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Synthesis of Deuterated Benzopyran Derivatives as Selective COX-2 Inhibitors with Improved Pharmacokinetic Properties

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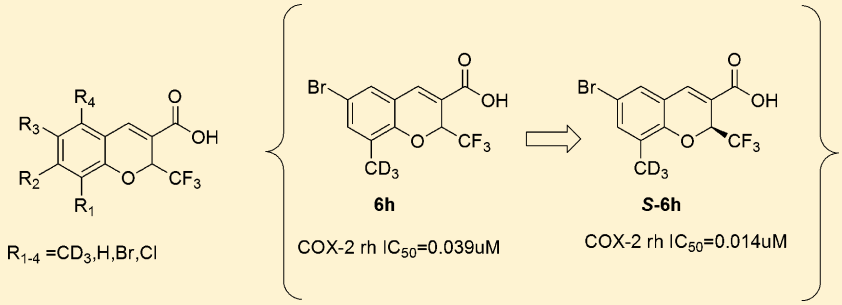
Supporting Information



ABSTRACT: We designed a series of specifically deuterated benzopyran analogues as new COX-2 inhibitors with the aim of improving their pharmacokinetic properties. As expected, the deuterated compounds retained potency and selectivity for COX-2. The new molecules possess improved pharmacokinetic profiles in rats compared to their nondeuterated congeners. Most importantly, the new compounds showed pharmacodynamic efficacy in several murine models of inflammation and pain. The benzopyran derivatives were separated into their enantiomers, and the activity was found to reside with the *S*-isomers. To streamline the synthesis of the desired *S*-isomers, an organocatalytic asymmetric domino oxa-Michael/aldol condensation reaction was developed for their preparation.

KEYWORDS: *COX-2, coxib, deuterium, benzopyran, NSAID*

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2 enzymes and have been a mainstay in clinical medicine for the treatment of inflammation and pain for many years. COX-2-selective inhibitors (coxibs)[1,2] developed in the mid 2000s supplanted traditional NSAIDs by virtue of their comparable efficacy with improved gastrointestinal safety.[3] Coxibs were initially thought to be able to avoid renal and cardiovascular side effects; however, this proved not to be entirely accurate.[4] In the kidney, COX-2 is expressed constitutively in certain regions (i.e., macula densa) and is highly regulated in response to changes in blood volume. COX-2-mediated metabolites (e.g., PGE_2 and PGI_2) play a mechanistic role in renin release, sodium excretion, and the maintenance of renal blood flow and glomerular filtration rate.[5] Coxibs fell into disfavor as clinical medicine because initial data linked them to cardiovascular risks of stroke and myocardial infarction compared with traditional NSAIDs.[6] However, data analysis from two recent clinical trials[7,8] clearly demonstrated that chronic and even short-term use of NSAIDs increased renal and cardiovascular side-effect risk no lesser than coxibs, and that the risks appeared to be drug-dependent rather than class-dependent. These data among other studies have inspired renewed interest in selective COX-2 inhibitors, particularly with coxibs that have a unique pharmacological profile, which could address unmet medical conditions.[9−12] Such clinical conditions include treating pain and inflammation without further compromising renal function and in treating or preventing certain types of cancer associated with inflammation mediated by COX-2.

Benzopyran compounds as selective COX-2 inhibitors were investigated.[13−15] It was reported that 2-trifluoromethyl, 3-carboxy, and 4-H substituents were key elements of the benzopyran pharmacophore. Chiral chromatographic separation of 2-trifluoromethyl enantiomers and evaluation of the individual isomers showed that *S*-isomers were far more effective in blocking COX-2 activity than

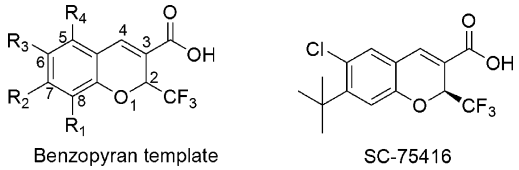


Figure 1. Benzopyran template and SC-75416.

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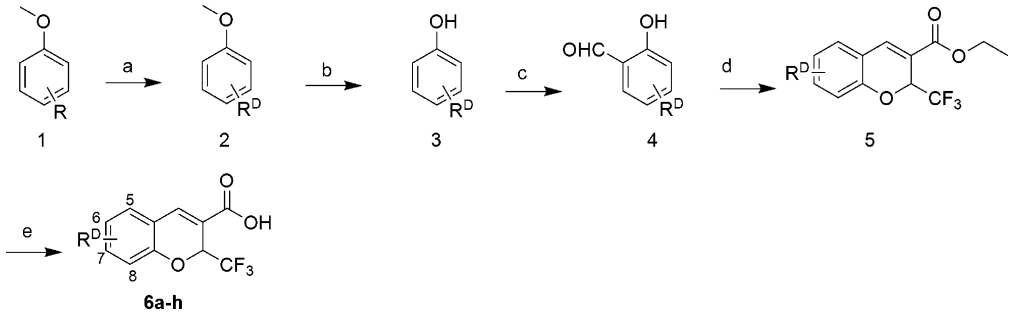
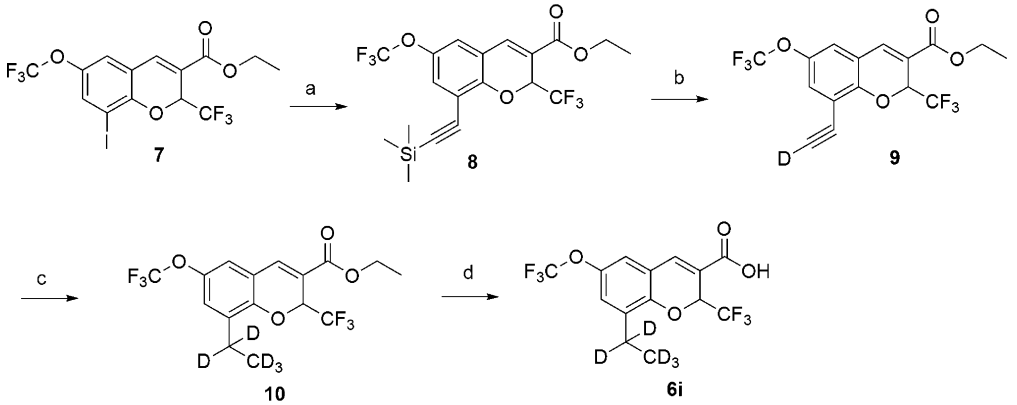
Scheme 1. Synthesis of Trideuteromethyl Derivatives[a]



[a]R represents substituents on C5, C6, C7, or C8 position; R^D represents deuterated substituents. Reagents and conditions: (a) potassium *t*-butoxide, DMSO-d_6, 110 °C 6 h; (b) BBr_3, DCM, 0 °C, 2 h; (c) HTMA, TFA, rt, 1 h; (d) ethyl 4,4,4-trifluorocrotonate, K_2CO_3, DMF, 80−100 °C, 2−4 h; (e) NaOH, THF/CH_3OH/H_2O.

Scheme 2. Synthesis of Pentadeuterated Analogue 6i[a]



[a]Reagents and conditions: (a) CuI, $Pd(PPh_3)_4$, ethynyltrimethylsilane, TEA, MeCN, rt, 24 h; (b) K_2CO_3, anhydrous ethanol, D_2O, rt, 30 min; (c) D_2, EtOAc, Pd/C, rt, 1 h; (d) NaOH, THF/CH_3OH/H_2O.

the corresponding *R*-isomers. Substitutions at the 5, 6, 7, and 8 positions were optimized for potency, efficacy, and pharmacokinetic profiles. Several clinical candidates were identified including SC-75416 and advanced into clinical trials (Figure 1).

Deuteration of compounds is a strategy for creating new chemical entities that has recently been used in drug discovery to make improved drugs. Carbon−deuterium bonds are stronger than the more common carbon−hydrogen bonds, and the replacement of hydrogen atoms with deuterium at metabolically labile positions can significantly improve the PK and thus efficacy of physiologically active compounds by slowing metabolism due to the kinetic isotope effect. Deuterium substituted compounds retain both biochemical potency and selectivity for their target, suggesting that deuterium atom substitution does not appreciably alter ligand−receptor binding. More importantly, replacing hydrogen with deuterium can enable substantial benefits to the overall pharmacological profile of the compounds.[16−18] In an effort to develop improved selective COX-2 inhibitors, we designed and synthesized a series of specifically deuterated analogues of benzopyran coxibs. The initial synthetic efforts focused on deuteration of the methyl group, which is outlined in Scheme 1. Commercially available anisoles **1** were deuterium labeled on the methyl group under strongly basic conditions in DMSO-d_6 to give compound **2**, which converted methyl or dimethyl into CD_3 or di-CD_3 derivatives.[19] Deuterium substituted phenols **3** were prepared by *O*-demethylation, followed by chlorination or bromination to provide the desired chlorinated or brominated products. Chlorination or bromination may also be conducted prior to *O*-demethylation if needed. Substituted salicylaldehydes **4** were synthesized by the Duff reaction.[20−22] Key intermediate **4** was then condensed with commercially available ethyl trifluorocrotonate to produce the specifically deuterium substituted benzopyran nucleus **5**, in a one-step procedure by heating in K_2CO_3 and DMF. The resulting esters **5** were hydrolyzed with sodium hydroxide yielding the acids **6a−h**; see Scheme 1 (see synthesis and characterization of compounds, Supporting Information).

Compound **6i** was prepared according to the procedure outlined in Scheme 2. The benzopyran **7** was prepared by a published procedure[23] and then coupled with ethynyltrimethylsilane in the presence of a base and a catalytic amount of cuprous iodide and tetrakis(triphenylphosphine)palladium(0) to afford **8**. Removal of the trimethylsilyl group was key to yield the terminal deuterated compound **9** (K_2CO_3 in D_2O), and reduction of **9** (D_2, Pd/C in ethyl acetate) and finally saponification of the ester with aqueous sodium hydroxide gave deuterated benzopyran **6i** (see Scheme 2 and synthesis and characterization of compounds in Supporting Information). The corresponding nondeuterated benzopyran derivatives **$6a^n$−i^n** were synthesized by known methods.[23]

The analogues **6a−i and $6a^n$−i^n** were tested for their inhibitory activity against recombinant human COX-1 and COX-2 enzymes, the results are shown in Table 1 (see *in vitro* COX enzyme assay in Supporting Information). There were no significant differences in the inhibitory profile against COX-1 or COX-2 between deuterated versus the corresponding

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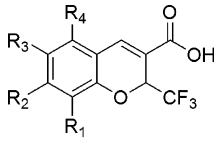
Table 1. Evaluation of Substituted Benzopyrans against COX-1 and COX-2 Enzymes



6a-i/6a^n-i^n

compd	R_1	R_2	R_3	R_4	rh IC_{50} (μM) COX-1	rh IC_{50} (μM) COX-2
6a	H	CD_3	Cl	CD_3		0.054 ± 0.013
6b	H	CD_3	Br	CD_3		0.043 ± 0.018
6c	Br	CD_3	Br	CD_3	>100	0.084 ± 0.020
6d	H	H	CD_3	H		>10
6e	Cl	H	CD_3	H		0.063 ± 0.015
6f	CD_3	H	CD_3	H	>100	0.15 ± 0.035
6g	CD_3	H	Cl	H		0.059 ± 0.009
6h	CD_3	H	Br	H		0.039 ± 0.005
6i	CD_2CD_3	H	OCF_3	H		0.061 ± 0.009
6a^n	H	CH_3	Cl	CH_3	>100	0.069 ± 0.025
6b^n	H	CH_3	Br	CH_3	>100	0.19 ± 0.042
6c^n	Br	CH_3	Br	CH_3	>100	0.069 ± 0.008
6d^n	H	H	CH_3	H		>10
6e^n	Cl	H	CH_3	H	>100	0.078 ± 0.022
6f^n	CH_3	H	CH_3	H		0.100 ± 0.024
6g^n	CH_3	H	Cl	H		0.051 ± 0.022
6h^n	CH_3	H	Br	H	>100	0.028 ± 0.001
6i^n	CH_2CH_3	H	OCF_3	H	>100	0.049 ± 0.007

nondeuterated analogues. Most analogues had potency for COX-2 with an IC_{50} < 100 nM and were relatively inactive against COX-1. Within this series of compounds, the analogues bearing a 6-chloro or 6-bromo substituent were the most potent and selective inhibitors of COX-2.

Table 4. *In Vivo* Murine Models of Inflammation and Pain

compd	air pouch EC_{50} (mg/kg)	edema EC_{50} (mg/kg)	hyperalgesia EC_{50} (mg/kg)	arthritis ED_{50} (mg/kg)
celecoxib	0.69 ± 0.10	2.81 ± 0.43	5.0 ± 0.64	1.57 ± 0.21
6a	0.47 ± 0.05	5.18 ± 1.01	2.77 ± 0.25	
6b	0.57 ± 0.10	2.26 ± 0.36	3.82 ± 0.75	
6g	0.45 ± 0.03	6.48 ± 1.25	3.33 ± 0.49	
6h	0.27 ± 0.02	3.00 ± 0.31	2.19 ± 0.32	0.42 ± 0.08
6a^n	0.77 ± 0.10			
6g^n	0.61 ± 0.09			
6h^n	0.47 ± 0.06	3.47 ± 0.62	3.52 ± 0.77	

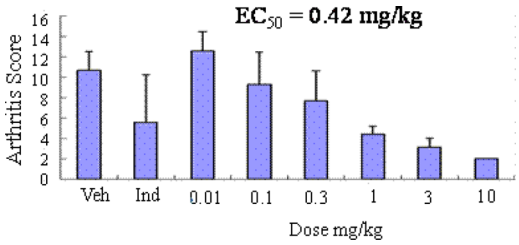


Figure 2. Dose-dependent inhibition of arthritis by compound **6h**. Indomethacin (2 mg/kg) was used a positive control and PBS was used as the vehicle (Veh).

The pharmacokinetic properties of analogues **6a−i and 6a^n−i^n** were studied in male SD rats following i.v. and oral administration, the results are described in Tables 2 and 3 (see rat po PK results of deuterated and nondeuterated analogues (Table 2) and rat iv PK results of deuterated and nondeuterated analogues (Table 3) in Supporting Information). There were significant

Table 2. Rat PK of Deuterated Analogues (PO)

	dose (mg/kg)	BA%	T_{max} (h)	C_{max} (μg/L)	V_d (L/kg)	$t_{1/2}$ (h)	$AUC_{(0-\infty)}$ (μg/L·h)	CLz/F (L/h/kg)
6a	10	92.8	1.167	20900	0.26	2.1	118331.438	0.086
6b	10	111.8	0.5	21300	0.57	3.35	84789.673	0.125
6g	2.5	110.7	0.5	8945	0.316	3.37	38881.983	0.066
6h	10	107.4	0.417	35300	0.53	5.2	142686.966	0.072
6i	30	60.2	1.25	33475	0.491	4.542	402662.508	0.075
6a^n	10	78.5	0.438	6592	1.25	3.09	12846.927	0.195
6b^n	2.5	56.7	0.375	5338	1.13	3.53	12529.512	0.211
6g^n	2.5	128.5	0.25	2720	1.37	1.75	4627.624	0.547
6h^n	5	46.3	0.438	11523	0.65	1.51	17190.28	0.298
6i^n	25	78.6	1.625	29525	0.678	9.542	511440.855	0.049
SC-75416	10	67.5	0.75	8152.5	2.314	6.68	42223.264	0.242

Table 3. Rat PK of Deuterated Analogues (IV)

	dose (mg/kg)	C_{max} (μg/L)	V_d (L/kg)	$t_{1/2}$ (h)	$AUC_{(0-\infty)}$ (μg/L·h)	CLz/F (L/h/kg)
6a	5	38750	0.287	2.525	63759.714	0.079
6b	5	26175	0.529	2.733	37914.156	0.135
6g	1	9068.75	0.404	3.909	14043.753	0.072
6h	5	38975	0.461	4.186	66436.832	0.077
6i	10	51625	0.39	5.946	222923.421	0.047
6a^n	1	5035	0.45	1.5	4898.988	0.207
6b^n	1	16681	0.38	2.30	8843.992	0.119
6g^n	1	4131	0.59	0.59	1440.446	0.706
6h^n	2.5	38581	0.15	0.58	14843.535	0.172
6i^n	5	37250	0.301	5.446	130985.986	0.038
SC-75416	5	37187	1.353	5.78	31271.923	0.16

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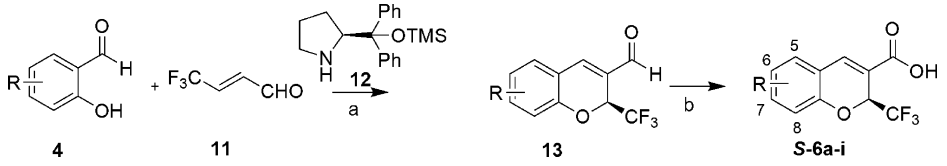
Scheme 3. Enantioselective Synthesis of (*S*)-2-(Trifluoromethyl)-2*H*-chromene-3-carboxylic Acids[a]



[a]R represents substituents on C5, C6, C7, or C8 position. Reagents and conditions: (a) 2-nitrobenzoic acid, CH_2Cl_2, rt, 24 h; (b) OXONE, DMF, rt, 24 h.

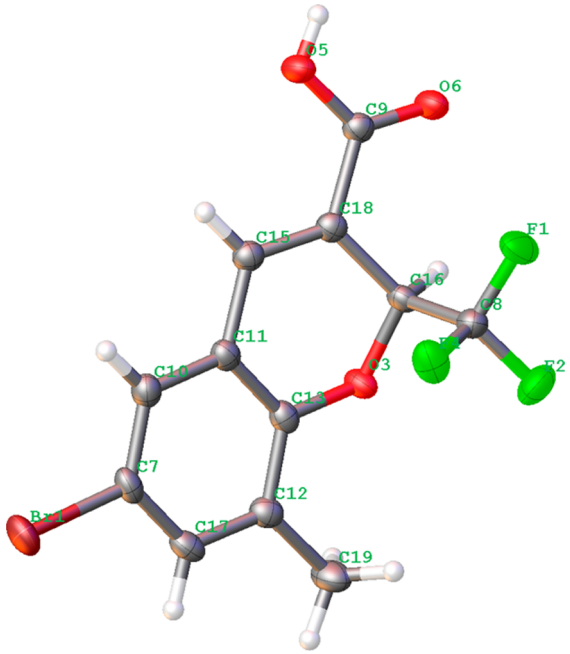
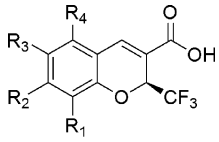


Figure 3. Ortep picture of *S*-**6h**.

Table 5. COX-2 Inhibition of *S*-Stereoisomers



***S*-6a-i**

	ee value (%)	rh IC_{50} (μM) COX-2	rh IC_{50} (μM) COX-1
***S*-6a**	86.5	0.016	>100
***S*-6b**	80.7	0.009	>100
***S*-6g**	89.7	0.02	>100
***S*-6h**	90.2	0.014	>100

changes in the overall pharmacokinetic profile between deuterated versus the corresponding nondeuterated analogues. Overall the deuterated analogues demonstrated a better PK profile. Analogue **6h** bearing a 6-bromo substituent was shown to have the longest half-life.

Moreover, compounds **6a**, **6b**, **6g**, and **6h** were efficacious in several key animal models used to assess the potency of NSAIDs including the air pouch model of PGE2 release and inflammation, paw edema, hyperalgesia in rats and the adjuvant induced arthritis model in mice; see Table 4. All compounds displayed potent efficacy and dose-dependent suppression in each of these disease models.

As an example of the dose-dependent efficacy that we observed for these compounds, a full dose response curve for compound **6h**, tested in the rat adjuvant arthritis model is shown in Figure 2.

Normally, separation of the enantiomers can be accomplished by classical diastereomeric salt formation (selective crystallization using chiral amines, such as α-methylbenzylamine) or by chiral chromatography. We discovered that the protected α,α-diphenyl-2-pyrrolidinemethanol[24−26] (compound **12** of Scheme 3) was able to catalyze the formation of *S*-stereoisomer with more than 80% ee, which is a much more efficient method for making the compound especially for large scale synthesis. Iminium activation of α,β-unsaturated aldehydes **11**[27] by **12** leads to enantioselective oxa-Michael addition with **4** and generates enamine intermediates that undergo subsequent intramolecular *6-exo-trig* aldol condensations to give the corresponding ***S*-6a−i**[24] (see Scheme 3 and page 9 of Supporting Information). X-ray analysis of ***S*-6h** established that the absolute configuration at C2 was ***S***; see Figure 3 (see crystal structure of ***S*-6h**, Supporting Information). As expected, *S*-stereoisomers were found to be 2−5 times more potent for COX-2 than their corresponding racemic mixtures; see Table 5.

In conclusion, we synthesized a series of specifically deuterium substituted benzopyran analogues as potent and selective COX-2 inhibitors. Analogues **6a**, **6b**, **6g**, and **6h** showed not only excellent selective COX-2 inhibition but also a significantly improved PK profile. These compounds were efficacious in the gold standard rodent models of inflammation and pain. We also developed a new enantioselective synthetic protocol for preparation of *S*-stereoisomers for this series of molecules. Collectively, these compounds deserve further evaluation as clinical candidates for the treatment of inflammatory mediated diseases.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details along with the characterizations of the synthesized compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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