

2-HETEROSUBSTITUTED-3-(4-METHYLSULFONYL)PHENYL- 5-TRIFLUOROMETHYL PYRIDINES AS SELECTIVE AND ORALLY ACTIVE CYCLOOXYGENASE-2 INHIBITORS

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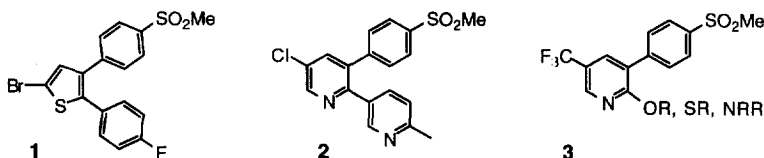
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Abstract: A series of novel 2-alkoxy, 2-thioalkoxy and 2-amino-3-(4-methylsulfonyl)phenylpyridines has been synthesized and shown to be highly potent and selective cyclooxygenase-2 (COX-2) inhibitors. Structure–activity relationship studies have demonstrated that central pyridine ring substituents play an important role in the COX-2 potency, selectivity vs the COX-1 enzyme, and oral activity. © 1999 Published by Elsevier Science Ltd. All rights reserved.

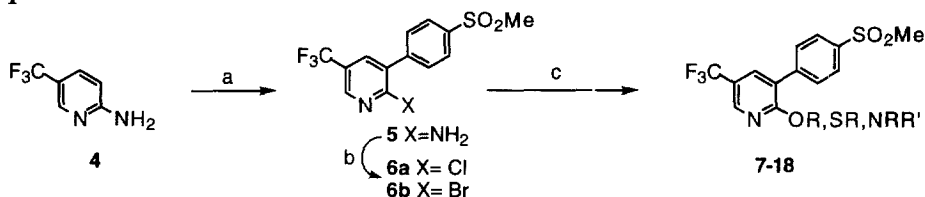
Introduction. The discovery of an inducible isoform of cyclooxygenase (COX-2) that is related primarily with inflammation has led to the identification of selective COX-2 inhibitors¹ which show reduced side effects as compared to the currently available nonsteroidal antiinflammatory drugs (NSAIDs), which are non-selective COX-1/COX-2 inhibitors. Indeed, several COX-2 selective inhibitors have been reported to have a safer *in vivo* profile in animal models with respect to the gastrointestinal side effects.^{1–3} The identification of Dup-697 (1),³ a selective COX-2 inhibitor, has led to extensive efforts by several laboratories¹ to develop improved analogs based on this lead structure or that of non-selective inhibitors such as indomethacin.^{4,5} From the Dup 697 (1) tricyclic class several groups have reported the successful replacement of the central thiophene ring by various rings including benzene,⁶ cyclobutene,⁷ cyclopentene,⁸ furanone,⁹ pyrazole,¹⁰ pyridine (2),^{11,12} thiazole,¹³ and triazole.¹⁴

The structure–activity relationship (SAR) studies on these analogs have confirmed that the (4-methylsulfonyl)phenyl or (4-sulfonamide)phenyl group attached to the central ring was essential for COX-2 inhibition.^{15,16} There are only few examples of successful replacement for the second aromatic moiety.^{1a} We have therefore investigated the replacement of this second aryl substituent with various other groups. Herein, we describe the discovery and SAR of a series of orally active 2-alkoxy, thioalkoxy, and 2-amino-3-(4-methylsulfonyl)phenylpyridines (3), which represent a new class of potent and selective COX-2 inhibitors.



Chemistry. The central pyridine nucleus was produced from the commercially available 2-aminopyridine **4** as shown in Scheme 1. Regioselective bromination and Suzuki¹⁷ coupling with 4-methylthiophenylboronic acid¹⁸ followed by oxidation to methylsulfone yielded the 2-amino-3-arylpyridine **5**. Conversion to the 2-bromopyridine (**6b**) was accomplished by treatment with sodium nitrite and bromine in 48% HBr. Alternatively, the 2-Cl (**6a**) analog was prepared by initial conversion of the 2-amino to the corresponding 2-pyridone with aqueous sodium nitrite in conc. HCl, followed by reaction with neat POCl₃ at 80 °C. The halogen at C2 can then be displaced with various alcohols, thiols or amines using standard conditions.

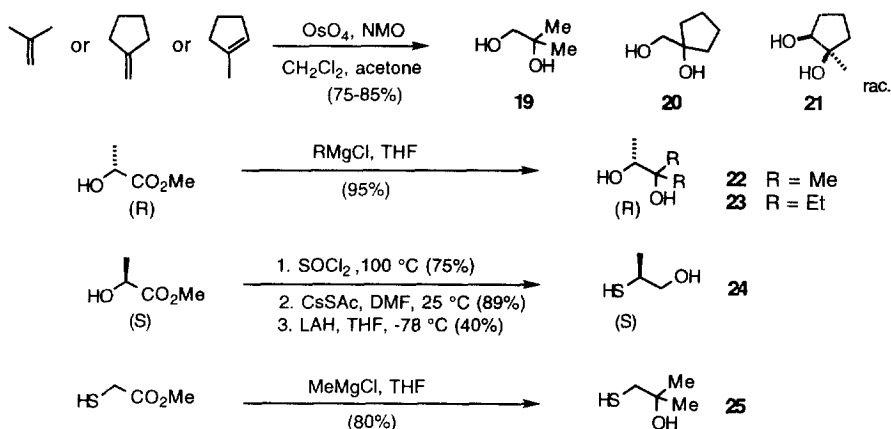
Scheme 1



Reagents: (a) i. Br₂, AcOH, 25 °C (91%) ii. 4-methylthiophenylboronic acid, P1(Ph₃P)₄ cat., 2 N Na₂CO₃, EtOH/PhH (1/1), reflux (93%) iii. OsO₄ cat., NMO, acetone/water (95:5) (90%) (b) Cl: NaNO₂, HCl, 25 °C then neat POCl₃, 80 °C (72%); Br: NaNO₂, 48% HBr, Br₂, 0–25 °C (67%). (c) ROH, KOt-Bu, DMF, 25 °C or RSH, Cs₂CO₃, DMF, 25 °C or RR'NH, neat 100 °C (76–85%)

The C2 side chains precursors containing a diol were obtained by osmium catalyzed *cis* hydroxylation of the corresponding commercially available olefins (Scheme 2, **19–21**). In the case of methylcyclopentene, we obtained a racemic mixture of *cis*-diols **21** that was used as such in the coupling with the pyridine nucleus. The enantiomers were then resolved using chiral HPLC.¹⁹ The tertiary carbinols **22**, **23**, and **25** were produced by addition of the desired Grignard reagents on the commercial methyl (*R*)-lactate or methyl thioglycolate.²⁰ Finally, the 2-(*S*)-mercaptoopropanol **24** was synthesized from (*S*)-lactate.²¹

Scheme 2



Results and Discussion.

Compounds **7–18** (Table 1) were tested *in vitro* for their ability to inhibit the enzymes COX-1 and COX-2. We measured IC_{50} values for the inhibition of PGE_2 produced by arachidonic acid stimulated CHO cells expressing human COX-2⁹, for the inhibition of PGE_2 produced by lipopolysaccharide (LPS) challenged human whole blood (HWB COX-2)²² and for the inhibition of TXB_2 synthesis induced by coagulation of human whole blood (HWB COX-1).²² Selected compounds were also tested *in vivo* for their pharmacokinetic parameters and their efficacy in the rat paw edema, rat pyresis and rat paw hyperalgesia assays.⁹

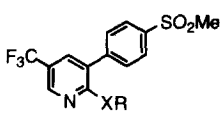
Structure–Activity Relationship, Bioavailability and *in vivo* Efficacy:

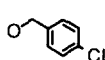
In a previous communication,¹¹ we have described briefly the SAR of the central pyridine ring and concluded that an electron withdrawing substituent such as a chlorine atom or trifluoromethyl group at the C5 position had an significant impact on COX-2 inhibition potency, especially in presence of human serum (HWB assay). Herein, we describe the SAR at C2 using oxygen, sulfur and nitrogen as linker atoms while keeping the 3-(4-methylsulfonyl)-5-trifluoromethylpyridine backbone fixed.

The data for the *in vitro* inhibition of COX-1 and COX-2 in the HWB assays are presented in Table 1 along with comparative values for indomethacin (Indo) and Dup-697 (**1**)³. All the examples cited in Table 1 are potent inhibitors of COX-2 in the CHO whole cells assays⁹ with IC_{50} values below 200 nM. For the SAR studies we have mainly used the HWB COX-2 assay²² as a marker for potential *in vivo* efficacy and the HWB COX-1 assay²² to assess, within our series, the selectivity between COX-1 and COX-2.

In general, phenoxy groups (such as entry **7**) gave analogs that were inhibitors of both COX-1 and COX-2 similar to indomethacin or Dup-697 (**1**). At the other extreme, longer and bulkier alkyl groups such as the *p*-chlorobenzyloxy (entry **8**) afforded less potent analogs based on the HWB COX-2 assay. The optimum steric requirement for good inhibitory potency and minimum protein shift reside in molecules bearing small aliphatic groups with 2 to 4 carbon units. The best nonpolar aliphatic groups were trifluoroethyl (entry **9**) or hexafluoroisopropyl (entry **10**). The latter was not orally absorbed in rats while the trifluoroethyl analog was only slowly absorbed with a C_{max} of 2.4 μM 6 h after oral dosing (20 mg/kg, P.O., suspension in 1% methocel). This compound showed efficacy in the rat paw edema model with an ED_{50} of 2.4 mg/kg.

To achieve better absorption in rats, a small polar function was introduced on the alkyl chain. As exemplified in Table 1, we observed good *in vitro* selectivity (IC_{50} COX-1/COX-2 > 50/1) and *in vivo* efficacy for analogs containing an alcohol group (entry **11–18**).

Table 1 *In vitro* and *in vivo* properties of 2,3,5-Substituted pyridine^a


entry	XR	HWB COX-2	HWB COX-1	Ratio	Rat Paw Edema	Rat Pyresis
		IC ₅₀ (μM) ^b	IC ₅₀ (μM) ^b	Cox-1/Cox-2	ED ₅₀ (mg/kg)	ED ₅₀ (mg/kg)
7	OPh	<0.4	<1.24	..	-	-
8		>33	>100	>3	-	-
9	OCH ₂ CF ₃	0.5	>100	>200	2.4	-
10	OCH(CF ₃) ₂	0.5	>100	>200	-	-
11		1.0	>100	>100	1.9	6.8
12		1.4	83	50	1.8	2.2
13		0.46	>100	>200	2.2	0.8
14		4.7	>100	>20	2.8	1.3
15 ^c	 (+)	1.4	>100	>70	0.4	1.6
16 ^d	 (rac.)	0.8	41	51	1.4	0.5
17		0.7	39	56	1.5	0.5
18		0.14	29	207	0.3	0.3
Indo		0.5	0.16	0.3	2.0	1.1
1 (Dup-697)		0.06	1.2	20	1.3	n.d.

^a All the examples cited in the table 1 were potent inhibitors of COX-2 in the CHO whole cell assay⁹ with IC₅₀'s below 200 nM^b Each IC₅₀ value corresponds to an average of at least three determinations ^c Absolute stereochemistry unknown^d Tested as a racemate.

The compounds with a sulfur link were usually slightly less selective than those with an oxygen link (entry 11 vs 17). We have demonstrated that the linker can also be a nitrogen atom (as exemplified by entry 16), although the SAR is significantly different than with oxygen or sulfur and will be the subject of a future publication.

All the analogs presented in the Table 1 that contain an alcohol on the side chain (11–18) were orally bioavailable in rats ($F > 75\%$) which translated into active anti-inflammatory (rat paw edema) and anti-pyretic (rat pyresis) agents. The isobutanol side chain containing an oxygen (entry 11) or a sulfur atom (entry 17) linker resulted in compounds having long half life in rats ($T_{1/2} > 12$ h). We therefore studied other substituents to provide more potential sites of metabolism that could help in the clearance of the compounds *in vivo*. For the tertiary alcohols we observed the same trend as with the nonpolar chains, the bulkier or longer alkyl chains are giving lower potency in the HWB assay (entry 13 vs 14), while an extra 2-methyl group provided slightly better *in vitro* potency but didn't shorten the half life significantly (entry 11 vs 13).

The replacement of the tertiary alcohol with a primary alcohol (entry 16, 18) resulted in shorter $T_{1/2}$ (≤ 2 h) in rats with metabolic oxidation of the primary alcohol to the corresponding carboxylic acid. The compounds with a cyclopentyl ring (entry 12, 15) also provided analogs with good pharmacokinetic parameters ($C_{max} \approx 9$ μ M at 1–2 h, $T_{1/2} \leq 4$ h). The best side chain analog based on *in vivo* efficacy in rats was the 2-(*S*)-mercaptopropanol derivative (entry 18) with excellent ED_{50} values; rat paw edema and rat pyresis: 0.3 mg/kg. Additional *in vivo* testing of 18 demonstrated that it is also effective in the model of carrageenan-induced hyperalgesia in rats ($ID_{50} = 0.65$ mg/kg compared with indomethacin $ID_{50} = 1.5$ mg/kg).

In summary, we have prepared a series of novel 2-alkoxy, 2-thioalkoxy or 2-aminopyridine as selective COX-2 inhibitors from which several potent and orally bioavailable analogs were found to be very active in rat models of inflammation, pyrexia and pain.

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