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Naphthalene/quinoline amides and sulfonylureas as potent and selective antagonists of the EP_4 receptor

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ABSTRACT

Two new series of EP_4 antagonists based on naphthalene/quinoline scaffolds have been identified as part of our on-going efforts to develop treatments for inflammatory pain. One series contains an acidic sulfonylurea pharmacophore, whereas the other is a neutral amide. Both series show subnanomolar intrinsic binding potency towards the EP_4 receptor, and excellent selectivity towards other prostanoid receptors. While the amide series generally displays poor pharmacokinetic parameters, the sulfonylureas exhibit greatly improved profile. **MF-592**, the optimal compound from the sulfonylurea series, has a desirable overall preclinical profile that suggests it is suitable for further development.

Prostanoids (prostaglandins and thromboxanes) are important lipid hormones formed from arachidonic acid metabolism. Prostaglandin E_2 (PGE_2), in particular, is the principal proinflammatory prostanoid and is implicated in the pathogenesis of a number of diseases such as pain, fever, arthritis and cancer. Inhibition of PGE_2 biosynthesis by NSAIDs and COX-2 inhibitors (Coxibs) constitutes an effective therapy to relieve inflammatory symptoms, leading to the widespread uses of these drugs as analgesics.[1] Unfortunately, their therapeutic utility is limited by their potential to cause either gastro-intestinal toxicity (by NSAIDs)[2] or cardiovascular (CV) side effects (by both NSAIDs and Coxibs).[3] Therefore, there is a vast unmet medical need to discover alternatives for treating chronic inflammatory conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA).

PGE_2 exerts its biological effects through four subtype EP receptors, EP_{1-4}. In a mouse model of collagen–antibody induced arthritis (CAIA), McCoy et al. demonstrated that the $EP_4^{-/-}$ mice are resistant to both the incidences and symptom scores of arthritis compared to the wild type controls. Conversely, $EP_{1-3}^{-/-}$ mice responded as wild type controls, suggesting that the effect of PGE_2 in chronic inflammation was mediated predominantly by the EP_4 receptor.[4] Lin et al. demonstrated that EP_4, not EP_{1-3}, contributed to inflammatory pain hypersensitivity in rats, providing further evidence that EP_4 antagonism is a valid strategy for treating inflammatory pain.[5] Using highly selective EP_1, EP_3 and EP_4 antagonists, we and others demonstrated pharmacologically that EP_4, not EP_1 or EP_3, was the primary receptor involved in joint inflammation and pain in rodent models of rheumatoid and osteoarthritis,[6,7] further supporting EP_4 antagonism as a valid strategy for treating inflammatory pain. Furthermore, EP_4 was also shown to mediate T_H1 cell differentiation and T_H17 cell expansion, and a selective EP_4 antagonist was effective in mouse models of immune inflammatory conditions such as multiple sclerosis (MS) and skin allergy.[8]

The CV adverse events associated with NSAIDs and Coxibs are not clearly understood although it is speculated that the prothrombotic and hypertensive effects are caused by inhibition of prostacyclin biosynthesis.[9] It is plausible that a selective EP_4 antagonist may ameliorate symptoms of chronic inflammation without the potential CV side effects observed with NSAIDs and COX-2 inhibitors since they should not interfere with the biosynthesis of any of the prostanoids including prostacyclin and thromboxanes. In addition to its role in inflammation, the EP_4 receptor has also been implicated in migraine headaches,[10] in destabilizing atherosclerotic plaques in human,[11] and in angiogenesis and tumor metastasis.[12] Therefore, EP_4 antagonists represent potential promising new therapeutic agents for treating pain, atherosclerosis and cancer.

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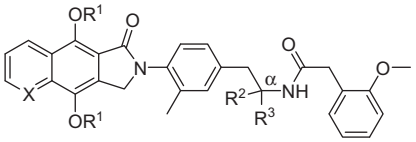
We have previously disclosed our progress in this area which led to the discovery of the quinoline acylsulfonamide series of EP_4 antagonists, typified by **MF-310** (Fig. 1).[13] This compound was a highly potent antagonist of the EP_4 receptor (K_i = 0.74 nM) and was only moderately protein-shifted (~five-fold in the presence of 10% human serum). A major drawback of this acylsulfonamide was its species dependent, CYP 3A mediated acylsufonamide hydrolysis, leading to variable drug levels of the parent and high levels of the corresponding sulfonamide **M1** as a circulating metabolite. We reported previously one of our successful strategies to alleviate this problem by replacing the acylsulfonamide pharmacophore with a carboxylic acid bioisostere.[14,15] We report herein another successful strategy to alleviate these problems by modifying the acylsulfonamide moiety with an alternative acidic (sulfonylurea) or non-acidic (amide) moiety and the discovery of a sulfonylurea analog **MF-592** (Fig. 1), a highly potent and selective EP_4 antagonist with vastly improved metabolic stability.

We initially focused on replacement with the amide pharmacophore. We have previously shown that *ortho*-methoxy phenyl acetate was a privileged substitution for the eastern portion of the acylsulfonamide class of EP_4 antagonists,[13] thus this moiety was selected as a starting point for optimization (Table 1). For the initial lead, diethoxy naphthalene substitution was selected for the scaffold, and the amide was unsubstituted at the α-position (**1a**, Table 1). Gratifyingly, it was found that this amide retained the excellent binding affinity and acceptable protein shift profile, indicating the acidic nature of the acylsulfonamide was not crucial for EP_4 affinity. As was shown for the acylsulfonamides, diethoxy substitution of the western aromatic framework was optimal, as difluoromethoxy (**1b**, Table 1) and trifluoroethoxy (**1c**, Table 1) replacements led to a reduction in potency and an increase in protein shift. Further, analogs with the quinoline template (**1d**, Table 1) were equipotent to the one containing a naphthalene (**1a**, Table 1), which was also observed for the acylsulfonamide series. Taken together, these observations indicated preferred structural features were common to the amides and acylsulfonamides, suggesting that the

Table 1
Scaffold SAR for the amide series of EP_4 antagonists



Entry	X	R^1	R^2	R^3	Compd	EP_4 K_i[a] (nM)	
						0% HS	10% HS
1	CH	CH_2CH_3	H	H	**1a**	0.32	2.7
2	CH	CHF_2	H	H	**1b**	0.71	8.4
3	CH	CH_2CF_3	H	H	**1c**	4.4	104
4	N	CH_2CH_3	H	H	**1d**	0.87	2.6
5	N	CH_2CH_3	H	Me	**1e**	0.67	1.3
6	CH	CH_2CH_3	$-CH_2CH_2-$		**1f**	0.20	0.68

[a] Values are means from at least three experiments; HS = human serum; For details of the EP_4 binding assay see Refs. 6 and 16.

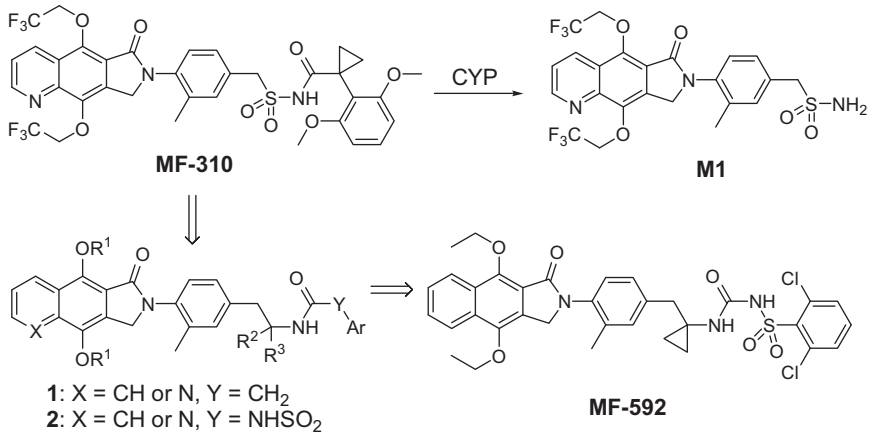


Figure 1. Metabolic liability of **MF-310** and structural-activity optimization to **MF-592**.

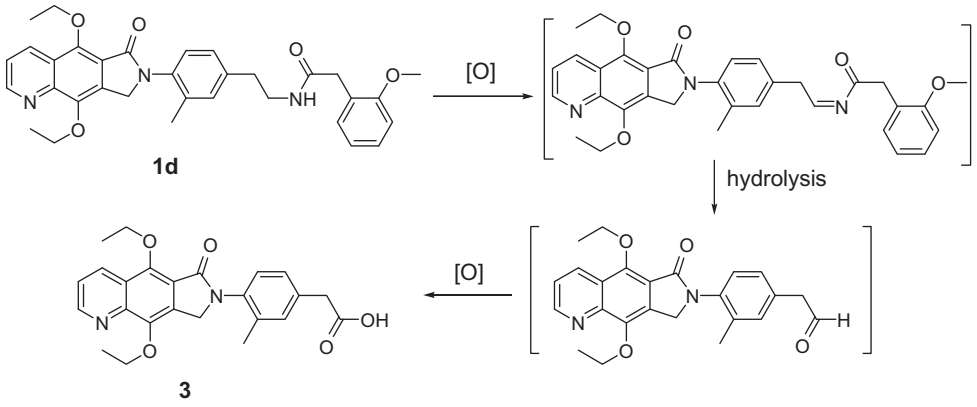
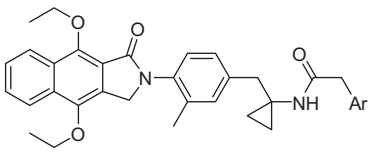
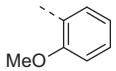
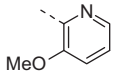
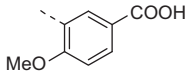
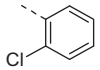
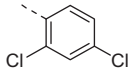


Figure 2. Proposed metabolic pathway for formation of acid **3** from dosing compound **1d** in rat.

Table 2
Phenacetyl SAR for the amide series of EP_4 antagonists



Entry	Ar	Compd	EP_4 K_i[a] (nM)		EP_4 IC_{50}[b] (nM)	
			0% HS	10% HS	0% HS	10% HS
1		**1f**	0.20	0.68	4.6	16.0
2		**1g**	0.16	1.44	4.9	23.6
3		**1h**	0.18	6.2	3.8	60.6
4		**1i**	0.32	1.3	6.0	35.1
5		**1j**	0.34	0.53	2.1	10.2

[a] Values are means from at least three experiments.
[b] Values are means from two to four experiments; HS = human serum; for details of the EP_4 binding and functional assays, see Refs. 6 and 16.

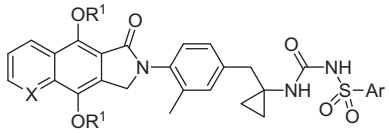
two series likely had a conserved binding mode. Substitution of the α-position of the amide was also tolerated (**1e** and **1f**, Table 1). The cyclopropyl substitution (**1f**), in particular, resulted in a significant reduction in protein shift. In addition, this substitution improved the metabolic stability of these molecules by preventing formation of the corresponding carboxylic acid **3** (observed as one of the major circulating metabolites after oral dosing of compound **1d** in rat), presumably by shutting down the formation of the imine from α-hydroxylation of the CH_2NH moiety and subsequent hydrolysis (to form the corresponding aldehyde) and further oxidation to acid **3** (Fig. 2).

With an optimal scaffold selected, further optimization of the phenacetyl moiety was investigated (Table 2). We were interested in modulation of the polarity of this region, and it was found that basic (**1g**, Table 2) and acidic (**1h**, Table 2) substitution were tolerated in terms of inherent binding potency, although the extent of protein shift was significantly increased when an acidic residue was present. Similar to the acylsulfonamide series, it was also found that chlorine was an adequate replacement for the methoxy substituent (**1i** and **1j**, Table 2). These compounds were also shown to exhibit excellent selectivity against other prostanoid (PG) receptors. For example, **1f** was found to be >2000-fold selective for EP_4 versus other receptors, namely EP_{1-4}, DP_1, DP_2, FP, IP and TP.

While the amide series of EP_4 antagonists generally showed excellent affinity and selectivity profile, these compounds suffered from poor pharmacokinetics in rat, with short elimination half-lives ($t_{1/2}$ <1 h) and high clearance rates. Further in vitro and in vivo metabolism studies indicated that extensive and complex oxidative metabolism were the likely culprit for the observed short $t_{1/2}$. As a result, we shifted our attention to the corresponding sulfonylurea analogs. Once again, the general SAR in this series tracked with that observed for the acylsulfonamide and the amide series so only a few representatives are shown in Table 3.

As shown, compounds incorporating the bis-trifluroethoxy-quinoline template seen in **MF-310** (**2c** and **2k**, Table 3) generally gave compounds with significantly higher serum protein shift. *para*-Substitution on the phenylsulfonamide moiety (**2a**, **2l** and **2m**, Table 3) also generally gave compounds with more significant protein shift. Other arylsulfonamides such as naphthalenesulfonamide (**2g** and **2k**, Table 3) were tolerated but had no advantage. *ortho*-Substitution on the phenylsulfonamide moiety was generally preferred (**2b–2e**, **2h** and **2j**, Table 3) and 2,6-bis-substitution (**2f**, **2i** and **2o**, Table 3) was optimal for potency in the human whole blood (HWB) assay.[15] The 2,6-di-Cl analog **2f** (**MF-592**), in particular, exhibited good EP_4 affinity (K_i = 0.3 nM, shifted to 3.1 nM in

Table 3
SAR of sulfonylurea series of EP_4 antagonist



Entry	Ar	R^1	X	Compd	EP_4 K_i[a] (nM)		EP_4 IC_{50}[b] (nM)		HWB IC_{50}[c] (nM)
					0% HS	10% HS	0% HS	10% HS	
1	*p*-MePh	Et	CH	**2a**	0.11	10	1.5	17	613
2	*o*-ClPh	Et	CH	**2b**	0.16	2.3	2.4	33	423
3	*o*-ClPh	CH_2CF_3	N	**2c**	0.48	14	3.0	48	ND[d]
4	*o*-MePh	Et	CH	**2d**	0.23	3.0	3.3	14	ND
5	*o*-MeOPh	Et	CH	**2e**	0.17	3.0	3.8	23	162
6	**2,6-Di-ClPh**	**Et**	**CH**	**2f** (**MF-592**)	**0.30**	**3.1**	**3.0**	**14**	**78**
7	2-Naphthyl	Et	CH	**2g**	0.52	6.3	2.5	37	ND
8	*o*-CF_3Ph	Et	CH	**2h**	0.39	8.9	3.3	28	ND
9	2,6-Di(MeO)Ph	Et	CH	**2i**	0.34	1.6	3.3	21	102
10	*o*-BrPh	Et	CH	**2j**	0.49	7.5	2.2	22	ND
11	2-Naphthyl	CH_2CF_3	N	**2k**	1.2	21	8.9	103	ND
12	*p*-CF_3OPh	Et	CH	**2l**	0.66	57	8.3	370	ND
13	*p*-FPh	Et	CH	**2m**	0.48	21	4.6	80	ND
14	2,3-Di-ClPh	Et	CH	**2n**	0.40	64	2.0	28	ND
15	2,6-Di-MePh	Et	CH	**2o**	0.40	1.6	3.2	19	77

[a] Values are means from at least three experiments.
[b] Values are means from one to eight experiments; HS = human serum; for details of the EP_4 binding and functional assays, see Refs. 6 and 16.
[c] Average of 2–4 experiments, for details of the human whole blood assay, see Ref. 15.
[d] ND = not done.

Table 4
Pharmacokinetic parameters of **MF-592**

Species	SD rat	Beagle dog
Dose[a] (iv/po, mg/kg)	5/20	1/4
CL (mL/kg/min)	11	1.2
$t_{1/2}$ (h)	6.6	4.3
F (%)	84	100
po AUC_{0-24} (μM·h)	37.4	101.1

[a] Both iv and po doses were administered as aqueous solutions of the sodium salt in 60% PEG-200.

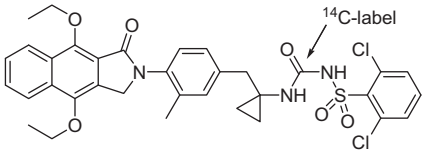


Figure 3. Structure of ^{14}C-labeled **MF-592**.

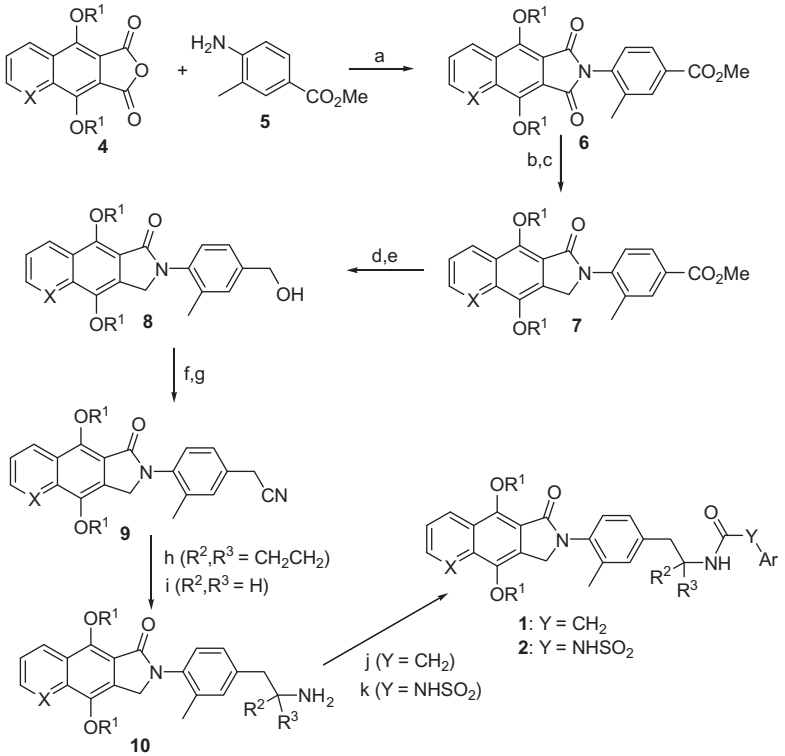
presence of 10% HS) and functional potency (IC_{50} = 3 nM, shifted to 14 nM in presence of 10% HS), and good potency in the whole blood assay with an IC_{50} of 78 nM. It also showed excellent selectivity (>1300-fold) against other PG receptors. This compound was profiled further and the results are discussed in the following sections.

First, the pharmacokinetic profile of **MF-592** was evaluated in SD rats and Beagle dogs, and the results are summarized in Table 4. As shown, this compound exhibited excellent oral bioavailability in both rats (F = 84%) and dogs (100%), along with moderate to low clearance rates (1.2–11 mL/kg/min) and good elimination $t_{1/2}$ (4.6–6.6 h). All these contributed to the observed high oral exposures, especially in dogs.

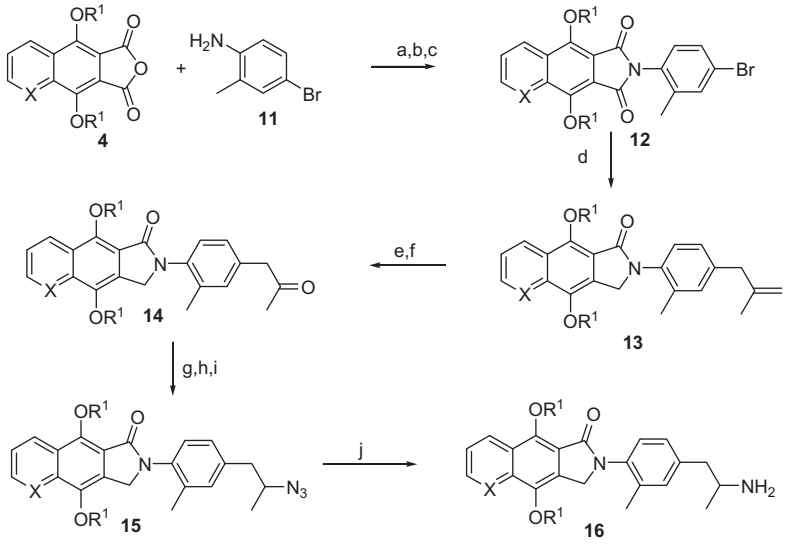
To ascertain that **MF-592** did not have the same liability as observed with **MF-310**, its metabolic profile was evaluated extensively in vitro and in vivo. When the ^{14}C-labeled **MF-592** (Fig. 3, prepared according to Scheme 1 using commercially available ^{14}C-labeled ethyl chloroformate) was incubated in NADPH fortified rat and human liver microsomes at 37 °C for 1 h, 97% and 90% of the parent was recovered, respectively. Acceptable levels of covalent protein labeling (31 and 23 pmol-equiv/mg-protein@1 h in rat and human liver microsomes, respectively) were observed in the same experiments. Similarly, when incubated in cryopreserved or freshly isolated rat and human hepatocytes for 2 h at 37 °C, 91% and 96% of the parent was recovered, respectively. Several very minor oxidative metabolites were also detected. The potential for covalent protein binding in vivo was evaluated in SD rats after oral dosing (20 mg/kg, 150 μCi/kg in 60% PEG-200). Very low levels of residual radioactivity (<10 pmol-equiv/mg-protein) was observed at 24 h in both the plasma and the liver, reflecting the observed robust metabolic stability and minimal potential for bioactivation observed in vitro. Furthermore, no sulfonylurea hydrolysis was detected from all these experiments. This is in direct contrast to the acylsulfonamide series which is plagued with species dependent, CYP mediated acylsulfonamide hydrolysis.

The in vivo potency and efficacy of **MF-592** was evaluated in the chronic rat adjuvant-induced-arthritis (AIA) model. The ED_{50} was established at 0.1 mg/kg/day, which was significantly more potent than has been reported for potent COX-2 inhibitors (0.5–0.7 mg/kg/day).[15]

The synthesis of these compounds can be accomplished according to Scheme 1 and Scheme 2. Starting with anhydride **4**,[13] condensation with methyl 4-amino-3-methylbenzoate (**5**) in refluxing acetic acid gave imide **6** in high yield. Deoxygenation was accomplished in two-steps, reduction with $NaBH_4$ to give the hemiaminal which was subsequently reduced to lactam **7** with triethylsilane in the presence of trifluoacetic acid. The methyl ester



Scheme 1. Reagents and conditions: (a) reflux AcOH; (b) $NaBH_4$, THF/MeOH; (c) Et_3SiH, TFA/CH_2Cl_2; (d) LiOH, THF/MeOH/H_2O; (e) BH_3–DMS, THF; (f) MsCl, triethylamine, CH_2Cl_2; (g) NaCN, DMF; (h) EtMgBr, Ti(O*i*Pr)$_4$, THF then BF_3–OEt_2; (i) BH_3–DMS, THF then MeOH and HCl; (j) $ArCH_2CO_2H$, EDC, DMAP, CH_2Cl_2; (k) $ArSO_2NHC(O)OEt$, Hünig's base, THF.



Scheme 2. Reagents and conditions: (a) reflux AcOH; (b) $NaBH_4$, THF/MeOH; (c) Et_3SiH, TFA/CH_2Cl_2; (d) 2-tri-*n*-butylstannylpropene, $Pd(PPh_3)_4$, tol.; (e) OsO_4, NMO, acetone/water; (f) $NaIO_4$, acetone; (g) $NaBH_4$, ethanol; (h) MsCl, triethylamine, CH_2Cl_2; (i) NaN_3, DMF; (j) H_2, Pd/C, ethanol.

was hydrolyzed to the acid which was reduced to alcohol **8** using BH_3–DMS. Conversion of the alcohol to the mesylate followed by treating with NaCN gave benzylic nitrile **9**. Nitrile **9** could be reduced directly with BH_3–DMS to amine **10** ($R^2 = R^3 = H$). Alternatively, **9** could be converted to the cyclopropylamine (R^2, $R^3 = CH_2CH_2$) according to the Szymoniak variation[17] of the Kulinkovich reaction. Standard amide coupling of amine **10** and an appropriate acid furnished the amide derivatives **1**. Alternatively, amine **10** was reacted with an appropriate ethyl (arylsulfonyl)carbamate (commercially available or easily prepared from arylsulfonamide and ethyl chloroformate in the presence of a suitable base[18]) to give the corresponding sulfonylurea analogs **2**.

Compounds bearing an α-Me substitution (e.g., **1e**) were prepared according to Scheme 2. Condensation of anhydride **4** with 4-bromo-2-methylaniline (**11**) followed by a similar deoxygenation sequence gave lactam **12**. Stille coupling of the bromide with 2-tri-*n*-butylstannylpropene using $Pd(PPh_3)_4$ as the catalyst gave alkene **13** which was converted to ketone **14** in two-steps: dihydroxylation with OsO_4 to give the diol; and oxidative diol cleavage with $NaIO_4$. Ketone **14** was then transformed to azide **15** in three-steps: reduction with $NaBH_4$, formation of mesylate and SN2 reaction of the mesylate with sodium azide. Reduction of azide **15** under the standard hydrogenation conditions gave amine **16** which was converted to the amide or sulfonylurea analogs under the aforementioned conditions.

In conclusion, we have described the identification and SAR optimization of two new series of EP_4 antagonists, the amides and sulfonylureas. While the neutral amide analogs suffered from poor pharmacokinetics due to extensive oxidative metabolism, the sulfonylureas exhibited a greatly improved metabolic stability and pharmacokinetic profile. **MF-592**, the optimal compound from these efforts, exhibited the desired potency, selectivity, metabolic stability and pharmacokinetic profiles that suggest that it is suitable for further development.

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