Journal of Medicinal Chemistry

Article

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Synthesis and Biological Evaluation of Derivatives of 2-{2-Fluoro-4-[(2-oxocyclopentyl)methyl]phenyl}propanoic Acid: Nonsteroidal Anti-Inflammatory Drugs with Low Gastric Ulcerogenic Activity

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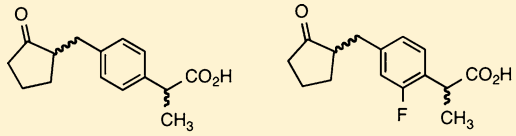
Supporting Information

ABSTRACT: We previously reported that 2-fluoroloxoprofen has lower gastric ulcerogenic activity than loxoprofen, a nonsteroidal anti-inflammatory drug (NSAID) without selectivity for COX-2. We synthesized derivatives of 2-fluoroloxoprofen and studied their properties. Compared to 2-fluoroloxoprofen, one derivative, **11a**, exhibited higher anti-inflammatory activity and an equivalent ulcerogenic effect. These results suggest that **11a** could be therapeutically beneficial for use as an NSAID.



Loxoprofen (1) | 2-Fluoroloxoprofen (2)

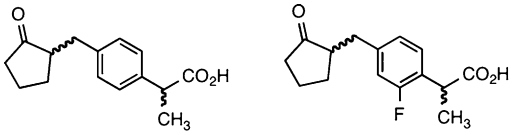
INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an important family of therapeutic agents, accounting for nearly 5% of all prescribed medications.[1] An inhibitory effect of NSAIDs on cyclooxygenase (COX) activity and a resulting decrease in prostaglandins (PGs) such as PGE_2 have been shown to be responsible for their anti-inflammatory actions. One downside of NSAID use is associated with gastrointestinal side effects.[2] Since PGE_2 has a strong protective effect on the gastrointestinal mucosa, it was considered that the adverse gastrointestinal effects of NSAIDs could also be due to their inhibitory action on COX activity.

COX has two main subtypes, COX-1 and COX-2, that are responsible for the majority of COX activity at the gastrointestinal mucosa and in tissue inflammation, respectively.[3,4] Thus, it stands to reason that a greatly reduced incidence of gastroduodenal lesions has been reported for selective COX-2 inhibitors.[5] However, a recently raised issue concerning the use of selective COX-2 inhibitors is their potential risk for cardiovascular thrombotic events.[6,7] This may be due to the fact that prostacyclin, a potent antiaggregator of platelets and a vasodilator, is mainly produced by the action of COX-2.[8,9] Thus, it is evident that NSAIDs other than COX-2-selective inhibitors that do not cause gastrointestinal problems need to be developed.

We recently suggested that COX-independent NSAID-induced cell death is also involved in NSAID-induced gastric lesions and that this direct cytotoxicity of NSAIDs is due to their membrane permeabilization activity.[10,11] Thus, we proposed that NSAIDs with lower membrane permeabilization activity would be safer on stomach tissue even if they had a reduced selectivity for COX-2.[11]

Loxoprofen (**1**) (Figure 1), an NSAID without selectivity for COX-2, has been used clinically for many years as a standard



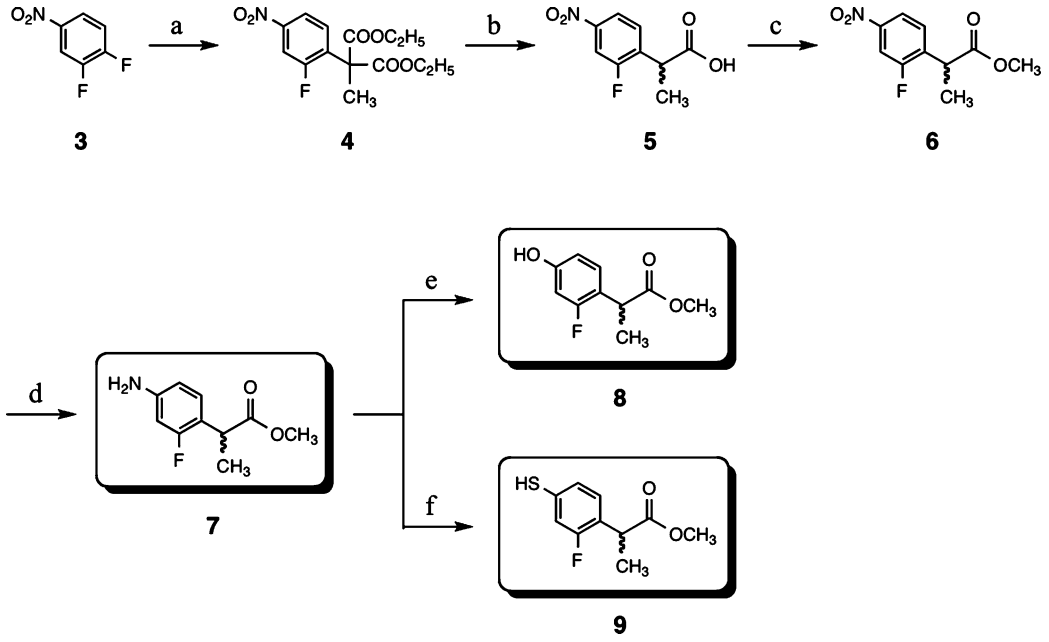
Loxoprofen (1) | 2-Fluoroloxoprofen (2)

Figure 1. Structures of loxoprofen and 2-fluoroloxoprofen.

NSAID in Japan, and clinical studies have suggested that it is safer to use than other NSAIDs, such as indomethacin.[12] Compound **1** is a prodrug that is converted to its active metabolite (the trans-alcohol form) after absorption in the gastrointestinal tract.[13] We recently reported that **1** has relatively lower membrane permeabilization activity than other NSAIDs[14] and considered that it could be used as a lead compound to obtain NSAIDs with even lower gastric ulcerogenic activity. We synthesized a series of its derivatives and obtained 2-fluoroloxoprofen (**2**) (Figure 1), which has lower gastric ulcerogenic activity but equivalent anti-inflammatory activity compared with **1**.[15] In order to obtain more clinically beneficial NSAIDs (higher anti-inflammatory activity and/or lower gastric ulcerogenic activity), we describe here details of the synthesis of a series of derivatives of **2** and the results of experiments

Received: January 12, 2012
Published: March 12, 2012

Scheme 1. Synthesis of Key Intermediates 7–9 for the Target Compounds[a]



[a]Reagents and conditions: (a) diethyl methylmalonate, NaOH, DMF; (b) conc H_2SO_4, AcOH, reflux; (c) MeOH, conc HCl, reflux; (d) H_2, 10% Pd/C, MeOH; (e) (i) 6 M H_2SO_4, $NaNO_2$, H_2O, (ii) 3 M H_2SO_4, reflux, (iii) MeOH, conc HCl, reflux; (f) (i) conc HCl, $NaNO_2$, H_2O, (ii) EtOCSSK, H_2O.

carried out to examine their ulcerogenic and anti-inflammatory activities.

CHEMISTRY

Compounds **1** and **2** were synthesized as described previously.[15,16]

The synthetic route for key intermediates **7**–**9** is outlined in Scheme 1. The commercially available 1, 2-difluoro-4-nitrobenzene (**3**) was converted to propanoic acid **5** via methylmalonate **4** as described previously.[17] Methyl esterification of **5** under acidic conditions gave methyl propanoate **6** that was subsequently treated with palladium on carbon under atmospheric H_2 pressure to provide key intermediate **7**. Another key intermediate **8** was obtained by hydrolyzing the diazonium salt that was formed by treatment of **7** with sodium nitrite ($NaNO_2$). On the other hand, the diazonium salt formed by treatment of **7** with $NaNO_2$ was reacted with potassium ethyl xanthate (EtOCSSK)[18] to yield key intermediate **9**.

The synthetic route for type-A target compounds (**10a**, **10b**, **11a**, **11b**, and **12**–**17**) having a heteroatom (O, N or S) bridge between two rings (Figure 2) is outlined in Scheme 2. The terminal ring is a cycloketone, cycloalkanol, or cycloalkane. The methyl ester precursor of final compounds **10a**, **10b**, **11a**, **11b**, and **12**–**17** were prepared from the corresponding intermediates **7**–**9**. Finally, these precursors were hydrolyzed with base to give the final compounds.

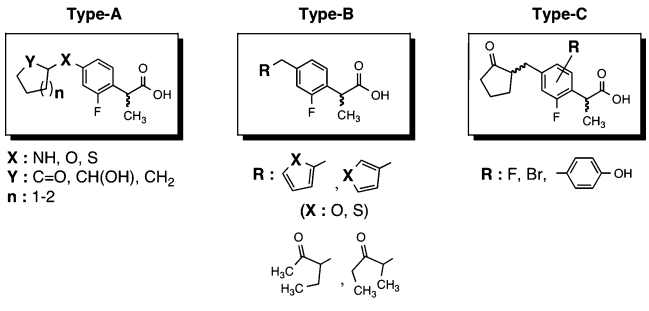


Figure 2. Structure of three types of derivative of 2-fluoroloxoprofen.

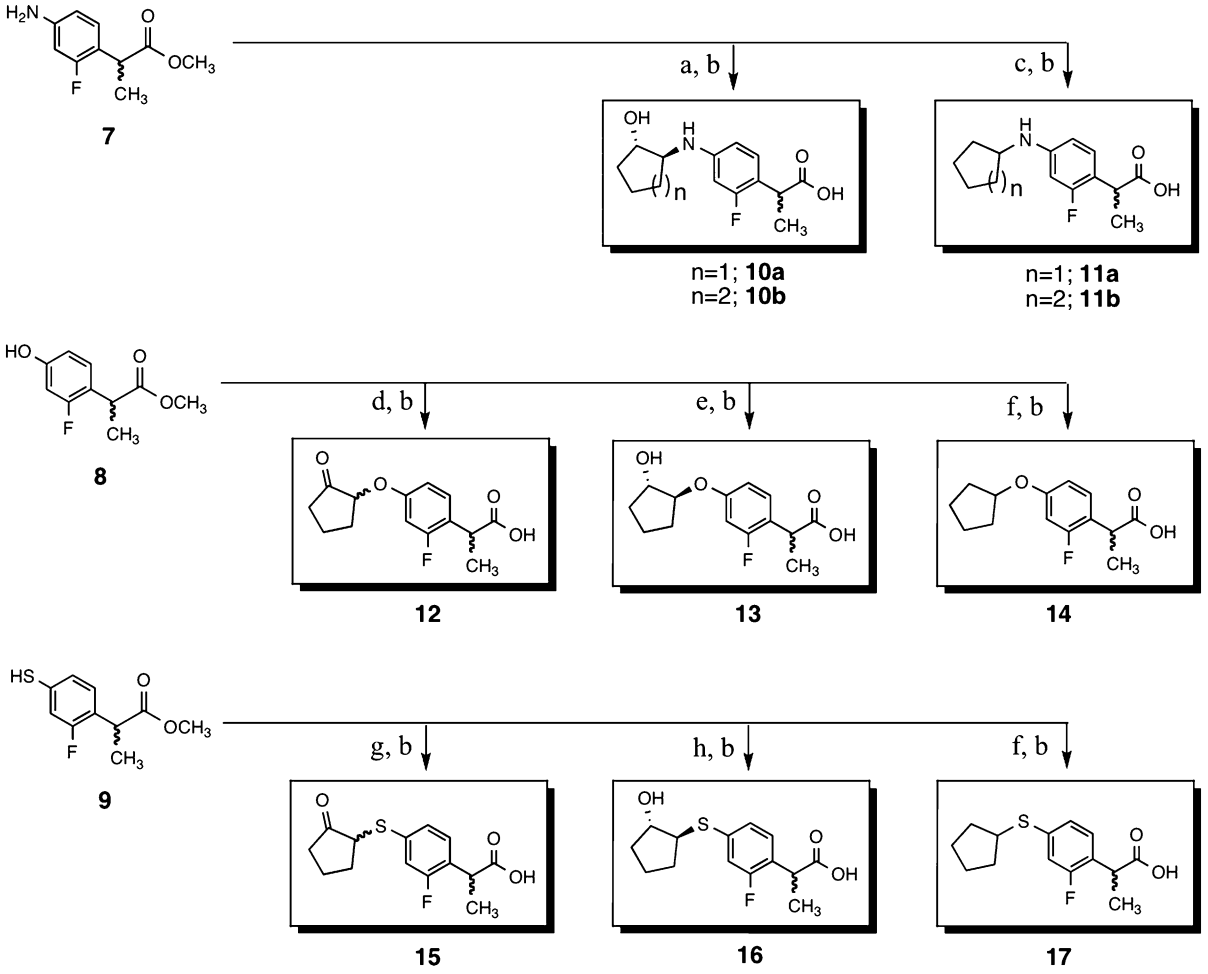
The synthetic route for type-B target compounds (**21a**, **21b**, **22a**, **22b**, **23**, and **24**) having an aromatic heteroring or an acyclic ketone (Figure 2) is outlined in Scheme 3. Treatment of **8** with trifluoromethanesulfonic anhydride ($(CF_3SO_2)_2O$)[19] provided **18**, which was then reacted with dimethylzinc ($Zn(CH_3)_2$)[20] to yield **19**. The methyl group of **19** was transformed into an active methylene group by treatment with *N*-bromosuccinimide (NBS) to yield the key intermediate **20**. Compound **20** was reacted with four kinds of boronic acid by the Suzuki–Miyaura coupling method[21] to yield the precursors for **21a**, **21b**, **22a**, and **22b**. Finally, these methyl ester precursors were hydrolyzed with base to give the final compounds. On the other hand, treatment of **20** with two kinds of acetoacetic ester derivatives provided the corresponding precursors for **23** and **24**. Finally, these precursors were subjected to decarboxylation and hydrolysis with acid to give the final compounds.

The synthetic route for type-C target compounds (**33a**, **33b**, **39**, and **40**), which were modified at the 5- or 6-position of the phenyl ring of **2** by halogen (F or Br) or para-phenol (Figure 2), is outlined in Schemes 4 and 5. Compounds **33a** and **33b** were synthesized from the corresponding commercially available starting materials **25a** and **25b**, respectively, in a manner similar to that described in Scheme 1. As part of the process, the amino group of **29a** and **29b** was transformed into a bromo group via a Sandmeyer reaction[22] and further converted into a methyl group by treatment with $Zn(CH_3)_2$ to yield the intermediates **31a** and **31b**.

On the other hand, **39** was synthesized from **34** according to a previously described method.[15] Compound **40** was synthesized via the Suzuki-Miyaura cross-coupling reaction

dx.doi.org/10.1021/jm300049g | J. Med. Chem. 2012, 55, 5143–5150

Scheme 2. Synthesis of the Type-A Target Compounds (10a, 10b, 11a, 11b, and 12−17)[a]



[a]Reagents and conditions: (a) 1,2-epoxycyclopentane or 1,2-epoxycyclohexane, LiBr, CH_2Cl_2; (b) NaOH, H_2O, MeOH, reflux; (c) cyclopentanone or cyclohexanone, $NaBH_3CN$, AcOH, MeOH; (d) chlorocyclopentanone, K_2CO_3, DMF; (e) 1,2-epoxycyclopentane, NaH, DMF; (f) bromocyclopentane, K_2CO_3,DMF; (g) cyclopentanone, NBS, CH_2Cl_2; (h) 1,2-epoxycyclopentane, borax, CH_2Cl_2.

between the methyl ester of **39** and 4-hydroxyphenylboronic acid as described previously.[16]

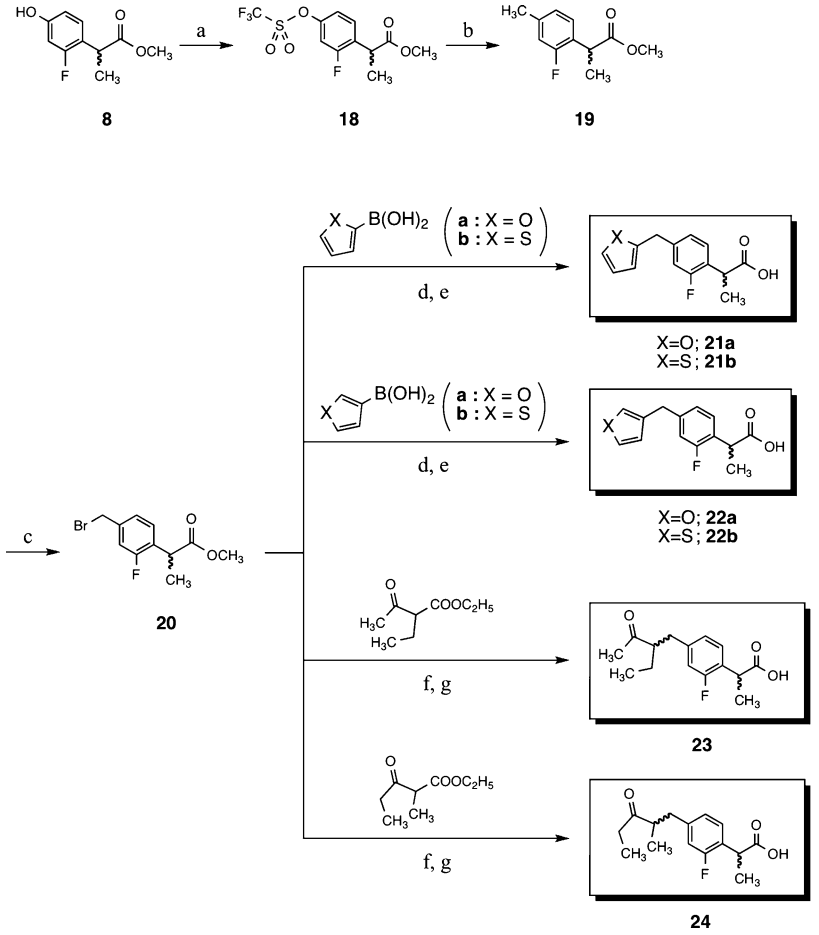
RESULTS AND DISCUSSION

We examined the inhibitory effects of synthesized derivatives of **2** on COX-1 and COX-2 activity using a human whole blood COX assay. To begin with, we determined COX inhibition at derivative concentrations of 10 and 100 μM and eliminated those derivatives that did not have an inhibitory action on either COX-1 or COX-2 activity when employed at 10 μM (Table 1). We also examined the anti-inflammatory effects of all derivatives by employing a rat carrageenan-induced footpad edema assay; derivatives were administered at a dose of 37.3 μM/kg (corresponding to 10 mg/kg for **1**), and those that did not show any anti-inflammatory effect (decrease in the volume of carrageenan-induced footpad edema) were not considered as candidates for further analysis (Table 1). We then examined the inhibitory effects on COX-1 or COX-2 of the remaining derivatives at various concentrations to determine IC_{50} values (concentration of each compound required for 50% inhibition of COX-1 or COX-2 activity) and selectivity for COX-2 (Table 1). Among the derivatives, compounds **10a**, **12**, and **21b** were eliminated as candidates for further analysis because of their low anti-inflammatory activity in the carrageenan-induced footpad edema assay. We also carried out a preliminary examination of the gastric ulcerogenic activity of the derivatives and found that the oral administration of **22b** produced more gastric lesions than **2** (data not shown). This compound was therefore also discounted from further analysis. The results in Table 1 also highlight the fact that, as well as **1** and **2**, some derivatives (**11a**, **14**, **21a**, and **22a**) did not exhibit any apparent selectvity for COX-2 (the COX-1/COX-2 value of COX-2-selective inhibitor celecoxib was found to be 22.7, measured using the same methodology as that used to generate the results presented in Table 1[23]).

We then evaluated the anti-inflammatory effects of selected derivatives (**11a**, **14**, **21a**, and **22a**) at various doses. As shown in Figure 3, the volume of carrageenan-induced footpad edema was significantly decreased after oral administration of **1** or **2**, confirming their previously described anti-inflammatory activities.[13,15,24] Of the selected derivatives, only **11a** showed a significantly more potent anti-inflammatory activity than **2** for various doses and at different time-points after the challenge with carrageenan (Figure 3). This result suggests that **11a** could be more effective than **2** for use as an NSAID. On the other hand, **21a** showed less anti-inflammatory activity than **2** at the lowest dose, 3 h after the administration of carrageenan (Figure 3).

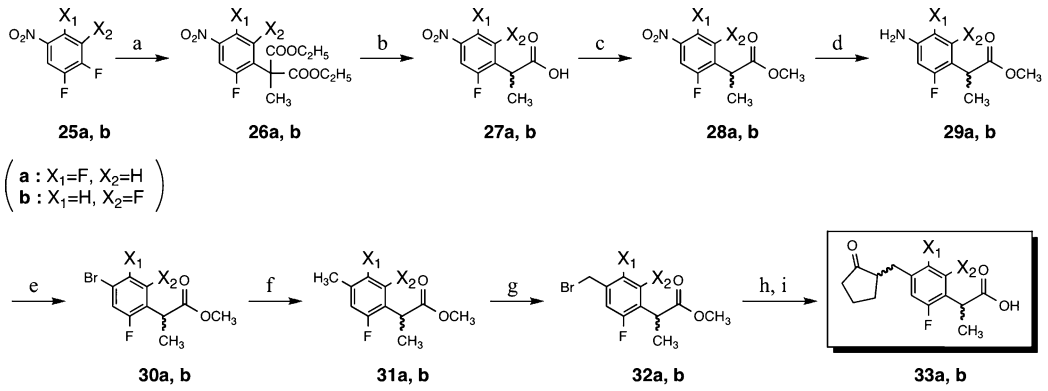
dx.doi.org/10.1021/jm300049g | J. Med. Chem. 2012, 55, 5143−5150

Scheme 3. Synthesis of the Type-B Target Compounds (21a, 21b, 22a, 22b, 23, and 24)[a]



[a]Reagents and conditions: (a) $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2; (b) $Zn(CH_3)_2$, Pd(dppe)Cl_2, 1,4-dioxane, reflux; (c) NBS, AIBN, CCl_4, reflux; (d) 3 M Na_2CO_3, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$, THF, reflux; (e) KOH, H_2O, EtOH, reflux; (f) dry Na_2CO_3, dry acetone, reflux; (g) conc HCl, AcOH, reflux.

Scheme 4. Synthesis of the Type-C Target Compounds with Modification at the 2 and 5 Positions or 2 and 6 Positions of the Phenyl Ring by Fluorine (33a and 33b)[a]

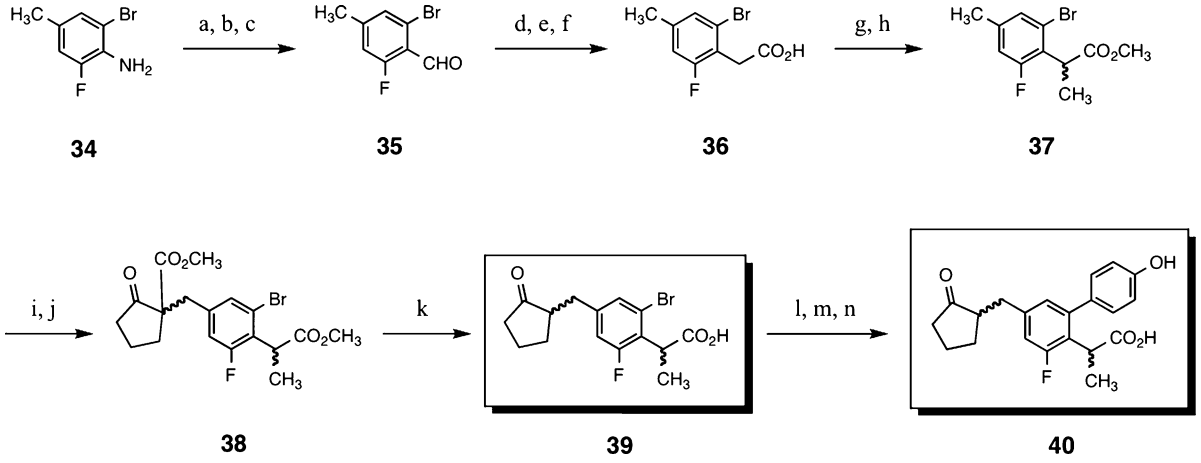


[a]Reagents and conditions: (a) diethyl methylmalonate, NaOH, DMF; (b) conc H_2SO_4, AcOH, reflux; (c) MeOH, conc HCl, reflux; (d) H_2, 10% Pd/C, MeOH; (e) (i) 40% HBr, $NaNO_2$, CuBr, H_2O, (ii) MeOH, conc HCl, reflux; (f) $Zn(CH_3)_2$, Pd(dppe)Cl_2, 1,4-dioxane, reflux; (g) NBS, AIBN, CCl_4, reflux; (h) dry Na_2CO_3, methyl 2-oxocyclopentanecarboxylate, dry acetone, reflux; (i) conc HCl, AcOH, reflux.

We then evaluated the gastric ulcerogenic activity of selected derivatives. Oral administration of **2** produced fewer gastric lesions in rats than **1** (Figure 4), as described previously.[15] All of the selected derivatives showed significantly lower ulcerogenic activity than **1** (Figure 4). Furthermore, compared with **2**, compounds **11a** and **14** showed significantly lower ulcerogenic activity at the dose of 7.45 mM/kg while **21a** and **22a** had significantly lower activity at 0.37 and 0.75 mM/kg, suggesting that these compounds could be more effective than **2** as potential NSAIDs. The mechanism for this lower ulcerogenic activity of **11a** and **14**, compared to **2** is unknown at present.

dx.doi.org/10.1021/jm300049g | *J. Med. Chem.* 2012, 55, 5143−5150

Scheme 5. Synthesis of the Type-C Target Compounds with Modification at the 2 and 6 Positions of the Phenyl Ring by Fluorine, Bromine, or the 4-Hydroxyphenyl Group (39 and 40)[a]



[a]Reagents and conditions: (a) 3 M HCl aq, $NaNO_2$, $CuSO_4$, Na_2SO_3, AcONa, H_2O, 0 °C; (b) NH_2OH·HCl, $(HCHO)_n$, AcONa, H_2O; (c) conc HCl, reflux; (d) $MeOCH_2P(Ph_3)Cl$, $C_6H_{18}KNSi_2$, toluene; (e) 3 M HCl aq, acetone, reflux; (f) PFC (2.0 mol %), H_5IO_6, acetonitrile; (g) conc HCl, CH_3OH, reflux; (h) 2.0 M LDA, CH_3I, dry THF, −78 to −40 °C; (i) NBS, AIBN, CCl_4, reflux; (j) dry Na_2CO_3, methyl 2-oxocyclopentanecarboxylate, dry acetone, reflux; (k) conc HCl, AcOH, reflux; (l) 4-DMAP, EDC, CH_3OH; (m) HO-C$_6$H$_4$-B(OH)$_2$, $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux; (n) KOH, C_2H_5OH, H_2O, reflux.

Table 1. Experimental Results of in Vitro Human Whole Blood Assay for Inhibition of COX-1- and COX-2-Derived PG Biosynthesis, And in Vivo Anti-Inflammatory Assay by Carrageenan-Induced Rat Paw Edema[a]

	COX-1 inhibition (%)		COX-2 inhibition (%)		IC_{50} (μM)			reduction in paw edema (%)	
compd	10 μM	100 μM	10 μM	100 μM	COX-1	COX-2	COX-1/COX-2	3 h	6 h
1	35.0 ± 5.9	87.5 ± 2.4	53.2 ± 5.9	97.4 ± 1.2	23.5[b] ± 4.8[b]	10.1[b] ± 1.3[b]	2.3	44.0 ± 0.2	53.1 ± 2.5
2	32.7 ± 5.1	85.7 ± 2.2	44.2 ± 2.4	81.8 ± 7.0	24.2[b] ± 8.6[b]	14.3[b] ± 6.8[b]	1.7	41.8 ± 0.4	54.1 ± 0.4
10a	54.6 ± 0.9	83.4 ± 1.1	45.3 ± 1.7	77.6 ± 1.7	9.0 ± 0.8	14.0 ± 0.4	0.7	20.6 ± 9.3	5.7 ± 0.3
10b	0	0	28.3 ± 3.7	76.7 ± 1.9				<0	<0
11a	34.7 ± 0.6	92.0 ± 2.3	40.7 ± 2.8	91.9 ± 1.6	15.6 ± 0.5	21.3 ± 2.8	0.7	45.5 ± 1.0	60.1 ± 1.9
11b	0	0	0	30.0 ± 7.2				<0	19.2 ± 4.3
12	80.6 ± 2.8	82.3 ± 1.5	27.6 ± 3.3	82.5 ± 0.5	1.5 ± 0.1	24.1 ± 6.2	0.1	30.3 ± 0.3	25.0 ± 4.2
13	10.4 ± 0.7	78.2 ± 2.2	25.4 ± 8.3	80.2 ± 7.0				<0	13.3 ± 4.8
14	65.0 ± 5.5	81.4 ± 0.9	39.7 ± 2.0	96.4 ± 1.1	3.0 ± 0.2	26.3 ± 8.8	0.1	40.4 ± 1.9	51.9 ± 6.1
15	0	60.7 ± 1.7	55.5 ± 7.4	93.1 ± 3.0				38.0 ± 1.1	27.2 ± 7.0
16	0	47.6 ± 4.6	0	64.4 ± 5.1				<0	<0
17	4.7 ± 0.7	87.9 ± 0.2	15.6 ± 3.0	80.1 ± 1.8				<0	9.5 ± 0.6
21a	26.3 ± 2.6	79.9 ± 6.0	64.1 ± 1.8	96.1 ± 2.1	21.6 ± 7.5	4.1 ± 2.8	5.3	38.9 ± 6.6	45.8 ± 3.5
21b	27.4 ± 1.1	76.5 ± 1.6	45.8 ± 0.6	89.2 ± 2.8	19.9 ± 5.7	13.0 ± 1.9	1.5	12.5 ± 8.1	28.0 ± 7.3
22a	30.9 ± 2.0	57.5 ± 5.6	58.7 ± 6.2	90.9 ± 2.2	30.1 ± 8.6	4.0 ± 1.1	7.6	32.7 ± 2.5	45.2 ± 0.01
22b	53.9 ± 2.0	87.4 ± 3.4	60.2 ± 4.4	99.5 ± 0.5	9.5 ± 1.4	8.3 ± 2.8	1.2	40.2 ± 3.1	33.4 ± 0.2
23	78.0 ± 6.5	98.1 ± 0.3	0	82.2 ± 2.9				20.9 ± 6.4	20.2 ± 6.7
24	0	13.5 ± 1.9	0	0				<0	<0
33a	0	81.0 ± 0.4	15.0 ± 4.9	84.8 ± 4.1				<0	<0
33b	11.3 ± 1.0	79.3 ± 5.6	0	70.9 ± 6.7				21.6 ± 2.6	17.7 ± 9.6
39	13.8 ± 2.6	49.7 ± 6.6	0	0				<0	<0
40	0	7.2 ± 1.0	15.4 ± 0.3	38.0 ± 3.2				<0	<0

[a]The inhibitory effect of each compound on COX-1- and COX-2-derived PG biosynthesis was measured. The relative inhibition of COX-1 or COX-2 (%) at 10 and 100 μM, IC_{50} values (concentration of each compound required for 50% inhibition of COX-1 or COX-2), and the COX-1/COX-2 ratio of IC_{50} values are shown. The values of IC_{50} were estimated from the sigmoid-like dose−response curve (four-parameter logistic curve model) drawn with the aid of logistic-curve fitting software (ImageJ, version 1.43u; National Institutes of Health, U.S.). Values are the mean ± SEM (n = 3−6). For the in vivo anti-inflammatory assay, rats were orally administered 37.3 μM/kg test compound and 1 h later received an intradermal injection of carrageenan (1%) into the left hindpaw. Footpad edema was measured 3 and 6 h after the administration of carrageenan, and the relative inhibition of the increase in edema volume by each compound was determined. Values are the mean ± SEM (n = 3−6). [b]Data from our previous report.[15]

Finally, the orientation of the selected derivatives in COX-2 and the interaction between these derivatives and amino acid residues in the active site of COX-2 were examined by molecular modeling and docking studies. Since **2** is a prodrug,[15] the

dx.doi.org/10.1021/jm300049g | J. Med. Chem. 2012, 55, 5143−5150

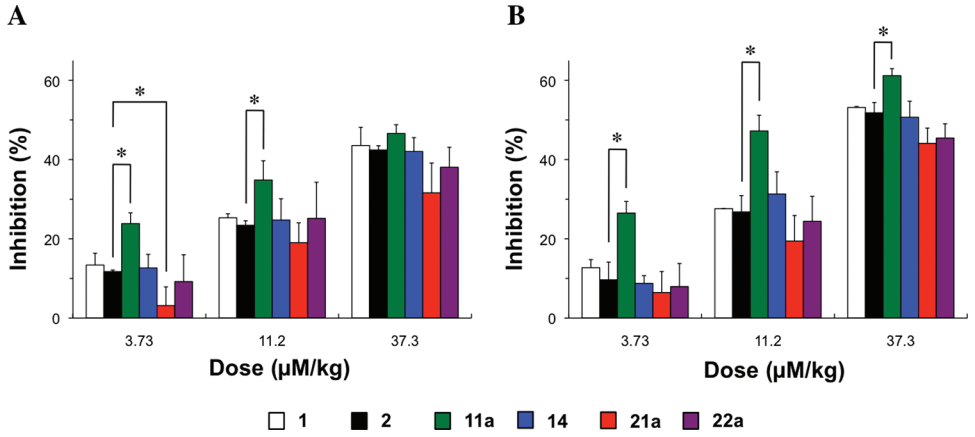


Figure 3. Anti-inflammatory activities of loxoprofen (**1**), 2-fluoroloxoprofen (**2**), and the latter's derivatives (**11a**, **14**, **21a**, and **22a**). Rats were orally administered 3.73, 11.2, or 37.3 μM/kg test compound and 1 h later received an intradermal injection of carrageenan (1%) into the left hindpaw. Footpad edema was measured 3 h (A) and 6 h (B) after the administration of carrageenan, and the relative inhibition of the increase in edema volume by each compound was determined. Values are the mean ± SEM (n = 3–6): (*) $P < 0.05$.

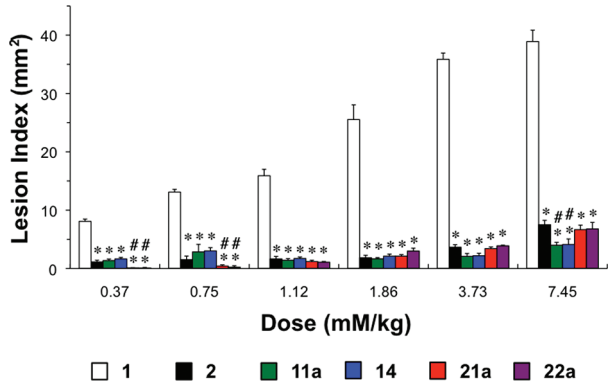


Figure 4. Production of gastric lesions in the presence of loxoprofen (**1**), 2-fluoroloxoprofen (**2**), and the latter's derivatives (**11a**, **14**, **21a**, and **22a**). Rats were orally administered 0.37, 0.75, 1.12, 1.86, 3.73, and 7.45 mM/kg test compound, and their stomachs were removed after 8 h. Stomachs were scored for hemorrhagic damage. Values are the mean ± SEM (n = 3–6): (*) $P < 0.05$ (vs **1**); (#) $P < 0.05$ (vs **2**).

active metabolite (2-[2-fluoro-4-{(2-hydroxycyclopentyl)-methyl}phenyl]propanoic acid) was subjected to the analysis. We recently reported results for **1** by this analysis, which showed that the cyclopentanone ring interacts with Y385 and S530, whereas propanoic acid interacts with R120 and Y355.[16] All of these amino acids were reported to be important for the interaction between COXs and NSAIDs.[25,26] Similar orientation and interactions were observed for **2** and its selected derivatives in this study (Figure 5).

We have thus not only identified here interesting and beneficial NSAIDs (see Conclusion) but also suggested structure–activity relationships of **2** for COX inhibition and anti-inflammatory effects, as follows:

For type-A derivatives, as described above, **2** is a prodrug and the trans-alcohol form of **2** showed a more potent inhibitory effect on both COX-1 and COX-2 activity than **2**.[15] However, **13** and **16**, corresponding to the trans-alcohol form of **12** and **15**, respectively, showed a weaker inhibitory effect on both COX-1 and COX-2 than **12** and **15**, respectively (Table 1). Thus, the alteration in bridge heteroatom (O or S) between the two rings may result in the disappearance of **2**'s property as a prodrug.

For type-B derivatives, **21a** and **22a** showed COX-inhibition and anti-inflammatory effects equivalent to **2**, suggesting that the furan ring can become a bioisostere of the cyclopentanone ring of **2**. On the other hand, **23** and **24** showed very weak COX-inhibition and anti-inflammatory effects, suggesting that the closed circular ring in **2** is important for its COX-inhibition and anti-inflammatory effects.

We previously reported that, as well as **2**, oral administration into rats of 2-bromoloxoprofen or 2-*p*-hydroxyphenylloxoprofen produced fewer gastric lesions but showed an equivalent anti-inflammatory effect compared to **1**.[15,16] Therefore, we examined here the effect of a similar modification of the aromatic ring of **2** by F, Br, or *p*-phenol on the anti-inflammatory effect of **2** (type-C derivatives). However, **33a**, **33b**, **39**, and **40** showed weaker COX inhibition and anti-inflammatory effects than **2**, suggesting that the introduction of a substituted group into the aromatic ring of **1** should be restricted to one position in order to maintain its anti-inflammatory activity.

CONCLUSION

Compound **11a** was found to have a more potent anti-inflammatory effect and an equivalent gastric ulcerogenic activity compared with **2**. Furthermore, as for **2**, **11a** has no apparent selectivity for COX-2. Thus, we consider that **11a** could be therapeutically beneficial for clinical use as an NSAID.

EXPERIMENTAL SECTION

The purity of the final compounds was greater than 95% as judged by HPLC (for details, see Supporting Information).

2-[4-(Cyclopentylamino)-2-fluorophenyl]propanoic Acid (11a). To a solution of **7** (1.50 g, 7.6 mmol) in a mixture of MeOH (10 mL) and AcOH (0.2 mL) were added cyclopentanone (1.4 mL, 15.2 mmol) and sodium cyanoborohydride ($NaBH_3CN$) (0.96 g, 15.2 mmol). The solution was stirred at room temperature for 12 h. The reaction mixture was evaporated to dryness, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated to dryness and the residue was purified on silica gel chromatography (*n*-hexane/AcOEt, 3:2) to afford the methyl ester precursor of **11a**. Hydrolysis with NaOH was done to give final compound **11a** as a brown powder solid (1.09 g, 54%). ^{1}H NMR ($CDCl_3$) δ: 1.28 (6H, d, J = 7.0 Hz), 1.33–1.68 (6H, m), 1.79–1.91 (2H, m), 3.56–3.64 (1H, m), 3.70 (1H, q, J = 7.3 Hz), 6.17–6.30 (2H, m), 6.90 (1H, t, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 18.1, 25.0, 33.9, 39.0, 55.7, 100.3, 110.4, 116.1, 116.3, 129.8, 130.0, 150.8, 161.2

dx.doi.org/10.1021/jm300049g | J. Med. Chem. 2012, 55, 5143–5150

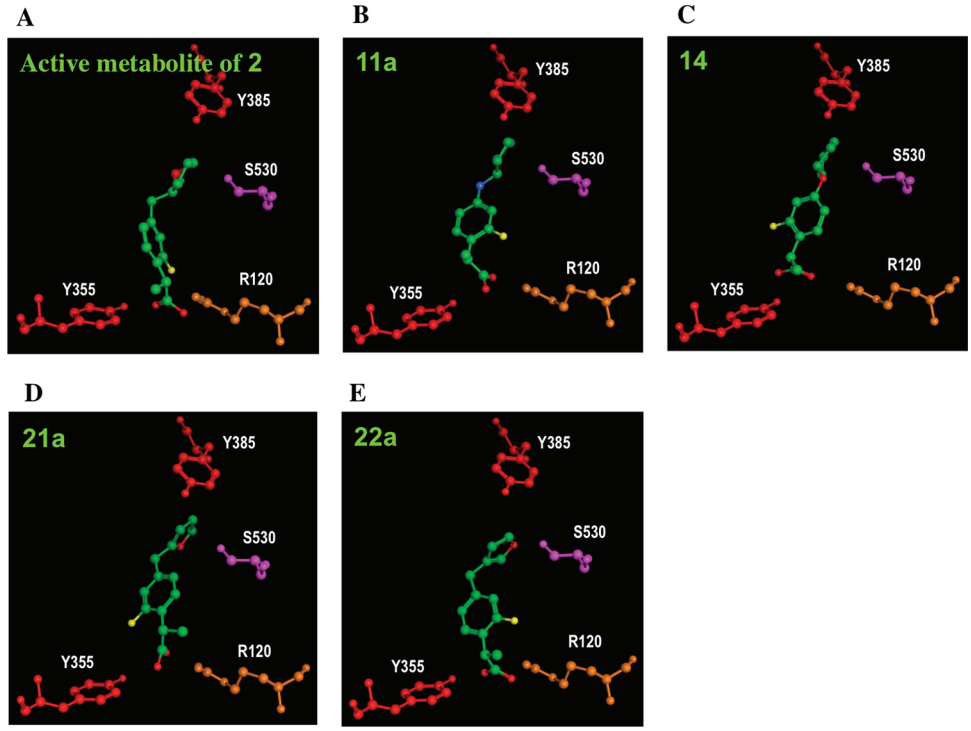


Figure 5. Potential binding mode of the active metabolite of **2** (A), **11a** (B), **14** (C), **21a** (D), and **22a** (E) to the active site of murine COX-2. Hydrogen atoms of the amino acid residues and the ligand have been removed.

(d, J_{C-F} = 242 Hz), 178.4. HR-FAB-MS (*m*/*z*): 251.1324 (M^+, calcd for $C_{14}H_{18}FNO_2$, 251.1322). Anal. Calcd for $C_{14}H_{18}FNO_2$: C, 66.91; H, 7.22; N, 5,57. Found: C, 67.05; H, 7.24; N, 5,46.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Health, Labour, and Welfare of Japan, Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Grants-in-Aid of the Japan Science and Technology Agency.

■ ABBREVIATIONS USED

NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; PG, prostaglandin; NBS, *N*-bromosuccinimide; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran

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