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Preliminary communication

Development of a prostaglandin D_2 receptor antagonist: discovery of a new chemical lead

Kazuhiko Torisu [a,*], Kaoru Kobayashi [a], Maki Iwahashi [a], Hiromu Egashira [a], Yoshihiko Nakai [a], Yutaka Okada [a], Fumio Nanbu [a], Shuichi Ohuchida [b], Hisao Nakai [a], Masaaki Toda [a]

[a] *Minase Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618-8585, Japan*
[b] *Fukui Research Institute, Ono Pharmaceutical Co., Ltd., Technoport, Yamagishi, Mikuni, Sakai, Fukui 913-8538, Japan*

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Abstract

A series of *N*-(*p*-alkoxy)benzoyl-5-methoxy-2-methylindole-3-acetic acids and *N*-(*p*-butoxy)benzoyl-2-methylindole-4-acetic acid were discovered as new chemical leads for a prostaglandin D_2 (PGD_2) receptor antagonist. Most of them exhibited PGD_2 receptor binding and blocked cyclic adenosine 3′,5′-monophosphate (cAMP) formation in vitro. In particular, 2-methylindole-4-acetic acid analog 1 showed markedly increased receptor affinity and cAMP antagonist activity. Chemistry and structure activity relationship (SAR) data are also presented.

Keywords: Prostaglandin; DP receptor; Antagonist

1. Introduction

Prostanoids (prostaglandins and thromboxanes) are products of cyclooxygenase derived from arachidonic acid. Cyclooxygenases metabolize arachidonic acid to five primary prostanoids, which are PGE_2, $PGF_{2\alpha}$, PGI_2, TXA_2(TX), and PGD_2. These lipid mediators interact with specific members of a family of distinct G-protein-coupled prostanoid receptors.

Coleman et al. [1,2] proposed the existence of specific receptors for TX, PGI, PGE, PGF, and PGD that are named TP, IP, EP, FP, and DP receptors, respectively. They further classified the EP receptor into four subtypes (EP_1, EP_2, EP_3 and EP_4), all of which respond to PGE_2 in different ways. A number of specific ligands for these receptors have already been described in the literature [3]. Among them, the DP receptor was the most recent prostanoid receptor to be cloned and is perhaps the least well characterized [4,5]. PGD_2 is the major prostanoid released from mast cells after challenge with IgE [6,7] and it has also been shown to affect the sleep cycle [8–11] and body temperature [12].

PGD_2 also promotes the migration of Th2 cells, eosinophils, and basophils by binding to the chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2) [13,14]. Thus, PGD_2 is an endogenous ligand that binds to both the DP receptor and CRTH2. Accordingly, the discovery of selective DP receptor antagonists [15–18] would offer a significant opportunity to elucidate the role of this receptor in various pathologies such as allergic diseases. However, the role of the DP receptor remains to be clarified because of the lack of potent and subtype-selective ligands. Here we report on the discovery of a chemical lead **1** for a new class of DP receptor antagonists starting from the chemical modification of Indomethacin analog **2d**, which could be an excellent chemical lead for developing an orally active drug (Fig. 1).

2. Chemistry

The synthesis of *N*-benzoyl-5-methoxy-2-methylindole-3-acetic acids **2a–j** is outlined in Scheme 1. Formation of a hydrazone of **12** with acetaldehyde in toluene, followed by *N*-acylation of another NH moiety with acid chlorides **13a–j**, afforded the *N*-acyl hydrazones **14a–j**, respectively. Acidic hydrolysis of **14a–j**, followed by conventional indole synthe-

* Corresponding author. Tel.: +81 75 961 1151; fax: +81 75 962 9314.
E-mail address: torisu@ono.co.jp (K. Torisu).

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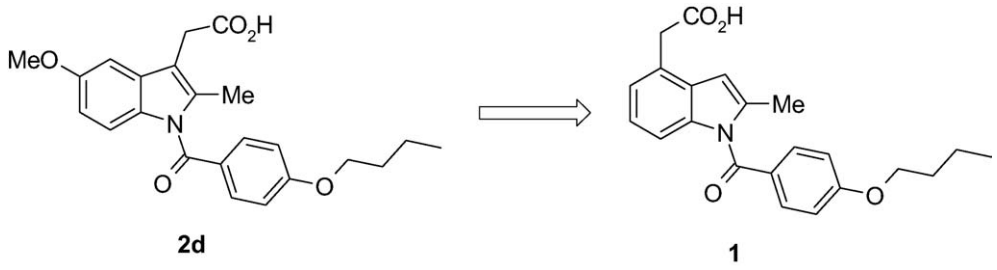
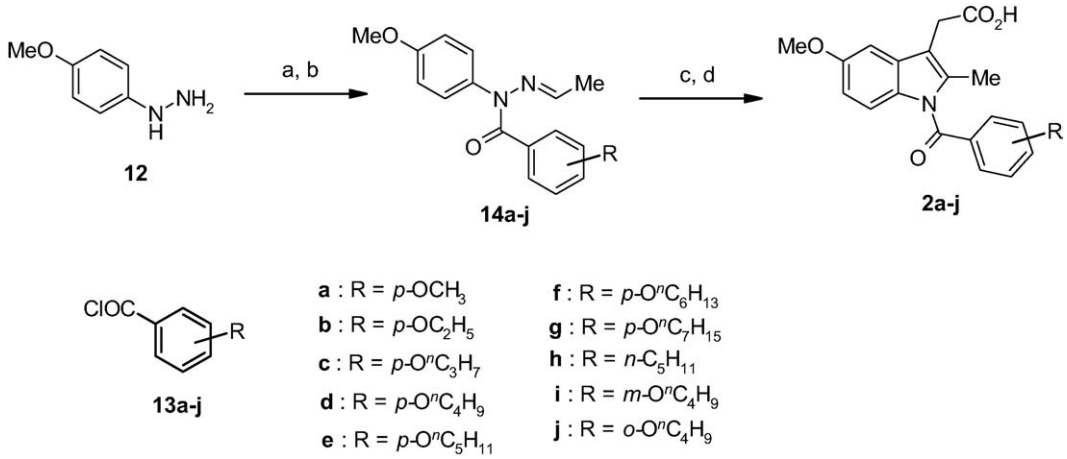


Fig. 1. Discovery of a new chemical lead **1**.



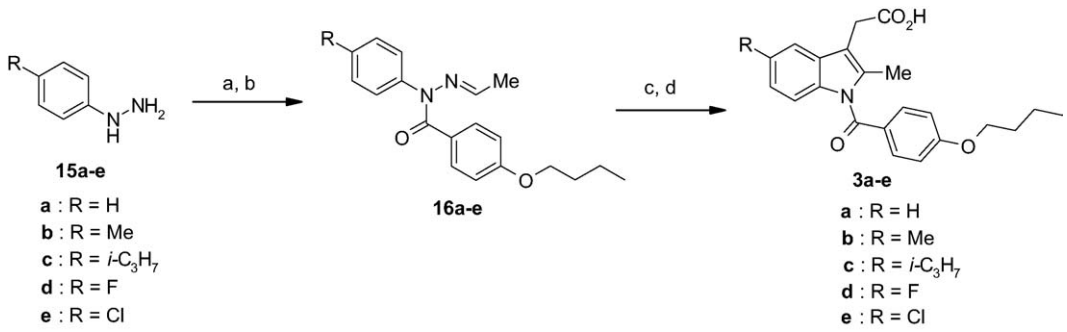
Scheme 1. Synthesis of **2a**–**j**. Reagents: (a) CH_3CHO, toluene; (b) **13a**–**j**, pyridine, CH_2Cl_2; (c) 4 N HCl, 1,4-dioxane; (d) levulinic acid, AcOH.

sis using levulinic acid, gave the *N*-benzoyl-5-methoxy-2-methylindole-3-acetic acids **2a**–**j**, respectively [19–21].

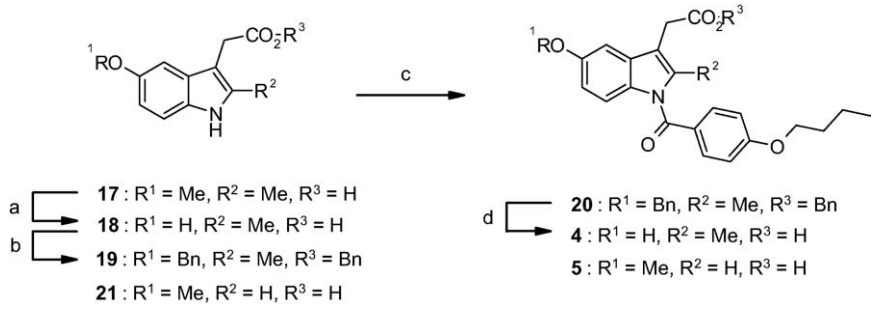
As shown in Scheme 2, compounds **3a**–**e** were prepared from their corresponding 4-subsituted phenylhydrazines (**15a**–**e**, respectively) according to the same procedures described above.

Synthesis of **4** and **5** is shown in Scheme 3. Replacement of the methoxy moiety of **17** with a benzyloxy moiety was successfully achieved as follows. Demethylation of the 5-methoxy group of **17** with pyridinium chloride at 180 °C, followed by benzylation of a formed phenol derivative **18** with benzyl bromide, afforded a benzyl ether **19**, *N*-acylation of which followed by catalytic hydrogenation gave **4**. Compound **5** was prepared from the corresponding indole derivative **21** according to the *N*-acylation procedure described above.

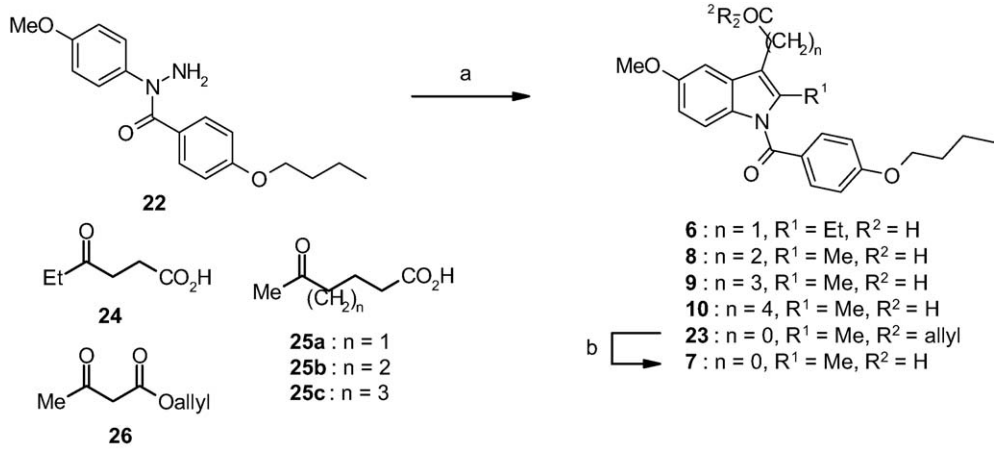
Synthesis of **6**–**10** is described in Scheme 4. Compounds **6** and **8**–**10** were prepared according to the usual indole synthesis procedure using *N*-acyl hydrazine **22** and the corresponding keto carboxylic acids **24** and **25a**–**c**, respectively. Compound **7** was prepared by deprotection of the allyl ester **23**, which was prepared from **22** and **26** by the indole synthesis procedure described above. An α,β-unsaturated carboxylic acid derivative **11** was prepared from 5-methoxy-2-methylindole **27** as outlined in Scheme 5. Treatment of **27** with dimethylformamide in the presence of phosphorus oxychloride gave **28**, C2 homologation of which by the Wittig reaction resulted in **29**. Alkaline hydrolysis of **29** provided the corresponding carboxylic acid **30**, *N*-acylation of which with 4-^{n}butoxybenzoylchloride in the presence of *n*-BuLi afforded **11**. Synthesis of 2-methylindole-4-acetic acid **1** is outlined in Scheme 6. Methoxycarbonylation of **32**, which



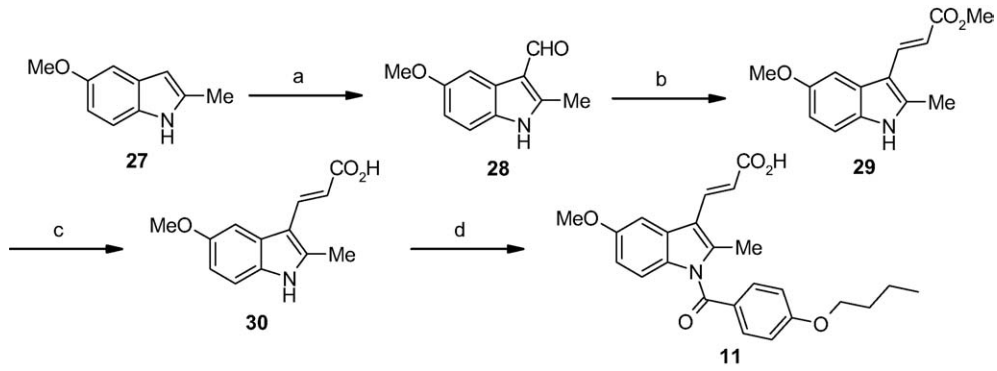
Scheme 2. Synthesis of **3a**–**e**. Reagents: (a) CH_3CHO, toluene; (b) **13d**, pyridine, CH_2Cl_2; (c) 4 N HCl, 1,4-dioxane; (d) levulinic acid, AcOH.



Scheme 3. Synthesis of **4** and **5**. Reagents: (a) HCl-pyridine, 180 °C; (b) benzyl bromide, K_2CO_3, DMF (c) NaH, **13d**, DMF; (d) H_2, Pd–C, *i*-PrOH, EtOAc.



Scheme 4. Synthesis of **6**–**10**. Reagents: (a) **24** or **25a**–**c** or **26**, AcOH; (b) morpholine, $Pd(PPh_3)_4$, THF.



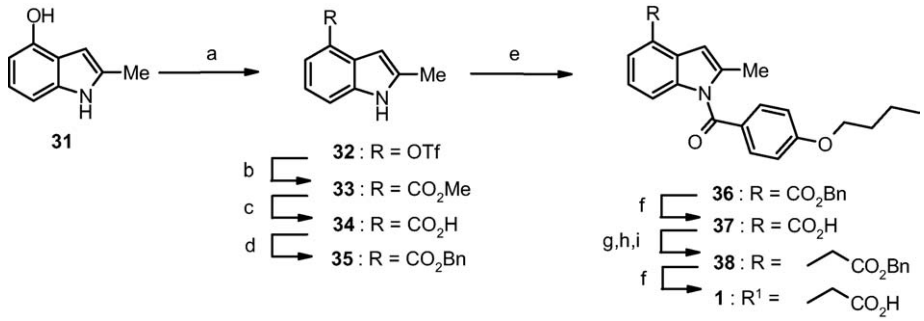
Scheme 5. Synthesis of **11**. Reagents: (a) $POCl_3$, DMF, –78 °C; (b) $Br^-Ph_3P^+CHCO_2Me$, benzene; (c) NaOH, H_2O; (d) *n*-BuLi, **13d**, THF.

was prepared from **31** by the usual method, was carried out by the palladium-catalyzed carbon monoxide insertion reaction in the presence of methanol. Alkaline hydrolysis of **33** [22–25], followed by *O*-benzylation, provided **35**, after which *N*-acylation of **35** with an acid chloride **13d** and deprotection with hydrogenolysis afforded a carboxylic acid **37**. Compound **37** was converted to **38** by the conventional C-1 homologation procedure [26], followed by *O*-benzylation. Deprotection of **38** with hydrogenolysis gave **1**.

3. Results and discussion

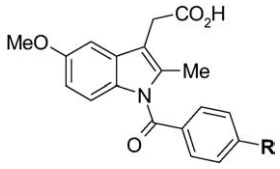
The test compounds listed in Tables 1–5 were biologically evaluated for inhibition of the specific binding of a radiolabeled ligand, [^{3}H]PGD_2, to membrane fractions prepared from cells stably expressing each prostanoid receptor and for their effect on cyclic adenosine 3′,5′-monophosphate (cAMP) formation evoked by PGD_2 in CHO cells [27] in the presence of bovine serum albumin (BSA). The compounds were also evaluated binding to all the subtypes of mouse PGE_2 (mEP1, mEP2, mEP3 and mEP4) [3].

In the course of screening our targeted library for lipid mediators, **2b** derived from Indomethacin was found to show weak binding to the mouse DP (mDP) receptor while Indomethacin did not show any binding at 10 μM. Based on this finding, structural optimization was initiated with chemical modification of the *p*-alkoxy substituent of the *N*-benzoyl residue of **2b**. As illustrated in the biological evaluation of



Scheme 6. Synthesis of **1**. Reagents: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C; (b) $Pd(PPh_3)_4$, CO, TEA, MeOH, DMF; (c) NaOH, MeOH, 1,4-dioxane; (d) benzyl bromide, K_2CO_3, DMF; (e) NaH, **13d**, DMF; (f) Pd–C, H_2, MeOH, EtOAc; (g) $(COCl)_2$, DMF, toluene; (h) $TMSCHN_2$, THF, CH_3CN; (i) 2,4,6-collidine, benzyl alcohol.

Table 1
Effect of the chain length of the *p*-substitutent of the *N*-benzoyl moiety on K_i values



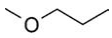
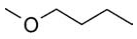
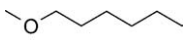
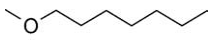
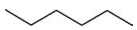
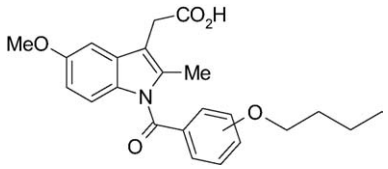
Compound	R	Binding K_i (μM)					IC_{50} (μM)
		mEP1	mEP2	mEP3	mEP4	mDP	mDP
1 Indomethacin	Cl	>10	>10	>10	>10	>10	NT
2a		>10	>10	>10	>10	>10	NT
2b		>10	>10	>10	>10	3.4	NT
2c		>10	4.1	>10	>10	0.61	5.9
2d		>10	4.7	>10	>10	0.27	1.6
2e		>10	0.020	>10	1.7	0.19	0.77
2f		>10	1.5	>10	1.9	0.50	2.5
2g		>10	0.58	>10	2.3	0.54	1.4
2h		4.5	1.3	>10	3.1	0.28	3.0

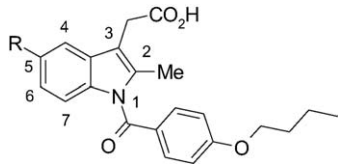
Table 2
Effect of the substitution pattern of the *N*-benzoyl moiety on K_i values



Compound	Position	Binding K_i (μM)					IC_{50} (μM)
		mEP1	mEP2	mEP3	mEP4	mDP	mDP
2i	*m*-	>10	1.7	>10	>10	0.41	2.5
2j	*o*-	6.5	>10	>10	>10	>10	NT
2d	*p*-	>10	4.7	>10	>10	0.27	1.6

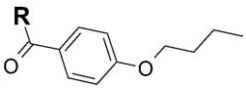
2a–**g** (Table 1), the chain length of the *p*-alkoxy moiety was optimized at the *n*-pentyloxy of **2e** with regard to both mDP receptor affinity and antagonist activity, showing increased mEP2 receptor affinity and mEP4 receptor affinity.

Table 3
Effect of a 5-substituent on K_i values



Compound	R	Binding K_i (μM)					IC_{50} (μM)
		mEP1	mEP2	mEP3	mEP4	mDP	mDP
2d	OMe	>10	4.7	>10	>10	0.27	1.6
3a	H	5.2	2.1	>10	>10	0.11	3.9
3b	Me	5.0	1.7	>10	2.2	0.15	2.9
3c	*i*-Pr	1.1	0.75	4.0	1.1	0.045	5.1
3d	F	>10	2.8	>10	>10	0.11	1.6
3e	Cl	7.4	0.98	>10	2.4	0.33	2.9
4	OH	>10	3.3	>10	>10	1.9	>10

Table 4
Effect of transformation of 2-methyl or 3-acetic acid residues on K_i values



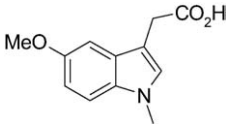
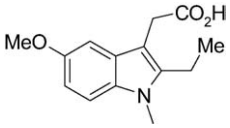
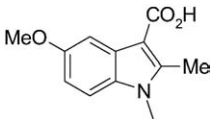
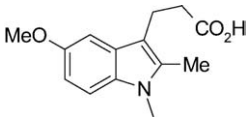
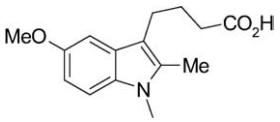
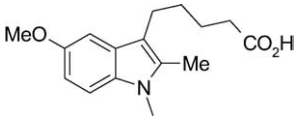
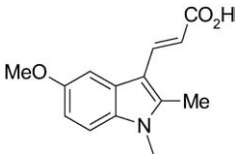
Compound	R	Binding K_i (μM)					IC_{50} (μM)
		mEP1	mEP2	mEP3	mEP4	mDP	mDP
5		>10	8.9	>10	>10	2.2	NT
6		3.8	2.9	>10	>10	1.5	NT
7		>10	>10	>10	>10	0.94	4.0
8		>10	5.7	>10	3.0	0.28	1.5
9		>10	2.7	2.4	1.5	0.19	0.91
10		>10	5.2	>10	4.2	0.40	4.5
11		>10	2.2	>10	3.0	1.4	NT

Table 5
Activity profiles of *N*-(*p*-butoxy)benzoyl-2-methylindole-4-acetic acid (**1**)

Compound	Binding K_i (μM)					IC_{50} (μM)
	mEP1	mEP2	mEP3	mEP4	mDP	mDP
2d	>10	4.7	>10	>10	0.27	1.6
1	>10	2.0	3.3	>10	0.010	0.30

As shown in Table 1, the increased mEP2 receptor affinity of **2e** was especially marked. But, subtype selectivity of **2e** remarkably decreased because compound **2e** showed nearly 10-fold higher mEP2 receptor affinity relative to its mDP receptor affinity. Compounds **2c**, **2d**, **2f** and **2g** also showed higher mDP receptor affinity than **2b**, while they showed relatively lower affinity for mEP2 and mEP4 receptors compared with their mDP receptor. As a result, compound **2d** was found to be most promising as a chemical lead for further chemical modification because of its activity profile and subtype selectivity.

Replacement of the ethoxy moiety of **2b** with an *n*-pentyl moiety provided **2h**, with a marked increase of mDP receptor affinity and increased affinity for the mEP1, mEP2 and mEP4 receptors. The mDP receptor antagonist activity of **2c**–**2h** was also evaluated in the presence of 0.1% of BSA.

When the structure activity relationship (SAR) of the *o*- and *m*- isomers of **2d** was also investigated, as shown in Table 2, *m*-isomer **2i** had slightly lower mDP receptor affin-

Table 6
Pharmacokinetic data for **1** in rats

	Dose (mg kg^{-1})	AUCinf (μg h ml^{-1})	T_{max} (h)	C_{max} (μg ml^{-1})	CL_{tot} (ml min^{-1}kg^{-1})	$T_{1/2}$ (h)	V_{ss} (ml kg^{-1})	BA (%)
iv	1	2.1			7.6	1.2	665	
po	1	2.0	1.0	1.1		1.5		95

ity than *p*-isomer **2d** with subtype selectivity close to that of *p*-isomer **2d**. The *o*-isomer **2j** did not show any mDP receptor affinity at 10 μM, while it showed weak affinity for the mEP1 receptor. Thus, the *p*-isomer was found to be the best of the three isomers.

As shown in Table 3, the effect of a 5-substituent on the indole ring was investigated. Replacement of the 5-methoxy moiety of **2d** with hydrogen afforded **3a**, which had increased affinity for the mEP1, mEP2 and mDP receptors, while **3a** showed weaker mDP receptor antagonist activity.

Replacement of the methoxy moiety of **2d** with a methyl moiety gave **3b**, with increased affinity for the mEP1, mEP2, mEP4 and mDP receptors, but weaker antagonist activity.

Replacement of the methoxy moiety of **2d** with an *i*-propyloxy moiety provided **3c**, which had increased affinity for the mEP1, mEP2, mEP3, mEP4 and mDP receptors, but showed weaker antagonist activity than **2d** despite its higher mDP receptor affinity.

Replacement of the methoxy moiety of **2d** with fluoro and chloro moieties afforded **3d** and **3e**, respectively, with increased affinity and slightly decreased affinity for the mDP receptor, respectively. In addition, **3d** and **3e** were equipotency and nearly twofold less potency relative to **2d**, respectively, with regard to mDP antagonist activity. Compound **3d** had a subtype selectivity analogous to that of **2d**, and showed weak affinity for the mEP2 receptor. Compound **3e** also showed weak affinity for the mEP1 and mEP4 receptors. Demethylation of the methoxy moiety of **2d** afforded a hydroxy derivative **4**, with lower affinity and slightly increased affinity for the mDP receptor and mEP2 receptor, respectively, while it showed no antagonist activity at 10 μM.

Thus, mDP receptor affinity was optimized by the 5-^{i}propyloxy derivative **3c**, but subtype selectivity was much lower than that of **2d**. The mDP receptor antagonist activity and subtype selectivity of **2d** and **3d** were greater than those of the other derivatives listed in Table 3.

Further modification of the 5-methoxy-2-methylindole-3-acetic acid skeleton was performed.

As shown in Table 4, removal of the 2-methyl moiety of **2d** afforded **5**, with nearly 10-fold and nearly twofold lower affinity for the mDP and mEP2 receptors, respectively.

Replacement of the 2-methyl moiety of **2d** with an ethyl moiety gave **6**, which had lower affinity and slightly higher affinity for the mDP receptor and mEP2 receptor, respectively, while **6** showed low affinity for the mEP1 receptor.

Replacement of the 3-acetic acid moiety of **2d** with a carboxy moiety gave **7**, with nearly fourfold lower affinity for the mDP receptor and threefold less potent antagonist activity. Replacement of the 3-acetic acid moiety of **2d** with a propionic acid moiety, butanoic acid moiety, and pentanoic acid moiety afforded **8**–**10**, respectively, which showed nearly equal affinity, slightly stronger affinity and slightly weaker affinity for the mDP receptor, respectively, while **8**–**10** were nearly equipotent, slightly stronger, and nearly threefold weaker with respect to antagonist activity. The subtype selectivity of **8**–**10** was reduced relative to that of **2d**. Compounds **8** and **10** showed weak affinity for the mEP2 and mEP4 receptors, while **9** showed weak affinity for the mEP2, mEP3 and mEP4 receptors.

The α,β-unsaturated acid derivative **11** showed nearly fivefold lower affinity for the mDP receptor relative to **2d**, while it showed nearly twofold higher affinity for the mEP2 receptor and also showed weak affinity for the mEP4 receptor.

An acidic function such as a carboxylic acid could be considered to play an important role in the binding of these ligands to PG receptors because of the similarity of these Indomethacin analogs to prostanoid structures consisting of an acidic α-chain and hydrophobic ω-chain. Based on this consideration, transfer of the 3-acetic acid moiety of the 2-methylindole-3-acetic acids was carried out to detect its optimized position.

A breakthrough was achieved by structural transformation of the 2-methylindole-3-acetic acid template to a 2-methylindole-4-acetic acid template. As described in Table 5, *N*-(*p*-butoxy)benzoyl-2-methylindole-4-acetic acid (**1**) demonstrated markedly increased mDP receptor affinity and antagonist activity. Compound **1** demonstrated 27-fold stronger mDP receptor affinity and nearly fivefold more potent antagonist activity relative to that of **2d**. These compounds were also evaluated for their TP receptor affinity, because PGD_2 has been known to be a TP agonist. All of the compounds listed in Tables 1–5 showed less than 1000-fold potent affinity to TP receptor.

The result of pharmacokinetic (PK) study of compound **1** was shown in Table 6 as a representative example. When **1** was administered orally to male rats at a dose of 10 mg kg^{-1} under fasting condition. Compound **1** had a good PK profile in rats (Table 6). Administration of this compound to rats (1 mg kg^{-1}, iv; 1 mg kg^{-1}, po; $n = 3$) led to detectable plasma levels, with a $T_{1/2}$ of 1.2 h (iv) and 1.5 h (po). The volume of distribution (V_{ss}) was calculated to be 665 ml kg^{-1}, indicating distribution to the tissues. Systemic clearance (CL) was 7.6 ml min^{-1} kg^{-1}. The peak plasma level (C_{max}) was 1.1 μg ml^{-1} at 1.0 h, and the oral bioavailability (BA) was 95% at a dose of 1 mg kg^{-1}. The AUC was 2.1 μg h ml^{-1} (iv) and 2.0 μg h ml^{-1} (po).

4. Conclusion

In summary, structural optimization of an mDP receptor antagonist was initiated by chemical modification of **2b**

derived from indomethacin, which is a well-known orally active drug. Optimization of the *N*-benzoyl moiety, 5-methoxy moiety, 2-methyl moiety, and 3-acetic acid moiety was carried out. As a result, *N*-(*p*-butoxy)benzoyl-5-methoxy-2-methylindole-3-acetic acid **2d** was found to be the best among this series of compounds with regard to mDP receptor affinity and antagonist activity. Synthesis and evaluation of *N*-(*p*-butoxy)benzoyl-2-methylindole-4-acetic acid (**1**) provided a breakthrough for further optimization. These findings strongly suggested that the discovery of a new class of more potent and orally active DP receptor antagonists could be achieved by continuing this approach. Further optimization of **1** will be reported in the following paper.

5. Experimental

5.1. General directions

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra (^{1}H 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), fast atom bombardment high-resolution mass spectra (FAB-HRMS) and electron ionization mass spectra (EI-MS, HRMS) 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 mass spectra (APCI-MS) were obtained on a HITACHI M1200H spectrometer. Infrared (IR) spectra were measured on a Perkin–Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyses were uncorrected. Column chromatography was carried out on silica gel [Merck silica gel 60 (0.063–0.200 mm), Wako gel C200 or Fuji Silysia BW235]. Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, silica gel 60 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).

5.2. General procedure for the preparation of N*-benzoyl-2-methyl-5-methoxyindole-3- acetic acids (**2a–j**)*

5.2.1. 4-Methoxy-N′-*[(1*E*)-ethylidene]*-N-*(4-methoxyphenyl)benzohydrazide (**14a**)*

To a stirred solution of 12 (500 mg, 3.04 mmol) and pyridine (0.37 ml, 4.57 mmol) in CH_2Cl_2 (4 ml) was added dropwise *p*-methoxybenzoyl chloride (519 mg, 3.04 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo to give an oily residue, which was purified by column chromatography on silica gel to yield **14a** (720 mg, 79% yield) as an oil. TLC R_f = 0.42 (*n*-hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.82 (q, J = 5.1 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 1.91 (d, J = 5.1 Hz, 3H).

5.2.2. 4-Ethoxy-N′-*[(1*E*)-ethylidene]*-N-*(4-methoxyphenyl)benzohydrazide (**14b**)*

81% yield; TLC R_f = 0.50 (*n*-hexane/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.82 (q, J = 5.1 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 1.91 (d, J = 5.1 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H).

5.2.3. N′-*[(1*E*)-Ethylidene]*-N-*(4-methoxyphenyl)-4-propoxybenzohydrazide (**14c**)*

74% yield; TLC R_f = 0.17 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.81 (q, J = 5.5 Hz, 1H), 3.96 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 1.90 (d, J = 5.5 Hz, 3H), 1.89–1.72 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H).

5.2.4. 4-Butoxy-N′-*[(1*E*)-ethylidene]*-N-*(4-methoxyphenyl)benzohydrazide (**14d**)*

73% yield; TLC R_f = 0.20 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.81 (q, J = 5.5 Hz, 1H), 4.05 (t, J = 7.0 Hz, 2H), 3.83 (s, 3H), 1.90 (d, J = 5.3 Hz, 3H), 1.88–1.74 (m, 2H), 1.60–1.43 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H).

5.2.5. N′-*[(1*E*)-Ethylidene]*-N-*(4-methoxyphenyl)-4-(pentyloxy)benzohydrazide (**14e**)*

73% yield; TLC R_f = 0.28 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.81 (q, J = 4.8 Hz, 1H), 3.99 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 1.90 (d, J = 4.8 Hz, 3H), 1.86–1.74 (m, 2H), 1.52–1.30 (m, 4H), 0.93 (t, J = 6.6 Hz, 3H).

5.2.6. N′-*[(1*E*)-Ethylidene]-4-(hexyloxy)*-N-*(4-methoxyphenyl)benzohydrazide (**14f**)*

92% yield; TLC R_f = 0.32 (*n*-hexane/EtOAc, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 9.2 Hz, 2H), 7.01 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.81 (q, J = 5.4 Hz, 1H), 3.99 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 1.90 (d, J = 5.4 Hz, 3H), 1.79 (m, 2H), 1.50–1.29 (m, 6H), 0.91 (t, J = 6.6 Hz, 3H).

5.2.7. N′-*[(1*E*)-Ethylidene]-4-(heptyloxy)*-N-*(4-methoxyphenyl)benzohydrazide (**14g**)*

82% yield; TLC R_f = 0.32 (*n*-hexane/EtOAc, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, J = 9.0 Hz, 2H), 7.10 (d,

J = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.81 (q, *J* = 5.4 Hz, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 1.90 (d, *J* = 5.4 Hz, 3H), 1.79 (m, 2H), 1.50–1.25 (m, 8H), 0.90 (t, *J* = 6.6 Hz, 3H).

5.2.8. N′*-[(1*E*)-Ethylidene]-*N*-(4-methoxyphenyl)-4-pentylbenzohydrazide (**14h**)*

80% yield; TLC R_f = 0.25 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.62 (m, 1H), 3.79 (s, 3H), 3.65 (s, 2H), 2.66 (t, 2H), 2.38 (s, 3H), 1.63 (m, 2H), 1.32 (m, 4H), 0.89 (t, 3H).

*5.2.9. 3-Butoxy-*N′*-[(1*E*)-ethylidene]-*N*-(4-methoxyphenyl)-benzohydrazide (**14i**)*

96% yield; TLC R_f = 0.19 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.05 (m, 6H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.81 (q, *J* = 5.4 Hz, 1H), 3.95 (t, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 1.91 (d, *J* = 5.4 Hz, 3H), 1.83–1.40 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H).

*5.2.10. 2-Butoxy-*N′*-[(1*E*)-ethylidene]-*N*-(4-methoxyphenyl)benzohydrazide (**14j**)*

14% yield; TLC R_f = 0.43 (*n*-hexane/AcOEt, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62–7.48 (m, 2H), 7.26–7.12 (m, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.81 (q, *J* = 5.4 Hz, 1H), 3.82 (s, 3H), 3.72 (t, *J* = 6.2 Hz, 2H), 1.90 (d, *J* = 5.4 Hz, 3H), 1.40–1.18 (m, 2H), 1.10–0.90 (m, 2H), 0.65 (t, *J* = 7.4 Hz, 3H).

*5.2.11. [1-(4-Methoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (**2a**)*

To a stirred solution of **14a** (720 mg, 2.41 mmol) in toluene (7 ml) and CH_3OH (7 ml) was added 4 M HCl dioxane (3.5 ml). After stirring for 40 min at room temperature, the reaction mixture was concentrated in vacuo to give a hydrazide , which was used for the next reaction without further purification. To a stirred solution of the above-described hydrazide (2.41 mmol) in AcOH (25 ml) was added levulinic acid (0.30 ml, 2.89 mmol) at room temperature. After stirring for 3 h at 80 °C, the reaction mixture was concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel to yield **2a** (403 mg, 47% yield) as a white powder; m.p. 154–156 °C, TLC R_f = 0.50 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 9.0 Hz, 2H), 6.99–6.92 (m, 3H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.66 (dd, *J* = 2.7, 9.0 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.71 (s, 2H), 2.40 (s, 3H); MS (APCI, Neg, 40 V) *m/z* 352 (M – H)$^-$, 308 (M-CO_2H)$^-$; HRMS (MALDI-TOF, Pos) Calc. for $C_{20}H_{19}NO_5$ + H^+: 354.1342; found: 354.1341; IR (neat) 2932, 1682, 1604, 1511, 1478, 1357, 1315, 1258, 1173, 1147, 1068, 1030, 913, 840, 763, 733 cm^{-1}.

*5.2.12. [1-(4-Ethoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (**2b**)*

69% yield; m.p. 142–143 °C; TLC R_f = 0.50 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 9.0 Hz, 2H), 6.98–6.90 (m, 3H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 2.4, 9.0 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 3.83 (s, 3H), 3.70 (s, 2H), 2.41 (s, 3H), 1.46 (t, *J* = 6.9 Hz, 3H); MS (APCI, Neg, 40 V) *m/z* 366 (M – H)$^-$, 322 (M–CO_2H)$^-$; HRMS (EI, Pos) Calc. for $C_{21}H_{21}NO_5$: 367.1420; found: 367.1435; IR (neat) 2932, 1713, 1682, 1604, 1509, 1478, 1357, 1315, 1256, 1173, 1147, 1068, 1039, 921, 842, 763, 733 cm^{-1}.

*5.2.13. [5-Methoxy-2-methyl-1-(4-propoxybenzoyl)-1*H*-indol-3-yl]acetic acid (**2c**)*

63% yield; TLC R_f = 0.42 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, *J* = 9.0 Hz, 2H), 6.98–6.91 (m, 3H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 2H), 2.40 (s, 3H), 1.92–1.78 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 380 (M – H)$^-$; HRMS (EI, Pos) Calc. for $C_{22}H_{23}NO_5$: 381.1576; found: 381.1581; IR (KBr) 3700–2800, 1698, 1605, 1513, 1473, 1380, 1322, 1220, 1181, 1154, 1079, 1039, 1008, 929, 846, 787, 763, 706, 613 cm^{-1}.

*5.2.14. [1-(4-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (**2d**)*

58% yield; m.p. 131–132 °C; TLC R_f = 0.49 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72–7.65 (m, 2H), 6.97–6.87 (m, 4H), 6.65 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.04 (t, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 2H), 2.40 (s, 3H), 1.88–1.74 (m, 2H), 1.61–1.43 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 394 (M – H)$^-$; HRMS (EI, Pos) Calc. for $C_{23}H_{25}NO_5$: 395.1733; found: 395.1811; IR (KBr) 2958, 1703, 1605, 1513, 1471, 1359, 1320, 1261, 1220, 1180, 1153, 1079, 1039, 929, 851, 786, 763, 614 cm^{-1}.

*5.2.15. {5-Methoxy-2-methyl-1-[4-(pentyloxy)benzoyl]-1*H*-indol-3-yl}acetic acid (**2e**)*

52% yield; m.p. 117–119 °C; TLC R_f = 0.56 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 9.0 Hz, 2H), 6.97–6.91 (m, 3H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.66 (dd, *J* = 2.4, 9.0 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.70 (s, 2H), 2.41 (s, 3H), 1.90–1.76 (m, 2H), 1.54–1.33 (m, 4H), 0.95 (t, *J* = 6.6 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 408 (M – H)$^-$; HRMS (EI, Pos) Calc. for $C_{24}H_{27}NO_5$: 409.1889; found: 409.1893; IR (neat) 2933, 1710, 1682, 1604, 1510, 1478, 1357, 1314, 1257, 1172, 1147, 1068, 1037, 927, 840, 763, 734, 671, 637 cm^{-1}.

*5.2.16. {1-[4-(Hexyloxy)benzoyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid (**2f**)*

69% yield; TLC R_f = 0.40 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 2H), 6.96–6.87 (m, 4H), 6.65 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 2H), 2.40 (s, 3H), 1.89–1.75 (m, 2H), 1.56–1.30 (m, 6H), 0.95–0.88 (m, 3H); MS (APCI, Neg, 20 V) *m/z* 422 (M – H)$^-$; HRMS (MALDI-TOF, Pos) Calc. for $C_{25}H_{29}NO_5$ + H^+: 424.2125; found: 424.2124; IR (KBr) 2931, 1684, 1606, 1479, 1359, 1312, 1254, 1149, 1069 cm^{-1}.

*5.2.17. {1-[4-(Heptyloxy)benzoyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid (**2g**)*

65% yield; m.p. 93–95 °C; TLC R_f = 0.42 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 2H), 6.96–6.87 (m, 4H), 6.65 (dd, J = 9.0, 3.0 Hz, 1H), 4.04 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.70 (s, 2H), 2.40 (s, 3H), 1.89–1.75 (m, 2H), 1.56–1.24 (m, 8H), 0.93–0.87 (m, 3H); MS (APCI, Neg, 20 V) *m/z* 436 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{26}H_{31}NO_5$: 437.2202; found: 437.2179; IR (KBr) 2931, 1699, 1671, 1608, 1513, 1463, 1355, 1321, 1262, 1225, 1178, 1153, 1073, 1038, 915, 846, 793, 763, 636 cm^{-1}.

*5.2.18. [5-Methoxy-2-methyl-1-(4-pentylbenzoyl)-1*H*-indol-3-yl]acetic acid (**2h**)*

80% yield; m.p. 119–120 °C; TLC R_f = 0.30 ($MeOH/CHCl_3$, 1:20); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.62 (m, 1H), 3.79 (s, 3H), 3.65 (s, 2H), 2.66 (t, 2H), 2.38 (s, 3H), 1.63 (m, 2H), 1.32 (m, 4H), 0.89 (t, 3H); MS (APCI, Neg, 20 V) *m/z* 392 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{24}H_{27}NO_4$: 393.1940; found: 393.1918.

*5.2.19. [1-(3-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (**2i**)*

48% yield; m.p. 133–134 °C; TLC R_f = 0.40 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 4H), 6.90 (m, 2H), 6.65 (m, 1H), 3.97 (t, J = 7.0 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 2H), 2.39 (s, 3H), 1.82–1.65 (m, 2H), 1.60–1.40 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); MS (EI, Pos) *m/z* 395 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{23}H_{25}NO_5$: 395.1733; found: 395.1752; IR (KBr) 2941, 1698, 1667, 1600, 1471, 1439, 1362, 1332, 1234, 1147, 1037 cm^{-1}.

*5.2.20. [1-(2-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid (**2j**)*

16% yield; TLC R_f = 0.38 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.42 (m, 2H), 7.18–7.01 (m, 2H), 6.95–6.88 (m, 2H), 6.64 (dd, J = 9.0, 2.8 Hz, 1H), 3.81 (s, 3H), 3.77 (t, J = 6.2 Hz, 2H), 3.65 (s, 2H), 2.30 (s, 3H), 1.39–1.23 (m, 2H), 1.11–0.90 (m, 2H), 0.64 (t, J = 7.4 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 394 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{23}H_{25}NO_5$: 395.1733; found: 395.1811; IR (neat) 2958, 2933, 2872, 1710, 1681, 1601, 1478, 1455, 1361, 1325, 1223, 1150, 1067, 1038, 914, 756 cm^{-1}.

5.3. General procedure for the preparation of N*-benzoyl-2-methyl-5-substituted indole-3-acetic acids (**3a–e**)*

*5.3.1. 4-Butoxy-*N′*-[(1*E*)-ethylidene]-*N*-(4-methylphenyl)-benzohydrazide (**16b**)*

To a stirred solution of *p*-tolylhydrazine **15b** (3.51 g, 28.7 mmol) in toluene (100 ml) was added acetaldehyde (1.6 ml, 28.7 mmol) at room temperature. After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo to give a residue, which was used for the next reaction without further purification. To a stirred solution of the above-described product (425 mg, 2.87 mmol) in pyridine (0.35 ml, 4.31 mmol) and CH_2Cl_2 (2 ml) at 0 °C was added dropwise a solution of *p*-butoxybenzoyl chloride (0.54 ml, 2.87 mmol) in CH_2Cl_2 (2 ml). After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuo to give a crude oil, which was purified by column chromatography on silica gel to yield **16b** (480 mg, 52% yield) as an oil; TLC R_f = 0.38 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.80 (q, J = 5.4 Hz, 1H), 4.00 (t, J = 6.6 Hz, 2H), 2.39 (s, 3H), 1.90 (d, J = 5.4 Hz, 3H), 1.85–1.72 (m, 2H), 1.58–1.40 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H).

*5.3.2. 4-Butoxy-*N′*-[(1*E*)-ethylidene]-*N*-phenylbenzohydrazide (**16a**)*

79% yield; TLC R_f = 0.43 (*n*-hexane/EtOAc, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82–7.77 (m, 2H), 7.54–7.36 (m, 3H), 7.22–7.17 (m, 2H), 6.90–6.86 (m, 2H), 6.79 (q, J = 5.0 Hz, 1H), 4.01 (t, J = 6.2 Hz, 2H), 1.91 (d, J = 5.0 Hz, 3H), 1.85–1.71 (m, 2H), 1.55–1.41 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H).

*5.3.3. 4-Butoxy-*N′*-[(1*E*)-ethylidene]-*N*-(4-isopropylphenyl)benzohydrazide (**16c**)*

60% yield; TLC R_f = 0.53 (*n*-hexane/EtOAc, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.80 (q, J = 5.4 Hz, 1H), 4.01 (t, J = 6.6 Hz, 2H), 2.95 (septet, J = 6.8 Hz, 1H), 1.90 (d, J = 5.4 Hz, 3H), 1.79 (m, 2H), 1.49 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H).

*5.3.4. 4-Ethoxy-*N′*-[(1*E*)-ethylidene]-*N*-(4-fluorophenyl)-benzohydrazide (**16d**)*

82% yield; TLC R_f = 0.39 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 8.7 Hz, 2H), 6.79 (q, J = 5.1 Hz, 1H), 4.01 (t, J = 6.6 Hz, 2H), 1.91 (d, J = 5.1 Hz, 3H), 1.85–1.72 (m, 2H), 1.58–1.44 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H).

*5.3.5. 4-Butoxy-*N*-(4-chlorophenyl)-*N′*-[(1*E*)-ethylidene]-benzohydrazide (**16e**)*

16% yield; TLC R_f = 0.47 (*n*-hexane/EtOAc, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82–7.77 (m, 2H), 7.50–7.46 (m, 2H), 7.16–7.12 (m, 2H), 6.91–6.87 (m, 2H), 6.85–6.76 (m, 1H), 4.01 (t, J = 6.0 Hz, 1H), 1.92 (d, J = 5.0 Hz, 3H), 1.86–1.72 (m, 2H), 1.6–1.4 (m, 2H), 0.98 (t, J = 7.0 Hz, 3H).

*5.3.6. [1-(4-Butoxybenzoyl)-2,5-dimethyl-1*H*-indol-3-yl]-acetic acid (**3b**)*

To a stirred solution of **16b** (480 mg, 1.48 mmol) in toluene (5 ml) and CH_3OH (5 ml) was added 4 M HCl dioxane (3 ml). After stirring for 40 min at room temperature, the reaction mixture was concentrated in vacuo to give a hydrazide,

which was used for the next reaction without further purification. To a stirred solution of the above-described hydrazide (1.48 mmol) in AcOH (10 ml) was added levulinic acid (0.30 ml, 2.96 mmol) at room temperature. After stirring for 3 h at 80 °C, the reaction mixture was concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel to yield **3b** (153 mg, 27% yield) as a white powder; m.p. 132–134 °C; TLC R_f = 0.57 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.0 Hz, 2H), 7.30–7.25 (m, 1H), 6.94 (d, J = 9.0 Hz, 2H), 6.85 (s, 2H), 4.05 (t, J = 6.3 Hz, 2H), 3.71 (s, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 1.87–1.75 (m, 2H), 1.59–1.45 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); MS (APCI, Neg, 20 V) m/z 378 (M – H)$^-$; HRMS (MALDI-TOF, Pos) Calc. for $C_{23}H_{25}NO_4$ + H^+: 380.1863; found: 380.1862; IR (neat) 2960, 2932, 2873, 1710, 1683, 1604, 1576, 1510, 1467, 1421, 1395, 1349, 1311, 1257, 1231, 1172, 1068, 1027, 970, 926, 840, 801, 763, 734, 670, 646, 592 cm^{-1}.

*5.3.7. [1-(4-Butoxybenzoyl)-2-methyl-1*H*-indol-3-yl]acetic acid (**3a**)*

8% yield; m.p. 118–120 °C; TLC R_f = 0.39 ($CHCl_3$/CH_3OH, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75–7.68 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.20–7.12 (m, 1H), 7.09–6.92 (m, 4H), 4.05 (t, J = 6.8 Hz, 2H), 3.74 (s, 2H), 2.42 (s, 3H), 1.88–1.75 (m, 2H), 1.60–1.43 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); MS (APCI, Neg, 20 V) m/z 364 (M – H)$^-$; HRMS (EI, Pos) Calc. for $C_{22}H_{23}NO_4$: 365.1627; found: 365.1611; IR (KBr) 2980, 1681, 1606, 1511, 1459, 1318, 1176, 1067, 843, 742, 621 cm^{-1}.

*5.3.8. [1-(4-Butoxybenzoyl)-5-isopropyl-2-methyl-1*H*-indol-3-yl]acetic acid (**3c**)*

15% yield; TLC R_f = 0.38 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (m, 2H), 7.32 (s, 1H), 6.93 (m, 4H), 4.05 (t, J = 6.6 Hz, 2H), 3.73 (s, 2H), 2.96 (septet, J = 6.8 Hz, 1H), 2.41 (s, 3H), 1.82 (m, 2H), 1.52 (m, 2H), 1.26 (d, J = 6.8 Hz, 6H), 1.00 (t, J = 7.4 Hz, 3H); MS (APCI, Neg, 20 V) m/z 406 (M – H)$^-$; HRMS (MALDI-TOF, Pos) Calc. for $C_{25}H_{29}NO_4$ + H^+: 408.2176; found: 408.2175; IR (neat) 2960, 1683, 1604, 1510, 1475, 1310, 1256, 1174, 1062, 843, 763 cm^{-1}.

*5.3.9. [5-Fluoro-2-methyl-1-(4-pentylbenzoyl)-1*H*-indol-3-yl]acetic acid (**3d**)*

3% yield; m.p. 146–147 °C; TLC R_f = 0.61 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, J = 9.0 Hz, 2H), 7.16 (dd, J = 8.7, 2.4 Hz, 1H), 7.00–6.90 (m, 3H), 6.77 (td, J = 9.3, 2.4 Hz, 1H), 4.05 (t, J = 6.4 Hz, 2H), 3.70 (s, 2H), 2.40 (s, 3H), 1.88–1.75 (m, 2H), 1.66–1.44 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); MS (APCI, Neg, 20 V) m/z 382 (M – H)$^-$; HRMS (EI, Pos) Calc. for $C_{22}H_{22}FNO_4$: 383.1533; found: 383.1611; IR (KBr) 3700–3300, 2941, 1714, 1682, 1510, 1473, 1375, 1355, 1313, 1260, 1175, 1137, 1069, 933, 845, 802, 764, 709, 671, 599 cm^{-1}.

*5.3.10. [1-(4-Butoxybenzoyl)-5-chloro-2-methyl-1*H*-indol-3-yl]acetic acid (**3e**)*

1% yield; m.p. 165–166 °C; TLC R_f = 0.32 (AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2H), 7.47 (m, 1H), 7.02–6.90 (m, 4H), 4.05 (t, J = 6.5 Hz, 2H), 3.71 (s, 2H), 2.41 (s, 3H), 1.86–1.77 (m, 2H), 1.58–1.46 (m, 2H), 1.00 (t, J = 6.0 Hz, 3H); MS (APCI, Neg, 20 V) m/z 398 (M – H)$^-$; HRMS (MALDI-TOF, Pos) Calc. for $C_{22}H_{22}ClNO_4$ + H^+: 400.1316; found: 400.1316; IR (neat) 3470, 1706, 1684, 1604, 1510, 1460, 1418, 1371, 1349, 1311, 1260, 1239, 1198, 1176, 1065, 926, 884, 859, 844, 800, 763, 710, 655 cm^{-1}.

*5.4. (5-Hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid (**18**)*

A mixture of 17 (5 g, 26.4 mmol) and pyridinium hydrochloride (50 g) was heated for 3 h at 190 °C. After cooling to room temperature, the reaction mixture was poured into water and extracted with EtOAc (×3). The combined organic layers were washed with 1 M HClaq, water, brine, dried over Na_2SO_4 and evaporated to yield 18 (2.32 g, 43% yield), which was used for the next reaction without further purification; TLC R_f = 0.10 ($CHCl_3$/CH_3OH, 9:1); MS (EI, Pos) m/z 205 (M)$^+$; HRMS (EI, Pos) Calc. for $C_{11}H_{11}NO_3$: 205.0739; found: 205.0747; IR (KBr) 3476, 3405, 2908, 1693, 1597, 1506, 1462, 1421, 1359, 1341, 1319, 1229, 1187, 1120, 1105, 925, 846, 831, 793, 648, 617, 596, 567 cm^{-1}.

*5.5. Benzyl [5-(benzyloxy)-2-methyl-1*H*-indol-3-yl]acetate (**19**)*

To a stirred solution of compound **18** (2.32 g, 11.4 mmol) in DMF (12 ml) were added K_2CO_3 (9.1 g, 66 mmol) and benzyl bromide (3.9 ml, 33 mmol) at room temperature under argon atmosphere. After stirring for 15 h, the reaction mixture was quenched with 1 M HClaq and extracted twice with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to give an oily residue, which was purified by column chromatography on silica gel to yield 19 (2.14 g, 42%); TLC R_f = 0.19 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (brs, 1H), 7.50–7.20 (m, 10H), 6.90–6.80 (m, 2H), 6.60 (m, 1H), 5.10 (s, 2H), 4.96 (s, 2H), 3.68 (s, 2H), 2.35 (s, 3H); MS (EI, Pos) m/z 385 (M)$^+$; HRMS (EI, Pos) Calc. for $C_{25}H_{23}NO_3$: 385.1678; found: 385.1675; IR (KBr) 3399, 3060, 3032, 2942, 1720, 1621, 1591, 1482, 1455, 1379, 1317, 1299, 1274, 1235, 1201, 1166, 1126, 1100, 1017, 1000, 939, 915, 861, 831, 797, 744, 711, 695, 634, 618 cm^{-1}.

*5.6. Benzyl [5-(benzyloxy)-1-(4-butoxybenzoyl)-2-methyl-1*H*-indol-3-yl]acetate (**20**)*

To a stirred solution of **19** (1.77 g, 4.60 mmol) in DMF (30 ml) was added sodium hydride (60% oil dispersion, 184 mg, 4.60 mmol) in several portions at 0 °C under argon atmosphere, and the resulting suspension was stirred for 1 h at 0 °C. After the addition of *p*-(*n*-butoxy) benzoyl chloride

(0.96 ml, 5.06 mmol) at 0 °C, the reaction mixture was stirred for 16 h, 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 a crude product, which was purified by column chromatography on silica gel to yield 20 (916 mg, 35%); TLC R_f = 0.48 (*n*-hexane/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 9.0 Hz, 2H), 7.50–7.20 (m, 10H), 7.03 (d, J = 2.7 Hz, 1H), 6.97–6.86 (m, 3H), 6.73 (m, 1H), 5.13 (s, 2H), 4.99 (s, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.71 (s, 2H), 2.39 (s, 3H), 1.93–1.77 (m, 2H), 1.75–1.45 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H); MS (EI, Pos) m/z 561 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{36}H_{35}NO_5$: 561.2515; found: 561.2521; IR (KBr) 3028, 2935, 2871, 1732, 1674, 1604, 1509, 1475, 1461, 1382, 1352, 1324, 1254, 1236, 1166, 1146, 1066, 1042, 1027, 1001, 917, 841, 793, 762, 737, 696, 630 cm^{-1}.

*5.7. [1-(4-Butoxybenzoyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid (**4**)*

To a stirred solution of **20** (795 mg, 1.42 mmol) in EtOAc (3 ml) was added 10% Pd–C (100 mg) at room temperature. The resulting suspension was stirred for 2 h at room temperature under hydrogen atmosphere. Insoluble substance was removed by filtration. The filtrate was concentrated in vacuo to give a crude product, which was purified by recrystallization from EtOAc/*n*-hexane to yield **4** (390 mg, 72%) as a white powder; m.p. 185–187 °C; TLC R_f = 0.16 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$/CD_3OD) δ 7.69 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.58 (dd, J = 8.8, 2.0 Hz, 1H), 4.05 (t, J = 6.4 Hz, 2H), 3.62 (s, 2H), 2.38 (s, 3H), 1.82 (m, 2H), 1.52 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H); MS (FAB, Pos) m/z 382 $(M + H)^+$; HRMS (EI, Pos) Calc. for $C_{22}H_{23}NO_5$: 381.1576; found: 381.1589; IR (KBr) 3239, 2960, 1706, 1669, 1605, 1576, 1512, 1468, 1387, 1351, 1310, 1256, 1180, 1148, 1074, 1027, 968, 931, 836, 799, 762, 707, 673, 637, 601 cm^{-1}.

*5.8. [1-(4-Butoxybenzoyl)-5-methoxy-1*H*-indol-3-yl]acetic acid (**5**)*

To a stirred solution of 21 (0.205 g, 1 mmol) in THF (3 ml) was added *n*-butyl lithium (1.6 M in *n*-hexane, 1.25 ml, 2 mmol) at –78 °C under argon atmosphere, and the resulting suspension was stirred for 1 h at –78 °C. After the addition of *p*-(*n*-butoxy) benzoyl chloride (0.255 g, 1.2 mmol) at –78 °C, the reaction mixture was stirred for 1 h at –20 °C, then quenched with saturated NH_4Claq 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 a crude product, which was purified by column chromatography on silica gel to yield 20 (0.016 mg, 4%); TLC R_f = 0.41 ($CHCl_3$/CH_3OH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, J = 9.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.35 (s, 1H), 7.06–6.93 (m, 4H), 4.05 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 3.72 (s, 2H), 1.82 (m, 2H), 1.52 (m, 2H), 1.00 (t, J = 8.0 Hz, 3H) ; MS (FAB, Pos) m/z 382 $(M + H)^+$; HRMS (EI, Pos) Calc. for $C_{22}H_{23}NO_5$: 381.1576; found: 381.1552; IR (neat) 2959, 1714, 1681, 1605, 1510, 1478, 1451, 1374, 1334, 1309, 1256, 1174, 1046, 912, 844, 760, 648 cm^{-1}.

*5.9. General procedure for the preparation of 4-^{n}butoxybenzoyl-2-methyl-5-methoxy indole-3-alkanoic acids derivatives **6**, **8**–**10** and **23***

*5.9.1. 3-[1-(4-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl] propanoic acid (**8**)*

To a stirred solution of **14d** (2.72 g, 7.99 mmol) in toluene (20 ml) and CH_3OH (20 ml) was added 4 M HCl-dioxane (2 ml). After stirring for 30 min at room temperature, the reaction mixture was concentrated in vacuo to give **22** (4.92 g), which was used for the next reaction without further purification.

To a stirred solution of **22** (376 mg, 1.07 mmol) in AcOH (10 ml) was added **24a** (0.158 ml, 1.28 mmol) at room temperature. After stirring for 2 h at 80 °C, the reaction mixture was concentrated in vacuo to give a crude solid, which was purified by column chromatography on silica gel to yield **8** (320 mg, 73% yield) as a pale yellow powder; m.p. 105–106 °C; TLC R_f = 0.31 ($CHCl_3$/CH_3OH, 20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 2H), 6.97–6.89 (m, 4H), 6.66 (dd, J = 9.4, 2.8 Hz, 1H), 4.05 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.03 (t, J = 7.8 Hz, 2H), 2.68 (m, 2H), 2.38 (s, 3H), 1.88–1.74 (m, 2H), 1.61–1.43 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); MS (APCI, Neg, 20 V) m/z 408 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{24}H_{27}NO_5$: 409.1889; found: 409.1889; IR (KBr) 2929, 1703, 1606, 1471, 1357, 1259, 1224, 1174, 1149, 1049, 794, 761 cm^{-1}.

*5.9.2. [1-(4-Butoxybenzoyl)-2-ethyl-5-methoxy-1*H*-indol-3-yl]acetic acid (**6**)*

1% yield; TLC R_f = 0.43 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J = 9.0 Hz, 2H), 6.98–6.92 (m, 3H), 6.71–6.60 (m, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 2H), 2.96 (q, J = 7.6 Hz, 2H), 1.89–1.74 (m, 2H), 1.62–1.42 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H); MS (APCI, Neg, 20 V) m/z 408 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{24}H_{27}NO_5$: 409.1889; found: 409.1888; IR (neat) 2931, 1680, 1604, 1478, 1259, 1042, 802 cm^{-1}.

*5.9.3. 4-[1-(4-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]butanoic acid (**9**)*

84% yield; TLC R_f = 0.34 ($CHCl_3$/MeOH, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70–7.65 (m, 2H), 6.98–6.87 (m, 4H), 6.64 (dd, J = 9.0, 2.4 Hz, 1H), 4.04 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 2.74 (dd, J = 7.8, 7.0 Hz, 2H), 2.44 (dd, J = 7.4, 7.0 Hz, 2H), 2.35 (s, 3H), 1.98 (dddd, J = 7.8, 7.4, 7.0, 7.0 Hz, 2H), 1.88–1.74 (m, 2H), 1.52 (qt, J = 7.4, 7.6 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H); MS (APCI, Neg, 20 V) m/z 422 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{25}H_{29}NO_5$: 423.2046; found: 423.2064; IR (neat) 2958, 1708, 1605, 1477, 1256, 1173, 763 cm^{-1}.

*5.9.4. 5-[1-(4-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]pentanoic acid (**10**)*

87% yield; TLC R_f = 0.28 ($CHCl_3$/MeOH, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71–7.64 (m, 2H), 6.95–6.89 (m, 4H), 6.64 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 2.69 (m, 2H), 2.40 (m, 2H), 2.35 (s, 3H), 1.88–1.65 (m, 6H), 1.60–1.43 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 436 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{26}H_{31}NO_5$: 437.2202; found: 437.2208; IR (KBr) 2936, 1675, 1606, 1512, 1478, 1373, 1324, 1259, 1217, 1175, 1069, 1039, 927, 847, 761, 633, 609 cm^{-1}.

*5.9.5. Allyl-1-(4-butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-carboxylate (**23**)*

85% yield; TLC R_f = 0.30 (*n*-hexane/EtOAc, 5:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74–7.66 (m, 3H), 7.00–6.91 (m, 3H), 6.73 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.22–6.02 (m, 1H), 5.47 (m, 1H), 5.31 (m, 1H), 4.90 (m, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 2.72 (s, 3H), 1.88–1.74 (m, 2H), 1.57–1.42 (m 2H), 0.99 (t, *J* = 7.2 Hz, 3H); MS (EI, Pos.) *m/z* 421 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{25}H_{27}NO_5$: 421.1889; found: 421.1895; IR (neat) 2957, 2873, 1695, 1602, 1556, 1509, 1475, 1455, 1393, 1356, 1311, 1258, 1198, 1164, 1112, 1038, 969, 925, 846, 764, 738, 649 cm^{-1}.

*5.10. 1-(4-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-carboxylic acid (**7**)*

To a stirred solution of compound **23** (220 mg, 0.522 mmol) in THF (3 ml) was added $Pd(PPh_3)_4$ (60 mg, 0.052 mmol) at room temperature under argon atmosphere, and stirring was continued for 15 min. To the stirred reaction mixture, morpholine (0.23 ml, 2.61 mmol) was added. After stirring for 1 h, reaction mixture was quenched with 1 M HClaq 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 an oily residue, which was purified by column chromatography on silica gel to yield **7** (139 mg, 34% in two steps) as a pale yellow powder; TLC R_f = 0.39 ($CHCl_3$/CH_3OH, 20:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75–7.69 (m, 3H), 6.99–6.93 (m, 3H), 6.75 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 3.91 (s, 3H), 2.79 (s, 3H), 1.89–1.75 (m, 2H), 1.52 (qt, *J* = 7.2, 7.6 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); MS (APCI, Neg, 20 V) *m/z* 380 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{22}H_{23}NO_5$: 381.1576; found: 381.1601; IR (KBr) 2957, 1698, 1604, 1476, 1358, 1260, 1208, 1170, 926, 848, 754 cm^{-1}.

*5.11. 5-Methoxy-2-methyl-1*H*-indole-3-carbaldehyde (**28**)*

Vilsmeier Reagent was prepared from $POCl_3$ (0.85 ml, 9.67 mmol) and DMF (3 ml) according to a reported procedure [11].

To a stirred solution of **27** (1.04 g, 6.45 mmol) in DMF (3 ml) was added dropwise above-described Vilsmeier Reagent at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was poured into 2 M NaOHaq and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated. The residue was purified by recrystallization from EtOAc to yield **28** (1.03 g, 92% yield) as a pale pink powder; m.p. 191–194 °C; TLC R_f = 0.28 (*n*-hexane/EtOAc, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.81 (s, 3H), 2.65 (s, 3H); MS (EI, Pos) *m/z* 189 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0773; IR (KBr) 3068, 2817, 2334, 1638, 1585, 1457, 1365, 1303, 1271, 1208, 1180, 1127, 1098, 1031, 982, 893, 844, 801, 720, 644, 621, 577 cm^{-1}.

*5.12. Methyl (2*E*)-3-(5-methoxy-2-methyl-1*H*-indol-3-yl)-acrylate (**29**)*

To a stirred solution of **28** (0.992 g, 5.66 mmol) in benzene (35 ml) was added methyl (triphenylphosphoranylidene) acetate (5.68 g, 17.0 mmol) at room temperature. After stirring for 50 h at 85 °C, the reaction mixture was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel to yield **29** (1.22 g, 89% yield) as a white powder; TLC R_f = 0.50 (*n*-hexane/EtOAc, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.34 (brs, 1H), 7.94 (d, *J* = 16.0 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.52 (s, 3H); MS (EI, Pos) *m/z* 245 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{14}H_{15}NO_3$: 245.1052; found: 245.1058; IR (KBr) 3276, 3001, 2940, 2836, 1693, 1605, 1483, 1456, 1427, 1315, 1284, 1224, 1150, 1105, 1032, 968, 879, 836, 818, 790, 728, 699, 643 cm^{-1}.

*5.13. (2*E*)-3-(5-Methoxy-2-methyl-1*H*-indol-3-yl)acrylic acid (**30**)*

To a stirred solution of methyl ester **29** (1.08 g, 4.39 mmol) in MeOH (5 ml) and 1,4-dioxane (15 ml) was added 2 M NaOHaq (5 ml). After stirring for 5 h at 50 °C, the reaction mixture was acidified with 1 M HClaq, 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 a residue, which was purified by recrystallization from EtOAc to yield **30** (344 mg, 96%) as a pale yellow powder; TLC R_f = 0.36 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR (200 MHz, CD_3OD) δ 7.97 (d, *J* = 16.0 Hz, 1H), 7.32 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.21 (s, 1H), 6.79 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.21 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.50 (s, 3H); MS (EI, Pos) *m/z* 231 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{13}H_{13}NO_3$: 231.0895; found: 231.0896; IR (KBr) 3349, 2942, 2835, 1674, 1602, 1482, 1408, 1316, 1284, 1219, 1192, 1176, 1103, 1032, 972, 884, 843, 794, 689, 607 cm^{-1}.

*5.14. (2*E*)-3-[1-(4-Butoxybenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acrylic acid (**31**)*

To a stirred solution of **30** (0.250 g, 1.08 mmol) in THF (4 ml) was added *n*-butyl lithium (1.53 M in *n*-hexane, 1.4 ml,

2.16 mmol) at –60 °C under argon atmosphere, and the resulting suspension was stirred for 1 h at –60 °C. After the addition of *p*-(*n*-butoxy) benzoyl chloride (0.246 ml, 1.3 mmol) at –78 °C, the reaction mixture was stirred for 2 h at –78 °C and for 1 h at –20 °C, then quenched with 1 M HClaq 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 a residue, which was purified by column chromatography on silica gel to yield **31** (0.198 g, 45%); m.p. 153–155 °C; TLC R_f = 0.53 ($CHCl_3$/MeOH, 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, J = 16.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.70–6.94 (m, 3H), 6.75 (dd, J = 8.8, 2.4 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 3.89 (s, 3H), 2.56 (s, 3H), 1.89–1.75 (m, 2H), 1.61–1.47 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H) ; MS (APCI, Neg. 20V) *m/z* 406 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{24}H_{25}NO_5$: 407.1733; found: 407.1740; IR (KBr) 2958, 1690, 1604, 1510, 1477, 1399, 1352, 1307, 1256, 1172, 1059, 927, 850, 802, 764, 671 cm^{-1}.

*5.15. 2-Methyl-1*H*-indol-4-yl trifluoromethanesulfonate (**32**)*

To a stirred solution of **31** (2-methyl-1*H*-indol-4-ol) (10.0 g, 67.9 mmol) in CH_2Cl_2 (100 ml) were added 2,6-lutidine (10.3 ml, 88.3 mmol) and Tf_2O (13.72 ml, 81.54 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was poured into water and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and evaporated to afford **32**, which was used for the next reaction without further purification; m.p. 69–70 °C; TLC R_f = 0.57 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21 (brs, 1H), 7.27 (m, *1*H), 7.09 (dd, J = 7.8, 7.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.33 (m, 1H), 2.47 (d, J = 0.6 Hz, 3H; MS (EI, Pos) *m/z* 279 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{10}H_8NF_3O_3S$: 279.0177; found: 279.0197; IR (KBr) 3951, 3444, 1892, 1633, 1585, 1552, 1496, 1450, 1405, 1351, 1336, 1286, 1251, 1206, 1151, 1054, 1010, 990, 886, 837, 786, 759, 729, 659, 621, 523 cm^{-1}.

*5.16. Methyl 2-methyl-1*H*-indole-4-carboxylate (**33**)*

To a stirred solution of **32** (6.34 g, 22.7 mmol) in MeOH (33 ml) and DMF (200 ml) were added TEA (6.3 ml, 45.29 mmol) and $Pd(PPh_3)_4$ (2.6 g, 2.26 mmol) at room temperature. After stirring over night at 60 °C under an atmosphere of carbon monoxide, the reaction mixture was filtered through a pad of Celite. The filtrate was poured into water and extracted with EtOAc (×2). The combined organic layers were washed with water, brine, and dried over Na_2SO_4 and evaporated to afford a residue, which was purified by column chromatography on silica gel to yield **33** (100% yield); m.p. 126–129 °C; TLC R_f = 0.18 (toluene); ^{1}H NMR (200 MHz, CDCl3) δ 8.14–8.00 (brs, 1H), 7.85 (m, 1H), 7.47 (m, 1H), 7.14 (t, J = 8.1 Hz, 1H), 6.87 (m, 1H), 3.97 (s, 3H), 2.50 (s, 3H); MS (EI, Pos) *m/z* 189 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0792; IR (KBr) 3339, 3065, 2951, 2845, 1698, 1615, 1577, 1552, 1494, 1464, 1442, 1407, 1388, 1355, 1337, 1293, 1234, 1195, 1172, 1136, 1058, 999, 944, 781, 752, 697, 682 cm^{-1}.

*5.17. 2-Methyl-1*H*-indole-4-carboxylic acid (**34**)*

To a stirred solution of methyl ester **33** (4.30 g, 22.7 mmol) in MeOH (10 ml) and 1,4-dioxane (10 ml) was added 5 M NaOHaq (10 ml). After stirring for 16 h at 60 °C, the reaction mixture was acidified with 2 M HClaq 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 a residue, which was purified by column chromatography on silica gel to yield **34** (1.6 g, 40%); m.p. 218–220 °C; TLC R_f = 0.48 ($CHCl_3$/MeOH, 9:1); ^{1}H NMR (300 MHz, CD_3OD) δ 8.14–8.04 (br, 1H), 7.93 (dd, J = 8.1, 0.9 Hz, 1H), 7.52 (m, 1H), 7.18 (dd, J = 8.1, 0.9 Hz, 1H), 6.94 (m, 1H), 3.71 (s, 3H); MS (EI, Pos) *m/z* 175 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{10}H_9NO_2$: 175.0633; found: 175.0641; IR (KBr) 3384, 2917, 2681, 2578, 1658, 1614, 1577, 1558, 1497, 1442, 1405, 1357, 1335, 1307, 1273, 1226, 1186, 1146, 1065, 1002, 918, 794, 749, 777, 749, 688, 647, 571, 549 cm^{-1}.

*5.18. Benzyl 2-methyl-1*H*-indole-4-carboxylate (**35**)*

To a stirred solution of **34** (690 mg, 3.94 mmol) in DMF (10 ml) were added K_2CO_3 (815 mg, 5.91 mmol) and benzyl bromide (0.7 ml, 5.91 mmol) at room temperature. After stirring for 2 h at 80 °C, the reaction mixture was poured into ice-water and extracted with EtOAc (×3). The combined organic layers were washed with water, brine, dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel to afford 35 (610 mg, 58%); TLC R_f = 0.44 (*n*-hexane/EtOAc, 8:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (brs, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.54–7.24 (m, 7H), 6.88 (m, 1H), 5.44 (s, 2H), 2.48 (s, 3H); MS (EI, Pos) *m/z* 265 $(M)^+$; HRMS (EI, Pos) Calc. for $C_{17}H_{15}NO_2$: 265.1103; found: 265.1112; IR (KBr) 3356, 3330, 1698, 1681, 1611, 1577, 1553, 1496, 1455, 1436, 1407, 1377, 1342, 1271, 1232, 1190, 1142, 1020, 952, 795, 755, 738, 695, 666, 632, 591 cm^{-1}.

*5.19. Benzyl 1-(4-butoxybenzoyl)-2-methyl-1*H*-indole-4-carboxylate (**36**)*

To a stirred solution of the **35** (690 mg, 2.60 mmol) in DMF (8 ml) was added sodium hydride (60% oil dispersion, 114 mg, 2.86 mmol) in several portions at 0 °C under argon atmosphere, and the resulting suspension was stirred for 30 min at 0 °C. After the addition of *p*-(*n*-butoxy) benzoyl chloride (0.54 ml, 2.86 mmol), the reaction mixture was stirred for 12 h at 0 °C, quenched with water and extracted with EtOAc (×3). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by column chromatogra-

phy on silica gel to yield **36** (1.02 g, 89%); TLC R_f = 0.61 (*n*-hexane/EtOAc, 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–6.90 (m, 13H), 5.45 (s, 2H), 4.05 (t, J = 6.3 Hz, 2H), 2.44 (s, 3H), 1.86–1.74 (m, 2H), 1.60–1.45 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H).

*5.20. 1-(4-Butoxybenzoyl)-2-methyl-1*H*-indole-4-carboxylic acid (**37**)*

To a stirred solution of the compound **36** (1.02 g, 2.31 mmol) in MeOH (10 ml) and EtOAc (5 ml) was added 10% Pd–C (100 mg) at room temperature, and the resulting mixture was stirred for 30 min at room temperature under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel to yield **37** (433 mg, 53%); m.p. 127–128 °C; TLC R_f = 0.59 ($CHCl_3$/MeOH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.21 (brs, 1H), 7.13 (t, J = 8.1 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 4.06 (t, J = 6.6 Hz, 2H), 2.48 (s, 3H), 1.88–1.76 (m, 2H), 1.60–1.46 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); MS (FAB, Pos) m/z 352 $(M + H)^+$; HRMS (EI, Pos) Calc. for $C_{21}H_{21}NO_4$: 351.1471; found: 351.1493; IR (neat) 2960, 1682, 1604, 1511, 1481, 1432, 1371, 1257, 1171, 912, 804, 757 cm^{-1}.

*5.21. Benzyl 4-[1-(4-butoxybenzoyl)-2-methyl-1*H*-indol-4-yl]acetate (**38**)*

To a stirred solution of **37** (290 mg, 0.825 mmol) in toluene (5 ml) were added oxalyl chloride (0.12 ml, 1.32 mmol) and DMF (a few drops) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was concentrated in vacuo to give an acid chloride, which was used for the next reaction without further purification. To a stirred solution of the above-described acid chloride in THF (4 ml) and CH_3CN (4 ml) was added (trimethylsilyl)diazomethane (2 M in ether, 0.83 ml, 1.65 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was concentrated in vacuo to afford a residue.

The residue described above was dissolved in benzyl alcohol (4 ml) and 2,4,6-collidine (4 ml) at room temperature. After stirring for 30 min at 180 °C, the reaction mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography on silica gel to yield **38** (110 mg, 29%); TLC R_f = 0.56 (*n*-hexane/EtOAc, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.0 Hz, 2H), 7.40–7.25 (m, 5H), 7.08–6.88 (m, 5H), 6.45 (s, 1H), 5.15 (s, 2H), 4.05 (t, J = 6.6 Hz, 2H), 3.87 (s, 2H), 2.45 (s, 3H), 1.90–1.74 (m, 2H), 1.60–1.45 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H).

*5.22. [1-(4-Butoxybenzoyl)-2-methyl-1*H*-indol-4-yl]acetic acid (**1**)*

To a stirred solution of the compound **38** (110 mg, 239 mmol) in EtOAc (4 ml) was added 10% Pd-C (15 mg) at room temperature. The resulting suspension was stirred for 2 h at room temperature under hydrogen atmosphere. Insoluble substance was removed by filtration. The filtrate was concentrated in vacuo to give a crude product, which was purified by recrystallization from EtOAc/*n*-hexane to yield **1** (25 mg, 28%); m.p. 95–97 °C; TLC R_f = 0.46 ($CHCl_3$/CH_3OH, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9.0 Hz, 2H), 7.08–6.90 (m, 5H), 6.49 (s, 1H), 4.05 (t, J = 6.6 Hz, 2H), 3.87 (s, 2H), 2.45 (s, 3H), 1.88–1.74 (m, 2H), 1.80–1.40 (br, 1H), 1.60–1.45 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); MS (APCI, Neg 20 V) m/z 364 $(M - H)^-$; HRMS (EI, Pos) Calc. for $C_{22}H_{23}NO_4$: 365.1627; found: 365.1619; IR (neat) 3369, 2959, 1682, 1604, 1574, 1511, 1472, 1434, 1369, 1299, 1257, 1222, 1169, 1016, 912, 837, 779, 641 cm^{-1}.

5.23. Prostanoid mEP and mDP 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 and mDP.

Membranes from CHO cells expressing prostanoid receptors were incubated with radioligand (2.5 nM of [^{3}H]PGE_2 for mEP1-4 or 2.5 nM of [^{3}H]PGD_2 for mDP) and the test compounds at various concentrations in assay buffer (10 mM KH_2PO_4–KOH buffer containing 100 mM NaCl, pH 6.0 for mEP1-4, 25 mM HEPES–NaOH buffer containing 1 mM EDTA, 5 mM $MgCl_2$ and 10 mM $MnCl_2$, pH 7.4 for mDP). Incubation was carried out at 25 °C for 60 min except for mEP1 and mDP (20 min). The incubation was terminated by filtration through Whatman GF/B filters. The filters were then washed with ice-cold buffer (10 mM KH_2PO_4–KOH buffer containing 100 mM NaCl, pH 6.0 for mEP1-4, 10 mM Tris–HCl buffer containing 100 mM NaCl and 0.01 w/v% BSA, pH 7.4 for mDP), 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) or unlabeled PGD_2 (for mDP) 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 radiolabeled ligand, K_d: dissociation constant of radiolabeled ligand towards the prostanoid receptors.

5.24. 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 PGD_2-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 1×10^5 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%) and the incubation mixture was frozen at –80 °C until the assay for cAMP.

The frozen incubation mixture was thawed, and the cells were detached with a cell scraper. 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 radioimmunoassay using a cAMP assay kit (Amersham). 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.

*5.25. Single dose rat PK study of **1***

Single dose PK of **1** was studied in rats. Formulation for intravenous injection was prepared using 30% HP-β-CD containing 5% DMSO (1 mg ml^{-1} kg^{-1}). Formulation for oral dosing was prepared using 0.5% MC (10 mg/5 ml kg^{-1}). Test compounds (1 mg kg^{-1}) were dosed intravenously to the fasted male rats ($n = 3$). Test compounds (1 mg kg^{-1}) were dosed orally to the fasted male rats ($n = 3$). After dosing, blood samples (250 μl) were collected from the jugular vein using a heparinized syringe at the selected time points (iv: pre-dosing, 2, 5, 15 and 30 min, 1, 2, 4, 6 and 8 h; po: pre-dosing, 15 and 30 min 1, 2, 4, 6 and 8 h, respectively). The blood samples were ice-chilled and then centrifuged at 12,000 rpm for 2 min at 4 °C to obtain plasma, which was preserved at –80 °C in a freezer. The AUC, C_{max}, T_{max}, $T_{1/2}$, V_{ss} and CL_{tot} were obtained by measuring the time course of the plasma concentration of the test compounds. BA was calculated according to the following equation:

$$BA\ (\%) = (AUC_{po}/D_{po})/AUC_{iv}/D_{iv}) \times 100$$

AUC_{po}: AUC after oral dosing; AUC_{iv}: AUC after intravenous dosing; D_{po}: dosage of oral administration; D_{iv}: dosage of intravenous administration.

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