. After being stirred for 20 min, the reaction mixture was diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to yield the corresponding methanesulfonate. To a stirred solution of pyrazole (100 mg, 1.47 mmol) in DMF (7 mL) was added NaH (62.7% in oil, 59 mg, 1.47 mmol) at 0 °C under argon atmosphere. After being stirred for 1 h, obtained methanesulfonate in DMF (3 mL) was added at 0 °C and the reaction mixture was stirred for 1 h at ambient temperature. The mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. 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) to yield **40** (215 mg, 50% in two steps) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, J = 16 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.00 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 16 Hz, 1H), 6.30 (t, J = 1.8 Hz, 1H), 5.31 (s, 2H), 5.22 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.48 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H).

5.1.21. Ethyl (2*E*)-3-{2-(methoxymethoxy)-4-[(2-oxopyrrolidin-1-yl)methyl]phenyl}acrylate (41)

The titled compound was synthesized in the same manner as described for **40** using 2-pyrrolidone instead of pyrazole as a colorless oil. Yield 75% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J = 16 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 16 Hz, 1H), 5.25 (s, 2H), 4.44 (s, 2H), 4.26 (d, J = 7.0 Hz, 2H), 3.50 (s, 3H), 3.29 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 8.1 Hz, 2H), 2.10–1.94 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H).

5.1.22. Ethyl (2*E*)-3-[2-(methoxymethoxy)-4-(phenoxymethyl)phenyl]acrylate (42)

The titled compound was synthesized in the same manner as described for **40** using phenol instead of pyrazole as a pale yellow oil. Yield 85% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, J = 16 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.36–7.21 (m, 3H), 7.10 (dd, J = 7.9, 1.1 Hz, 1H), 7.02–6.92 (m, 3H), 6.50 (d, J = 16 Hz, 1H), 5.27 (s, 2H), 5.05 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.50 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H).

5.1.23. Methyl 2-hydroxy-4-iodobenzoate (44)

To a stirred solution of **43** (5.00 g, 32.6 mmol) in 14% H_2SO_4 was added sodium nitrite (2.40 g, 34.8 mmol) in water (10 mL) at 0 °C. After being stirred for 10 min, potassium iodide (8.70 g, 52.4 mmol) in water (20 mL) was added and the reaction mixture was stirred for 1 h at 60 °C. After cooling to the room temperature, the mixture was filtered through a pad of Celite and the filtrate was extracted with Et_2O. The organic layer was washed successively with aqueous $Na_2S_2O_3$, water and brine, dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was treated with concd H_2SO_4 (2.5 mL) in MeOH (70 mL). After being stirred for 3 days, the reaction mixture was concentrated to half the volume and then poured into ice-cold water. The mixture was extracted with Et_2O and 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, 1/20) to yield **44** (3.26 g, 36% in two steps) as a white powder. ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 8.6, 1.6 Hz, 1H), 3.95 (s, 3H).

5.1.24. Methyl 4-iodo-2-(methoxymethoxy)benzoate (45)

The titled compound was synthesized in the same manner as described for **30** using **44** instead of **29** as a white powder. Yield 99%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (d, J = 1.4 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.40 (dd, J = 8.0, 1.4 Hz, 1H), 5.23 (s, 2H), 3.89 (s, 3H), 3.52 (s, 3H).

5.1.25. Methyl 4-benzyl-2-(methoxymethoxy)benzoate (46)

To a stirred solution of **45** (330 mg, 1.02 mmol), DPPF (17 mg, 31.0 μmol) and $Pd_2(dba)_3$ (9.0 mg, 15.5 μmol) in THF (1 mL) was added benzylzinc bromide (1.6 mL, 1.60 mmol), which was prepared from zinc (392 mg, 6.00 mmol) and benzyl bromide (513 mg, 3.00 mmol) in THF (3 mL) according to the literature[14], at 0 °C under argon atmosphere. After being stirred for 12 h at 50 °C, the reaction mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. 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) to yield **46** (240 mg, 82%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H), 7.35–7.12 (m, 5H), 7.03 (d, J = 1.4 Hz, 1H), 6.85 (dd, J = 8.0, 1.4 Hz, 1H), 5.22 (s, 2H), 3.98 (s, 2H), 3.87 (s, 3H), 3.51 (s, 3H).

5.1.26. [4-Benzyl-2-(methoxymethoxy)phenyl]methanol (48)

To a stirred suspension of $LiAlH_4$ (41 mg, 1.08 mmol) in THF (2.5 mL) was added **46** (238 mg, 0.830 mmol) in THF (1.5 mL) at 0 °C. After being stirred for 30 min, aqueous Na_2SO_4 was added and the resultant mixture was filtered through a pad of Celite to remove the white precipitate. The filtrate was evaporated to yield **48** (206 mg, 96%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.14 (m, 6H), 6.95 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 5.20 (s, 2H), 4.67 (s, 2H), 3.96 (s, 2H), 3.48 (s, 3H).

5.1.27. Ethyl (2*E*)-3-[4-benzyl-2-(methoxymethoxy)phenyl]acrylate (50)

To a stirred solution of **48** (200 mg, 0.770 mmol) and TEA (0.530 ml, 3.85 mmol) in DMSO (3.8 mL) and CH_2Cl_2 (2.5 mL) was added sulfur trioxide–pyridine complex (616 mg, 3.87 mmol) at 0 °C. After being stirred for 1 h at room temperature, the reaction

mixture was poured into ice-cold water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to yield the corresponding aldehyde, which was converted into **50** in the same manner as described for **32**. Yield 97% in two steps. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J = 16 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.36–7.16 (m, 5H), 7.00 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 16 Hz, 1H), 5.22 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.97 (s, 2H), 3.49 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

5.1.28. Methyl 2-(methoxymethoxy)-4-(2-thienylmethyl)benzoate (47)

The titled compound was synthesized in the same manner as described for **46** using 2-bromomethylthiophene instead of benzyl bromide as a pale yellow oil. Yield 57%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, J = 7.8 Hz, 1H), 7.60–7.36 (m, 2H), 7.19–6.78 (m, 3H), 5.23 (s, 2H), 4.27 (s, 2H), 3.87 (s, 3H), 3.52 (s, 3H).

5.1.29. [2-(Methoxymethoxy)-4-(2-thienylmethyl)phenyl]methanol (49)

The titled compound was synthesized in the same manner as described for **48** using **47** instead of **46** as a colorless oil. Yield 68%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–6.78 (m, 6H), 5.21 (s, 2H), 4.68 (s, 2H), 4.13 (s, 2H), 3.49 (s, 3H).

5.1.30. Ethyl (2*E*)-3-[2-(methoxymethoxy)-4-(2-thienylmethyl)phenyl]acrylate (51)

The titled compound was synthesized in the same manner as described for **50** using **49** instead of **48** as a pale yellow oil. Yield 33% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, J = 16 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.16 (dd, J = 5.0, 1.0 Hz, 1H), 6.95 (s, 1H), 6.98–6.79 (m, 3H), 6.47 (d, J = 16 Hz, 1H), 5.23 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.14 (s, 2H), 3.49 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

5.1.31. Ethyl (2*E*)-3-{2-[2-(2-naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl}acrylate (52)

To a stirred solution of **40** (390 mg, 1.23 mmol) in EtOH (4 mL) was added 4 M HCl in dioxane (1.5 mL) at room temperature. After being stirred for 2 h, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The resultant residue was treated with 2-(naphthalen-2-yl)ethanol (224 mg, 1.42 mmol), Ph_3P (464 mg, 1.77 mmol) and ADDP (447 mg, 1.77 mmol) in THF (13 mL) at room temperature under argon atmosphere. After being stirred for 12 h, the reaction mixture was evaporated and the resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1) to yield **52** (452 mg, 90% in two steps) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (d, J = 16 Hz, 1H), 7.88–7.70 (m, 4H), 7.58–7.34 (m, 6H), 6.76 (d, J = 8.2 Hz, 1H), 6.70 (s, 1H), 6.49 (d, J = 16 Hz, 1H), 6.28 (t, J = 4.2 Hz, 1H), 5.28 (s, 2H), 4.35–4.15 (m, 4H), 3.29 (t, J = 6.6 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).

According to the same procedure as described above, **53–56** were prepared from **41**, **42**, **50** and **51**, respectively.

5.1.32. Ethyl (2*E*)-3-{2-[2-(2-naphthyl)ethoxy]-4-[(2-oxopyrrolidin-1-yl)methyl]phenyl}acrylate (53)

Yield 23% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, J = 16 Hz, 1H), 7.86–7.74 (m, 4H), 7.52–7.36 (m, 4H), 6.84–6.74 (m, 2H), 6.51 (d, J = 16 Hz, 1H), 4.39 (s, 2H), 4.35–4.22 (m, 4H), 3.32 (t, J = 6.8 Hz, 2H), 3.23 (t, J = 7.2 Hz, 2H), 2.42 (t, J = 8.1 Hz, 2H), 2.06–1.88 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H).

5.1.33. Ethyl (2*E*)-3-[2-[2-(2-naphthyl)ethoxy]-4-(phenoxymethyl)phenyl]acrylate (54)

Yield 69% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, J = 16 Hz, 1H), 7.86–7.74 (m, 4H), 7.53–7.40 (m, 4H), 7.35–7.21 (m, 2H), 7.03–6.90 (m, 5H), 6.52 (d, J = 16 Hz, 1H), 5.03 (s, 2H), 4.34 (t, J = 7.0 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.32 (t, J = 7.0 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).

5.1.34. Ethyl (2*E*)-3-{4-benzyl-2-[2-(2-naphthyl)ethoxy]phenyl}acrylate (55)

Yield 74% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J = 16 Hz, 1H), 7.86–7.72 (m, 4H), 7.50–7.37 (m, 4H), 7.35–7.12 (m, 5H), 6.77 (d, J = 7.8 Hz, 1H), 6.71 (s, 1H), 6.48 (d, J = 16 Hz, 1H), 4.33–4.20 (m, 4H), 3.94 (s, 2H), 3.29 (t, J = 7.0 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).

5.1.35. Ethyl (2*E*)-3-[2-[2-(2-naphthyl)ethoxy]-4-(2-thienylmethyl)phenyl]acrylate (56)

Yield 66% in two steps; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J = 16 Hz, 1H), 7.86–7.73 (m, 4H), 7.50–7.38 (m, 4H), 7.18–7.12 (m, 1H), 6.96–6.76 (m, 4H), 6.50 (d, J = 16 Hz, 1H), 4.34–4.20 (m, 4H), 4.12 (s, 2H), 3.31 (t, J = 6.8 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

5.1.36. (2*E*)-3-[2-[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl]acrylic acid (4)

To a stirred solution of **52** (445 mg, 1.04 mmol) in THF (3 mL) and MeOH (3 mL) was added 2 M NaOH (3 mL). After being stirred for 2 h at 50 °C, the reaction mixture was acidified with 1 M HCl and extracted with EtOAc. 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, 2/3–3/2) to yield **4** (281 mg, 68%) as a colorless amorphous. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, J = 16 Hz, 1H), 7.88–7.72 (m, 4H), 7.57 (d, J = 2.0 Hz, 1H), 7.51–7.35 (m, 5H), 6.77 (d, J = 7.8 Hz, 1H), 6.72 (s, 1H), 6.51 (d, J = 16 Hz, 1H), 6.29 (t, J = 2.0 Hz, 1H), 5.30 (s, 2H), 4.25 (t, J = 6.6 Hz, 2H), 3.28 (t, J = 6.6 Hz, 2H); IR (KBr) 1689, 1610, 1431, 1266, 1170, 819, 749, 479 cm^{-1}; MS (APCI, Neg.) *m/e* 397 $(M-H)^-$; HRMS (Pos.) calcd for $C_{25}H_{23}N_2O_3$: 399.1709; found: 399.1717.

According to the same procedure as described above, **13, 16, 14** and **15** were prepared from **54**, **55**, **56** and **57**, respectively.

5.1.37. (2*E*)-3-{2-[2-(2-Naphthyl)ethoxy]-4-[(2-oxopyrrolidin-1-yl)methyl]phenyl}acrylic acid (13)

Yield 79%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, J = 16 Hz, 1H), 7.90–7.76 (m, 4H), 7.52–7.36 (m, 4H), 6.86–6.76 (m, 2H), 6.54 (d, J = 16 Hz, 1H), 4.41 (s, 2H), 4.31 (t, J = 6.5 Hz, 2H), 3.32 (t, J = 6.5 Hz, 2H), 3.24 (t, J = 7.0 Hz, 2H), 2.45 (t, J = 8.0 Hz, 2H), 2.10–1.88 (m, 2H); IR (neat) 1685, 1500, 1429, 1266, 1173, 732 cm^{-1}; MS (APCI, Neg.) *m/e* 414 $(M-H)^-$; HRMS (Pos.) calcd for $C_{26}H_{26}NO_4$: 416.1862; found: 416.1840.

5.1.38. (2*E*)-3-{2-[2-(2-Naphthyl)ethoxy]-4-(phenoxymethyl)phenyl}acrylic acid (16)

Yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 16 Hz, 1H), 7.87–7.76 (m, 4H), 7.57–7.39 (m, 4H), 7.34–7.24 (m, 2H), 7.06–6.92 (m, 5H), 6.56 (d, J = 16 Hz, 1H), 5.05 (s, 2H), 4.35 (t, J = 6.8 Hz, 2H), 3.33 (t, J = 6.8 Hz, 2H); IR (KBr) 3427, 2947, 1690, 1624, 1598, 1497, 1433, 1379, 1329, 1239, 1220, 1118, 1036, 991, 822, 750, 692, 481 cm^{-1}; MS (APCI, Neg.) *m/e* 423 $(M-H)^-$; HRMS (Neg.) calcd for $C_{28}H_{23}O_4$: 423.1596; found: 423.1599.

5.1.39. (2*E*)-3-{4-Benzyl-2-[2-(2-naphthyl)ethoxy]phenyl}acrylic acid (14)

Yield 86%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.12 (d, J = 16 Hz, 1H), 7.88–7.74 (m, 4H), 7.52–7.10 (m, 9H), 6.79 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 6.52 (d, J = 16 Hz, 1H), 4.26 (t, J = 6.6 Hz, 2H), 3.95 (s, 2H), 3.29 (t, J = 6.6 Hz, 2H); IR (KBr) 3026, 1678, 1615, 1418, 1263, 1209, 1020, 820, 700, 477 cm^{-1}; MS (APCI, Neg.) *m/e* 407

(M−H)⁻; HRMS (Neg.) calcd for $C_{28}H_{23}O_3$: 407.1647; found: 407.1655.

5.1.40. (2*E*)-3-[2-[2-(2-Naphthyl)ethoxy]-4-(thien-2-ylmethyl)phenyl]acrylic acid (15)

Yield 61%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 16 Hz, 1H), 7.86–7.74 (m, 4H), 7.50–7.38 (m, 4H), 7.15 (dd, J = 5.1, 1.2 Hz, 1H), 6.92 (dd, J = 5.1, 3.6 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.82–6.76 (m, 2H), 6.53 (d, J = 16 Hz, 1H), 4.29 (t, J = 6.8 Hz, 2H), 4.12 (s, 2H), 3.31 (t, J = 6.8 Hz, 2H); IR (KBr) 1665, 1606, 1435, 1318, 1285, 1258, 1211, 814, 744, 706 cm^{-1}; MS (APCI, Neg.) *m/e* 413 (M−H)⁻; HRMS (Neg.) calcd for $C_{26}H_{21}O_3S$: 413.1211; found: 413.1217.

5.1.41. Ethyl 3-[2-[2-(2-naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl]propanoate (57)

To a stirred solution of **52** (1.97 g, 4.62 mmol), $NiCl_2$·$6H_2O$ (1.21 g, 5.08 mmol) in THF (32 mL) and EtOH (8 mL) was added $NaBH_4$ (699 mg, 18.5 mmol) at 0 °C under argon atmosphere. After being stirred for 1 h at ambient temperature, the reaction mixture was quenched with water and filtered through a pad of Celite. The filtrate was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 2/3) to yield **57** (1.61 g, 81%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.76 (m, 3H), 7.72 (s, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.49–7.38 (m, 3H), 7.35 (d, J = 2.1 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.73–6.65 (m, 2H), 6.26 (t, J = 2.1 Hz, 1H), 5.24 (s, 2H), 4.20 (t, J = 6.6 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.23 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.47 (t, J = 7.7 Hz, 2H) 1.22 (t, J = 7.1 Hz, 3H).

5.1.42. 3-[2-[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl]propanoic acid (5)

The titled compound was synthesized in the same manner as described for **4** using **57** instead of **52** as a white powder. Yield 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.75 (m, 3H), 7.71 (s, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.48–7.32 (m, 4H), 7.08 (d, J = 7.8 Hz, 1H), 6.73–6.66 (m, 2H), 6.26 (t, J = 2.1 Hz, 1H), 5.24 (s, 2H), 4.20 (t, J = 6.6 Hz, 2H), 3.23 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.51 (t, J = 7.7 Hz, 2H); IR (KBr) 3048, 2930, 2878, 1709, 1613, 1582, 1508, 1427, 1261, 1211, 1194, 1124, 1034, 820, 770, 754, 619, cm^{-1}; MS (APCI, Neg.) *m/e* 399 (M−H)⁻; HRMS (Pos.) calcd for $C_{25}H_{25}N_2O_3$: 401.1865; found: 401.1880.

5.1.43. 4-(Benzyloxy)-2-hydroxybenzaldehyde (59)

A solution of **58** (1.04 g, 7.50 mmol), $NaHCO_3$ (725 mg, 8.63 mmol), KI (125 mg, 0.750 mmol) benzyl chloride (1.12 mL, 9.75 mmol) in acetonitrile (7 mL) was refluxed for 20 h under argon atmosphere. The reaction mixture was quenched with water at 0 °C and extracted with Et_2O. 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, 1/3) to yield **59** (1.30 g, 76%) as an off-white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.47 (s, 1H), 9.72 (s, 1H), 7.45–7.32 (m, 6H), 6.61 (dd, J = 8.6, 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 5.11 (s, 2H).

5.1.44. 4-(Benzyloxy)-2-[2-(2-naphthyl)ethoxy]benzaldehyde (60)

To a stirred solution of **59** (400 mg, 1.75 mmol), 2-(naphthalen-2-yl)ethanol (362 mg, 2.10 mmol), Ph_3P (690 mg, 2.63 mmol) in THF (5 mL) was added ADDP (662 mg, 2.63 mmol) at room temperature under argon atmosphere. After being stirred for 12 h, the reaction mixture was concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/5) to yield **60** (486 mg, 73%) as a pale yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.31 (d, J = 0.8 Hz, 1H), 7.86–7.70 (m, 5H), 7.53–7.31 (m, 8H), 6.60 (dd, J = 8.7, 1.5 Hz, 1H), 6.51 (d, J = 2.1 Hz, 1H), 5.08 (s, 2H), 4.32 (t, J = 6.6 Hz, 2H), 3.30 (t, J = 6.6 Hz, 2H).

5.1.45. (2*E*)-3-{4-(Benzyloxy)-2-[2-(2-naphthyl)ethoxy]phenyl}acrylic acid (17)

A solution of **60** (288 mg, 0.753 mmol), malonic acid (141 mg, 1.36 mmol), piperidine (0.100 mL) in pyridine (3 mL) was stirred for 1 h at 100 °C. The reaction mixture was quenched with water and 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 from EtOAc–hexane to yield **17** (292 mg, 91%) as a pale yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 16 Hz, 1H), 7.87–7.76 (m, 4H), 7.50–7.29 (m, 9H), 6.60–6.51 (m, 2H), 6.46 (d, J = 16 Hz, 1H), 5.05 (s, 2H), 4.29 (t, J = 6.8 Hz, 2H), 3.33 (t, J = 6.8 Hz, 2H); IR (KBr) 3038, 2935, 1682, 1600, 1567, 1504, 1321, 1263, 1208, 1181, 1117, 1027, 815, 742, 699, 619, 476 cm^{-1}; MS (APCI, Neg.) *m/e* 423 (M−H)⁻; HRMS (Neg.) calcd for $C_{28}H_{23}O_4$: 423.1596; found: 423.1608.

5.1.46. 3-[2-(2-Naphthyl)ethoxy]-4-nitrobenzaldehyde (62)

The titled compound was synthesized in the same manner as described for **60** using **61** instead of **59** as a white powder. Yield 30%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.93–7.74 (m, 5H), 7.55–7.38 (m, 5H), 4.45 (t, J = 6.6 Hz, 2H), 3.33 (t, J = 6.6 Hz, 2H).

5.1.47. 4-Hydroxy-3-[2-(2-naphthyl)ethoxy]benzaldehyde (63)

To a stirred solution of benzaldoxime (565 mg, 4.66 mmol) in DMSO (10 mL) was added potassium *t*-butoxide (522 mg, 4.66 mmol) at 0 °C under argon atmosphere. After being stirred for 20 min, **62** (680 mg, 2.12 mmol) in DMSO (5 mL) was added and then the reaction mixture was stirred for 2 h. The mixture was poured into 1 M HCl and extracted with Et_2O. 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) to yield **63** (297 mg, 48%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.96–7.76 (m, 3H), 7.72 (s, 1H), 7.54–7.36 (m, 6H), 7.01 (d, J = 8.4 Hz, 1H), 4.45 (t, J = 6.8 Hz, 2H), 3.32 (t, J = 6.8 Hz, 2H).

5.1.48. 4-(Hydroxymethyl)-2-[2-(2-naphthyl)ethoxy]phenol (64)

To a stirred solution of **63** (297 mg, 1.02 mmol) in EtOH (5 mL) was added $NaBH_4$ (46 mg, 1.22 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with acetic acid and then poured into 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, 1/2) to yield **64** (188 mg, 63%) as a yellow powder. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78–7.68 (m, 4H), 7.54–7.36 (m, 3H), 6.96–6.80 (m, 3H), 5.52 (s, 1H), 4.58 (s, 2H), 4.38 (t, J = 6.9 Hz, 2H), 3.29 (t, J = 6.9 Hz, 2H).

5.1.49. Ethyl {4-(hydroxymethyl)-2-[2-(2-naphthyl)ethoxy]phenoxy}acetate (65)

To a stirred solution of **64** (188 mg, 0.640 mmol) in DMF (4 mL) was added NaH (62.7% in oil, 25 mg, 0.670 mmol) at 0 °C under argon atmosphere. After being stirred for 1 h, ethyl bromoacetate (0.100 mL, 0.770 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. 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, 2/3) to yield **65** (211 mg, 87%) as a pale

yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86–7.73 (m, 4H), 7.52–7.38 (m, 3H), 6.97–6.79 (m, 3H), 4.62–4.55 (m, 4H), 4.33 (t, J = 7.1 Hz, 2H), 4.22 (q, J = 7.4 Hz, 2H), 3.31 (t, J = 7.1 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H).

5.1.50. Ethyl [2-[2-(2-naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenoxy] acetate (66)

To a stirred solution of **65** (70 mg, 0.184 mmol) in CH_2Cl_2 (1 mL) was added phosphorus tribromide (26 μL, 0.276 mmol) at 0 °C under argon atmosphere. After being stirred for 10 min, the reaction mixture was quenched with water and diluted with EtOAc. The mixture was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to yield the corresponding bromide, which was used for the next step without purification. To a stirred solution of pyrazole (19 mg, 0.276 mmol) in DMF (0.5 mL) was added NaH (62.7% in oil, 11 mg, 0.276 mmol) at room temperature under argon atmosphere. After being stirred for 30 min, the obtained bromide in DMF (1.5 mL) was added and the reaction mixture was stirred for 1 h at room temperature. The mixture was quenched with aqueous NH_4Cl and extracted with Et_2O. 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, 2/3) to yield **66** (30 mg, 38% in two steps) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86–7.70 (m, 4H), 7.61 (d, J = 2.1 Hz, 1H), 7.50–7.37 (m, 4H), 6.88–6.70 (m, 3H), 6.25 (t, J = 2.1 Hz, 1H), 5.21 (s, 2H), 4.58 (s, 2H), 4.26 (t, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.28 (t, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

5.1.51. [2-[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenoxy]acetic acid (19)

The titled compound was synthesized in the same manner as described for **4** using **66** instead of **52** as a colorless amorphous. Yield 35%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.75 (m, 3H), 7.70 (s, 1H), 7.55 (dd, J = 1.8, 0.6 Hz, 1H), 7.49–7.32 (m, 4H), 6.84 (d, J = 7.8 Hz, 1H), 6.78–6.71 (m, 2H), 6.26 (t, J = 2.1 Hz, 1H), 5.22 (s, 2H), 4.59 (s, 2H), 4.25 (t, J = 7.1 Hz, 2H), 3.25 (t, J = 7.1 Hz, 2H); IR (KBr) 2929, 1733, 1515, 1434, 1260, 1212, 1143, 1063, 1030, 858, 820, 753, 667, 621, 479 cm^{-1}; MS (APCI, Neg.) *m/e* 401 $(M-H)^-$; HRMS (Pos.) calcd for $C_{24}H_{23}N_2O_4$: 403.1658; found: 403.1660.

5.1.52. Methyl 3-hydroxy-4-iodobenzoate (68)

The titled compound was synthesized in the same manner as described for **44** using **67** instead of **43** as a pale brown powder. Yield 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 8.1, 2.0 Hz, 1H), 5.50 (s, 1H), 3.91 (s, 3H).

5.1.53. Methyl 4-iodo-3-[2-(2-naphthyl)ethoxy]benzoate (69)

The titled compound was synthesized in the same manner as described for **60** using **68** instead of **59** as a colorless oil. Yield 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.78 (m, 5H), 7.51 (dd, J = 8.4, 1.5 Hz, 1H), 7.49–7.43 (m, 2H), 7.40 (d, J = 1.7 Hz, 1H), 7.35 (dd, J = 8.1, 1.7 Hz, 1H), 4.35 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 3.34 (t, J = 6.6 Hz, 2H).

5.1.54. {4-Iodo-3-[2-(2-naphthyl)ethoxy]phenyl}methanol (70)

To a stirred solution of **69** (4.61 g, 10.7 mmol) in CH_2Cl_2 (40 mL) was added diisobutylaluminum hydride (0.95 M in hexane, 28.0 mL, 26.7 mmol) at −70 °C under argon atmosphere. The reaction mixture was allowed to warm to −40 °C over 1 h and then quenched with aqueous Na_2SO_4. The resultant mixture was filtered through a pad of Celite to remove the precipitate and the filtrate was evaporated. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/4–1/3) to yield **70** (4.21 g, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.78 (m, 4H), 7.72 (d, J = 8.0 Hz, 1H), 7.51 (dd, J = 8.6, 1.7 Hz, 1H). 7.48–7.41 (m, 2H), 6.83 (d, J = 2.0 Hz, 1H), 6.67 (dd, J = 8.0, 2.0 Hz, 1H), 4.62 (d, J = 5.7 Hz, 2H), 4.31 (t, J = 6.6 Hz, 2H), 3.33 (t, J = 6.6 Hz, 2H).

5.1.55. 1-{4-Iodo-3-[2-(2-naphthyl)ethoxy]benzyl}-1*H*-pyrazole (71)

The titled compound was synthesized in the same manner as described for **40** using **70** instead of **33** as a colorless oil. Yield 87% in two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.77 (m, 4H), 7.70 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.51–7.40 (m, 3H), 7.34 (d, J = 2.1 Hz, 1H), 6.59 (d, J = 1.9 Hz, 1H), 6.54 (dd, J = 8.0, 1.9 Hz, 1H), 6.26 (t, J = 2.1 Hz, 1H), 5.22 (s, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.28 (t, J = 6.6 Hz, 2H).

5.1.56. 3-{[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl}prop-2-yn-1-ol (72)

A solution of **71** (1.50 g, 3.18 mmol), propargyl alcohol (370 μL, 6.36 mmol), CuI (30 mg, 0.159 mmol), $PdCl_2(Ph_3P)_2$ (112 mg, 0.159 mmol), tetrabutylammonium iodide (59 mg, 0.159 mmol), TEA (1.27 mL, 9.11 mmol) in DMF (7 mL) was stirred at 75 °C for 3 h under argon atmosphere. The reaction mixture was diluted with Et_2O 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 Na_2SO_4 and concentrated in vacuo. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1) to yield **72** (495 mg, 37%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.72 (m, 4H), 7.55 (d, J = 2.1 Hz, 1H), 7.51–7.31 (m, 5H), 6.71 (d, J = 7.8 Hz, 1H), 6.67 (s, 1H), 6.28 (t, J = 2.1 Hz, 1H), 5.27 (s, 2H), 4.46 (d, J = 6.3 Hz, 2H), 4.25 (t, J = 6.6 Hz, 2H), 3.26 (t, J = 6.6 Hz, 2H).

5.1.57. 3-{2-[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl}prop-2-ynoic acid (18)

To a stirred solution of **72** (349 mg, 0.870 mmol) in CH_2Cl_2 (4 mL) was added Dess–Martin periodinate (738 mg, 1.74 mmol) at 0 °C. After being stirred for 4 h, the reaction mixture was quenched with aqueous $Na_2S_2O_3$ and aqueous $NaHCO_3$, and then stirred for an additional 30 min. The mixture was extracted with EtOAc and the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to afford **73**, which was used for the next step without purification. To a stirred solution of **73** and 2-methyl-2-butene (7 mL) in *t*-BuOH (7 mL) were added NaH_2PO_4 (163 mg, 1.04 mmol) in water (7 mL) and $NaClO_2$ (157 mg, 1.74 mmol). After being stirred for 12 h, 1 M HCl was added and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant residue was recrystallized with EtOAc–hexane to afford **18** (150 mg, 44% in two steps) as a white powder. ^{1}H NMR (300 MHz, CD_3OD) δ 7.85–7.73 (m, 4H), 7.66 (d, J = 2.3 Hz, 1H), 7.54–7.49 (m, 2H), 7.44–7.34 (m, 3H), 6.78 (s, 1H), 6.71 (dd, J = 7.8, 1.5 Hz, 1H), 6.31 (t, J = 2.3 Hz, 1H), 5.30 (s, 2H), 4.24 (t, J = 6.5 Hz, 2H), 3.23 (t, J = 6.5 Hz, 2H); IR (KBr) 3363, 2923, 2209, 1563, 1505, 1428, 1393, 1289, 753 cm^{-1}; MS (FAB, Pos.) *m/e* 397 $(M+H)^+$; HRMS (Pos.) calcd for $C_{25}H_{21}N_2O_3$: 397.1552; found: 397.1556.

5.1.58. Ethyl 4-[2-[2-(2-naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl]butanoate (74)

To a stirred solution of **71** (120 mg, 0.264 mmol), $PdCl_2$(dppf) (22 mg, 26.4 μmol) in THF (0.5 mL) was added 4-ethoxy-4-oxobutylzinc bromide (0.5 M in THF, 2.11 mL, 1.06 mmol) at room temperature under argon atmosphere. After being stirred for 12 h at 50 °C, the reaction mixture was quenched with 1 M HCl at 0 °C and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant

residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1) to yield **74** (94 mg, 80%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.75 (m, 3H), 7.70 (s, 1H), 7.52 (d, J = 2.1 Hz, 1H), 7.49–7.37 (m, 3H), 7.33, (d, J = 2.1 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.71 (dd, J = 7.6, 1.7 Hz, 1H), 6.66 (d, J = 1.5 Hz, 1H), 6.25 (t, J = 2.1 Hz, 1H), 5.24 (s, 2H), 4.19 (t, J = 6.7 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.23 (t, J = 6.7 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.83–1.74 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H).

5.1.59. 4-[2-[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl]butanoic acid (20)

The titled compound was synthesized in the same manner as described for **4** using **74** instead of **52** as a white powder. Yield 85%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84–7.73 (m, 3H), 7.69 (s, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.50–7.32 (m, 4H), 7.02 (d, J = 7.6 Hz, 1H), 6.74–6.64 (m, 2H), 6.25 (t, J = 2.1 Hz, 1H), 5.24 (s, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.21 (t, J = 6.6 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.4 Hz, 2H), 1.88–1.68 (m, 2H); IR (KBr) 1708, 1510, 1427, 1273, 1145, 1041, 821, 760, 623 cm^{-1}; MS (APCI, Neg.) *m/e* 413 $(M-H)^-$; HRMS (Pos.) calcd for $C_{26}H_{27}N_2O_3$: 415.2022; found: 415.2014.

5.1.60. Methyl 2-[2-(2-naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)benzoate (75)

A solution of **71** (2.29 g, 5.04 mmol), TEA (2.10 mL, 15.0 mmol), DPPF (139 mg, 0.250 mmol) $Pd(OAc)_2$ (57 mg, 0.250 mmol) in DMF (5 mL) and MeOH (5 mL) was stirred for 12 h at 60 °C under carbon monoxide atmosphere. The mixture was diluted with EtOAc and water, and then filtered through a pad of Celite. The filtrate was extracted with EtOAc and the organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated. The resultant residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/1) to yield **75** (2.10 g, 99%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.73 (m, 5H), 7.55 (m, 1H), 7.47–7.42 (m, 3H), 7.36 (m, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.73 (s, 1H), 6.29 (t, J = 2.1 Hz, 1H), 5.30 (s, 2H), 4.25 (t, J = 6.9 Hz, 2H), 3.84 (s, 3H), 3.27 (t, J = 6.9 Hz, 2H).

5.1.61. {[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)phenyl}methanol (76)

The titled compound was synthesized in the same manner as described for **48** using **75** instead of **46** as a colorless oil. Yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.79 (m, 3H), 7.71 (s, 1H), 7.54–7.35 (m, 5H), 7.20 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.72 (s, 1H), 6.27 (t, J = 2.1 Hz, 1H), 5.27 (s, 2H), 4.58 (d, J = 6.0 Hz, 2H), 4.27 (t, J = 6.6 Hz, 2H), 3.25 (t, J = 6.6 Hz, 2H).

5.1.62. *tert*-Butyl {[2-[2-(2-naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)benzyl]oxy}acetate (77)

To a stirred solution of **76** (200 mg, 0.561 mmol), *t*-butyl bromoacetate (0.250 mL. 1.70 mmol), tetrabutylammonium hydrogen sulfate (19 mg, 56.0 μmol) in toluene (1 mL) was added 40% NaOH (1 mL) at room temperature. After being stirred for 10 h, 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, 1/1) to yield **77** (231 mg, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.70 (m, 4H), 7.54–7.34 (m, 6H), 6.81 (dd, J = 7.8, 1.5 Hz, 1H), 6.69 (d, J = 1.5 Hz, 1H), 6.26 (t, J = 2.1 Hz, 1H), 5.27 (s, 2H), 4.58 (s, 2H), 4.21 (t, J = 6.6 Hz, 2H), 3.94 (s, 2H), 3.23 (t, J = 6.6 Hz, 2H), 1.47 (s, 9H).

5.1.63. {[2-[2-(2-Naphthyl)ethoxy]-4-(1*H*-pyrazol-1-ylmethyl)benzyl]oxy}acetic acid (21)

To a solution of **77** (231 mg, 0.489 mmol), anisole (0.1 mL) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (0.2 mL) at room temperature and the reaction mixture was stirred for 12 h. Concentration in vacuo followed by purification by column chromatography on silica gel ($CHCl_3$/MeOH, 50/1) afforded **21** (93 mg, 45%) as an ivory powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.80 (m, 3H), 7.68 (s, 1H), 7.56–7.23 (m, 6H), 6.80–6.74 (m, 2H), 6.28 (m, 1H), 5.29 (s, 2H), 4.52 (s, 2H), 4.26 (t, J = 6.9 Hz, 2H), 4.01 (s, 2H), 3.23 (t, J = 6.9 Hz, 2H); IR (KBr) 3105, 2902, 2520, 1732, 1613, 1586, 1507, 1430, 1400, 1263, 1216, 1159, 1136, 1110, 1065, 1040, 965, 866, 817, 753, 624 cm^{-1}; MS (APCI, Neg.) *m/e* 415 $(M-H)^-$; HRMS (Pos.) calcd for $C_{25}H_{25}N_2O_4$: 417.1814; found: 417.1795.

5.2. Pharmacology

5.2.1. Measurement of the prostanoid mEP1-4 receptors 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 that 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.

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

[L]: Concentration of radiolabeled ligand. K_d; Dissociation constant of radiolabeled ligand for the prostanoid receptors.

5.2.2. Measurement of the mEP3 receptor antagonist activity

To confirm that test compounds antagonized the mEP3 receptor and estimate potencies 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 2 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, 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 0.1% (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 an assay buffer, intracellular calcium concentration was measured with a Fluorescence drug screening system (FDSS-3000, Hamamatsu Photonics). The fluorescence intensities emitted 500 nm by an excitation wavelength of 340 nm and 380 nm was measured. The percent inhibition on the increase of 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%) to estimate the IC_{50} value.

References and notes

1. Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev.* **1994**, *46*, 205.
2. Minami, T.; Nakano, H.; Kobayashi, T.; Sugimoto, Y.; Ushikubi, F.; Ichikawa, A.; Narumiya, S.; Ito, S. *Br. J. Pharmacol.* **2001**, *133*, 438.
3. Ushikubi, F.; Segi, E.; Sugimoto, Y.; Murata, T.; Matsuoka, T.; Kobayashi, T.; Hizaki, H.; Tuboi, K.; Katsuyama, M.; Ichikawa, A.; Tanaka, T.; Yoshida, N.; Narumiya, S. *Nature* **1998**, *395*, 281.
4. (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.
5. Chen, M. C. Y.; Amirian, D. A.; Toomey, M.; Sanders, M. J.; Soll, A. H. *Gastroenterology* **1988**, *94*, 1121.
6. Ma, H.; Hara, A.; Xiao, C. Y.; Okada, Y.; Takahata, O.; Nakaya, K.; Sugimoto, Y.; Ichikawa, A.; Narumiya, S.; Ushikubi, F. *Circulation* **2001**, *104*, 1176.
7. Gross, S.; Tilly, P.; Hentsch, D.; Vonesch, J. L.; Fabre, J. E. *J. Exp. Med.* **2007**, *204*, 311.
8. (a) Juteau, H.; Gareau, Y.; Labelle, M.; Lamontagne, S.; Tremblay, N.; Carriere, M. C.; Sawyer, N.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 747; (b) Juteau, H.; Gareau, Y.; Labelle, M.; Sturino, C. F.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carriere, M. C.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem.* **2001**, *9*, 1977; (c) Gallant, M.; Carriere, M. C.; Chateauneuf, A.; Denis, D.; Gareau, Y.; Godbout, C.; Greig, G.; Juteau, H.; Lachance, N.; Lacombe, P.; Lamontagne, S.; Metters, K. M.; Rochette, C.; Ruel, D.; Slipetz, D.; Sawyer, N.; Tremblay, N.; Labelle, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2583; (d) Gallant, M.; Belley, M.; Carriere, M. C.; Chateauneuf, A.; Denis, D.; Lachance, N.; Lamontagne, S.; Metters, K. M.; Sawyer, N.; Slipetz, D.; Truchon, J. F.; Labelle, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3813; (e) Belley, M.; Gallant, M.; Roy, B.; Houde, K.; Lachance, N.; Labelle, M.; Trimble, L. A.; Chauret, N.; Li, C.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carriere, M. C.; Denis, D.; Greig, G. M.; Slipetz, D.; Metters, K. M.; Gordon, R.; Chan, C. C.; Zamboni, R. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 527; (f) Belley, M.; Chan, C. C.; Gareau, Y.; Gallant, M.; Juteau, H.; Houde, K.; Lachance, N.; Labelle, M.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carriere, M. C.; Denis, D.; Greig, G. M.; Slipetz, D.; Gordon, R.; Chauret, N.; Li, C.; Zamboni, R. J.; Metters, K. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5639.
9. (a) Zhou, N.; Zeller, W.; Krohn, M.; Anderson, H.; Zhang, J.; Onua, E.; Kiselyov, A. S.; Ramirez, J.; Halldorsdottir, G.; Andresson, T.; Gurney, M. E.; Singh, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 123; (b) O'Connell, M.; Zeller, W.; Burgeson, J.; Mishra, R. K.; Ramirez, J.; Kiselyov, A. S.; Andresson, T.; Gurney, M. E.; Singh, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 778; (c) Zhou, N.; Zeller, W.; Zhang, J.; Onua, E.; Kiselyov, A. S.; Ramirez, J.; Palsdottir, G.; Halldorsdottir, G.; Andresson, T.; Gurney, M. E.; Singh, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1528; (d) Zegar, S.; Tokar, C.; Enache, L. A.; Rajagopol, V.; Zeller, W.; O'Connell, M.; Singh, J.; Muellner, F. W.; Zembower, D. E. *Org. Process Res. Dev.* **2007**, *11*, 747; (e) 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.
10. Ohuchida, S.; Toda, M.; Miyamoto, T. U.S. Patent 5,055,598, 1991.
11. Mendelson, W. L.; Holmes, M.; Dougherty, J. *Synth. Commun.* **1996**, *26*, 593.
12. Sweeney, Z. K. PCT Publication No. WO2008/009613, 2008.
13. Shigeyasu, M.; Kuwahara, M.; Sisido, M.; Ishikawa, T. *Chem. Lett.* **2001**, *30*, 634.
14. Knochel, P.; Yeh, M. C.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392.