Bioorganic & Medicinal Chemistry 19 (2011) 4574–4588

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

# Discovery of selective indole-based prostaglandin $D_2$ receptor antagonist

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ARTICLE INFO

*Article history:*
Received 10 May 2011
Revised 3 June 2011
Accepted 3 June 2011
Available online 16 June 2011

*Keywords:*
Prostaglandin
DP receptor
Antagonist
Indole

ABSTRACT

A series of *N*-benzoyl-2-methylindole-3-acetic acids were synthesized and biologically evaluated as prostaglandin (PG) $D_2$ receptor antagonists. Some of the selected compounds significantly inhibited OVA-induced vascular permeability in guinea pig conjunctiva after oral dosing. Structure–activity relationship study is presented.



## 1. Introduction

Coleman et al.[1] proposed the existence of specific receptors for thromboxane (TX), prostaglandin (PG)$I_2$, $PGE_2$, $PGF_{2\alpha}$, and $PGD_2$ such as TP, IP, EP, FP, and DP receptors, respectively. Among them, the DP receptor is the most recently cloned prostanoid receptor and perhaps the least characterized.[2] $PGD_2$ is the major prostanoid released from mast cells after challenge with IgE[3] and it has also been shown to affect the sleep cycle[4] and body temperature.[5] The discovery of a DP selective receptor antagonist[6,7] seems to offer significant advantages, for investigating the role of this receptor in the various pathologies described above. However, the role of the DP receptor remains unclear because of the lack of potent and subtype-selective ligands.

Several patent applications claim the use of indolyl acetic acid derivatives as orphan receptor CRTH2 antagonists.[8] Blockade of the above-described receptors is known to inhibit much of the pro-inflammatory effects of $PGD_2$.[9]

$PGD_2$ receptor antagonists might have therapeutic potential for allergic disorders because $PGD_2$ is considered to play an important role in various allergic diseases such as allergic rhinitis,[10] atopic asthma,[3b] allergic conjunctivitis,[11] and atopic dermatitis.[12]

In our previous paper,[7d] we reported discovery of *N*-benzoyl-2-methylindole-4-acetic acid analog **2** as an optimized human DP (hDP) receptor antagonist starting with chemical modification of indomethacin **1** (Fig. 1). Synthetic study of the indole-based hDP antagonist **2** prompted us to carry out molecular design of more cost-effective structure as a chemical lead of a drug candidate because of the synthetic difficulty of '*N*-benzoyl-2-methylindole-4-acetic acid' scaffold. Besides, low hIP/DP receptor selectivity of **2** (Table 1) was considered a risk factor that might cause serious side effects such as platelet aggregation. To solve the problems described above, further optimization of the indole-3-acetic

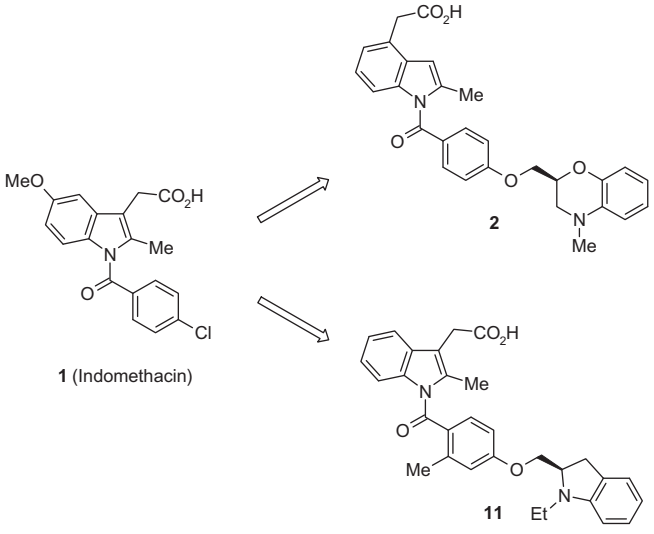


**Figure 1.** Molecular design of indole-based DP antagonists.

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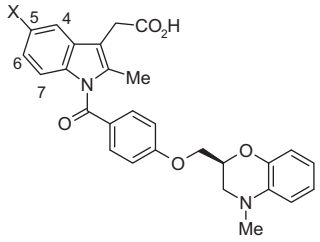
doi:10.1016/j.bmc.2011.06.014

**Table 1**
Effect of the 5-substituent of the indole moiety on the activity profiles



| Compound | X | Binding $K_i$ (nM) | | | | | | | | $IC_{50}$[a] (nM) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | mEP1 | mEP2 | mEP3 | mEP4 | mFP | hTP | hIP | mDP | mDP |
| **1** | | >10,000 | >10,000 | >10,000 | >10,000 | NT[b] | NT[b] | NT[b] | >10,000 | NT[b] |
| **2** | | 6200 | 99 | 1700 | >10,000 | 3100 | 260 | 37 | 16 | 2.4 |
| **3a** | H | >10,000 | 210 | 1700 | >10,000 | 2100 | >10,000 | 200 | 7.7 | NT[b] |
| **3b** | Me | 5200 | 340 | 2800 | 3600 | 1700 | >10,000 | 1100 | 28 | 4.3 |
| **3c** | Cl | >10,000 | 330 | >10,000 | >10,000 | 2200 | NT[b] | 49 | 29 | 3.1 |
| **3d** | F | >10,000 | 250 | 1900 | >10,000 | 1700 | >10,000 | 320 | 5.7 | 1.8 |
| **3e** | OMe | >10,000 | 310 | 2500 | 3000 | NT[b] | NT[b] | 1000 | 9.9 | NT[b] |

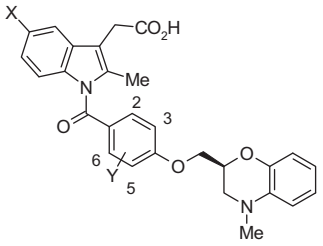
[a] $IC_{50}$ (nM): mDP receptor antagonist activity.
[b] NT: not tested.

acid-based chemical lead was carried out. We here report the discovery process of new indole-based mouse DP (mDP) antagonist **11** starting from chemical modification of indomethacin **1**, which could be an excellent chemical lead for developing an orally active drug candidate.

## 2. Chemistry

Synthesis of the test compounds listed in Tables 1–3 is outlined in Schemes 1 and 2. Synthesis of **3a**–**e**, **4a**–**i** and **5a**–**g** is described in Scheme 1. O-Alkylation of appropriately substituted methyl 4-hydroxybenzoates **18a**–**j** with a tosylate **13**, prepared from *N*-methyl benzomorpholine **12**,[7d] afforded **14a**–**j**, alkaline hydrolysis of which provided the corresponding carboxylic acids **15a**–**j**. The carboxylic acids **15a**–**j** were converted to the corresponding acid chlorides **16a**–**j**, which were used for the next N-acylation reaction of the benzyl 2-methylindole-3-acetic acetates **19a**–**e**. N-Acylation of **19a**–**e**, which were prepared from the corresponding *para*-substituted phenylhyrazine hydrochloride and levulinic acid by Fisher's indole synthesis, with an optional acid chloride selected among **16a**–**j** under the reported reaction condition[7d] afforded **17a**–**u**. Deprotection of **17a**–**e**, **17f**–**n**, and **17o**–**u** by catalytic hydrogenation afforded **3a**–**e**, **4a**–**i**, and **5a**–**g**, respectively. Synthesis of **6**–**11** is described in Scheme 2a. N-Acylation of **19a** with 4-acetoxy-2-methylbenzoyl chloride in the presence of 20 M sodium hydroxide aq gave **20**, which was transformed to the corresponding carboxylic acid **21** by catalytic hydrogenation. Treatment of carboxylic acid **21** with a resin in the presence of diisopropylethylamine afforded resin-supported intermediate **22**, deacetylation of which with piperidine provided phenol **23**. Mitsunobu reaction[13] of alcohols **24–29**[7d,14] with the resin-supported phenol **23** followed by acidic cleavage from the supporting resin[15] resulted in the production of **6–11**. Among the bicyclic alcohols, **25a**–**b** were prepared as described in Scheme 2b. *O*-Alkylation of **30a**–**b** with (*S*)-(+)-glycidyl 3-nitrobenzenesulfonate in the presence of cesium carbonate afforded epoxides **31a**–**b**. Intramolecular ring opening reaction of epoxides **31a**–**b** by addition of *n*-butyllithium resulted in dihydrofurans **25a**–**b**. As shown in Scheme 2c, racemic **28b** and optically active **29** were prepared from commercially available **32a** and **32b**, respectively. Concurrent N-ethylation and O-ethylation of **32a** with ethyl iodide in the presence of cesium carbonate afforded **33a**, reduction of which with lithium aluminum hydride gave **28b**. According to the same procedure as described for the preparation of **28b** from **32a**, **29** was prepared from the corresponding 2*R*-enantiomer **32b**.

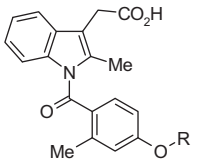
**Table 2**
Effect of substitution of the *N*-benzoyl moiety on the activity profiles

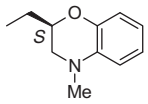
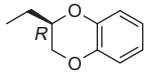
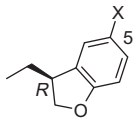
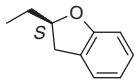
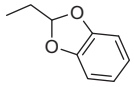
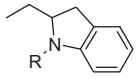
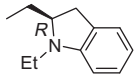


| Compound | X | Y | Binding $K_i$ (nM) | $IC_{50}$[a] (nM) | Binding $K_i$ (nM) |
|---|---|---|---|---|---|
| | | | mDP | | hIP |
| **3a** | H | H | 7.7 | NT[b] | 200 |
| **4a** | H | 2-Me | 3.5 | 1.1 | 130 |
| **4b** | H | 2-Cl | 4.4 | 2.2 | 92 |
| **4c** | H | 2-F | 3.8 | 2.5 | 110 |
| **4d** | H | 3-Me | 140 | NT[b] | 72 |
| **4e** | H | 3-Cl | 380 | NT[b] | 91 |
| **4f** | H | 3-F | 240 | NT[b] | 210 |
| **4g** | H | 3-OMe | 340 | NT[b] | 430 |
| **4h** | H | 2,3-Me | 380 | NT[b] | 98 |
| **4i** | H | 2,5-Me | 360 | NT[b] | 94 |
| **3d** | F | H | 5.7 | 1.8 | 320 |
| **5a** | F | 2-Me | 2.7 | 3.2 | 130 |
| **5b** | F | 2-Cl | 5.2 | 1.6 | 200 |
| **5c** | F | 2-F | 3.8 | 0.7 | 320 |
| **5d** | F | 3-Me | 59 | 42 | 160 |
| **5e** | F | 3-OMe | NT[b] | 68 | 1500 |
| **5f** | F | 2,3-Me | NT[b] | 32 | 230 |
| **5g** | F | 2,5-Me | 14 | 2.8 | 93 |

[a] $IC_{50}$ (nM): mDP receptor antagonist activity.
[b] NT: not tested.

**Table 3**
Effect of chemical modification of *N*-methyl benzomorpholine moiety on the activity profiles




| Compound | R | | Binding $K_i$ (nM) | $IC_{50}$[a] (nM) | Binding $K_i$ (nM) |
|---|---|---|---|---|---|
| | | | mDP | | hIP |
| **4a** |  | | 3.5 | 1.1 | 130 |
| **6** |  | | 22 | 3.8 | 570 |
| **7** |  | a X = H | 43 | 72 | 2100 |
| | | b X = F | 5.4 | 1.8 | 520 |
| **8** |  | | 7.1 | 7.0 | 280 |
| **9** |  | | NT[b] | 43 | 3000 |
| **10** |  | a R = Me | NT[b] | 6.2 | >10,000 |
| | | b R = Et | 22 | 3.1 | 5100 |
| **11** |  | | 4.8 | 2.2 | 2200 |

[a] $IC_{50}$ (nM): mDP receptor antagonist activity.
[b] NT: not tested.

## 3. Results and discussion

The test compounds listed in Tables 1–3 were all tested for inhibition of the specific binding of a radiolabeled ligand, [$^3$H]$PGD_2$, to membrane fractions prepared from cells stably expressing mDP receptor. They were also evaluated for their potency to antagonize mDP receptors by measuring $PGD_2$-stimulated changes in intracellular second messenger cAMP as an indicator of receptor function. The mDP antagonism was measured in the presence of 0.1% bovine serum albumin (BSA) for the discovery of potent antagonists in protein-rich in vivo animal models. Because of their close homology to human receptors, all the DP receptor affinities and antagonist activities are assayed by mouse receptor unless otherwise noted. Our purpose was to identify more DP-selective antagonist compared with **2**, which showed relatively higher IP receptor affinity. As such, our focus was placed on the binding affinity ($K_i$) of the newly synthesized compounds for mEP1–4, mFP, hTP, and hIP in addition to their $K_i$ values for the mDP receptor. Compounds **3a**–**e** (Table 1), **4a**–**i** (Table 2), and **5a**–**g** (Table 2), in which *para*-position of the *N*-benzoyl residue is substituted with the *para*-*N*-methyl benzomorpholinomethoxy moiety, were synthesized and evaluated. On the basis of the previously optimized structure **2**,[7d] a series of 2*R*-enantiomers **3a**–**e** were synthesized and evaluated.

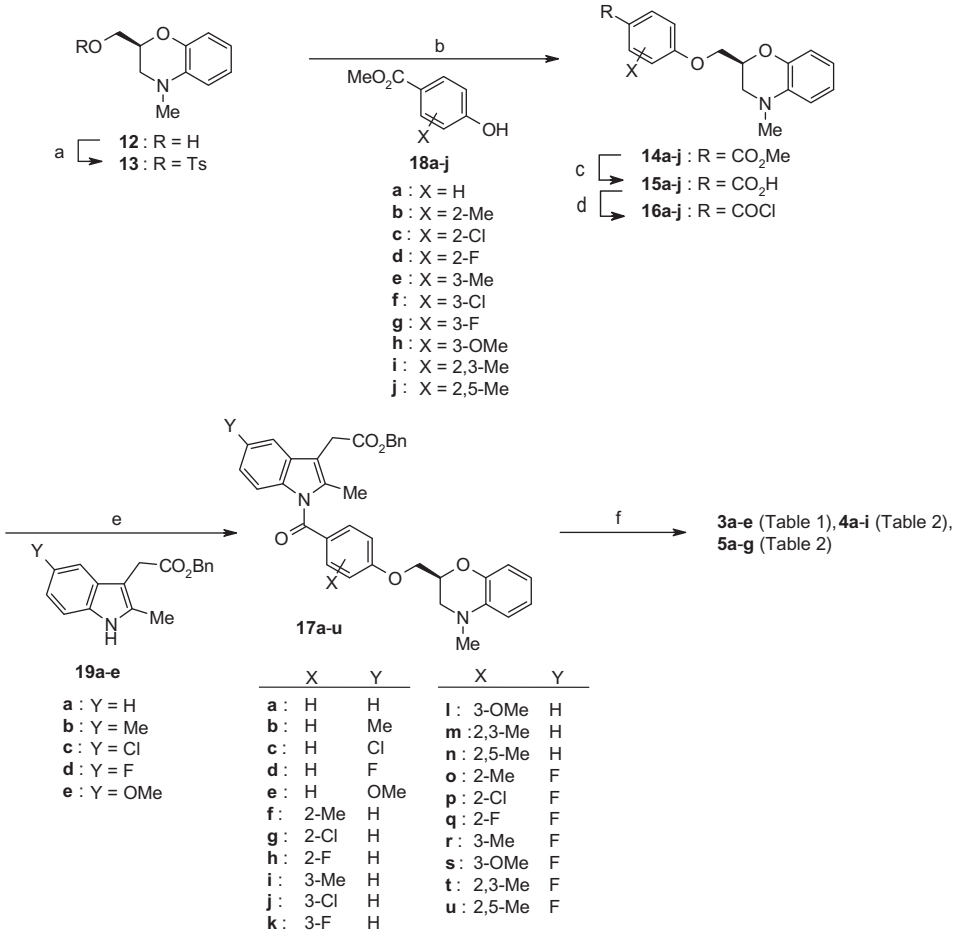
Table 1 displays the effect of the 5-substituent of the indole moiety on the activity profiles. Compound **3a** demonstrated slightly more potent DP receptor affinity and 5.4-fold less potent hIP receptor affinity relative to **2**. Introduction of 5-methyl and 5-chloro residues into the 2-methyl indole-3-acetic acid scaffold afforded **3b** and **3c**, respectively, with nearly equipotent binding affinity for DP receptor and 30-fold less potent and equipotent hIP receptor affinity, respectively. Introduction of 5-fluoro and 5-methoxy residues into the 2-methyl indole-3-acetic acid scaffold afforded **3d** and **3e**, respectively, with slightly increased and nearly equipotent binding affinity.

Among them, **3a**, **3d** and **3e** tended to show slightly more DP selectivity than **2**.

Regarding hIP receptor affinity, compound **3c** afforded nearly the same hIP receptor affinity as **2**. Compounds **3a**–**b** and **3d**–**e** showed less potent hIP receptor affinity relative to **2**. 4-Substituted and 6-substituted analogs were also synthesized but they were not evaluated as a single product because of the difficulty in their separation. 7-Substituted indole analogs were not synthesized because of predicted difficulty of their N-acylation. As a result, most of the tested compounds **3b**–**c** and **3d** showed potent antagonist activity.

Table 2 displays the effect of simultaneous substitution of the indole moiety and phenyl moiety of the *N*-benzoyl residue on the activity profiles. As illustrated by the biological results of **4a**–**c**, 2-methyl, 2-chloro, and 2-fluoro substitutions resulted in retention of potent DP receptor affinity relative to unsubstituted **3a** while as illustrated by **4d**–**i**, 3-methyl, 3-chloro, 3-fluoro, 3-methoxy, 2, 3-dimethyl, and 2,5-dimethyl substitution resulted in a decrease of DP receptor affinity. A series of 5-fluoro indole analogs were synthesized and evaluated. As illustrated by **5a**–**c**, introduction of 2-methyl, 2-chloro, and 2-fluoro residues was effective for retention of potent DP receptor affinity whereas introduction of 3-methyl, 3-methoxy, and 2,3-dimethylbenzoyl residues resulted in reduced activities relative to **3d** as illustrated by **5d**–**f**. Compounds **4a**–**c**, **5a**–**c**, and **5g** showed very potent antagonist activity as expected from their corresponding $K_i$ values. Regarding hIP receptor affinity, compounds **4b**, **4d**–**e**, **4h**–**i**, and **5g** tended to show increased affinity relative to **3a** while they still retained selectivity ($K_i$ values, hIP/mDP). As a result, the 2-substituted *N*-benzoyl analogs tended to show increased activity versus 3-substituted *N*-benzoyl analogs whereas **4i** and **5g** showed unexpected results in their binding affinity.

Table 3 displays the effect of chemical modification of *N*-methyl benzomorpholine moiety of **4a**, which is the partial structure of the previously optimized 2-methylindole-4-acetic acid analog **2**.[7d] Transformation of the terminal *N*-methyl benzomorpholine moiety to a benzodioxane moiety provided **6** with 6.3-fold reduction of DP receptor affinity. Replacement of the benzomorpholine moiety of **4a** with benzofuran-3-yl moiety provided **7a** with 12-fold reduction of DP receptor affinity, whereas introduction of 5-fluoro residue into the benzofuran moiety afforded **7b** with nearly equipotent receptor affinity and 4.1-fold less potent hIP receptor affinity relative to **4a**. Replacement of the benzomorpholine moiety of **4a** with benzofuran-2-yl moiety afforded **8** with nearly retained DP receptor affinity and nearly 2-fold less potent hIP receptor affinity. Introduction of another oxygen into the benzofuran moiety of **8** afforded **9** with a reduction of antagonist activity. Replacement of the oxygen atom of the benzofuran moiety of **8** with *N*-methyl moiety afforded **10a** with nearly equipotent antagonist activity. Replacement of the oxygen moiety of **8** with *N*-ethyl moiety afforded **10b** tended to increase DP receptor antagonist activity. Based on the information mentioned above, an optically active form **11** was prepared and evaluated for DP receptor affinity and hIP receptor affinity. The compound **11** showed potent DP receptor affinity and equipotent antagonist activity relative to **4a**. Besides, DP receptor affinity of **11** showed remarkable improvement in selectivity for the hIP receptor (**11**, hIP/DP = 458; **2**, hIP/DP = 2.3).




**Scheme 1.** Synthesis of **3a**–**e**, **4a**–**i** and **5a**–**g**. Reagents: (a) TsCl, $Et_3N$, DMAP, THF; (b) **18a**–**j**, $K_2CO_3$, DMF; (c) NaOH, MeOH, THF; (d) $(COCl)_2$, DMF, DME; (e) NaOH, TBACl, $CH_2Cl_2$; or $Et_3N$, DMAP, $CH_3CN$, EtOAc; (f) $H_2$, $Pd(OH)_2$–C, EtOAc.

As shown in Table 4, representative compounds **4a**, **4b**, **5b**, and **11** were evaluated for their potency to inhibit OVA-induced vascular permeability in guinea pig conjunctiva. Among the tested compounds, **4b**, **5b**, and **11** showed significant inhibition after their oral dosing (3, 3, and 1 mg/kg, respectively) whereas **4a** (3 mg/kg) did not show significant DP receptor antagonist activity because of the presumed PK problem and/or species difference of DP receptor affinity between mouse and guinea pig. Weaker in vivo potency of **4a** relative to **4b**, **5b** and **11** was considered to be due to its less potent antagonist activity and/or its lower blood level in guinea pig.

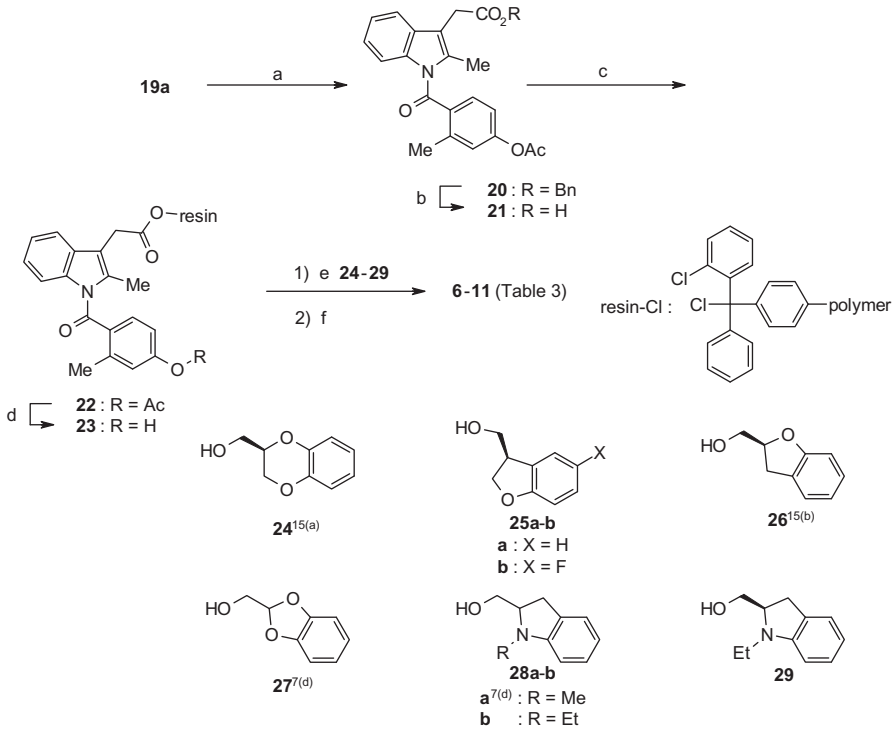
Table 5 displays activity profiles of **4a**, **4b**, **5b**, and **11** including other mEP receptors, mFP receptor, hTP receptor, hIP receptor, mDP receptor, and mDP antagonist activity. As shown in Table 5, **4a**, **4b**, **5b**, and **11** demonstrated much better IP/DP selectivity relative to the previously reported compound **2** (Table 1). Especially, compound **11** showed better selectivity compared with **2** because of its markedly reduced hIP receptor affinity and retained mDP receptor affinity. Compounds **4a**, **4b**, and **5b** also showed a similar tendency as **11** regarding hIP/DP selectivity although reduction of their hIP receptor affinity was not so much as that of **11**. Based on these results, more receptor-selective indole-based DP antagonist relative to **2** was discovered starting with the chemical modification of indomethacin **1**.

In summary, we have discovered two series of indole-based DP antagonists possessing 2-methylindole-4-acetic acid[7] and 2-methylindole-3-acetic acid as scaffolds starting with chemical modification of indomethacin **1**. An optimized compound **11** demonstrated efficacy in OVA-induced vascular permeability in guinea pig conjunctiva. The newly identified DP antagonist **11** showed remarkable improvement of hIP/mDP selectivity in its receptor affinity compared with **2**.

## 4. Experimental

### 4.1. General directions

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra ($^1H$ NMR) were taken on a Varian Mercury 300 spectrometer or Varian GEMINI-200 or VXR-200s spectrometer using deuterated chloroform ($CDCl_3$) or deuterated methanol ($CD_3OD$) or deuterated dimethylsulfoxide (DMSO-$d_6$) as the solvent. Fast atom bombardment mass spectra (FAB-MS) and electron ionization (EI) were obtained on a JEOL JMS-DX303HF spectrometer. The matrix assisted laser desorption ionization-time of flight high-resolution mass spectra (MALDI-TOF, HRMS) were obtained on a PerSeptive Voyager Elite spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a HITACHI M1200H spectrometer. Infrared spectra (IR) were measured on a Perkin-Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyses were uncorrected. Optical rotations were measured in a JASCO DIP-1000 digital polarimeter. Column chromatography was carried out on silica gel [Merck Silica Gel 60 (0.063–0.200 mm), Wako gel C200 or Fuji Silysia BW235]. Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, Silica Gel 60

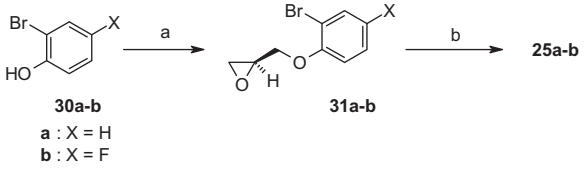



**Scheme 2a.** Synthesis of **6**–**11**. Reagents: (a) 4-acetoxy-2-methylbenzoyl chloride, NaOH, TBACl, $CH_2Cl_2$; (b) $H_2$, $Pd(OH)_2$–C, EtOAc; (c) resin-Cl, diisopropylethylamine, $CH_2Cl_2$; (d) piperidine, $CH_2Cl_2$; (e) DEAD, $PPh_3$, $CH_2Cl_2$; (f) AcOH, $CF_3CH_2OH$, $CH_2Cl_2$.

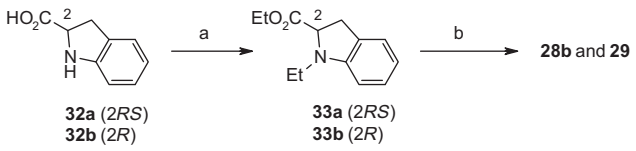
$F_{254}$). The following abbreviations for solvents and reagents are used; tetrahydrofuran (THF), ethyl acetate (EtOAc), dimethylformamide (DMF), dichloromethane ($CH_2Cl_2$), chloroform ($CHCl_3$), methanol (MeOH), acetic acid (AcOH), triethylamine (TEA), diisopropylethylamine (DIPEA), 4-dimethylaminopyridine (DMAP), *tert*-butyl methyl ether (MTBE), 2-propanol (IPA), 1,2-dimethoxyethane (DME), tetrabutylammonium chloride (TBACl), divinylbenzene (DVB), *p*-toluenesulfonyl chloride (TsCl), and diethylazodi-carboxylate (DEAD).

### 4.2. [(2*S*)-4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methyl 4-methylbenzenesulfonate (13)

To a stirred solution of **12** (4.27 g, 23.8 mmol) in THF (10.5 mL) were successively added a solution of TEA (8.0 mL, 57.2 mmol) and DMAP (0.29 g, 2.38 mmol) in THF (1.5 mL) and a solution of TsCl (5.45 g, 28.6 mmol) in THF (18 mL) at 0 °C. After stirring for 4 h at room temperature, the reaction mixture was quenched with water and extracted with MTBE (×2). The combined organic layers were washed with 1 M HCl aq, water, $NaHCO_3$ aq, brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by recrystalization from MTBE (7.9 mL) and IPA (39 mL) to yield **13** (5.53 g, 70%); TLC $R_f$ = 0.45 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J$ = 8.4 Hz, 2H), 7.35 (d, $J$ = 8.4 Hz, 2H), 6.87–6.81 (m, 1H), 6.70–6.61 (m, 3H), 4.50–4.42 (m, 1H), 4.23–4.12 (m, 2H), 3.24 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.09 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.83 (s, 3H), 2.45 (s, 3H).




**Scheme 2b.** Synthesis of **25a**–**b**. Reagents: (a) (*S*)-(+)-glycidyl 3-nitrobenzenesulfonate, $Cs_2CO_3$, DMF; (b) *n*-BuLi, THF.




**Scheme 2c.** Synthesis of **28b** and **29**. Reagents: (a) ethyl iodide, $Cs_2CO_3$, DMF; (b) $LiAlH_4$, THF.

### 4.3. General procedure for the preparation of 16a–j

#### 4.3.1. Methyl 4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14a)

To a stirred solution of methyl-4-hydroxybenzoic acid (2.43 g, 16.0 mmol) and **13** (5.43 g, 16.3 mmol) in DMF (10.8 mL) was added $K_2CO_3$ (4.94 g, 35.2 mmol). After stirring for 10 h at 80 °C, the reaction mixture was quenched with water and extracted with MTBE (×2). The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and evaporated to give **14a**, which was used for the next reaction without further purification; TLC $R_f$ = 0.46 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 8.7 Hz, 2H), 6.96 (d, $J$ = 8.7 Hz, 2H), 6.92–6.80 (m, 2H), 6.74–6.66 (m, 2H), 4.70–4.61 (m, 1H), 4.28 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.17 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.89 (s, 3H), 3.39 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.26 (dd, $J$ = 11.7, 6.6 Hz, 1H), 2.90 (s, 3H).

#### 4.3.2. 4-{[(2*S*)-4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15a)

To a stirred solution of **14a** in MeOH (25 mL)–THF (25 mL) was added 5 M NaOH aq (25 mL). After stirring for 3 h at 50 °C, the reaction mixture was diluted with water and extracted with MTBE. The

**Table 4**
Inhibitory effects of **4a**, **4b**, **5b** and **11** on OVA-induced vascular permeability in guinea pig conjunctiva ($n = 8$)

| Compound | Dose (mg/kg, po) | % Inhibition |
|---|---|---|
| **2** | 1 | 23 |
| | 3 | 41[a] |
| **4a** | 3 | 29 |
| **4b** | 3 | 48[a] |
| **5b** | 3 | 52[a] |
| **11** | 1 | 42[a] |
| Pyrilamine | 1 (mg/kg, iv) | 68 |

Inhibition of increase in conjunctival vascular permeability caused by topical application of OVA (1%, 20 μL/eye) in actively sensitized guinea pigs. All antagonists were orally administered 1 h before the antigen challenge.
[a] 0.05 versus control with Student's *t*-test.

aqueous layer was acidified with 2 M HCl aq and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and evaporated to yield **15a** (4.26 g, 87% in two steps); TLC $R_f = 0.47$ ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 8.7$ Hz, 2H), 6.92–6.80 (m, 2H), 6.74–6.66 (m, 2H), 4.72–4.62 (m, 1H), 4.30 (dd, $J = 9.6$, 5.1 Hz, 1H), 4.19 (dd, $J = 9.6$, 6.6 Hz, 1H), 3.40 (dd, $J = 11.4$, 3.0 Hz, 1H), 3.27 (dd, $J = 11.4$, 6.9 Hz, 1H), 2.91 (s, 3H).

#### 4.3.3. 4-{[(2*S*)-4-Methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl] methoxy}benzoyl chloride (16a)

To a stirred solution of **15a** (120 mg, 0.4 mmol) in DME (5 mL) were added $(COCl)_2$ (0.09 mL, mmol) and DMF (0.3 μL, 0.004 mmol). After stirring for 1 h at 40 °C, the reaction mixture was concentrated in vacuo to give **16a**, which was used for the next reaction without further purification; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J = 9.0$ Hz, 2H), 7.01 (d, $J = 9.0$ Hz, 2H), 6.98–6.80 (m, 4H), 4.80–4.70 (m, 1H), 4.34 (dd, $J = 9.9$, 4.5 Hz, 1H), 4.26 (dd, $J = 9.9$, 5.7 Hz, 1H), 3.47 (dd, $J = 12.0$, 2.7 Hz, 1H), 3.34 (dd, $J = 12.0$, 7.2 Hz, 1H), 2.98 (s, 3H).

According to the same procedure as described above for the conversion of **13** to**16a**, **13** were converted to **16b**–**j**.

#### 4.3.4. Methyl 2-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14b)

TLC $R_f = 0.61$ (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.93 (d, $J = 9.3$ Hz, 1H), 6.91–6.75 (m, 4H), 6.75–6.61 (m, 2H), 4.68–4.60 (m, 1H), 4.26 (dd, $J = 9.6$, 5.1 Hz, 1H), 4.15 (dd, $J = 9.6$, 6.6 Hz, 1H), 3.86 (s, 3H), 3.38 (dd, $J = 11.4$, 2.7 Hz, 1H), 3.24 (dd, $J = 11.4$, 6.6 Hz, 1H), 2.90 (s, 3H), 2.60 (s, 3H).

#### 4.3.5. 2-Methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15b)

56% yield in two steps; TLC $R_f = 0.27$ (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J = 9.6$ Hz, 1H), 6.92–6.78 (m, 4H), 6.75–6.66 (m, 2H), 4.70–4.60 (m, 1H), 4.28 (dd, $J = 9.6$, 5.1 Hz, 1H), 4.17 (dd, $J = 9.6$, 6.3 Hz, 1H), 3.39 (dd, $J = 11.7$, 3.0 Hz, 1H), 3.25 (dd, $J = 11.7$, 6.3 Hz, 1H), 2.91 (s, 3H), 2.63 (s, 3H).

#### 4.3.6. 2-Methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16b)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J = 8.7$ Hz, 1H), 7.10–6.80 (m, 6H), 4.86–4.78 (m, 1H), 4.40–4.28 (m, 2H), 3.58 (dd, $J = 11.7$, 2.7 Hz, 1H), 3.45 (dd, $J = 11.7$, 2.7 Hz, 1H), 3.08 (s, 3H), 2.57 (s, 3H).

#### 4.3.7. Methyl 2-chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14c)

TLC $R_f = 0.58$ (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J = 8.7$ Hz, 1H), 7.02 (d, $J = 2.7$ Hz, 1H), 6.92–6.80 (m, 3H), 6.73–6.65 (m, 2H), 4.69–4.60 (m, 1H), 4.25 (dd, $J = 9.6$, 5.1 Hz, 1H), 4.16 (dd, $J = 9.6$, 6.3 Hz, 1H), 3.90 (s, 3H), 3.37 (dd, $J = 11.7$, 3.0 Hz, 1H), 3.24 (dd, $J = 11.7$, 6.3 Hz, 1H), 2.91 (s, 3H).

#### 4.3.8. 2-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15c)

68% yield in two steps; TLC $R_f = 0.43$ ($CHCl_3$/$CH_3OH$, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J = 9.0$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 1H), 6.94–6.80 (m, 3H), 6.75–6.67 (m, 2H), 4.70–4.61 (m, 1H), 4.27 (dd, $J = 9.9$, 5.4 Hz, 1H), 4.18 (dd, $J = 9.9$, 6.3 Hz, 1H), 3.35 (dd, $J = 11.7$, 3.0 Hz, 1H), 3.25 (dd, $J = 11.7$, 6.3 Hz, 1H), 2.91 (s, 3H).

#### 4.3.9. 2-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16c)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.21 (d, $J = 9.3$ Hz, 1H), 7.10–6.90 (m, 6H), 4.88–4.78 (m, 1H), 4.40–4.30 (m, 2H), 3.59 (dd, $J = 12.3$, 2.4 Hz, 1H), 3.43 (dd, $J = 12.3$, 8.4 Hz, 1H), 3.08 (s, 3H).

#### 4.3.10. Methyl 2-fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14d)

TLC $R_f = 0.36$ (*n*-hexane/EtOAc, 3:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90 (t, $J = 8.4$ Hz, 1H), 6.90–6.79 (m, 2H), 6.78–6.64 (m, 4H), 4.68–4.60 (m, 1H), 4.24 (dd, $J = 9.6$, 5.1 Hz, 1H), 4.15 (dd, $J = 9.6$, 6.3 Hz, 1H), 3.90 (s, 3H), 3.37 (dd, $J = 11.7$, 2.7 Hz, 1H), 3.24 (dd, $J = 11.7$, 6.3 Hz, 1H), 2.90 (s, 3H).

#### 4.3.11. 2-Fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15d)

96% yield in two steps; TLC $R_f = 0.45$ ($CHCl_3$/$CH_3OH$, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.96 (t, $J = 8.4$ Hz, 1H), 6.92–6.75 (m, 3H), 6.75–6.65 (m, 3H), 4.70–4.61 (m, 1H), 4.26 (dd, $J = 9.9$, 5.1 Hz, 1H), 4.17 (dd, $J = 9.9$, 6.3 Hz, 1H), 3.37 (dd, $J = 11.7$, 2.7 Hz, 1H), 3.24 (dd, $J = 11.7$, 6.3 Hz, 1H), 2.90 (s, 3H).

#### 4.3.12. 2-Fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16d)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.13 (t, $J = 8.4$ Hz, 1H), 7.42–7.33 (m, 1H), 7.27–7.20 (m, 1H), 7.12–6.98 (m, 2H), 6.85 (dd, $J = 8.7$,

**Table 5**
Activity profiles of **4a**, **4b**, **5b** and **11** on all the tested receptors

| Compound | Binding $K_i$ (nM) | | | | | | | | $IC_{50}$[a] (nM) |
|---|---|---|---|---|---|---|---|---|---|
| | mEP1 | mEP2 | mEP3 | mEP4 | mFP | hTP | hIP | mDP | mDP |
| **4a** | 2900 | 500 | 3600 | >10,000 | 2600 | >10,000 | 130 | 3.5 | 1.1 |
| **4b** | >10,000 | 600 | >10,000 | >10,000 | NT[b] | NT[b] | 92 | 4.4 | 2.2 |
| **5b** | >10,000 | 370 | 3200 | 4100 | 1200 | >10,000 | 200 | 5.2 | 1.6 |
| **11** | >10,000 | 2700 | 2800 | 1600 | 1400 | 7600 | 2200 | 4.8 | 2.2 |

[a] $IC_{50}$ (nM): mDP receptor antagonist activity.
[b] NT: not tested.

2.4 Hz, 1H), 6.75 (dd, $J$ = 12.3, 2.4 Hz, 1H), 5.02–4.92 (m, 1H), 4.48–4.38 (m, 2H), 3.84–3.54 (m, 2H), 3.23 (s, 3H).

#### 4.3.13. Methyl 3-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14e)

TLC $R_f$ = 0.69 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90–7.81 (m, 2H), 6.91–6.80 (m, 3H), 6.75–6.65 (m, 2H), 4.72–4.63 (m, 1H), 4.28 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.18 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.88 (s, 3H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.9 Hz, 1H), 2.91 (s, 3H), 2.26 (s, 3H).

#### 4.3.14. 3-Methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15e)

90% yield in two steps; TLC $R_f$ = 0.19 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.94 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.91–7.87 (m, 1H), 6.91–6.80 (m, 3H), 6.73–6.66 (m, 2H), 4.72–4.64 (m, 1H), 4.30 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.20 (dd, $J$ = 9.9, 6.9 Hz, 1H), 3.41 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.29 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.91 (s, 3H), 2.28 (s, 3H).

#### 4.3.15. 3-Methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16e)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.99 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.92 (s, 1H), 6.97–6.78 (m, 5H), 4.80–4.72 (m, 1H), 4.35 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.27 (dd, $J$ = 9.9, 6.0 Hz, 1H), 3.48 (dd, $J$ = 11.7, 2.4 Hz, 1H), 3.35 (dd, $J$ = 11.7, 7.2 Hz, 1H), 2.98 (s, 3H), 2.28 (s, 3H).

#### 4.3.16. Methyl 3-chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14f)

TLC $R_f$ = 0.30 (*n*-hexane/EtOAc, 4:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J$ = 2.1 Hz, 1H), 7.91 (dd, $J$ = 8.7, 2.1 Hz, 1H), 6.97 (d, $J$ = 8.7 Hz, 1H), 6.91–6.79 (m, 2H), 6.72–6.64 (m, 2H), 4.75–4.67 (m, 1H), 4.34 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.22 (dd, $J$ = 9.6, 7.2 Hz, 1H), 3.89 (s, 3H), 3.43 (dd, $J$ = 11.7, 3.0 Hz, 1H), 3.33 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.91 (s, 3H).

#### 4.3.17. 3-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15f)

45% yield in two steps; TLC $R_f$ = 0.38 ($CHCl_3$/$CH_3OH$, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.12 (s, 1H), 7.98 (d, $J$ = 9.0 Hz, 1H), 7.01 (d, $J$ = 9.0 Hz, 1H), 6.93–6.80 (m, 2H), 6.75–6.65 (m, 2H), 4.78–4.68 (m, 1H), 4.36 (dd, $J$ = 9.9, 5.4 Hz, 1H), 4.24 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.44 (dd, $J$ = 11.7, 3.0 Hz, 1H), 3.34 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.91 (s, 3H).

#### 4.3.18. 3-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16f)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J$ = 2.4 Hz, 1H), 8.08 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.46 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.32 (dt, $J$ = 8.1, 1.5 Hz, 1H), 7.15–7.03 (m, 3H), 5.13–5.03 (m, 1H), 4.57–4.50 (m, 2H), 3.88 (dd, $J$ = 12.9, 2.1 Hz, 1H), 3.71 (dd, $J$ = 12.9, 10.2 Hz, 1H), 3.29 (s, 3H).

#### 4.3.19. Methyl 3-fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14g)

TLC $R_f$ = 0.30 (*n*-hexane/EtOAc, 4:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.82–7.71 (m, 2H), 7.01 (t, $J$ = 8.1 Hz, 1H), 6.90–6.79 (m, 2H), 6.72–6.65 (m, 2H), 4.73–4.64 (m, 1H), 4.33 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.23 (dd, $J$ = 9.9, 6.6 Hz, 1H), 3.89 (s, 3H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.90 (s, 3H).

#### 4.3.20. 3-Fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15g)

69% yield in two steps; TLC $R_f$ = 0.57 ($CHCl_3$/$CH_3OH$/$CH_3CO_2H$, 9:1:0.1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.89–7.83 (m, 1H), 7.80 (dd, $J$ = 11.4, 1.8 Hz, 1H), 7.04 (t, $J$ = 8.4 Hz, 1H), 6.91–6.79 (m, 2H), 6.73–6.65 (m, 2H), 4.74–4.65 (m, 1H), 4.35 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.25 (dd, $J$ = 9.9, 6.6 Hz, 1H), 3.41 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.90 (s, 3H).

#### 4.3.21. 3-Fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16g)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.99–7.93 (m, 1H), 7.86 (dd, $J$ = 11.4, 2.4 Hz, 1H), 7.30–7.24 (m, 1H), 7.20–6.96 (m, 4H), 5.02–4.93 (m, 1H), 4.52–4.46 (m, 2H), 3.74 (dd, $J$ = 12.6, 2.4 Hz, 1H), 3.59 (dd, $J$ = 12.6, 9.3 Hz, 1H), 3.19 (s, 3H).

#### 4.3.22. Methyl 3-methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14h)

TLC $R_f$ = 0.24 (*n*-hexane/EtOAc, 4:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.64 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.55 (d, $J$ = 1.8 Hz, 1H), 6.94 (d, $J$ = 8.1 Hz, 1H), 6.90–6.79 (m, 2H), 6.71–6.64 (m, 2H), 4.74–4.66 (m, 1H), 4.32 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.21 (dd, $J$ = 9.9, 6.9 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.41 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.26 (dd, $J$ = 11.7, 6.6 Hz, 1H), 2.89 (s, 3H).

#### 4.3.23. 3-Methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15h)

85% yield in two steps; TLC $R_f$ = 0.57 ($CHCl_3$/$CH_3OH$/$CH_3CO_2H$, 9:1:0.1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.73 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.60 (d, $J$ = 2.1 Hz, 1H), 6.98 (d, $J$ = 8.4 Hz, 1H), 6.91–6.81 (m, 2H), 6.73–6.66 (m, 2H), 4.76–4.67 (m, 1H), 4.35 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.23 (dd, $J$ = 9.9, 6.9 Hz, 1H), 3.93 (s, 3H), 3.42 (dd, $J$ = 11.1, 2.4 Hz, 1H), 3.28 (dd, $J$ = 11.1, 6.3 Hz, 1H), 2.90 (s, 3H).

#### 4.3.24. 3-Methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16h)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.84 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.56 (d, $J$ = 2.1 Hz, 1H), 7.44 (d, $J$ = 8.4 Hz, 1H), 7.32–7.25 (m, 1H), 7.13–6.98 (m, 3H), 5.04–4.95 (m, 1H), 4.49–4.44 (m, 2H), 3.91 (s, 3H), 3.84–3.76 (m, 1H), 3.74–3.64 (m, 1H), 3.26 (s, 3H).

#### 4.3.25. Methyl 2,3-dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14i)

TLC $R_f$ = 0.66 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$ = 8.7 Hz, 1H), 6.91–6.80 (m, 2H), 6.77–6.66 (m, 3H), 4.72–4.63 (m, 1H), 4.26 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.15 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.86 (s, 3H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.29 (dd, $J$ = 11.4, 6.9 Hz, 1H), 2.91 (s, 3H), 2.51 (s, 3H), 2.21 (s, 3H).

#### 4.3.26. 2,3-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15i)

88% yield in two steps; TLC $R_f$ = 0.26 (*n*-hexane/EtOAc, 1:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 9.0 Hz, 1H), 6.91–6.65 (m, 5H), 4.72–4.63 (m, 1H), 4.27 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.17 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.29 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.91 (s, 3H), 2.57 (s, 3H), 2.22 (s, 3H).

#### 4.3.27. 2,3-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16i)

$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.12 (d, $J$ = 9.3 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.33 (t, $J$ = 7.8 Hz, 1H), 7.15–7.02 (m, 2H), 6.82 (d, $J$ = 9.3 Hz, 1H), 5.07–4.96 (m, 1H), 4.47–4.40 (m, 2H), 3.89–3.81 (m, 1H), 3.72–3.58 (m, 1H), 3.29 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H).

#### 4.3.28. Methyl 2,5-dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoate (14j)

TLC $R_f$ = 0.57 (toluene/EtOAc, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.76 (s, 1H), 6.92–6.80 (m, 2H), 6.74–6.65 (m, 3H), 4.71–4.63 (m, 1H), 4.27 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.15 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.85 (s, 3H), 3.40 (dd, $J$ = 11.7, 3.0 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.6 Hz, 1H), 2.91 (s, 3H), 2.57 (s, 3H), 2.21 (s, 3H).

#### 4.3.29. 2,5-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoic acid (15j)

97% yield in two steps; TLC $R_f$ = 0.50 ($CHCl_3$/$CH_3OH$, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.87 (s, 1H), 6.91–6.80 (m, 2H), 6.74–6.65 (m, 3H), 4.72–4.63 (m, 1H), 4.28 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.17 (dd, $J$ = 9.6, 6.9 Hz, 1H), 3.40 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.91 (s, 3H), 2.61 (s, 3H), 2.22 (s, 3H).

#### 4.3.30. 2,5-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl chloride (16j)

$^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.06 (s, 1H), 7.44 (d, $J$ = 8.1 Hz, 1H), 7.33–7.23 (m, 1H), 7.14–7.00 (m, 2H), 6.71 (s, 1H), 5.05–4.95 (m, 1H), 4.47–4.38 (m, 2H), 3.85–3.76 (m, 1H), 3.72–3.56 (m, 1H), 3.26 (s, 3H), 2.57 (s, 3H), 2.24 (s, 3H).

### 4.4. General procedure for the preparation of 17a–u

#### 4.4.1. Benzyl [2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17a)

*Method A:* To a stirred solution of **19a** (1 g, 3.58 mmol) and **16a** (1.52 g, 5.37 mmol) in $CH_2Cl_2$ (10 mL) were added 20 M NaOH aq (0.9 mL, 17.9 mmol) and TBACl (99 mg, 0.358 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with water and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **17a** (462 mg, 23%); TLC $R_f$ = 0.63 (toluene/EtOAc, 9:1);$^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.76–6.67 (m, 17H), 5.13 (s, 2H), 4.74–4.62 (m, 1H), 4.32 (dd, $J$ = 9.9, 5.4 Hz, 1H), 4.21 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.76 (s, 2H), 3.41 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.40 (s, 3H).

#### 4.4.2. Benzyl [2,5-dimethyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17b)

*Method B:* To a stirred solution of **19b** (410 mg, 1.40 mmol) in $CH_3CN$ (4 mL) and EtOAc (4 mL) were added TEA (1.17 mL, 8.40 mmol), DMAP (51.3 mg, 0.42 mmol) and then **16a** (593 mg, 2.10 mmol). After stirring for 14 h at 40 °C, the reaction mixture was quenched with water and extracted with MTBE (×2). The combined organic layers were washed with $NaHCO_3$ aq, brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **17b** (370 mg, 46%); TLC $R_f$ = 0.46 (*n*-hexane/EtOAc, 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (dd, $J$ = 6.9, 2.1 Hz, 2H), 7.34–7.27 (m, 5H), 7.01 (dd, $J$ = 6.9, 2.1 Hz, 2H), 6.92–6.83 (m, 5H), 6.73–6.67 (m, 2H), 6.67 (s, 2H), 4.68 (m, 1H), 4.31 (dd, $J$ = 9.6, 4.0 Hz, 1H), 4.20 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.73 (s, 2H), 3.43 (dd, $J$ = 12.0, 4.0 Hz, 1H), 3.28 (dd, $J$ = 12.0, 6.6 Hz, 1H), 2.92 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H).

#### 4.4.3. Benzyl [5-chloro-2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17c)

*Method B:* 42% yield; TLC $R_f$ = 0.81 (*n*-hexane/EtOAc, 2:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 9.0 Hz, 2H), 7.47 (d, $J$ = 2.1 Hz, 1H), 7.40–7.27 (m, 5H), 7.02–6.96 (m, 3H), 6.93–6.82 (m, 3H), 6.74–6.66 (m, 2H), 5.15 (s, 2H), 4.73–4.63 (m, 1H), 4.31 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.21 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.71 (s, 2H), 3.41 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.38 (s, 3H).

#### 4.4.4. Benzyl [5-fluoro-2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17d)

*Method B:* 85% yield; TLC $R_f$ = 0.46 (*n*-hexane/EtOAc, 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.68 (dd, $J$ = 14.4 Hz, 2H), 7.33–7.25 (m, 5H), 7.20–7.10 (m, 2H), 7.02–6.65 (m, 7H), 5.15 (m, 2H), 4.70 (m, 1H), 4.31 (dd, $J$ = 9.6, 2.1 Hz, 1H), 4.21 (dd, $J$ = 9.6, 6.3 Hz, 1H), 3.71 (s, 2H), 3.40 (dd, $J$ = 11.4, 2.1 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.92 (s, 3H), 2.37 (s, 3H).

#### 4.4.5. Benzyl [5-methoxy-2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17e)

*Method A*: 26% yield; TLC $R_f$ = 0.53 (toluene/EtOAc, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 9.0 Hz, 2H), 7.38–7.28 (m, 5H), 7.04–6.62 (m, 9H), 5.14 (s, 2H), 4.74–4.62 (m, 1H), 4.31 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.21 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 2H), 3.41 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.92 (s, 3H), 2.39 (s, 3H).

#### 4.4.6. Benzyl [2-methyl-1-(2-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17f)

*Method A:* 20% yield; TLC $R_f$ = 0.48 (*n*-hexane/EtOAc, 7:3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 7.5 Hz, 1H), 7.40–7.25 (m, 7H), 7.20–7.00 (m, 3H), 6.93–6.76 (m, 3H), 6.75–6.67 (m, 2H), 5.13 (s, 2H), 4.73–4.63 (m, 1H), 4.29 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.18 (dd, $J$ = 9.6, 6.3 Hz, 1H), 3.74 (s, 2H), 3.41 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H).

#### 4.4.7. Benzyl [1-(2-chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17g)

*Method A:* 60% yield; TLC $R_f$ = 0.42 (*n*-hexane/EtOAc, 7:3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.54–7.40 (m, 2H), 7.40–7.03 (m, 9H), 6.97–6.82 (m, 3H), 6.75–6.67 (m, 2H), 5.12 (s, 2H), 4.72–4.64 (m, 1H), 4.29 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.20 (dd, $J$ = 9.9, 6.0 Hz, 1H), 3.73 (s, 2H), 3.40 (dd, $J$ = 12.0, 2.7 Hz, 1H), 3.27 (dd, $J$ = 12.0, 6.0 Hz, 1H), 2.92 (s, 3H), 2.30 (s, 3H).

#### 4.4.8. Benzyl [1-(2-fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17h)

*Method A:* 41% yield; TLC $R_f$ = 0.53 (*n*-hexane/EtOAc, 2:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.56–7.47 (m, 3H), 7.34–7.26 (m, 4H), 7.21–7.05 (m, 3H), 6.92–6.82 (m, 3H), 6.74–6.68 (m, 3H), 5.13 (s, 2H), 4.72–4.64 (m, 1H), 4.32–4.09 (m, 2H), 3.74 (s, 2H), 3.42–3.25 (m, 2H), 2.92 (s, 3H), 2.38 (s, 3H).

#### 4.4.9. Benzyl [2-methyl-1-(3-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17i)

*Method A:* 70% yield; TLC $R_f$ = 0.51 (*n*-hexane/EtOAc, 2:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.61 (d, $J$ = 2.1 Hz, 1H), 7.54 (dd, $J$ = 8.1, 2.1 Hz, 1H), 7.50 (d, $J$ = 7.8 Hz, 1H), 7.34–7.29 (m, 5H), 7.18–6.98 (m, 3H), 6.92–6.80 (m, 3H), 6.75–6.65 (m, 2H), 5.14 (s, 2H), 4.75–4.65 (m, 1H), 4.34–4.17 (m, 2H), 3.76 (s, 2H), 3.45–3.28 (m, 2H), 2.92 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H).

#### 4.4.10. Benzyl [1-(3-chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17j)

*Method A*: 75% yield; TLC $R_f$ = 0.42 (toluene/EtOAc, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J$ = 1.8 Hz, 1H), 7.60 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.50 (d, $J$ = 7.2 Hz, 1H), 7.34–7.29 (m, 5H), 7.20–6.98 (m, 4H),

6.92–6.82 (m, 2H), 6.73–6.68 (m, 2H), 5.14 (s, 2H), 4.76–4.72 (m, 1H), 4.41–4.24 (m, 2H), 3.76 (s, 2H), 3.46 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.36 (dd, $J$ = 11.4, 6.0 Hz, 1H), 2.93 (s, 3H), 2.40 (s, 3H).

#### 4.4.11. Benzyl [1-(3-fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17k)

*Method A:* 38% yield; TLC $R_f$ = 0.30 (*n*-hexane/EtOAc, 3:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.56–6.68 (m, 16H), 5.14 (s, 2H), 4.76–4.65 (m, 1H), 4.40–4.25 (m, 2H), 3.75 (s, 2H), 3.45–3.28 (m, 2H), 2.92 (s, 3H), 2.40 (s, 3H).

#### 4.4.12. Benzyl [1-(3-methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17l)

*Method A:* 64% yield; TLC $R_f$ = 0.38 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J$ = 8.1 Hz, 1H), 7.36 (d, $J$ = 2.4 Hz, 1H), 7.33–7.26 (m, 6H), 7.18–7.03 (m, 3H), 6.94–6.82 (m, 3H), 6.72–6.67 (m, 2H), 5.14 (s, 2H), 4.78–4.70 (m, 1H), 4.38–4.22 (m, 2H), 3.87 (s, 3H), 3.76 (s, 2H), 3.43 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.30 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.91 (s, 3H), 2.41 (s, 3H).

#### 4.4.13. Benzyl [1-(2,3-dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17m)

*Method A:* 68% yield; TLC $R_f$ = 0.57 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 7.5 Hz, 1H), 7.35–7.27 (m, 5H), 7.19–7.14 (m, 2H), 7.10–7.03 (m, 2H), 6.92–6.83 (m, 2H), 6.77–6.67 (m, 3H), 5.13 (s, 2H), 4.72–4.67 (m, 1H), 4.30–4.08 (m, 2H), 3.74 (s, 2H), 3.45–3.29 (m, 2H), 2.93 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H).

#### 4.4.14. Benzyl [1-(2,5-dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17n)

*Method A*: 47% yield; TLC $R_f$ = 0.60 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.46 (d, $J$ = 7.8 Hz, 1H), 7.34–7.22 (m, 5H), 7.20–7.12 (m, 2H), 7.06–7.00 (m, 2H), 6.92–6.81 (m, 2H), 6.74–6.66 (m, 3H), 5.12 (s, 2H), 4.73–4.64 (m, 1H), 4.29 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.19 (dd, $J$ = 9.9, 6.6 Hz, 1H), 3.73 (s, 2H), 3.42 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.31 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.92 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H), 2.17 (s, 3H).

#### 4.4.15. Benzyl [5-fluoro-2-methyl-1-(2-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17o)

*Method A*: 24% yield; TLC $R_f$ = 0.48 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38–7.24 (m, 6H), 7.12 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.03 (dd, $J$ = 9.0, 4.2 Hz, 1H), 6.93–6.67 (m, 7H), 5.13 (s, 2H), 4.72–4.62 (m, 1H), 4.29 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.17 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.68 (s, 2H), 3.41 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H).

#### 4.4.16. Benzyl [1-(2-chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]acetate (17p)

*Method A*: 40% yield; TLC $R_f$ = 0.40 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.42 (d, $J$ = 8.4 Hz, 1H), 7.40–7.10 (m, 7H), 7.04 (d, $J$ = 2.7 Hz, 1H), 6.98–6.80 (m, 4H), 6.76–6.68 (m, 2H), 5.13 (s, 2H), 4.73–4.63 (m, 1H), 4.29 (dd, $J$ = 9.6, 5.4 Hz, 1H), 4.20 (dd, $J$ = 9.6, 5.7 Hz, 1H), 3.67 (s, 2H), 3.40 (dd, $J$ = 11.1, 2.4 Hz, 1H), 3.27 (dd, $J$ = 11.1, 6.3 Hz, 1H), 2.92 (s, 3H), 2.24 (s, 3H).

#### 4.4.17. Benzyl [5-fluoro-1-(2-fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17q)

*Method A*: 82% yield; TLC $R_f$ = 0.55 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.53 (t, $J$ = 8.4 Hz, 1H), 7.38–7.08 (m, 7H), 6.93–6.76 (m, 4H), 6.76–6.66 (m, 3H), 5.13 (s, 2H), 4.73–4.63 (m, 1H), 4.29 (dd, $J$ = 9.6, 5.1 Hz, 1H), 4.20 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.68 (s, 2H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.27 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.92 (s, 3H), 2.33 (s, 3H).

#### 4.4.18. Benzyl [5-fluoro-2-methyl-1-(3-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetate (17r)

*Method A*: 84% yield; TLC $R_f$ = 0.55 (toluene/EtOAc, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.60–7.56 (m, 1H), 7.51 (dd, $J$ = 8.7, 2.7 Hz, 1H), 7.38–7.27 (m, 5H), 7.14 (dd, $J$ = 9.0, 2.7 Hz, 1H), 6.95 (dd, $J$ = 9.0, 4.5 Hz, 1H), 6.93–6.67 (m, 6H), 5.15 (s, 2H), 4.74–4.65 (m, 1H), 4.31 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.22 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.71 (s, 2H), 3.42 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.31 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.37 (s, 3H), 2.27 (s, 3H).

#### 4.4.19. Benzyl [5-fluoro-1-(3-methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetate (17s)

*Method A*: 58% yield; TLC $R_f$ = 0.55 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38–7.20 (m, 7H), 7.14 (dd, $J$ = 6.0, 2.7 Hz, 1H), 7.02–6.65 (m, 7H), 5.15 (s, 2H), 4.78–4.68 (m, 1H), 4.35 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.25 (dd, $J$ = 9.9, 6.6 Hz, 1H), 3.87 (s, 3H), 3.71 (s, 2H), 3.42 (dd, $J$ = 11.7, 3.0 Hz, 1H), 3.30 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.91 (s, 3H), 2.38 (s, 3H).

#### 4.4.20. Benzyl [1-(2,3-dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]acetate (17t)

*Method A*: 65% yield; TLC $R_f$ = 0.54 (*n*-hexane/EtOAc, 2:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38–7.23 (m, 5H), 7.17–7.03 (m, 3H), 6.92–6.66 (m, 6H), 5.13 (s, 2H), 4.74–4.65 (m, 1H), 4.27 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.18 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.67 (s, 2H), 3.43 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.32 (dd, $J$ = 11.4, 6.9 Hz, 1H), 2.93 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H).

#### 4.4.21. Benzyl [1-(2,5-dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]acetate (17u)

*Method A*: 73% yield; TLC $R_f$ = 0.52 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40–7.23 (m, 5H), 7.20–7.08 (m, 2H), 7.07–6.97 (m, 1H), 6.93–6.66 (m, 6H), 5.13 (s, 2H), 4.74–4.64 (m, 1H), 4.30 (dd, $J$ = 9.6, 4.5 Hz, 1H), 4.20 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.68 (s, 2H), 3.42 (dd, $J$ = 11.4, 3.0 Hz, 1H), 3.31 (dd, $J$ = 11.4, 6.0 Hz, 1H), 2.93 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H).

### 4.5. General procedure for the preparation of 3a–e, 4a–i, 5a–g

#### 4.5.1. [2-Methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (3a)

To a stirred solution of **17a** (462 mg, 0.82 mmol) in EtOAc (20 mL) was added 20% $Pd(OH)_2$/C (100 mg) at room temperature. The resulting suspension was vigorously stirred for 80 min at room temperature under hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **3a** (380 mg, quant); TLC $R_f$ = 0.42 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 8.7 Hz, 2H), 7.51 (d, $J$ = 8.1 Hz, 1H), 7.17 (dt, $J$ = 1.5, 8.1 Hz, 1H), 7.09–6.94 (m, 4H), 6.93–6.81 (m, 2H), 6.75–6.66 (m, 2H), 4.74–4.64 (m, 1H),

4.32 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.21 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.75 (s, 2H), 3.41 (dd, $J$ = 11.7, 2.4 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.6 Hz, 1H), 2.93 (s, 3H), 2.43 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 469 $(M-H)^-$; IR (KBr) 3046, 2928, 1735, 1709, 1682, 1604, 1577, 1505, 1474, 1457, 1420, 1396, 1351, 1316, 1246, 1224, 1175, 1065, 1041, 924, 874, 840, 743, 662, 624, 525, 465 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +10.88 ($c$ 0.75, DMSO).

#### 4.5.2. [2,5-Dimethyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (3b)

37% yield; TLC $R_f$ = 0.39 ($CHCl_3$/MeOH, 10:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 9.6 Hz, 2H), 7.28 (s, 1H), 6.99 (d, $J$ = 9.6 Hz, 2H), 6.90–6.80 (m, 4H), 6.73–6.70 (m, 2H), 4.67 (m, 1H), 4.30 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.21 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.71 (s, 2H), 3.40 (dd, $J$ = 11.7, 3.0 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.6 Hz, 1H), 2.92 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 483 $(M-H)^-$; IR (KBr) 2925, 1710, 1681, 1604, 1578, 1505, 1463, 1350, 1307, 1225, 1174, 1138, 1068, 1041, 926, 842, 805, 762, 744 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +9.70 ($c$ 0.75, DMSO).

#### 4.5.3. [5-Chloro-2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (3c)

50% yield; TLC $R_f$ = 0.40 ($CHCl_3$/MeOH, 10:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 9.0 Hz, 2H), 7.47 (d, $J$ = 1.8 Hz, 1H), 7.05–6.95 (m, 3H), 6.92–6.80 (m, 3H), 6.73–6.70 (m, 2H), 4.69 (m, 1H), 4.31 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.22 (dd, $J$ = 9.9, 6.0 Hz, 1H), 3.71 (s, 2H), 3.40 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.92 (s, 3H), 2.41 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 503 $(M-H)^-$; IR (KBr) 2928, 1686, 1604, 1505, 1458, 1347, 1308, 1224, 1175, 1137, 1061, 1042, 842, 745 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +10.19 ($c$ 0.75, DMSO).

#### 4.5.4. [5-Fluoro-2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (3d)

12% yield; TLC $R_f$ = 0.42 ($CHCl_3$/MeOH, 10:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$ = 9.0 Hz, 2H), 7.15 (m, 1H), 7.00 (d, $J$ = 9.0 Hz, 2H), 6.95–6.65 (m, 6H), 4.68 (m, 1H), 4.30 (dd, $J$ = 9.6, 4.8 Hz, 1H), 4.21 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.68 (s, 2H), 3.39 (dd, $J$ = 11.7, 2.7 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.6 Hz, 1H), 2.91 (s, 3H), 2.39 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 487 $(M-H)^-$; IR (KBr) 3069, 2930, 1711, 1684, 1604, 1472, 1459, 1373, 1355, 1314, 1248, 1224, 1173, 1136, 1065, 1042, 930, 844, 806, 762, 745 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +14.68 ($c$ 0.60, DMSO).

#### 4.5.6. [5-Methoxy-2-methyl-1-(4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (3e)

99% yield; TLC $R_f$ = 0.42 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 8.7 Hz, 2H), 7.04–6.94 (m, 3H), 6.94–6.80 (m, 3H), 6.76–6.62 (m, 3H), 4.74–4.64 (m, 1H), 4.31 (dd, $J$ = 9.6, 5.1 Hz, 1H), 4.21 (dd, $J$ = 9.6, 6.0 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 2H), 3.41 (dd, $J$ = 11.7, 2.4 Hz, 1H), 3.28 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.91 (s, 3H), 2.42 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 499 $(M-H)^-$; IR (KBr) 2929, 2831, 1735, 1709, 1679, 1604, 1578, 1505, 1477, 1458, 1357, 1314, 1224, 1173, 1143, 1067, 1037, 992, 926, 840, 808, 762, 744, 676, 608, 461 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +9.69 ($c$ 0.75, DMSO).

#### 4.5.7. [2-Methyl-1-(2-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (4a)

50% yield; TLC $R_f$ = 0.52 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 7.8 Hz, 1H), 7.40–7.28 (m, 2H), 7.23–7.13 (m, 1H), 7.11–6.95 (m, 2H), 6.94–6.76 (m, 3H), 6.76–6.65 (m, 2H), 4.72–4.62 (m, 1H), 4.29 (dd, $J$ = 9.9, 5.1 Hz, 1H), 4.19 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.72 (s, 2H), 3.40 (dd, $J$ = 11.4, 1.8 Hz, 1H), 3.27 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 483 $(M-H)^-$; IR (KBr) 3065, 2926, 2871, 2249, 1710, 1684, 1605, 1572, 1503, 1474, 1457, 1383, 1351, 1316, 1241, 1225, 1176, 1131, 1115, 1046, 1026, 909, 856, 822, 742, 647, 619, 571 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +9.03 ($c$ 0.75, DMSO).

#### 4.5.8. [1-(2-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4b)

75% yield; TLC $R_f$ = 0.53 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.52–7.42 (m, 2H), 7.33–7.04 (m, 4H), 6.98–6.82 (m, 3H), 6.76–6.68 (m, 2H), 4.72–4.64 (m, 1H), 4.29 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.20 (dd, $J$ = 9.9, 6.0 Hz, 1H), 3.72 (s, 2H), 3.40 (dd, $J$ = 12.0, 2.7 Hz, 1H), 3.27 (dd, $J$ = 12.0, 6.0 Hz, 1H), 2.92 (s, 3H), 2.32 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 503 $(M-H)^-$; IR (KBr) 3042, 2928, 2871, 2821, 1733, 1709, 1685, 1600, 1561, 1504, 1474, 1458, 1355, 1319, 1299, 1221, 1136, 1075, 1044, 983, 964, 931, 914, 854, 821, 743, 607, 571, 487 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +8.80 ($c$ 0.75, DMSO).

#### 4.5.9. [1-(2-Fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4c)

63% yield; TLC $R_f$ = 0.63 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.55 (t, $J$ = 8.4 Hz, 1H), 7.49 (d, $J$ = 7.5 Hz, 1H), 7.20 (dt, $J$ = 6.6, 1.5 Hz, 1H), 7.15–7.06 (m, 2H), 6.92–6.83 (m, 3H), 6.75–6.68 (m, 3H), 4.72–4.65 (m, 1H), 4.32–4.17 (m, 2H), 3.72 (s, 2H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.27 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.92 (s, 3H), 2.42 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 487 $(M-H)^-$; IR (KBr) 3068, 2929, 2871, 2822, 2616, 1709, 1685, 1619, 1578, 1504, 1474, 1458, 1397, 1355, 1320, 1297, 1225, 1168, 1131, 1119, 1066, 1040, 984, 918, 859, 745, 615, 528 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +8.41 ($c$ 0.75, DMSO).

#### 4.5.10. [2-Methyl-1-(3-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (4d)

32% yield; TLC $R_f$ = 0.52 ($CHCl_3$/MeOH/AcOH, 9:1:0.1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.61 (d, $J$ = 1.2 Hz, 1H), 7.56 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.50 (d, $J$ = 7.8 Hz, 1H), 7.16 (dt, $J$ = 6.9, 1.2 Hz, 1H), 7.04 (dt, $J$ = 8.4, 1.2 Hz, 1H), 6.99 (d, $J$ = 7.8 Hz, 1H), 6.92–6.82 (m, 3H), 6.73–6.68 (m, 2H), 4.74–4.66 (m, 1H), 4.34–4.19 (m, 2H), 3.74 (s, 2H), 3.42 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.31 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 483 $(M-H)^-$; IR (KBr) 3048, 2927, 2821, 1682, 1604, 1580, 1504, 1474, 1457, 1415, 1397, 1351, 1317, 1265, 1225, 1191, 1133, 1122, 1071, 1041, 962, 913, 822, 744, 607, 598, 573, 545, 527, 499, 488, 479, 464, 455 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +11.52 ($c$ 0.75, DMSO).

#### 4.5.11. [1-(3-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4e)

46% yield; TLC $R_f$ = 0.52 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J$ = 2.1 Hz, 1H), 7.62 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.51 (d, $J$ = 7.8 Hz, 1H), 7.19 (dt, $J$ = 6.9, 1.2 Hz, 1H), 7.09–6.96 (m, 3H), 6.92–6.82 (m, 2H), 6.73–6.67 (m, 2H), 4.78–4.71 (m, 1H), 4.41–4.24 (m, 2H), 3.74 (s, 2H), 3.45 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.36 (dd, $J$ = 11.4, 6.0 Hz, 1H), 2.93 (s, 3H), 2.42 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 503 $(M-H)^-$; IR (KBr) 3067, 2928, 2870, 2822, 1710, 1684, 1596, 1503, 1474, 1458, 1405, 1351, 1317, 1277, 1271, 1244, 1224, 1159, 1137, 1065, 1027, 944, 915, 822, 745, 610, 571, 464, 454 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +17.78 ($c$ 0.75, DMSO).

#### 4.5.12. [1-(3-Fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4f)

32% yield; TLC $R_f$ = 0.55 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.57–7.48 (m, 3H), 7.19 (dt, $J$ = 7.4, 1.2 Hz, 1H), 7.09–7.03 (m, 2H), 6.97 (d, $J$ = 8.1 Hz, 1H), 6.92–6.81 (m, 2H), 6.73–6.67 (m, 2H), 4.75–4.68 (m, 1H), 4.40–4.25 (m, 2H), 3.74 (s, 2H), 3.45–3.28 (m, 2H), 2.92 (s, 3H), 2.42 (s, 3H), 1.90 (br s, 1H) *m/z* 487 $(M-H)^-$; IR (KBr) 3069, 2931, 1689, 1604, 1578, 1506, 1459, 1318, 1173, 1117, 1056, 745 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +11.38 (*c* 0.75, DMSO).

#### 4.5.13. [1-(3-Methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4g)

56% yield; TLC $R_f$ = 0.65 ($CHCl_3$/MeOH/AcOH, 9:1:0.1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50 (d, $J$ = 7.5 Hz, 1H), 7.35 (d, $J$ = 1.8 Hz, 1H), 7.30 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.20–7.15 (m, 1H), 7.08–6.81 (m, 5H), 6.72–6.66 (m, 2H), 4.77–4.69 (m, 1H), 4.38–4.22 (m, 2H), 3.87 (s, 3H), 3.74 (s, 2H), 3.45–3.26 (m, 2H), 2.91 (s, 3H), 2.42 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 499 $(M-H)^-$; IR (KBr) 3067, 2932, 2871, 2827, 2617, 1710, 1682, 1598, 1506, 1458, 1417, 1350, 1317, 1273, 1244, 1215, 1183, 1137, 1072, 1028, 943, 871, 820, 787, 746, 611, 577, 462 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +13.37 (*c* 0.75, DMSO).

#### 4.5.14. [1-(2,3-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4h)

56% yield; TLC $R_f$ = 0.63 ($CHCl_3$/MeOH/AcOH, 9:1:0.1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 7.8 Hz, 1H), 7.21–7.16 (m, 2H), 7.06–7.04 (m, 2H), 6.91–6.83 (m, 2H), 6.77–6.67 (m, 3H), 4.73–4.66 (m, 1H), 4.30–4.15 (m, 2H), 3.71 (s, 2H), 3.45–3.28 (m, 2H), 2.93 (s, 3H), 2.31 (s, 3H), 2.24 (s, 6H); MS (APCI, Neg, 20 V) *m/z* 497 $(M-H)^-$; IR (KBr) 3044, 2927, 2819, 2626, 2564, 1685, 1607, 1592, 1580, 1504, 1476, 1458, 1378, 1352, 1317, 1301, 1268, 1243, 1227, 1188, 1132, 1112, 1091, 1043, 957, 913, 866, 800, 764, 741, 687, 608, 567, 524, 514, 489, 469, 459 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +11.53 (*c* 0.75, DMSO).

#### 4.5.15. [1-(2,5-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (4i)

12% yield; TLC $R_f$ = 0.35 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (t, $J$ = 7.5 Hz, 1H), 7.21–7.15 (m, 2H), 7.09–6.99 (m, 2H), 6.92–6.82 (m, 2H), 6.75–6.68 (m, 3H), 4.73–4.66 (m, 1H), 4.33–4.18 (m, 2H), 3.72 (s, 2H), 3.42 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.31 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.93 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 497 $(M-H)^-$; IR (KBr) 2927, 2871, 1769, 1710, 1684, 1656, 1637, 1610, 1570, 1543, 1505, 1473, 1458, 1376, 1350, 1319, 1262, 1224, 1176, 1132, 1104, 1040, 986, 915, 859, 805, 744, 684, 671, 657, 638, 628, 618, 612, 603, 596, 578, 563, 552, 486, 478, 468, 462 $cm^{-1}$; Optical rotation $[\alpha]_D^{24}$ +11.08 (*c* 0.88, DMSO).

#### 4.5.16. [5-Fluoro-2-methyl-1-(2-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (5a)

50% yield; TLC $R_f$ = 0.43 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.31 (d, $J$ = 8.7 Hz, 1H), 7.14 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.01 (dd, $J$ = 9.3, 4.5 Hz, 1H), 6.92–6.74 (m, 5H), 6.74–6.66 (m, 2H), 4.72–4.62 (m, 1H), 4.29 (dd, $J$ = 9.9, 4.8 Hz, 1H), 4.18 (dd, $J$ = 9.9, 6.3 Hz, 1H), 3.68 (s, 2H), 3.41 (dd, $J$ = 11.4, 2.1 Hz, 1H), 3.27 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 501 $(M-H)^-$; IR (KBr) 2927, 2611, 2360, 2249, 1865, 1686, 1604, 1573, 1504, 1471, 1459, 1384, 1372, 1355, 1317, 1279, 1241, 1224, 1198, 1174, 1118, 1064, 1049, 1024, 996, 911, 850, 807, 764, 737, 693, 673, 658, 620, 599, 589, 571, 523, 465, 454 $cm^{-1}$; Optical rotation $[\alpha]_D^{24}$ +7.71 (*c* 0.75, DMSO).

#### 4.5.17. [1-(2-Chloro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]acetic acid (5b)

75% yield; TLC $R_f$ = 0.48 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 8.7 Hz, 1H), 7.22 (dd, $J$ = 8.7, 4.5 Hz, 1H), 7.15 (dd, $J$ = 8.7, 2.1 Hz, 1H), 7.05 (d, $J$ = 2.1 Hz, 1H), 7.00–6.80 (m, 4H), 6.75–6.68 (m, 2H), 4.73–4.63 (m, 1H), 4.29 (dd, $J$ = 9.9, 5.4 Hz, 1H), 4.20 (dd, $J$ = 9.9, 6.0 Hz, 1H), 3.67 (s, 2H), 3.40 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.27 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.92 (s, 3H), 2.27 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 521 $(M-H)^-$; IR (KBr) 3068, 2930, 2871, 2822, 1908, 1710, 1688, 1601, 1561, 1504, 1471, 1460, 1359, 1322, 1300, 1278, 1223, 1139, 1072, 1046, 996, 935, 926, 850, 811, 745, 621, 593, 585, 572, 515, 485, 475 $cm^{-1}$; Optical rotation $[\alpha]_D^{24}$ +6.49 (*c* 0.75, DMSO).

#### 4.5.18. [5-Fluoro-1-(2-fluoro-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (5c)

43% yield; TLC $R_f$ = 0.40 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.53 (t, $J$ = 8.1 Hz, 1H), 7.17–7.12 (m, 2H), 6.92–6.68 (m, 7H), 4.75–4.64 (m, 1H), 4.31–4.17 (m, 2H), 3.64 (s, 2H), 3.39 (dd, $J$ = 11.4, 3.0 Hz, 1H), 3.26 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.92 (s, 3H), 2.34 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 505 $(M-H)^-$; IR (KBr) 3070, 2929, 2871, 2612, 1688, 1619, 1578, 1505, 1472, 1460, 1395, 1372, 1358, 1324, 1297, 1277, 1224, 1197, 1172, 1118, 1065, 1040, 997, 923, 850, 809, 745, 594 $cm^{-1}$; Optical rotation $[\alpha]_D^{24}$ +8.67 (*c* 0.75, DMSO).

#### 4.5.19. [5-Fluoro-2-methyl-1-(3-methyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-1*H*-indol-3-yl]acetic acid (5d)

76% yield; TLC $R_f$ = 0.48 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.61–7.51 (m, 2H), 7.15 (dd, $J$ = 8.7, 2.1 Hz, 1H), 6.98–6.67 (m, 7H), 4.74–4.66 (m, 1H), 4.32 (dd, $J$ = 9.6, 5.1 Hz, 1H), 4.22 (dd, $J$ = 9.6, 6.3 Hz, 1H), 3.69 (s, 2H), 3.42 (dd, $J$ = 11.4, 2.4 Hz, 1H), 3.31 (dd, $J$ = 11.4, 6.6 Hz, 1H), 2.92 (s, 3H), 2.39 (s, 3H), 2.27 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 501 $(M-H)^-$; IR (KBr) 3067, 2927, 2822, 1711, 1685, 1604, 1561, 1504, 1472, 1459, 1415, 1395, 1373, 1354, 1317, 1265, 1225, 1204, 1122, 1069, 1041, 993, 910, 808, 759, 744, 638, 600, 459 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +10.81 (*c* 0.75, DMSO).

#### 4.5.20. [5-Fluoro-1-(3-methoxy-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (5e)

43% yield; TLC $R_f$ = 0.58 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33 (d, $J$ = 1.8 Hz, 1H), 7.27 (dd, $J$ = 8.7, 1.8 Hz, 1H), 7.19–7.14 (m, 1H), 7.00–6.66 (m, 7H), 4.77–4.69 (m, 1H), 4.38–4.22 (m, 2H), 3.88 (s, 3H), 3.70 (s, 2H), 3.43 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.30 (dd, $J$ = 11.4, 6.3 Hz, 1H), 2.91 (s, 3H), 2.40 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 517 $(M-H)^-$; IR (KBr) 3069, 2933, 2871, 2622, 2360, 1710, 1684, 1598, 1506, 1472, 1459, 1417, 1395, 1373, 1355, 1316, 1272, 1244, 1218, 1177, 1129, 1070, 1028, 911, 850, 808, 753, 669, 648, 582, 501, 471, 461 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +9.73 (*c* 0.75, DMSO).

#### 4.5.21. [1-(2,3-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]acetic acid (5f)

41% yield; TLC $R_f$ = 0.54 ($CHCl_3$/MeOH, 9:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.18–7.02 (m, 3H), 6.92–6.67 (m, 6H), 4.73–4.66 (m, 1H),

4.30–4.16 (m, 2H), 3.66 (s, 2H), 3.43 (dd, $J$ = 11.4, 2.7 Hz, 1H), 3.32 (dd, $J$ = 11.4, 6.9 Hz, 1H), 2.93 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 515 $(M-H)^-$; IR (KBr) 3041, 2929, 2871, 2372, 1710, 1686, 1649, 1606, 1593, 1561, 1543, 1505, 1472, 1459, 1372, 1355, 1317, 1302, 1269, 1243, 1225, 1203, 1149, 1110, 1086, 1042, 994, 915, 852, 803, 766, 743, 617, 603, 593, 567, 548, 527, 505, 487, 459 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +8.63 ($c$ 0.75, DMSO).

#### 4.5.22. [1-(2,5-Dimethyl-4-{[(2*S*)-4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methoxy}benzoyl)-5-fluoro-2-methyl-1*H*-indol-3-yl]acetic acid (5g)

39% yield; TLC $R_f$ = 0.44 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.19–7.11 (m, 2H), 7.06–6.96 (m, 1H), 6.93–6.67 (m, 6H), 4.74–4.64 (m, 1H), 4.31 (dd, $J$ = 9.6, 3.9 Hz, 1H), 4.20 (dd, $J$ = 9.6, 6.6 Hz, 1H), 3.68 (s, 2H), 3.42 (dd, $J$ = 11.7, 3.0 Hz, 1H), 3.31 (dd, $J$ = 11.7, 6.3 Hz, 1H), 2.93 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 515 $(M-H)^-$; IR (KBr) 3041, 2927, 2870, 1711, 1685, 1609, 1578, 1505, 1472, 1459, 1407, 1396, 1372, 1354, 1321, 1279, 1261, 1242, 1224, 1200, 1153, 1137, 1120, 1102, 1063, 1040, 981, 921, 849, 803, 766, 743, 655, 593, 572, 459 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +7.95 ($c$ 0.75, DMSO).

### 4.6. Benzyl {1-[4-(acetyloxy)-2-methylbenzoyl]-2-methyl-1*H*-indol-3-yl}acetate (20)

To a stirred solution of **19a** (2.3 g, 8.3 mmol) in $CH_2Cl_2$ (15 mL) were added 20 M NaOH aq (2.1 mL, 41.5 mmol), TBACl (231 mg, 0.83 mmol) and then a solution of 4-acetoxy-2-methylbenzoyl chloride (2.3 g, 10.8 mmol) in $CH_2Cl_2$ (5 mL). After stirring for 1 h at room temperature, the reaction mixture was quenched with water and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **20** (3.5 g, 92%); TLC $R_f$ = 0.49 ($n$-hexane/EtOAc, 7:3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 7.5 Hz, 1H), 7.39 (d, $J$ = 8.4 Hz, 1H), 7.36–7.25 (m, 6H), 7.22–7.15 (m, 1H), 7.13–7.06 (m, 2H), 7.02 (dd, $J$ = 8.4, 2.4 Hz, 1H), 5.13 (s, 2H), 3.73 (s, 2H), 2.33 (s, 3H), 2.28 (s, 6H).

### 4.7. {1-[4-(Acetyloxy)-2-methylbenzoyl]-2-methyl-1*H*-indol-3-yl}acetic acid (21)

To a stirred solution of **20** (3.5 g, 8.0 mmol) in EtOAc (20 mL) was added 20% $Pd(OH)_2$/C (820 mg) at room temperature. The resulting suspension was vigorously stirred for 30 min at room temperature under hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to give **21**, which was used for the next reaction without further purification; TLC $R_f$ = 0.56 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 7.5 Hz, 1H), 7.40 (d, $J$ = 8.4 Hz, 1H), 7.24–7.17 (m, 1H), 7.15–7.00 (m, 4H), 3.72 (s, 2H), 2.33 (s, 3H), 2.31 (s, 6H).

### 4.8. Polymer supported {1-[4-(acetyloxy)-2-methylbenzoyl]-2-methyl-1*H*-indol-3-yl}acetate (22)

To an agitated solution of **21** (2.63 g, 7.5 mmol) and DIPEA (5.2 mL, 30 mmol) in $CH_2Cl_2$ (60 mL) was added a polymer supported 2-chloro triphenylmethyl chloride (1.22 mmol/g, 100–200 mesh, 1% DVB) (6.15 g, 7.5 mmol) at room temperature. After agitating for 2.5 h at room temperature, the reaction mixture was filtered to collect insoluble substance, which was washed with $CH_2Cl_2$ (×5).

To a suspension of the insoluble substance in $CH_2Cl_2$ (70 mL) were added a solution of AcOH (4.3 mL, 75 mmol) and DIPEA (26 mL, 150 mmol). After agitating for 1 h at room temperature, the reaction mixture was filtered, washed with $CH_2Cl_2$ (×5) to afford **22** (8.55 g, quant); IR (KBr) 3568, 3058, 3024, 2920, 2849, 1950, 1807, 1767, 1742, 1686, 1601, 1568, 1505, 1492, 1446, 1415, 1347, 1314, 1265, 1197, 1154, 1125, 1056, 1039, 1013, 902, 827, 755, 698, 632, 551 $cm^{-1}$.

### 4.9. Polymer supported [1-(4-hydroxy-2-methylbenzoyl)-2-methyl-1*H*-indol-3-yl]acetate (23)

To an agitated mixture of **22** (8.55 g, 7.5 mmol) in $CH_2Cl_2$ (95 mL) was added piperidine (5 mL, mmol) at room temperature. After agitating for 30 min at room temperature, the reaction mixture was filtered, washed with $CH_2Cl_2$ (×5), dried in vacuo to afford **23** (8.23 g, quant); IR (KBr) 3564, 3058, 3025, 2922, 2850, 1951, 1808, 1739, 1682, 1601, 1492, 1446, 1348, 1310, 1219, 1153, 1055, 1013, 858, 825, 754, 697, 631, 553 $cm^{-1}$.

### 4.10. General procedure for the preparation of *N*-(4-(alkyloxy)-2-methylbenzoyl)-2-methylindol-3-acetic acids (6–11)

#### 4.10.1. (1-{4-[(2*R*)-2,3-Dihydro-1,4-benzodioxin-2-ylmethoxy]-2-methylbenzoyl}-2-methyl-1*H*-indol-3-yl)acetic acid (6)

To an agitated mixture of 23 (300 mg, 0.3 mmol) in $CH_2Cl_2$ (4 mL) were added a solution of 24 (299 mg, 1.8 mmol) in $CH_2Cl_2$ (1 mL), $Ph_3P$ (472 mg, 1.8 mmol) and DEAD (40% in toluene, 0.82 mL, 1.8 mmol) at room temperature. After agitating for 2 h at room temperature, the reaction mixture was filtered to collect insoluble substance, which was washed with $CH_2Cl_2$ (×5), and dried in vacuo.

To a stirred suspension of the insoluble substance described above in $CH_2Cl_2$ (2.1 mL) and $CF_3CH_2OH$ (0.6 mL) was added acetic acid (0.3 mL) at room temperature. After agitating for 2 h at room temperature, insoluble substance was removed by filtration. The filtrate was concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel to yield 6 (50 mg, 35%); TLC $R_f$ = 0.44 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 7.8 Hz, 1H), 7.33 (d, $J$ = 8.4 Hz, 1H), 7.18 (t, $J$ = 7.8 Hz, 1H), 7.10–6.84 (m, 7H), 6.79 (dd, $J$ = 8.4, 2.4 Hz, 1H), 4.64–4.56 (m, 1H), 4.42 (dd, $J$ = 11.7, 2.4 Hz, 1H), 4.35–4.18 (m, 3H), 3.71 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 470 $(M-H)^-$; IR (KBr) 3049, 2927, 2612, 2360, 2251, 1892, 1709, 1684, 1638, 1604, 1572, 1542, 1494, 1475, 1457, 1440, 1351, 1316, 1266, 1243, 1176, 1113, 1047, 909, 849, 747, 669, 647, 637, 542, 463 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +19.85 ($c$ 0.75, DMSO).

#### 4.10.2. (1-{4-[(3*R*)-2,3-Dihydro-1-benzofuran-3-ylmethoxy]-2-methylbenzoyl}-2-methyl-1*H*-indol-3-yl)acetic acid (7a)

50% yield; TLC $R_f$ = 0.49 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.51–7.45 (m, 1H), 7.35–7.28 (m, 2H), 7.25–6.80 (m, 7H), 6.79–6.73 (m, 1H), 4.73 (t, $J$ = 8.4 Hz, 1H), 4.55 (dd, $J$ = 9.3, 5.1 Hz, 1H), 4.21 (dd, $J$ = 9.3, 5.7 Hz, 1H), 4.08 (t, $J$ = 8.4 Hz, 1H), 4.02–3.90 (m, 1H), 3.72 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H); MS (APCI, Neg, 20 V) $m/z$ 454 $(M-H)^-$; IR (KBr) 3050, 2927, 2616, 2564, 2362, 1711, 1685, 1603, 1571, 1498, 1483, 1458, 1351, 1316, 1240, 1174, 1128, 1111, 1026, 968, 853, 815, 749, 636, 605, 453 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +19.15 ($c$ 0.75, DMSO).

#### 4.10.3. [1-(4-{[(3*R*)-5-Fluoro-2,3-dihydro-1-benzofuran-3-yl]methoxy}-2-methylbenzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (7b)

68% yield; TLC $R_f$ = 0.53 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, $J$ = 7.8 Hz, 1H), 7.32 (d, $J$ = 8.4 Hz, 1H), 7.22–6.97 (m, 4H), 6.84 (d, $J$ = 2.4 Hz, 1H), 6.76 (dd, $J$ = 8.4, 2.4 Hz, 1H), 6.67–6.57 (m, 2H), 4.80–4.64 (m, 2H), 4.44–4.36 (m, 1H),

4.18–4.03 (m, 2H), 3.72 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 472 $(M-H)^-$; IR (KBr) 3052, 2965, 2928, 1712, 1684, 1625, 1603, 1498, 1475, 1457, 1351, 1316, 1241, 1174, 1129, 1111, 1015, 956, 857, 816, 779, 764, 756, 746, 618, 478 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +27.43 (*c* 0.66, DMSO).

#### 4.10.4. (1-{4-[(2*S*)-2,3-Dihydro-1-benzofuran-2-ylmethoxy]-2-methylbenzoyl}-2-methyl-1*H*-indol-3-yl)acetic acid (8)

34% yield; TLC $R_f$ = 0.56 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.24–7.10 (m, 3H), 7.10–6.94 (m, 2H), 6.92–6.75 (m, 4H), 5.24–5.12 (m, 1H), 4.27 (dd, *J* = 10.5, 6.3 Hz, 1H), 4.17 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.71 (s, 2H), 3.41 (dd, *J* = 15.6, 9.6 Hz, 1H), 3.16 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.34 (s, 3H), 2.31 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 454 $(M-H)^-$; IR (KBr) 3050, 2927, 2562, 1734, 1710, 1685, 1603, 1571, 1499, 1481, 1458, 1351, 1316, 1228, 1173, 1129, 1111, 1047, 1026, 982, 905, 868, 747, 711, 607, 469, 458 $cm^{-1}$; Optical rotation $[\alpha]_D^{23}$ +37.42 (*c* 0.59, $CHCl_3$).

#### 4.10.5. {1-[4-(1,3-Benzodioxol-2-ylmethoxy)-2-methylbenzoyl]-2-methyl-1*H*-indol-3-yl}acetic acid (9)

47% yield; TLC $R_f$ = 0.50 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.24–6.94 (m, 3H), 6.92–6.84 (m, 5H), 6.79 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.48 (t, *J* = 3.9 Hz, 2H), 4.33 (t, *J* = 3.9 Hz, 1H), 3.72 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 456 $(M-H)^-$; IR (KBr) 1711, 1684, 1604, 1484, 1457, 1352, 1316, 1230, 1176, 1108, 742 $cm^{-1}$.

#### 4.10.6. (2-Methyl-1-{2-methyl-4-[(1-methyl-2,3-dihydro-1*H*-indol-2-yl)methoxy]benzoyl}-1*H*-indol-3-yl)acetic acid (10a)

32% yield; TLC $R_f$ = 0.50 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.54–6.48 (m, 11H), 4.26 (dd, *J* = 9.6. 5.7 Hz, 1H), 4.21–4.04 (m, 2H), 3.90–3.80 (m, 1H), 3.72 (s, 2H), 3.27 (dd, *J* = 15.3, 8.4 Hz, 1H), 2.91 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H); MS (APCI, Neg, 20 V) *m/z* 467 $(M-H)^-$; IR (KBr) 3050, 2926, 2857, 1710, 1684, 1604, 1569, 1497, 1487, 1475, 1457, 1351, 1316, 1242, 1174, 1128, 1113, 1042, 984, 941, 854, 815, 746, 715, 611, 537, 526, 492, 461 $cm^{-1}$.

#### 4.10.7. (1-{4-[(1-Ethyl-2,3-dihydro-1H-indol-2-yl)methoxy]-2-methylbenzoyl}-2-methyl-1*H*-indol-3-yl)acetic acid (10b)

45% yield; TLC $R_f$ = 0.55 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.22–6.97 (m, 5H), 6.86 (d, *J* = 2.1 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.66 (t, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 4.30–4.04 (m, 3H), 3.72 (s, 2H), 3.47–3.22 (m, 3H), 2.89 (dd, *J* = 16.2, 7.2 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 1.17 (t, *J* = 7.5 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 481 $(M-H)^-$; IR (KBr) 3048, 2966, 2927, 2871, 2558, 2353, 1732, 1683, 1604, 1540, 1486, 1457, 1416, 1395, 1374, 1351, 1316, 1241, 1174, 1128, 1109, 1024, 940, 856, 808, 744, 712, 682, 612, 580 $cm^{-1}$.

#### 4.10.8. [1-(4-{[(2*R*)-1-Ethyl-2,3-dihydro-1*H*-indol-2-yl]methoxy}-2-methylbenzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (11)

36% yield; TLC $R_f$ = 0.55 ($CHCl_3$/MeOH, 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.22–6.96 (m, 5H), 6.90–6.74 (m, 2H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 8.1 Hz, 1H), 4.26–4.04 (m, 3H), 3.72 (s, 2H), 3.57–3.16 (m, 3H), 2.89 (dd, *J* = 15.3, 7.2 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 1.17 (t, *J* = 6.9 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 481 $(M-H)^-$; IR (KBr) 3049, 2970, 2928, 2869, 2563, 2345, 2233, 1892, 1709, 1685, 1604, 1570, 1486, 1458, 1351, 1316, 1242, 1175, 1129, 1111, 1024, 945, 863, 820, 764, 746, 725, 711, 696, 666, 625, 612, 599, 558, 546, 537, 524, 514, 502, 489, 477, 470, 464 $cm^{-1}$; Optical rotation $[\alpha]_D^{24}$ -6.49 (*c* 0.75, DMSO).

### 4.11. General procedure for the preparation of 25a–b

#### 4.11.1. (2*S*)-2-[(2-Bromophenoxy)methyl]oxirane (31a)

To a stirred solution of 2-bromophenol **30a** (3.5 g, 20 mmol) in DMF (20 mL) were added $Cs_2CO_3$ (9.9 g, 30 mmol) and (*S*)-(+)-glycidyl 3-nitrobenzenesulfonate (3.9 g, 20 mmol) at room temperature under argon atmosphere, and stirring was continued for 1 h. The reaction mixture was quenched with water and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and concentrated in vacuo to give **31a** (3.95 g, 86%), which was used for the next reaction without further purification; TLC $R_f$ = 0.50 (*n*-hexane/EtOAc, 5:1).

#### 4.11.2. (3*R*)-2,3-Dihydro-1-benzofuran-3-ylmethanol (25a)

To a stirred solution of the above-described crude product **31a** (3.92 g, 17 mmol) in THF (20 mL) was added dropwise a 1.6 M solution of *n*-butyl lithium in hexane (11.3 mL, 17.9 mmol) at −78 °C. After stirring for 1 h at −78 °C and 1 h while gradually warmed up to room temperature, the reaction mixture was quenched with 1 M HCl aq and extracted with EtOAc (×2). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel to yield **25a** (3.24 g, quant); TLC $R_f$ = 0.70 (*n*-hexane/EtOAc, 1:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.24–7.12 (m, 2H), 6.90–6.78 (m, 2H), 4.64 (t, *J* = 9.0 Hz, 1H), 4.48 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.86–3.77 (m, 2H), 3.70–3.58 (m, 1H).

According to the same procedure as described above for the conversion of **30a** to **25a**, **30b** was converted to **25b**.

#### 4.11.3. (2*S*)-2-[(2-Bromo-4-fluorophenoxy)methyl]oxirane (31b)

93% yield; TLC $R_f$ = 0.57 (*n*-hexane/EtOAc, 2:1).

#### 4.11.4. [(3*R*)-5-Fluoro-2,3-dihydro-1-benzofuran-3-yl]methanol (25b)

34% yield; TLC $R_f$ = 0.35 (*n*-hexane/EtOAc, 2:1); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.10 (dd, *J* = 8.1, 6.0 Hz, 1H), 6.63–6.53 (m, 2H), 4.67 (t, *J* = 9.0 Hz, 1H), 4.59 (dd, *J* = 9.0, 5.1 Hz, 1H), 4.00–3.74 (m, 3H).

### 4.12. General procedure for the preparation of 28b, 29

#### 4.12.1. Ethyl 1-ethylindoline-2-carboxylate (33a)

To a stirred solution of **32a** (150 mg, 0.9 mmol) in DMF (3 mL) were added $Cs_2CO_3$ (1.2 g, 3.7 mmol) and ethyl iodide (0.28 mL, 3.5 mmol) at room temperature. After stirring for 3 h at 40 °C, The reaction mixture was diluted with water and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and concentrated in vacuo to give **33a**, which was used for the next reaction without further purification; TLC $R_f$ = 0.78 (*n*-hexane/EtOAc, 7:3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.11–7.00 (m, 2H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 4.30–4.18 (m, 3H), 3.41–3.18 (m, 3H), 3.12 (dd, *J* = 15.9, 8.7 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H).

#### 4.12.2. (1-Ethyl-2,3-dihydro-1*H*-indol-2-yl)methanol (28b)

To a stirred suspension of lithium aluminium hydride (42 mg, 1.1 mmol) in THF (3 mL) was added a solution of the above-described crude product **33a** (0.90 mmol) in THF (3 mL) at room temperature. After stirring for 30 min at room temperature, the reaction mixture was diluted with ether and quenched with brine

under cooling. The resulting mixture was stirred for additional 10 min at room temperature and dried over $MgSO_4$. Insoluble substance was removed by filtration and the filtrate was evaporated to give a crude product, which was purified by column chromatography on silica gel to yield **28b** (90 mg, 56% in two steps); TLC $R_f$ = 0.38 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.11–7.04 (m, 2H), 6.68 (td, *J* = 7.8, 0.9 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 3.92–3.84 (m, 1H), 3.83–3.73 (m, 1H), 3.68–3.58 (m, 1H), 3.38–3.12 (m, 2H), 3.06 (d, *J* = 9.9 Hz, 2H), 1.86 (dd, *J* = 9.9, 2.1 Hz, 1H), 1.12 (t, *J* = 7.2 Hz, 3H).

According to the same procedure as described above for the conversion of **33a** to **28b**, **32b** was converted to **29**.

#### 4.12.3. Ethyl (2R)-1-ethylindoline-2-carboxylate (33b)

TLC $R_f$ = 0.78 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.11–7.00 (m, 2H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 4.30–4.18 (m, 3H), 3.41–3.18 (m, 3H), 3.12 (dd, *J* = 15.9, 8.7 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H).

#### 4.12.4. [(2R)-1-ethyl-2,3-dihydro-1*H*-indol-2-yl]methanol (29)

60% yield in two steps; TLC $R_f$ = 0.38 (*n*-hexane/EtOAc, 7:3); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.11–7.04 (m, 2H), 6.68 (td, *J* = 7.8, 0.9 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 3.92–3.84 (m, 1H), 3.83–3.73 (m, 1H), 3.68–3.58 (m, 1H), 3.38–3.12 (m, 2H), 3.06 (d, *J* = 9.9 Hz, 2H), 1.86 (dd, *J* = 9.9, 2.1 Hz, 1H), 1.12 (t, *J* = 7.2 Hz, 3H).

## 5. Biological assay method

### 5.1. Prostanoid mEP1–4, mDP, hTP, mFP and hIP receptor binding assay

Competitive binding studies were conducted using radiolabeled ligands and membrane fractions prepared from Chinese hamster ovary (CHO) cells stably expressing the respective prostanoid receptors, mEP1, mEP2, mEP3α, mEP4, mDP, hTP mFP, and hIP.

Membranes from CHO cells expressing prostanoid receptors were incubated with radioligands (2.5 nM of [$^3$H]$PGE_2$ for mEP1–4; 2.5 nM of [$^3$H]$PGD_2$ for mDP; 5.0 nM [$^3$H]-SQ29548 for hTP; 2.5 nM [$^3$H]PGF2α for mFP; 5.0 nM of [$^3$H]Iloprost for hIP) and the test compounds at various concentrations in assay buffer (10 mM $KH_2PO_4$–KOH buffer containing 1 mM EDTA, 10 mM $MgCl_2$, and 100 mM NaCl, pH 6.0 for mEP1–4 and mFP; 25 mM HEPES–NaOH buffer containing 1 mM EDTA, 5 mM $MgCl_2$ and 10 mM $MnCl_2$, pH 7.4 for mDP; 10 mM Tris–HCl buffer containing 100 mM NaCl, pH 7.5, for hTP; 50 mM Tris–HCl buffer containing 1 mM EDTA and 10 mM $MgCl_2$, pH 7.5, for hIP). Incubation was carried out at room temperature for 60 min except for mEP1, and mDP (20 min), and hTP and hIP (30 min). The incubation was terminated by filtration through Whatman GF/B filters. The filters were washed with ice-cold buffer (10 mM $KH_2PO_4$–KOH buffer containing 100 mM NaCl, pH 6.0 for mEP1–4 and mFP; 10 mM Tris–HCl buffer containing 100 mM NaCl and 0.01 w/v% BSA, pH 7.4 for mDP; 10 mM Tris–HCl buffer containing 100 mM NaCl, pH 7.5, for hTP and hIP), dried for 60 min at 60 °C 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 $PGE_2$ (for mEP1–4), unlabeled $PGD_2$ (for mDP), unlabeled SQ29548 (for hTP), unlabeled PGF2α (for mFP) or unlabeled Iloprost (for IP) with assay buffer. The concentrations of the test substance required to inhibit the amounts of the specific binding in the vehicle group by 50% ($IC_{50}$ value) were estimated from the regression curve. The $K_i$ value (M) was calculated according to the following equation.

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

[L] : Concentration of radioligand

$K_d$ : Dissociation constant of radiolabeled ligand towards the prostanoid receptors

### 5.2. Measurement of the mDP receptor antagonist activity

To confirm that test compounds antagonize the mDP receptor and to estimate potencies of antagonism for the mDP receptor, a functional assay was performed by measuring PGD2-stimulated changes in intracellular second messenger cAMP as an indicator of receptor function.

For the assessment of the antagonist activity of test compounds, a suspension of CHO cells expressing mDP receptor was seeded at a cell density of $1 \times 10^5$ cells per well and cultivated for 2 days. The cells in each well were rinsed with minimum essential medium (MEM), and MEM containing 2 μM of Diclofenac was added to each well. The cells were incubated for approximately 10 min at 37 °C and the culture medium was removed. The assay medium (MEM containing 0.1% BSA, 1 mM IBMX and 2 μM Diclofenac) was added to each well and the cells were incubated for approximately 10 min at 37 °C. The assay medium, assay medium containing 10 nM of $PGD_2$, or assay medium containing various concentrations of test compounds and 10 nM of $PGD_2$ was added to each well and the cells were further incubated for 10 min at 37 °C. The reaction was terminated by the addition of ice-cold trichloroacetic acid (TCA; 10 w/v%).

After centrifugation of the reaction mixture, TCA was extracted by adding a mixture of tri-*n*-octylamine and chloroform (5:18 v/v) to the resultant supernatant, mixing and re-centrifugation. The cAMP level in the resultant aqueous layer (upper layer) was determined by enzymeimmunoassay using a cAMP assay kit (GE Healthcare UK Ltd). The relative responsiveness (%) of cAMP production was calculated relative to the maximum increase in cAMP that occurred in the absence of test compound (100%) to estimate of the $IC_{50}$ values.

### 5.3. Inhibitory effects of 4a, 4b, 5b and 11 on ovalbumin-induced vascular permeability in guinea pig conjunctiva

Male Hartley guinea pigs were sensitized by intraperitoneal injection of a mixture of ovalbumin (OVA) (1 mg) and inactivated *Bordetella pertussis* ($5 \times 10^9$). Two weeks later, animals were challenged by topical application of OVA (1%, 20 μL/eye) to the eye, and then Evans blue dye (20 mg/kg, iv) was immediately injected as a marker of plasma exudation. All antagonists were orally administered 1 h before the antigen challenge. After 30 min, the guinea pigs were exsanguinated, and the eye tissue including conjunctiva were extracted. Isolated conjunctiva was incubated in DMF (1 mL) at 37 °C to extract the extravasated dye, and the incubation mixture was centrifuged. The absorption of the supernatant at 620 nm was determined, and the amount of Evans blue dye leaked into the tissues was quantified by interpolation on the standard curve.

## References and notes


1. (a) Coleman, R. A. Prostanoids Receptors. In *The IUPHAR Compendium of Receptor Characterization and Classification*; Girdlestne, D., Ed.; Burlington Press: Cambridge, 1998; pp 229–244; (b) Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev.* **1994**, *46*, 205–229.
2. (a) Boie, Y.; Sawyer, N.; Slipetz, D. M.; Metters, K. M.; Abramovitz, M. *J. Biol. Chem.* **1995**, *270*, 18910; (b) Hirata, M.; Kakizuka, A.; Kimura, M.; Aizawa, Y.; Ushikubi, F.; Narumiya, S. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11192.
3. (a) Lewis, R. A.; Soter, N. A.; Diamond, P. T.; Austen, K. F.; Oates, J. A.; Roverts, L. J., II *J. Immunol.* **1982**, *129*, 1627; (b) Matsuoka, T.; Hirata, M.; Tanaka, H.; Takahashi, Y.; Murata, T.; Kabashima, K.; Sugimoto, Y.; Kobayashi, T.; Ushikubi, F.; Aze, Y.; Yoshida, N.; Honda, Y.; Nagai, H.; Narumiya, S. *Science* **2000**, *287*, 2013.

4. (a) Hayaishi, O. *FASEB J.* **1991**, *5*, 2575; (b) Oida, H.; Hirata, M.; Sugimoto, Y.; Ushikubi, F.; Ohishi, H.; Mizuno, N.; Ichikawa, A.; Narumiya, S. *FEBS Lett.* **1997**, *417*, 53; (c) Matsumura, H.; Nakajima, T.; Osaka, T.; Satoh, S.; Kawase, K.; Kubo, E.; Kasahara, K.; Hayaishi, O. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11998; (d) Mizoguchi, A.; Eguchi, N.; Kimura, K.; Kiyohara, Y.; Qu, W.-M.; Huang, Z.-L.; Mochizuki, T.; Lazarus, M.; Kobayashi, T.; Kaneko, T.; Narumiya, S.; Urade, Y.; Hayaishi, O. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 11674.
5. Ueno, R.; Narumiya, S.; Ogorochi, T.; Nakayama, T.; Ishikawa, Y.; Hayaishi, O. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 6093.
6. (a) Giles, H.; Leff, P.; Bolofo, M. L.; Kelly, M. G.; Robertson, A. D. *Br. J. Pharmacol.* **1989**, *96*, 291; (b) Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Mitsumori, S.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **1997**, *40*, 3504; (c) Mitsumori, S.; Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **2003**, *46*, 2436; (d) Mitsumori, S.; Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **2003**, *46*, 2446; (e) Liu, J.; Fu, Z.; Wang, Y.; Schmitt, M.; Huang, A.; Marshall, D.; Tonn, G.; Seitz, L.; Sullivan, T.; Tang, H. L.; Collins, T.; Medina, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6419; (f) Sturino, C. F.; Lachance, N.; Boyd, M.; Berthelette, C.; Labelle, M.; Li, L.; Roy, B.; Scheigetz, J.; Tsou, N.; Brideau, C.; Cauchon, E.; Carriere, M. C.; Denis, D.; Greig, G.; Kargman, S.; Lamontagne, S.; Mathieu, M. C.; Sawyer, N.; Slipetz, D.; O'Neill, G.; Wang, Z.; Zamboni, R.; Metters, K. M.; Young, R. N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3043; (g) Beaulieu, C.; Guay, D.; Wang, Z.; Leblanc, Y.; Roy, P.; Dufresne, C.; Zamboni, R.; Berthelette, C.; Day, S.; Tsou, N.; Denis, D.; Greig, G.; Mathieu, M. C.; O'Neill, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2696; (h) Leblanc, Y.; Roy, P.; Dufresne, C.; Lachance, N.; Wang, Z.; O'Neill, G.; Greig, G.; Denis, D.; Mathieu, M. C.; Slipetz, D.; Sawyer, N.; Tsou, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2125; (i) Li, L.; Beaulieu, C.; Carriere, M. C.; Denis, D.; Greig, G.; Guay, D.; O'Neill, G.; Zamboni, R.; Wang, Z. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7462; (j) Sturino, C. F.; O'Neill, G.; Lachance, N.; Boyd, M.; Berthelette, C.; Labelle, M.; Li, L.; Roy, B.; Scheigetz, J.; Tsou, N.; Aubin, Y.; Bateman, K. P.; Chauret, N.; Day, S. H.; Lévesque, J. F.; Seto, C.; Silva, J. H.; Trimble, L. A.; Carriere, M. C.; Denis, D.; Greig, G.; Kargman, S.; Lamontagne, S.; Mathieu, M. C.; Sawyer, N.; Slipetz, D.; Abraham, W. M.; Jones, T.; McAuliffe, M.; Piechuta, H.; Nicoll-Griffith, D. A.; Wang, Z.; Zamboni, R.; Young, R. N.; Metters, K. M. *J. Med. Chem.* **2007**, *50*, 794.
7. (a) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Egashira, H.; Nakai, Y.; Okada, Y.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4557; (b) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem. Bioorg. Med. Chem. Lett.* **2004**, *14*, 4891; (c) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 4685; (d) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 5361.
8. (a) Middlemiss, D.; Ashton, M. R.; Boyd, E. A.; et al. WO2005040112, 2005.; (b) Arimura, A.; Kishino, J.; Tanimoto, N. WO2003097042, 2003.; (c) Tanimoto, N.; Hiramatsu, Y.; Mitsumori, S.; Inagaki, M. WO2003097598, 2003.; (d) Middlemiss, D.; Ashton, M. R.; Boyd, E. A.; et al. WO2005040114, 2005.; (e) Middlemiss, D.; Ashton, M. R.; Boyd, E.A.; Brookfield, F.A. WO2005044260, 2005.; (f) Middlemiss, D.; Ashton, M. R.; Boyd, E. A.; Brookfield, F. A. GB2407318, 2005.; (g) Armer, R. E.; Boyd, E. A.; Hay, P. A. WO2006095183, 2006.; (h) Armer, R. E.; Wynne, G. M. WO2008012511, 2008.; (i) Armer, R. E.; Pettipher, E. R.; Whittaker, M.; et al. WO2009090414, 2009.; (j) Armer, R. E.; Wynne, G. M. WO2009093026, 2009.; (k) Armer, R. E.; Maillol, C. E. A.; Dorgan, C. R.; et al. WO2009093029, 2009.; (l) Bonnert, R.; Brough, S.; Cook, T.; et al. WO2003101961, 2003.; (m) Bonnert, R.; Dickinson, M.; Rasul, R.; et al. WO2004007451, 2004.; (n) Bonnert, R. V.; Luker, T. J.; Cumming, J. WO2007138282, 2007.; (o) Bennani, Y. L.; Tumey, L. N.; Gleason, E. A.; Robarge, M. J. WO2006034419, 2006.; (p) Hynd, G.; Montana, J. G.; Finch, H.; et al. WO2009077728, 2009.
9. (a) Pettipher, R. *Br. J. Pharmacol.* **2008**, *153*, S191; (b) Pettipher, R.; Hansel, T. T.; Armer, R. *Nat. Rev. Drug Disc.* **2007**, *6*, 313; (c) Kostenis, E.; Ulven, T. *Trends Mol. Med.* **2006**, *12*, 148; (d) Herlong, J. L.; Scott, T. R. *Immunol. Lett.* **2006**, *102*, 121; (e) Moore, M. L.; Peebles, R. S., Jr. *J. Allergy Clin. Immunol.* **2006**, *117*, 1036; (f) Xue, L.; Gyles, S. L.; Wettey, F. R.; Gazi, L.; Townsend, E.; Hunter, M. G.; Pettipher, R. *J. Immunol.* **2005**, *175*, 6531.
10. (a) Doyle, W. J.; Boehm, S.; Skoner, D. P. *J. Allergy Clin. Immunol.* **1990**, *86*, 924; (b) Johnston, S. L.; Smith, S.; Harrison, J.; Ritter, W.; Hawarth, P. H. *J. Allergy Clin. Immunol.* **1993**, *91*, 903; (c) Alving, K.; Matran, R.; Lundberg, J. M. *Acta Physiol. Scand.* **1991**, *143*, 93.
11. (a) Woodward, D. F.; Hawley, S. B.; Williams, L. S.; Ralston, T. R.; Protzman, C. E.; Spada, C. S.; Nieves, A. L. *Invest. Ophthalmol. Vis. Sci.* **1990**, *31*, 138; (b) Woodward, D. F.; Nieves, A. L.; Friedlaender, J. *Pharmacol. Exp. Ther.* **1996**, *279*, 137.
12. (a) Soter, N. A.; Lewis, R. A.; Corey, E. J.; Austen, K. F. *J. Invest. Dermatol.* **1983**, *80*, 115; (b) Flower, R. J.; Harvey, E. A.; Kingston, W. P. *Br. J. Pharmacol.* **1976**, *56*, 229.
13. Mitsunobu, O. *Synthesis* **1981**, 1.
14. (a) Delgado, A.; Leclerc, G.; Lobato, C.; Mauleon, D. *Tetrahedron Lett.* **1988**, *29*, 3671; Ramadas, S.; Krupadanam, G. L.; David *Tetrahedron: Asymmetry* **2000**, *11*, 3375.
15. Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenqing, Y.; Schafer, W. *Tetrahedron Lett.* **1989**, *30*, 3943.