Brief Articles

3-[4-(Methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl) Phenyl Ketone as a Potent and Orally Active Cyclooxygenase-2 Selective Inhibitor: Synthesis and Biological Evaluation

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Incorporation of a spacer group between the central scaffold and the aryl ring resulted in a new cyclooxygenase-2 (COX-2) selective inhibitor core structure, 3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl) phenyl ketone (**20**), with COX-2 $IC_{50} = 0.25\ \mu M$ and COX-1 $IC_{50} = 14\ \mu M$ (human whole blood assay). Compound **20** was orally active in the rat air pouch model of inflammation, inhibiting white blood cell infiltration and COX-2-derived PG production. Our data support the identification of a novel COX-2 selective inhibitor core structure exemplified by **20**.

Introduction

One mammalian cyclooxygenase (COX) isozyme, COX-1, is constitutively present in platelets and all tissues and produces prostaglandins (PGs) with homeostatic functions including gastric mucosal cytoprotection, renal blood flow regulation, and vascular antithrombotic activity. Although constitutive in a few tissues, COX-2 isozyme is transiently induced by proinflammatory stimuli to generate PGs that mediate the inflammatory response.[1] As inhibitors of COX isozymes, traditional nonsteroidal antiinflammatory drugs (NSAIDs) relieve the signs and symptoms of inflammation by decreasing PG production but may cause serious gastrointestinal (GI) and renal damage, especially with long-term use.[1,2]

By reduction of PG synthesis at sites of inflammation, COX-2 selective inhibitors have been clinically validated as antiinflammatory therapeutics for indications such as rheumatoid arthritis.[3−5] Enhanced GI safety is the major clinical advantage of COX-2 selective inhibitors over traditional NSAIDs.[6,7] Prior to completion of this work, three COX-2 selective inhibitors were marketed in the U.S.: celecoxib (**1**),[8] rofecoxib (**2**),[9] and valdecoxib (**3**)[10] (Figure 1). Rofecoxib (Vioxx) was recently withdrawn[11] worldwide because of evidence of increased cardiovascular risk in select, high-dose patients that may reflect rofecoxib's greater COX-2 selectivity.[12] The moderately COX-2 selective inhibitor celecoxib has not shown similar adverse cardiovascular effects,[13] but valdecoxib, with greater COX-2 selectivity, has.[12] Celecoxib and valdecoxib are comparable to conventional NSAIDs in terms of analgesic, antipyretic and antiinflammatory activity.[8,10]

The COX-2 selective inhibitor etoricoxib (**4**)[14,15] is an approved drug in Europe. Containing a pyridyl ring as a central scaffold, etoricoxib validated the importance of pyridyl analogues as COX-2 selective antiinflammatory therapeutics. Lumiracoxib (**5**) is a new COX-2 selective inhibitor that is structurally and pharmacologically distinctive (Figure 1). Although it contains an acid group similar to classical nonselective NSAIDs, lumiracoxib still shows superior GI tolerance, suggesting that PG synthesis inhibition is more critical to NSAID-induced GI toxicity than an acidic drug−mucosal interaction. In phase III clinical trials, the GI tolerability of lumiracoxib is superior to that of ibuprofen and equivalent to that of celecoxib and rofecoxib.[16,17]

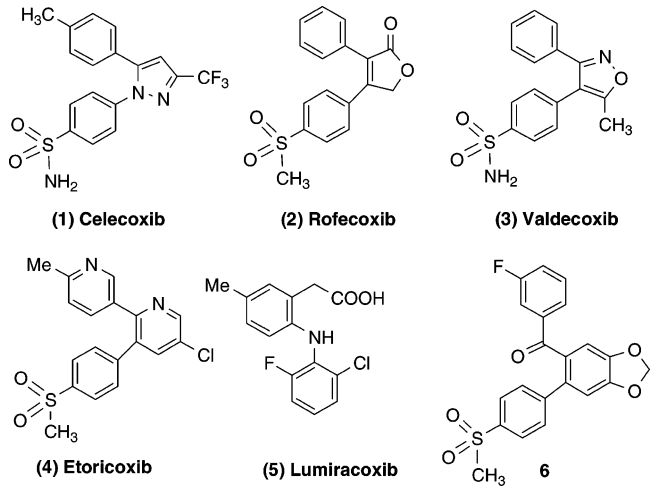

Figure 1.

The nonabsolute GI safety of extant COX-2 selective antiinflammatory agents and their pharmacological and side effect limitations invite improvement and development of new core inhibitor structures. We recently described a new series of metharyl COX-2 selective inhibitors and showed that a spacer group between the

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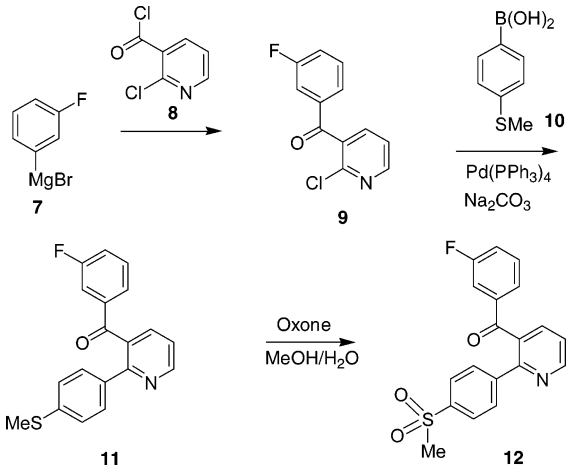
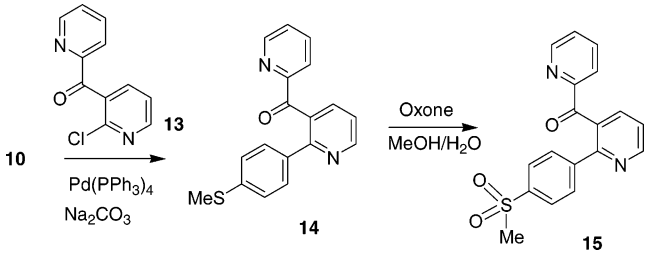
Scheme 1



Scheme 2



aryl ring and the central benzo-1,3-dioxolane ring (scaffold) significantly increased COX-2 inhibitory potency.[18] Within this metharyl series, **6** was identified as a potent COX-2 selective inhibitor in vitro [COX-2 $IC_{50} = 1.0\ \mu M$ and COX-1 $IC_{50} = 20\ \mu M$ in human whole blood (HWB)] that inhibited COX-2-driven PGE_2 production when administered in vivo directly at the site of inflammation in a rat air pouch model but not when administered orally.

This lack of oral in vivo antiinflammatory activity by COX-2 selective inhibitor **6** presumably reflected poor absorption, distribution, metabolism, and excretion properties and prompted us to explore the pyridyl ring as the central scaffold in view of the enhanced bioavailability it can afford because of salt formation in GI tract.[14,15] Recently, pyridinic nimesulide analogues were found to be preferential COX-2 selective inhibitors with antiinflammatory properties similar to those of nimesulide in vivo.[19] Herein, we report that 3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl) phenyl ketone (**20**) is a potent COX-2 selective inhibitor. Synthesis and biological evaluation of this compound are presented.[20]

Chemistry

We initially investigated the pyridyl analogue **12** to determine whether incorporating a carbonyl spacer group between the central pyridyl ring and the aryl ring might lead to a potent COX-2 inhibitor. The general synthesis of 3-fluorophenyl 2-[4-(methylsulfonyl)phenyl]-(3-pyridyl) ketone (**12**) is illustrated in Scheme 1. 2-[4-(Methylsulfonyl)phenyl](3-pyridyl) 2-pyridyl ketone (**15**) was prepared using a similar synthetic pathway as described in Scheme 1 but starting from 2-chloro(3-pyridyl) 2-pyridyl ketone (**13**) (Scheme 2).

Our initial route to **12** (Scheme 1) did not allow the installation of the 4-sulfonylphenyl COX-2 pharmacophore at the 3-position and a metharyl group at the 2-position of the central pyridine ring because of the lack of a suitably substituted commercial starting material. Therefore, the synthesis was modified to incorporate a nitrile functionality in the spacer group that could be converted to a ketone by oxidative decyanation,[21] as shown in Scheme 3a. Alternatively, the nitrile group in **16** was converted into ketone **21** prior to the Suzuki–Miyaura coupling (Scheme 3b). Reaction of **16** with

Scheme 3

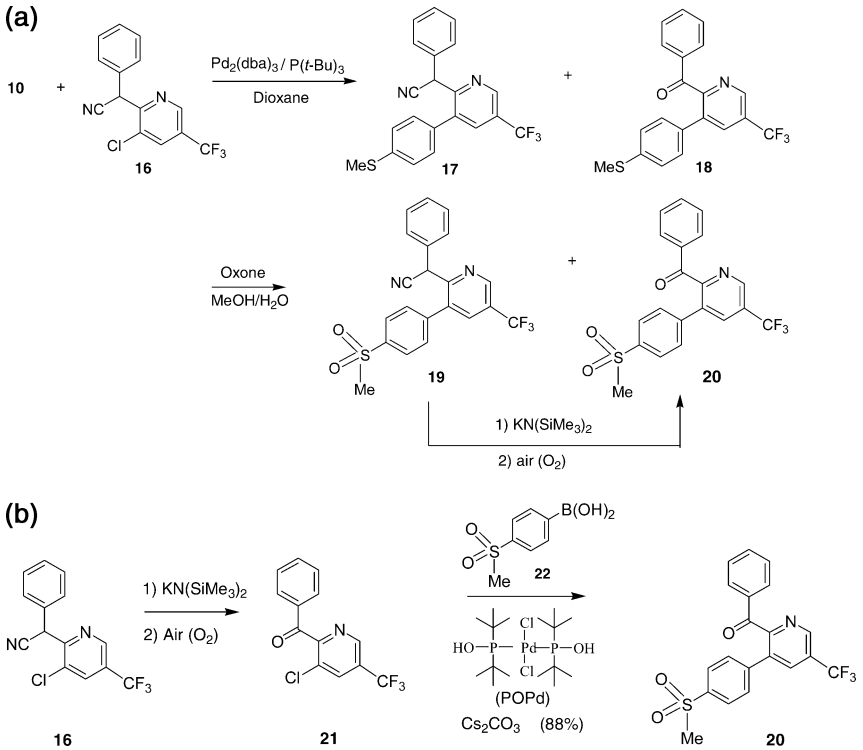


Table 1. IC_{50} Values[a] of Select COX-2 Inhibitors in HWB

compd	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	COX-2/COX-1 selectivity
20	14	0.25	56
etoricoxib	>200	2	>100
celecoxib	14	1.2	11
rofecoxib	62	0.5	124

[a] Average of two blood donors.

boronic acid **10** under classical $Pd(PPh_3)_4$-mediated cross-coupling reaction conditions failed to yield the desired product **17**. The reaction of **21** and **22** using $Pd(dba)_2$/P(*t*-Bu)$_3$ and cesium carbonate as base in dioxane gave **20** in 39% yield. Our recently developed method[22] for the optimized Suzuki−Miyaura cross-coupling of less reactive heteroaryl chlorides and arylboronic acids using an air-stable palladium phosphinous acid complex [(*t*-Bu)$_2$P(OH)]$_2PdCl_2$ (POPd) as a catalyst was found to be very effective and convenient for the Pd-catalyzed coupling of **21** and **22** to give the desired product **20** in very high yield (88%) (Scheme 3b).

Results and Discussion

In Vitro Studies. Compounds were initially evaluated in a standard HWB assay for their ability to inhibit COX-1 at 100 μM and COX-2 at 10 and 1 μM (table in Supporting Information). Compounds that showed good COX-2 inhibition at 10 μM were also evaluated for their COX-2 and COX-1 IC_{50} values to index COX-2 selectivity. Standard COX-2 inhibitors were evaluated in parallel (Table 1).

Compound **12,** in which a 3-fluorophenyl group was linked by a carbonyl spacer at the 3-position, was initially screened for COX-2 inhibitory activity in human whole blood (table in Supporting Information). It was moderately active (55% inhibition of COX-2 at 10 μM). We next explored the effect of an additional pyridyl moiety by replacing the aryl ring at position 3 of central pyridine scaffold to increase the hydrophilicity of the molecule. Increased aqueous solubility often improves compound absorption, bioavailability, and in vivo potency.[14] But the 2-pyridyl derivative **15** exhibited poor COX-2 inhibitory activity (table in Supporting Information).

Compound **20,** in which a phenyl substituent is linked to the central pyridyl ring by a carbonyl spacer, was a potent, highly selective COX-2 inhibitor (COX-2 IC_{50} = 0.25 μM and COX-1 IC_{50} = 14 μM in HWB). Thus, our earlier finding in the metharyl series of compounds that the spacer group was critical for optimizing COX-2 inhibition[18] was equally applicable to the pyridylmetharyl compound **20**. The spacer group presumably increases flexibility to allow for attainment of a molecular conformation that enahnces inhibitor interaction with the COX-2 active site. Additionally, the trifluoromethyl group on the pyridine ring may have contributed to the improved activity of **20**. A trifluoromethyl group on the central ring of the celecoxib is essential for COX-2 activity; it acts as an acceptor to form a hydrogen bond with the NH group of arginine-120.[23] Elimination of the trifluoromethyl group of celecoxib dramatically decreased COX-2 inhibitory activity because of a change in disolvation energy and loss of van der Waals interaction with COX.[24]

Table 2. Oral Antiinflammatory Potency of **20** in the Rat Air Pouch Model[a]

compd	oral dose mg/kg (mmol)	% inhibition of WBC infiltration	% inhibition of PGE_2
20	6.1 (15)	46.2 ± 3.05	58.9 ± 5.0
etoricoxib	5.4 (15)	45 ± 6.7	61 ± 6.7

[a] n = 11 rats.

To our knowledge, **20** is the most potent COX-2 inhibitor in the HWB COX assay yet reported. Thus, **20** represents a COX-2 selective inhibitor in a novel chemical series for this drug class. It is not, however, the most selective, which would increase its attractiveness as a therapeutic were the hypothesis to be proven that the cardiovascular liability of certain COX-2 inhibitors reflects their very high selectivity for this COX isozyme.[12]

In Vivo Antiinflammatory Activity. Rat Air Pouch Model. We evaluated **20** in vivo in the rat carrageenan-induced air pouch inflammation model, a standard and reliable model for COX-2 inhibitor pharmacological profiling and, more specifically, assessment of in vivo COX-2 driven PGE_2 production.[10,18] In this model, **20** showed good oral activity with 59% inhibition of PGE_2 formation and 46% inhibition of white blood cell (WBC) infiltration at a 15 μmol/kg dose, a profile similar to that of etoricoxib (Table 2).

Conclusion

We have discovered a novel compound **20** that is a very potent COX-2 selective inhibitor with appreciable in vivo antiinflammatory activity.

Experimental Section

For general comments, see our earlier publication in this series.[18] 2-Chloro(3-pyridyl) 2-pyridyl ketone (**9**) and 2-[3-chloro-5-(trifluoromethyl)(2-pyridyl)]-2-phenylethanenitrile (**16**) were purchased from Ryan Scientific, Inc., SC.

COX-1 and COX-2 Enzyme Assay in HWB. The assay for COX-1 and COX-2 enzyme activity in HWB was performed essentially as described by Young et al.[25] and as we have previously described.[18]

Rat Air Pouch Inflammation Model. An air pouch inflammation model was established in male Sprague Dawley (SD) rats (200−250 g, Charles River Laboratories) previously detailed.[18] Upon pouch development on day 6, vehicle or test compound in 0.5% methyl cellulose was administered by oral gavage. One hour later, inflammation was induced by injecting 1 mL of 1% carrageenan into the air pouch. Three hours after carrageenan injection, the rats were sacrificed and the pouch exudates were collected. Exudate white blood cells were quantified by automated counting, and exudate PGE_2 was determined by enzyme immunoassay (Cayman).

General Procedures. Suzuki−Miyaura Coupling Reaction: Method A. The chloropyridyl compound (5 mmol) and the corresponding benzeneboronic acid (5 mmol) were dissolved in toluene (50 mL), and sodium carbonate (2 M, 5 mL, 10 mmol) was added. To this reaction mixture was added ethanol (20 mL) followed by tetrakis(triphenylphosphine)palladium (0.34 g, 0.25 mmol). The reaction mixture was refluxed overnight under a nitrogen atmosphere and then diluted with water (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 75 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. The product was purified by trituration with ethyl acetate/hexane or by chromatography

on silica gel and elution with hexanes/EtOAc (8:2 to 6:4) to give the title compound as a white solid.

Oxone Oxidation Reaction: Method B. The thiomethyl compound (4 mmol) was dissolved in methanol (60 mL) with stirring at room temperature. A solution of oxone (8 mmol) in water (20 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The solvent methanol was evaporated at reduced pressure, and the remainder was diluted with water (25 mL), neutralized with ammonium hydroxide, and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 25 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure, and the product was purified by trituration with ethyl acetate/hexane or by chromatography on silica gel and elution with hexanes/EtOAc (19:1) to give the desired methylsulfonyl compound as a white solid in excellent yield.

Suzuki−Miyaura Coupling Reaction Using POPd Catalyst: Method C. To a solution of chloropyridine (2 mmol) in DME (8 mL) was added boronic acid (**10**) (500 mg, 2.5 mmol) followed by Cs_2CO_3 (5 mmol) and POPd (25 mg, 0.05 mmol, 0.02 mol %). The reaction mixture was refluxed overnight and then cooled to room temperature and filtered. The filtrate was evaporated at reduced pressure, and the residue was extracted with ethyl acetate, washed with aqueous saturated Na_2CO_3, water, and brine, and dried. The solvent was evaporated and the residue obtained was purified by trituration with ethyl acetate/hexane or by chromatography on silica gel and elution with hexanes/EtOAc (6:4) to give the desired methylsulfonyl compound as a white solid in excellent yield.

3-[4-(Methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl) Phenyl Ketone (20). Compound **20** was prepared, using method C, in 88% yield as a colorless crystalline solid, mp 141−142 °C. ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1 H), 8.14 (d, J = 1.3 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 7.85 (dd, J = 7.2 and 1.0 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.51 (t, J = 7.5 Hz, 2 H), 3.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 193.1, 158.2, 145.05, 141.5, 140.7, 135.3, 134.3, 130.3 (2 C), 129.7 (2 C), 128.2 (2 C), 127.8, (2 C), 127 0 (q, J = 33 Hz, CF_3), 124.6, 121.0, 44.3; LRMS (APIMS) m/z 406 $(M + H)^+$.

Procedure Using $Pd_2(dba)_3$/$P(Ph_3)_4$ Catalyst: 3-[4-(Methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl) Phenyl Ketone (20) and 2-{3-[4-(Methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl)}-2-phenylethanenitrile (19). 2-[3-Chloro-5-(trifluoromethyl)(2-pyridyl)]-2-phenylethanenitrile (**16**) (4.8 g, 16.17 mmol) and 4-(methylthio)benzeneboronic acid (**10**) (4.15 g, 25 mmol) were dissolved in anhydrous dioxane (80 mL). To this reaction mixture were added successively tris(dibenzylideneacetone)dipalladium(0) (0.58 g, 0.633 mmol), tri-*tert*-butylphosphine (150 mg, 0.724 mmol), and cesium carbonate (6.5 g, 20 mmol), and the mixture was refluxed overnight under nitrogen atmosphere. Reaction was monitored by thin-layer chromatography, which indicated the starting material and the product. Additional 4-(methylthio)-benzeneboronic acid (**10**) (4.15 g, 25 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.58 g, 0.633 mmol), tri-*tert*-butylphosphine (150 mg, 0.724 mmol), and base cesium carbonate (6.5 g, 20 mmol) were added, and the mixture was further refluxed for another 24 h. The mixture was then cooled to room temperature, and solvent was evaporated at reduced pressure. The residue was treated with water and extracted with ethyl acetate (1 × 250 mL). The combined extracts were washed with water (4 × 250 mL) and brine (1 × 250 mL), dried over sodium sulfate, treated with charcoal, filtered, and concentrated at reduced pressure to give the crude product. Purification by column chromatography over silica gel using 5% ethyl acetate in hexane gave 1.3 g of thick oil that was a mixture (85:15) of 2-[3-(4-methylthiophenyl)-5-(trifluoromethyl)(2-pyridyl)]-2-phenylethanenitrile (**17**) and 3-(4-methylthiophenyl)-5-(trifluoromethyl)(2-pyridyl) phenyl ketone (**18**). This mixture was dissolved in methanol (60 mL). OXONE (4.35 g, 7.1 mmol) in water (15 mL) was added, and the mixture was stirred at room temperature for 1.5 h. It was then neutralized with ammonium hydroxide, solvent methanol was evaporated at reduced pressure, and the residue extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and brine (1 × 25 mL), dried over sodium sulfate, and filtered, and the solvent was evaporated at reduced pressure to give the crude product. Purification by column chromatography over silica gel using gradient 20−40% ethyl acetate in hexane gave the less polar compound as a white crystalline product (**20**) (85 mg), mp 141−142 °C. ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1 H), 8.14 (d, J = 1.3 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 7.85 (dd, J = 7.2 and 1.0 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.51 (t, J = 7.5 Hz, 2 H), 3.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 193.1, 158.2, 145.05, 141.5, 140.7, 135.3, 134.3, 130.3 (2 x C), 129.7 (2 C), 128.2 (2 C), 127.8, (2 C), 127 0 (q, J = 33 Hz, CF_3), 124.6, 121.0, 44.3; LRMS (APIMS) m/z 406 $(M + H)^+$. From the more polar fractions, 490 mg of 2-{3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl)}-2-phenylethanenitrile (**19**) was isolated as a light-yellow solid, mp 78 °C. ^{1}H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 8.1 (d, J = 1.6 Hz, 1 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.33 (m, 1 H), 7.16 (m, 2 H), 5.42 (s, 1 H), 3.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.0, 146.6, 141.6, 141.4, 135.5, 135.1, 133.6, 130.1 (2 x C), 129.2 (2 C), 128.1, 127.8, (2 C), 127.0 (2 C), 126.3 (q, J = 33 Hz, CF_3), 124.6, 121.0, 118.1, 44.4, 42.3; LRMS (APIMS) m/z 417 $(M + H)^+$.

Oxidative Decyanation of Compound 19 To Give 20. Nitrile **19** (208 mg, 0.5 mmol) was dissolved in anhydrous THF (4 mL). The solution was cooled to −78 °C, and under nitrogen atmosphere 0.5 M potassium bishexamethylsilazide (1.1 mL) was added slowly. The solution turned dark-red and was further stirred at −78 °C for 15 min and then slowly allowed to warm to 0 °C over a period of 1 h. Then air was bubbled through the solution for 1 h at room temperature, and then the reaction flask was left open to air overnight. Product was extracted with dichloromethane, and the usual workup gave the crude product that was purified by column chromatography over silica gel using 20% ethyl acetate in hexane to give the pure product **20**, 110 mg in 54% yield. The spectral data were identical to the spectral data of the product obtained by method C as described above.

3-Chloro-5-(trifluoromethyl)(2-pyridyl) Phenyl Ketone (21). Nitrile **16** (4 g, 13.48 mmol) was dissolved in anhydrous THF (25 mL). The solution was cooled to −78 °C, and under nitrogen atmosphere 0.5 M potassium bishexamethylsilazide (27 mL) was added slowly. The solution was further stirred at −78 °C for 15 min and then slowly allowed to warm to 0 °C over a period of 1 h. Then dry air was bubbled through the solution for 1 h at room temperature while allowing it to warm to room temperature. Product was extracted with ethyl acetate, and the usual workup gave the crude product that was purified by column chromatography over silica gel using 10% ethyl acetate in hexane to give the pure product ketone **21** (3.8 g in 98% yield) as a white solid, mp 58 °C. ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1 H), 8.09 (s, 1 H), 8.09 (d, J = 7.4, 2 H), 7.64 (t, J = 7.3 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 191.3, 157.7, 143.9, 143.8, 135.1, 134.5, 130.2 (2 C), 129.7, 128.8 (2 C), 128.3 (d, J_{C-F} = 33.75 Hz), 122.27 (q, J_{C-F} = 271 Hz, CF_3); LRMS (APIMS) m/z 286 $(M + H)^+$, 288 $[(M + H) + 2]^+$.

Supporting Information Available: COX-2 and COX-1 percentage inhibition in HWB, elemental analysis data, experimental procedures, and spectroscopic data for **9**, **11**, **12**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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