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

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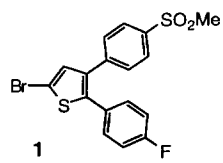
Abstract: A series of novel 2-alkoxy, 2-thioalkoxy and 2-amino-3-(4-methylsulfonyl)phenylpyridines has been synthesized and shown to be highly potent and selective cyclooxygenase-2 (COX-2) inhibitors. Structure–activity relationship studies have demonstrated that central pyridine ring substituents play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

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 inhibitors,[1] 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 laboratories[1] 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.



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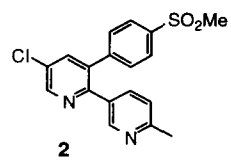

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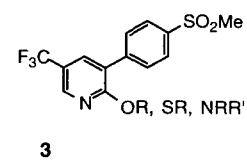

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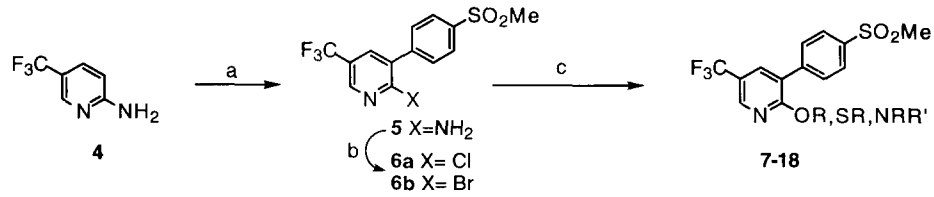
Chemistry. The central pyridine nucleus was produced from the commercially available 2-aminopyridine **4** as shown in Scheme 1. Regioselective bromination and Suzuki[17] coupling with 4-methylthiophenylboronic acid[18] followed by oxidation to methylsulfone yielded the 2-amino-3-arylpyridine **5**. 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 $POCl_3$ at 80 °C. The halogen at C2 can then be displaced with various alcohols, thiols or amines using standard conditions.

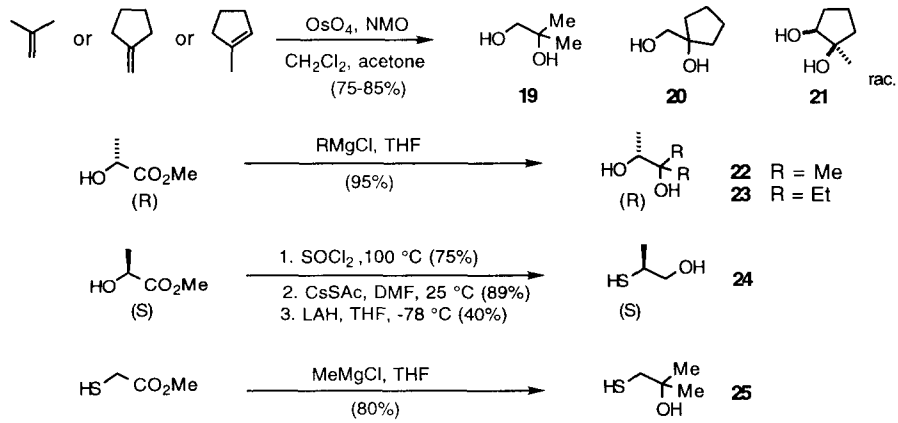
Scheme 1



Reagents: (a) *i.* Br_2, AcOH, 25 °C (91%) *ii.* 4-methylthiophenylboronic acid, $Pd(Ph_3P)_4$ cat., 2 N Na_2CO_3, EtOH/PhH (1/1), reflux (93%) *iii.* OsO_4 cat., NMO, acetone/water (95:5) (90%) (b) Cl: $NaNO_2$, HCl, 25 °C then neat $POCl_3$ 80°C (72%); Br: $NaNO_2$, 48% HBr, Br_2, 0-25 °C (67%). (c) ROH, KOt-Bu, DMF, 25 °C or RSH, Cs_2CO_3, 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*)-mercaptopropanol **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-2[9], 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:

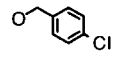
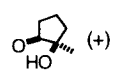
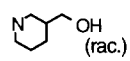
In a previous communication,[11] we have described briefly the SAR of the central pyridine ring and concluded that an electron withdrawing substituent such as a chlorine atom or trifluoromethyl group at the C5 position had an significant impact on COX-2 inhibition potency, especially in presence of human 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 assays[9] with IC_{50} values below 200 nM. For the SAR studies we have mainly used the HWB COX-2 assay[22] as a marker for potential *in vivo* efficacy and the HWB COX-1 assay[22] 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 Cmax 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 IC_{50} (μM)[b]	HWB COX-1 IC_{50} (μM)[b]	Ratio Cox-1/Cox-2	Rat Paw Edema ED_{50} (mg/kg)	Rat Pyresis ED_{50} (mg/kg)
7	OPh	<0.4	<1.24	-	-	-
8		>33	>100	>3	-	-
9	OCH_2CF_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	59	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 exemples cited in the table 1 were potent inhibitors of COX-2 in the CHO whole cell assay[9] with IC_{50}'S below 200 nM

[b] Each IC_{50} 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 (Cmax ≈ 9 μM at 1–2 h, $T_{1/2}$ ≤ 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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