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Naphthalene Derivatives: A New Series of Selective Cyclooxygenase-2 Inhibitors

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Abstract—A new series of potent and selective cyclooxygenase-2 inhibitors have been prepared. Some of these compounds show good oral anti-inflammatory activity in rats.

Introduction

Various laboratories have developed extensive libraries of selective COX-2 inhibitors in recent years.[1] Most of the compounds fit into three main categories: (1) acidic sulfonamides such as NS-398, L-745337, and flosulide, (2) diarylheterocycles such as rofecoxib and celecoxib, and (3) modifications of classical NSAIDs such as zomepirac and indomethacin derivatives.

In this paper, we describe our efforts in developing a new series of selective COX-2 inhibitors. This new series fits into the third category, due to its structural similarity to the classical NSAID indomethacin. Compounds of type **I** (Fig. 1) can yield selective inhibitors of COX-2 through modification at the 1- and 3-positions of indomethacin.[2] From these findings, we considered that COX-2 selectivity could be maintained or even improved in a compound where the benzyl group and alkanoic acid moiety were connected to a naphthalene ring (**II**) instead of to the indole nucleus of indomethacin.

Chemistry

In order to confirm our hypothesis, variously substituted benzylnaphthalene derivatives were synthesized using the sequences described below.

Derivatives **1** and **4** were prepared from the commercially available tetralone **III** following the routes described in Scheme 1. $POCl_3$ promoted dehydration of the alcohol **IV**, followed by a DDQ oxidation, afforded compound **1**. The same alcohol **IV** was used in a Vilsmeier reaction and oxidation sequence to produce the aldehyde **V** which was converted into acid **4** by using a four-step procedure (Scheme 1).

The key intermediates **XI** used in the synthesis of naphthylacetic acid derivatives were prepared as shown in Scheme 2. Protection of the commercially available acids **VII** as oxazolidines followed a two-step procedure, formation of the amides **VIII** and cyclodehydration to provide ketones **IX**. Grignard reaction of the ketones **IX**

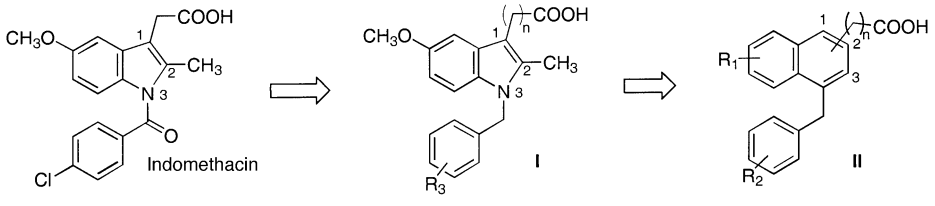

Figure 1.

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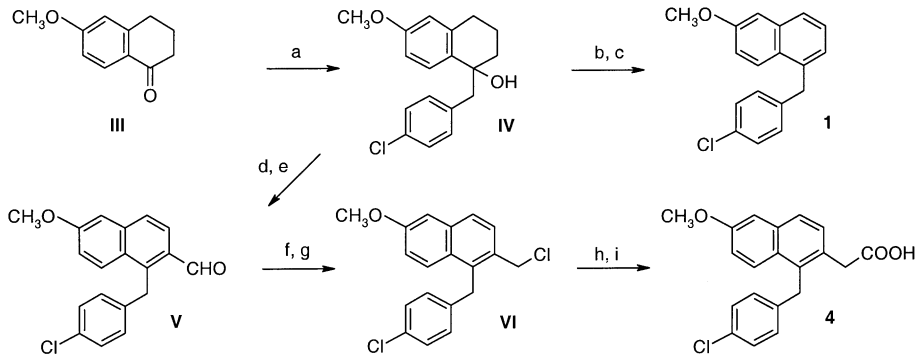
with the appropriate benzyl magnesium halides, followed by reduction of the resultant benzyl alcohols and concomitant hydrolysis of the oxazolidines with HI/AcOH, yielded acid **X**. Final cyclization with PPA resulted in the desired intermediates **XI**.

The naphthylacetic derivatives **2** and **5**–**23** were typically prepared starting from the tetralones **XI** through a Reformatsky reaction, dehydration and final DDQ aromatization sequence outlined below (Scheme 3). Alternatively, the condensation of the glyoxylic acid hydrate with **XI** followed by Zn(Hg)/HCl reduction of the carbonyl group in **XIII** and final DDQ oxidation led to compound **3**.

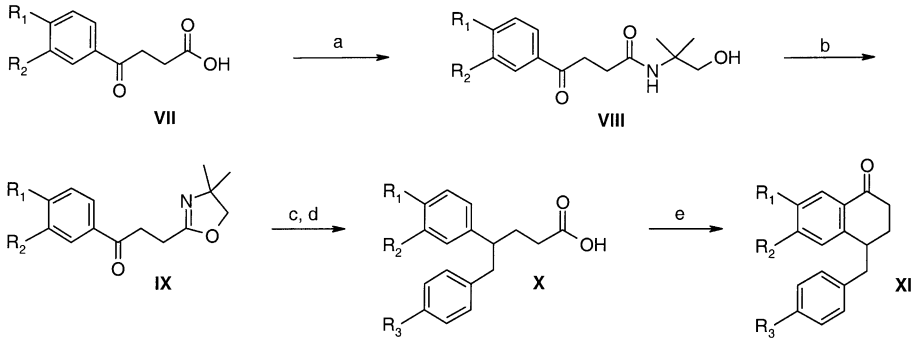
The alkylation of the corresponding enolates of esters **XII** with the appropriate alkyl halides yielded, after final hydrolysis, compounds **5** to **23** (compound **2** arose from the direct hydrolysis of the corresponding ester **XII**).

Results and Discussion

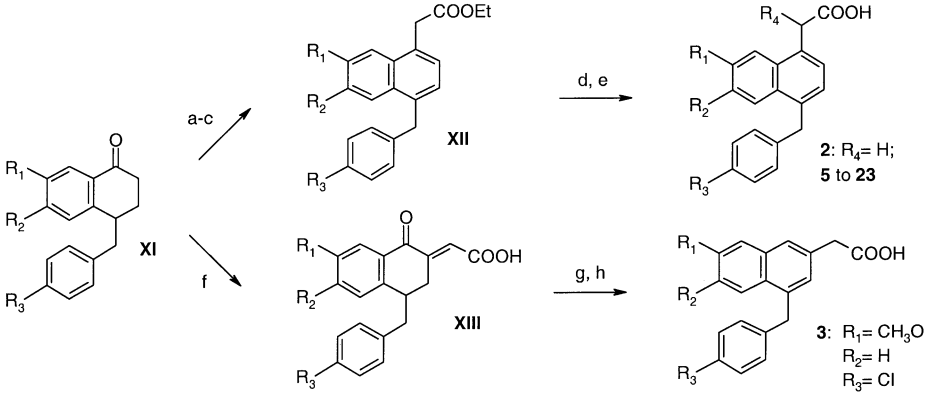
Indomethacin is a non-selective cyclooxygenase inhibitor. In our whole blood assay, it has an IC_{50} of 0.22 μM for COX-2 and 0.19 μM for COX-1, and causes gastrointestinal ulceration in rats at a dose of 10 mg/kg with a 100% incidence.[3] To avoid this gastrointestinal toxicity we pursued modifications of indomethacin that



Scheme 1. (a) $ClPhCH_2Cl$, Mg, THF; (b) $POCl_3$, benzene, reflux; (c) DDQ, benzene, reflux; (d) $POCl_3$, DMF; (e) DDQ, benzene, reflux; (f) $NaBH_4$, MeOH; (g) $SOCl_2$, CH_2Cl_2; (h) NaCN, NaI, $(CH_3)_2CO$; (i) KOH, EtOH, reflux.



Scheme 2. (a) ClCOOEt, Et_3N, $NH_2C(CH_3)_2CH_2OH$, THF; (b) p-TsOH, Xylene, reflux; (c) R_3PhCH_2X, Mg, THF; (d) HI, AcOH reflux; (e) when R_1 or $R_2 = CH_3O$; (i) K_2CO_3, Me_2SO_4, reflux; (ii) NaOH 2 N, EtOH, reflux; (iii) PPA, 70 °C. When R_1 or R_2 are not CH_3O: (i) NaOH 2 N, EtOH, reflux; (ii) PPA, 70 °C.



Scheme 3. (a) $BrCH_2COOEt$, Zn, benzene, reflux; (b) $POCl_3$, benzene, reflux; (c) DDQ, toluene, reflux; (d) LDA, R_4-X; (e) NaOH 2 N, EtOH, reflux; (f) $(HO)_2CHCOOH$, NaOH, $EtOH/H_2O$; (g) Zn(Hg), HCl; (h) DDQ, benzene, reflux.

would confer COX-2 selectivity. The first compound synthesized was structure **1** lacking the acidic moiety. This simplified structure was completely inactive at both the COX-1 and COX-2 isoenzymes (Table 1). Introduction of an alkanoic side chain at the 2- and 3-positions of the naphthalene ring also yielded inactive compounds (**3** and **4**), but substitution at position 1 (structure **2**) gave a submicromolar inhibitor of COX-2 that was essentially inactive at COX-1. This encouraging result prompted us to evaluate **2** in the carrageenan paw edema assay[3] in which it gave good anti-inflammatory activity (see Table 1). Analogues of **2** with different substituents either on the benzyl ring or on the naphthalene ring did not have any activity against either enzyme (data not shown). So, curiously, **2** was the only 2-naphthylacetic derivative that inhibited COX-2. It has been reported that the whole blood assay, originally developed by Patrignani et al.,[4] should be the model of choice to test COX inhibitors and selectivity,[5] and for that reason we routinely use it for screening purposes with slight modifications.[3] Nevertheless, because this assay does not discriminate between COX-2 and PLA_2 inhibitors, we performed an alternative assay using an endothelial cell line[6] in which arachidonic acid was provided exogenously. For all the compounds tested, we observed COX-2 inhibition in the latter assay that was completely compatible with the results of the whole blood assay, and thus discarded the involvement of PLA_2.

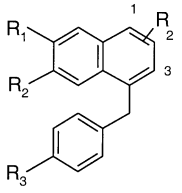
In an attempt to obtain good COX-2/COX-1 selectivity whilst maintaining in vivo activity, we prepared compounds **5**–**8** in which the acidic chain had different substituents such as methyl, dimethyl and ethyl. For ease of synthesis, we utilized the 4-fluoro substituted benzyl (**6**) as a standard, even though it was slightly less selective for COX-2. Compound **5** was more potent in COX-2 when compared with compound **2**, but in addition, it also dramatically improved its potency in COX-1. Ethyl and dimethyl substituted compounds (**7**, **8**) were weaker at COX-2. The 2-naphthylpropionic acid derivative **5** exhibited excellent activity in the carrageenan assay. Unfortunately, it also produced ulceration in rats with an $ED_{50} = 40$ mg/kg when administered daily for 4 days. This was probably due to its inhibition of the COX-1 isoenzyme ($IC_{50} = 4.10\,\mu M$).

Taking compounds **5** and **6** as leads, we explored several substitutions at the R_1 position. Among these, we introduced chlorine (**9**), ethyl (**10**), methylthio (**11**), methylsulfone (**12**) (a group typical of some selective COX-2 inhibitors) and hydrogen (**13**). All of these groups resulted in IC_{50} values for COX-2 inhibition well above 3 μM. In an attempt to mimic the methoxy substitution of naproxen, we moved the methoxy group from position 7 to 6 of the naphthalene ring to provide **14**, but again lost inhibitory activity at both enzymes.

In Table 2, we present the results of varying substitution at the benzyl ring. For the chlorine substitution, it is clear that the *para* position is the most preferred for both potency in COX-2 and selectivity (**5**, **15** and **16**). Introduction of hydrogen instead of chlorine (**17**) led to an improved potency at both enzymes but an overall decrease in selectivity.

We evaluated the effect of *para*-alkyl substitution. In the case of the methyl group (**18**) we saw an improvement in both COX-2 and COX-1 potency, and in selectivity for COX-2. The sterically demanding *t*-butyl group (**20**) produced a significant loss in both COX-1 and COX-2 activity. The ethyl group (**19**) prompted a loss in

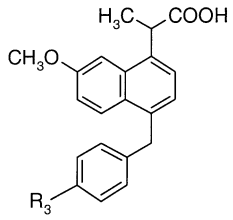
Table 1. In vitro and in vivo results for 4-benzylnaphthylacetic acids



Compound	R	R_1	R_2	R_3	COX-2[a]	COX-1[a]	Carrageenan[b] % inhib. (mg/kg)
1	H	CH_3O	H	Cl	50.4±15.2	>100	IN (30)
2	1-CH_2COOH	CH_3O	H	Cl	0.88±0.50	>100	52% (30)*
3	2-CH_2COOH	CH_3O	H	Cl	10.5±0.50	>100	IN (30)
4	3-CH_2COOH	CH_3O	H	Cl	11.0±1.40	>100	IN (30)
5	1-$CH(CH_3)COOH$	CH_3O	H	Cl	0.52±0.32	4.10±2.16	50% (30)*
6	1-$CH(CH_3)COOH$	CH_3O	H	F	0.74±0.34	1.70±0.57	53% (30)*
7	1-$CH(CH_3CH_2)COOH$	CH_3O	H	F	2.00±1.20	7.30±0.25	IN (30)
8	1-$C(CH_3)_2COOH$	CH_3O	H	F	6.38±1.45	35.80±3.14	IN (30)
9	1-$CH(CH_3)COOH$	Cl	H	Cl	11.0±2.1	>100	IN (30)
10	1-$CH(CH_3)COOH$	CH_3CH_2	H	Cl	8.20±0.79	61.00±10.2	IN (30)
11	1-$CH(CH_3)COOH$	CH_3S	H	Cl	4.20±0.87	19.90±0.35	16% (30)
12	1-$CH(CH_3)COOH$	CH_3SO_2	H	Cl	4.90±0.62	>100	IN (30)
13	1-$CH(CH_3)COOH$	H	H	F	3.50±0.14	2.40±0.36	16% (30)
14	1-$CH(CH_3)COOH$	H	CH_3O	F	11.40±1.18	>100	IN (30)

*$p < 0.05$.
[a]Data are indicated as IC_{50} (μM)±SEM ($n = 3$).
[b]6–7 animals per group.

Table 2. In vitro and in vivo results of benzyl-monosubstituted naphthalenes



Compound	R_3	COX-2[a]	COX-1[a]	Selectivity	Carrageenan[b] % inhib (mg/kg)
5	4-Cl	0.52±0.32	4.10±2.16	7.9	35 (3)*, 50 (30)*
6	4-F	0.74±0.34	1.70±0.57	2.3	35 (3)*, 53 (30)*
15	3-Cl	14.70±1.26	N.D.	—	0 (3), 0 (30)
16	2-Cl	1.70±0.38	2.30±0.06	1.4	5 (3), 13 (30)
17	H	0.39±0.05	1.50±0.45	3.8	30 (3)*, 58 (30)*
18	4-Me	0.22±0.04	2.80±2.13	12.7	30 (3)*, 49 (30)*
19	4-Et	1.03±0.01	>100	>97	32 (30)*
20	4-*t*-Bu	7.50±1.23	40.8±4.30	5.4	IN (3), 32 (30)*
21	4-Ac	6.60±4.15	218±6	33.0	IN (3), IN (30)
22	4-MeO	0.33±0.12	8.80±2.05	26.6	22 (3), 45 (30)*
23	4-EtO	1.70±0.53	>100	>59.0	27 (3)*, 52 (30)*
Celecoxib	—	1.10±0.20	14.2±4.40	12.9	41 (3)*, 40 (30)*
Rofecoxib	—	0.76±0.33	11.4±0.81	15.0	41 (3)*, 34 (30)*

*$p < 0.05$.
[a]Data are indicated as IC_{50} (μM)±SEM ($n = 3$).
[b]6–7 animals per group.

potency, particularly at COX-1, which resulted in a selectivity of around 100-fold. Unfortunately, this interesting result did not translate into good in vivo activity, producing only a 32% inhibition at 30 mg/kg in the carrageenan model.

The effect of 4-acetyl substitution (**21**) was loss of activity at COX-2, whereas 4-MeO substitution (**22**) produced good inhibition at this enzyme, giving rise to a 26-fold selectivity. This ratio could be increased to >59-fold with the homologous 4-ethoxy substitution but with some loss of COX-2 activity. It can be deduced from these examples that selectivity can be profoundly affected by substitution at the *para* position of the benzyl ring and that the more potent and selective structures come from smallish groups such as methyl and methoxy, giving rise to very active and selective molecules which elicit promising in vivo activity.

In conclusion, we have identified a new series of selective COX-2 inhibitors that are active in an acute in vivo model of inflammation. We have also gained an insight into the structure–activity relationships that will allow us to improve the properties of the series in the future. Further work is underway and will be reported in due course.

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