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2-PYRIDINYL-3-(4-METHYLSULFONYL)PHENYLPYRIDINES: SELECTIVE AND ORALLY ACTIVE CYCLOOXYGENASE-2 INHIBITORS

Richard W. Friesen,* Christine Brideau, Chi Chung Chan, Stella Charleson, Denis Deschênes, Daniel Dubé, Diane Ethier, Réjean Fortin, Jacques Yves Gauthier, Yves Girard, Robert Gordon, Gillian M. Greig, Denis Riendeau, Chantal Savoie, Zhaoyin Wang, Elizabeth Wong, Denise Visco, Li Jing Xu, and Robert N. Young

Merck Frosst Centre for Therapeutic Research
P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8

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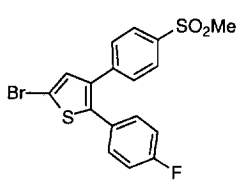
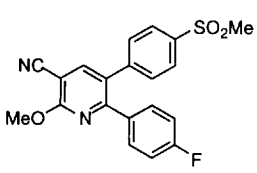
Abstract. A series of novel 2-pyridinyl-3-(4-methylsulfonyl)phenylpyridines has been synthesized and evaluated with respect to their ability to inhibit the isozymes of cyclooxygenase, COX-1, and COX-2. Optimum COX-2 activity is observed by introduction of a substituent at C5 of the central pyridine. 5-Chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine **33** was identified as the optimum compound in this series.

Nonsteroidal antiinflammatory drugs (NSAIDs) used for the treatment of inflammatory conditions act by inhibition of cyclooxygenase (COX), the first enzyme involved in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid. The major COX isozyme, COX-1, is expressed as a constitutive enzyme and is involved in homeostasis of the gastrointestinal (GI) tract (in addition to other functions).[1] Recently, the discovery[2] of an inducible COX isozyme, commonly referred to as COX-2 and expressed principally in inflammatory tissue, has led several groups to search for selective inhibitors of COX-2.[3] The rationale behind these investigations is that such a selective COX-2 inhibitor will greatly reduce the side-effect profile, including gastric ulceration, that is commonly associated with the chronic use of traditional NSAIDs.[1] One series of selective COX-2 inhibitor that has been described is characterized by a 1,2-bisaryl pharmacophore and is illustrated by the original lead for this class, DuP 697.[4] Not surprisingly, both benzene[5] and pyridine[5c,6] rings have been used as replacements for the central thiophene ring. In the pyridine series, several substituted analogs such as **1**[6a] and **2**[6b] were reported to be highly selective COX-2 inhibitors but the in vitro potency did not translate in vivo (16 and 12% inhibition, respectively, at 10 and 20 mg/kg in the rat paw edema assay). Herein, we describe the discovery and SAR of a series of orally active 2-pyridinyl-3-(4-methylsulfonyl)phenylpyridines **A**, which are potent and selective COX-2 inhibitors.[7]



DuP-697



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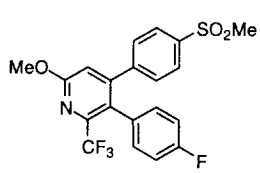

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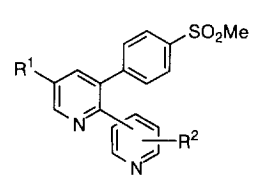

A

Chemistry

In general, the synthetic strategy used to prepare the substituted pyridines **A** was based on palladium-catalyzed cross-coupling reactions of pyridine halides or triflates, employing either pyridinyl boronic acids or

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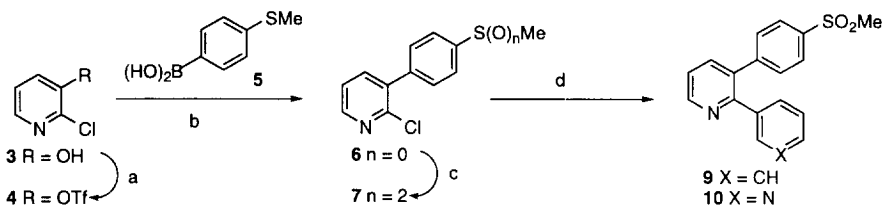
boronates (Suzuki reaction[8]) or pyridinyl stannanes (Stille reaction[9]) as the organometallic partner. The 2,3-disubstituted pyridines were prepared as is shown in Scheme 1. Conversion of the hydroxy pyridine **3** to the corresponding triflate **4** followed by Suzuki coupling with one equivalent of 4-methylthiobenzene boronic acid **5**[10] yielded the mono-coupled product **6** (22%) together with bis-coupled product and starting material. Oxidation to the sulfone **7** (95%) followed by a second Suzuki coupling with benzene boronic acid or 3-pyridinyl boronate **8** provided the 2-phenylpyridine **9** (75%) and the bispyridine **10** (82%), respectively.

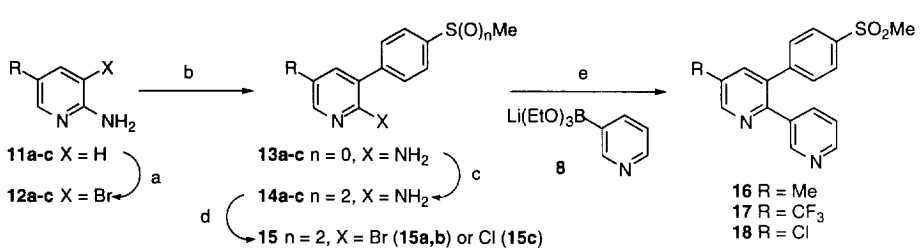
Scheme 1



Reagents: (a) Tf_2O, Et_3N, CH_2Cl_2, -78 to 0 °C (95%); (b) $Pd(Ph_3P)_4$ (cat.), 2 N Na_2CO_3, EtOH/PhH (1/1), reflux (22%); (c) OsO_4 (cat.), NMO•H_2O, acetone/H_2O (95/5) (95%); (d) benzene boronic acid or **8**, $Pd(Ph_3P)_2Br_2$ (cat.), 2 N Na_2CO_3, PhMe/*n*-PrOH (1/1), reflux.

The 2,3,5-trisubstituted pyridines were typically prepared as shown in Schemes 2 and 3 from commercially available 2-amino-5-substituted pyridines **11** (R = Me (**11a**); R = CF_3 (**11b**); R = Cl (**11c**)). Regioselective bromination using bromine in acetic acid afforded the 3-bromo derivatives **12**. Suzuki coupling with **5** followed by oxidation yielded the 2-aminopyridines **14**. Conversion of **14a,b** to the 2-bromopyridines **15a,b** was accomplished by treatment with sodium nitrite and bromine in 48% HBr. Alternatively, the 2,5-dichloropyridine **15c** was prepared by initial conversion of **14c** to the corresponding 2-pyridone with aqueous sodium nitrite in concentrated HCl, followed by reaction with neat $POCl_3$ at 150 °C. Again, Suzuki coupling with 3-pyridinyl boronate **8** yielded the bispyridines **16–18** (35–88%).

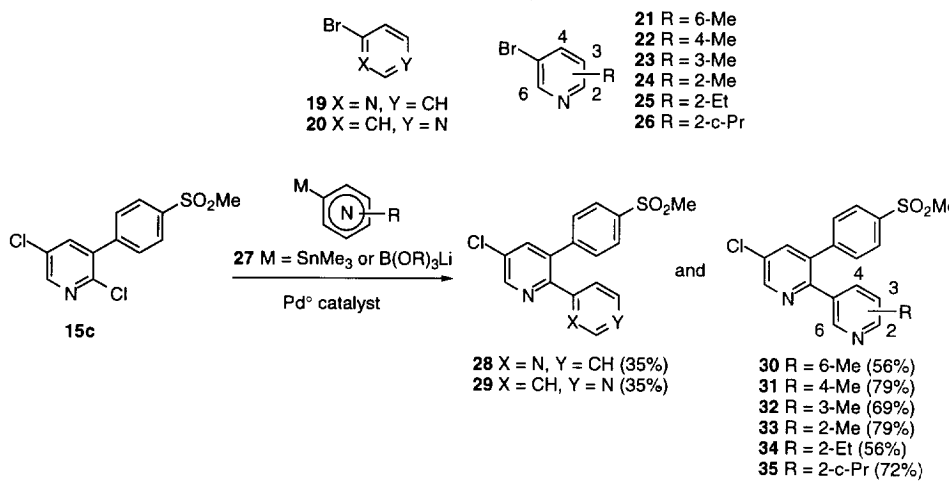
Scheme 2



Reagents: (a) Br_2, HOAc, 25 °C (83–91%); (b) **5**, $Pd(Ph_3P)_4$ (cat.), 2 N Na_2CO_3, EtOH/PhH (1/1), reflux (83–93%); (c) OsO_4 (cat.), NMO•H_2O, acetone/H_2O (95/5) (86–93%); (d) X = Br: $NaNO_2$, 48% HBr, Br_2, 0–25 °C (64–67%); X = Cl: $NaNO_2$, HCl, 25 °C; neat $POCl_3$, 150 °C (72%); (e) $Pd(Ph_3P)_2Br_2$ or $Pd(Ph_3P)_2Cl_2$ (cat.), 2 N Na_2CO_3, PhMe/*n*-PrOH (1/1) or EtOH/PhH (1/1), reflux (35–88%).

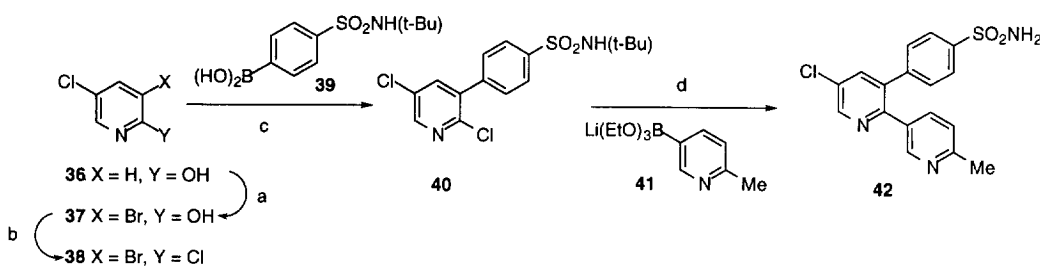
The bispyridines **28–35** were prepared via Suzuki or Stille cross-coupling reactions of 2,5-dichloropyridine **15c** (Scheme 3). The metalated pyridines **27** were derived from commercially available pyridines **19** and **20** or readily prepared bromo pyridines **21–26**[11] by lithium-halogen exchange with n-BuLi in ether at -78 °C, followed by the addition of trimethyltin chloride (**19**) or triisopropyl borate (**20–26**) and warming to 0 °C. We have found that the resulting crude boronates are suitable for subsequent use in the Suzuki reaction.

Scheme 3



Finally, the pyridinyl sulfonamide **42** was prepared as shown in Scheme 4 from 5-chloro-2-hydroxypyridine **36** via the intermediacy of dichloride **38**. Sequential Suzuki couplings with the 4-t-butylaminosulfonylbenzene boronic acid **39**[12] and the pyridinyl boronate **41**, followed by TFA hydrolysis of the t-butyl protecting group, provided the sulfonamide **42**.

Scheme 4



Reagents: (a) Br_2, HOAc, 25 °C (58%); (b) neat $POCl_3$, reflux (92%); (c) $Pd(Ph_3P)_2Cl_2$ (cat.), 2 N Na_2CO_3, EtOH/PhH (1/1), reflux (35%); (d) conditions (c) followed by neat TFA, 25 °C (51%).

Results and Discussion

The in vitro inhibition of the COX-1 and COX-2 isozymes by the pyridines **9**, **10**, **16–18**, **28**, **29**, **30-35** and **42** is presented in Table 1, together with comparative data for indomethacin (Indo) and DuP-697.

Inhibition of COX-1 was determined using a highly sensitive microsomal assay at subsaturating arachadonic acid concentration.[13] Also tabulated is the data generated from in vivo testing of a number of the more potent compounds (IC_{50} in human whole blood (HWB) assay <2 μM), namely the oral absorption in rats (as reflected by the maximal plasma concentration (C_{max})) and the efficacy in both the rat paw edema and rat pyresis assays upon oral administration.

Table 1. Bispyridine Cyclooxygenase Inhibitors

Compound	COX-2		COX-1[c]	Plasma	Rat Models	
	CHO[a]	HWB[b]	IC_{50} (μM)	Concentration[d]	Paw Edema[e]	Pyresis[e]
	IC_{50} (μM)			C_{max} (μM), Time (h)	ED_{50} (mg/kg)	
9	0.06 ± 0.03	7.9 ± 2.1	20 ± 2	40, 0.5	>10	
10	0.61 ± 0.13	>33	>100			
16	0.35 ± 0.05	2.1 ± 0.6	59 ± 2			
17	0.090 ± 0.001	1.8 ± 0.4	31 ± 9	24, 2	1.7	1.4
18	0.034 ± 0.011	0.9 ± 0.3	19 ± 2	52, 2	2.3	0.8
28	0.068 ± 0.001	5.8 ± 1.0	63 ± 2			
29	0.101 ± 0.003	7.0 ± 0.6	81 ± 3			
30	1.33 ± 0.25	2.6 ± 0.2	45 ± 7			
31	0.83 ± 0.11	2.7 ± 0.7	>100			
32	0.087 ± 0.009	3.8 ± 1.1	>100			
33	0.081 ± 0.010	1.1 ± 0.1	12 ± 2	30, 1	0.6	0.5
34	0.050 ± 0.020	1.7 ± 0.5	13 ± 3	9, 0.5	1.6	2.6
35	0.016 ± 0.008	1.8 ± 0.5	6 ± 1	9, 2	2.0	4.9
42	0.023 ± 0.010	2.4 ± 0.3	0.8 ± 0.2			
Indo	0.026 ± 0.006	0.5 ± 0.1	0.020 ± 0.001		2.0	1.1
DuP-697	0.002 ± 0.001	0.06 ± 0.01	0.007 ± 0.003	0.7, 2	1.3	n.d.

[a] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid-stimulated CHO cells stably expressing human COX-2 as described in ref 14. [b] IC_{50} values for inhibition of PGE_2 produced by lipopolysaccharide-challenged HWB as described in ref 15. [c] IC_{50} values for inhibition of PGE_2 produced by microsomes from U937 cells incubated with a low concentration of arachidonic acid as described in ref 13. For all the in vitro assays, each value is reported as either ± a range of values (n = 2) or ± SEM (n ≥ 3). [d] Plasma concentration in rats when administered at 20 mg/kg in 1% methocel. [e] Ref 16.

The lead pyridine compound, 2-phenyl-3-(4-methylsulfonyl)phenylpyridine **9**, had previously been described by the group from Dupont-Merck[5c] and they concluded that preferred inhibitors of COX-2 possessed a nonpolar central scaffolding ring. Indeed, we have found that although **9** is a potent inhibitor of COX-2 in the CHO assay (IC_{50} = 60 nM) and is selective (COX-1 IC_{50} = 20 μM), the IC_{50} for COX-2 inhibition is highly shifted in the presence of human serum. As a result, the in vitro potency observed in the CHO cell assay does not translate in vivo (ED_{50} >10 mg/kg in the rat paw edema model). By introducing

appropriate substituents on the central pyridine moiety in conjunction with replacing the phenyl moiety by substituted pyridine derivatives, we have discovered a new class of COX-2 inhibitors in which the in vitro potency translates into orally active antiinflammatory agents.

Replacement of the phenyl substituent in **9** by a 3-pyridinyl moiety (**10**) reduced the inhibitory potency against COX-2 by an order of magnitude. However, by replacing the proton at C5 on the central pyridine ring with substitutents of varying electronegativity (**16–18**), the IC_{50} against COX-2 was found to decrease in the order Me>CF_3>Cl. Indeed, the COX-2 inhibitory potency and selectivity of the trifluoromethyl and chloro analogs (**17** and **18**, respectively) are similar to **9**. This substituent effect on potency suggests that the basicity of the pyridine nitrogen atoms may have an important effect in modulating the binding of these inhibitors to COX-1 and COX-2. Of equal importance, **18** exhibits a 10-fold improvement in potency in the COX-2 HWB assay when compared with **9**. Moreover, this improvement in HWB in vitro potency translates in vivo, as evidenced by efficacy in models of both inflammation (rat paw edema) and pyrexia (rat pyresis). In this series, the position of attachment of the pendant pyridine isomer is important. Although both the 2- and 4-pyridinyl isomers of **18**, (**28** and **29**, respectively) are potent and selective COX-2 inhibitors, they are significantly shifted in the HWB assay.

It was found that upon oral dosing of **18** in rats at 20 mg/kg, the plasma levels after 24 h were in excess of 4 μM, suggesting an extremely long half-life. We therefore explored the effect of introducing an alkyl substituent on the 2-pyridinyl moiety of **18** with the aim of providing a potential site of metabolism which may aid in the clearance of the drug in vivo. The four methyl substituted isomers of **18** (**30–33**) were prepared and, as can be seen from Table 1, the in vitro potency against COX-2 is significantly affected by this substituent. The optimum compound is the 2-methyl isomer **33**, which retains good COX-2 inhibitory potency (IC_{50} = 81 nM) and selectivity while still possessing good potency in the whole blood assay and in the in vivo assays. While the 2-ethyl and 2-cyclopropyl analogs of **33** (**34** and **35**, respectively) are 1.5–5 times more potent inhibitors of COX-2 in CHO cells than **33**, their potency in HWB is more highly shifted and, thus, they exhibit slightly reduced efficacy in the in vivo models when compared with **33**. Finally, as has been observed in other related series,[3] the sulfonamide analog of **33** (**42**), displays a 3.5-fold increase in potency against COX-2 but this is accompanied by a 15-fold increase in COX-1 inhibition.

The selective, bispyridine COX-2 inhibitor **33** (L-791,456) is orally bioavailable and well behaved in rats with a half-life of approximately 2 h. The in vivo profile of **33** compares favourably with indomethacin and DuP-697. On the basis of its in vitro and in vivo profile, bispyridine **33** was selected for further evaluation and, as a result, was subjected to the highly stringent ^{51}Cr excretion model of ulcerogenicity[16] in order to address the issue of GI toxicity. Dosing of **33** in rats at 100 mg/kg (note that this dose is 170 times the efficacious dose based on the rat paw edema assay (ED_{50} = 0.6 mg/kg)), bid, for 10 days had no effect on urinary ^{51}Cr excretion. In contrast, single doses (10 mg/kg) of the nonselective NSAIDs indomethacin and diclofenac resulted in ^{51}Cr leakage 20–50 times that of controls.[16] Additional in vivo testing of **33** demonstrated that it was effective in models of carrageenan-induced hyperalgesia in rats[16] (ID_{50} = 0.3 mg/kg compared to indomethacin ID_{50} = 1.5 mg/kg) and adjuvant-induced arthritis in rats[17] (ID_{50} = 0.7 mg/kg/day/bid compared to indomethacin ID_{50} = 0.2 mg/kg/day/bid).

In summary, we have prepared a series of novel bispyridine COX-2 inhibitors from which **33** (L-791,456) was identified as a very potent and selective COX-2 inhibitor in vitro. Bispyridine **33** was found to

be very active in models of inflammation, pyrexia, pain and arthritis. No evidence of GI toxicity was observed upon dosing of **33** to rats at 100 mg/kg, bid for 10 days, suggesting that development of bispyridine COX-2 inhibitors such as **33** may provide therapeutically useful alternatives to traditional NSAIDs with a greater GI safety profile.

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