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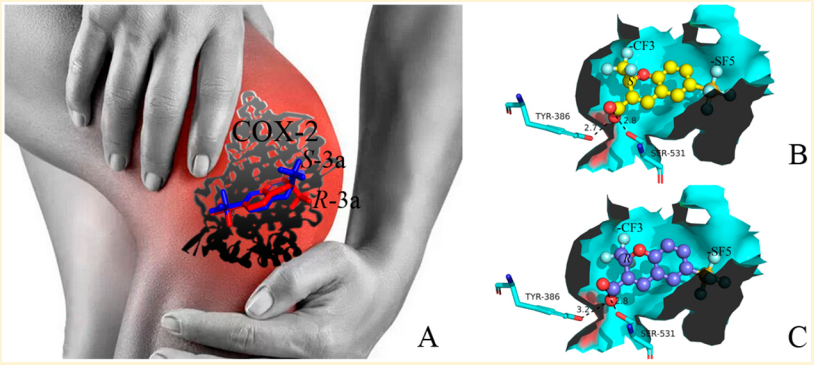
Pentafluorosulfanyl-Substituted Benzopyran Analogues As New Cyclooxygenase-2 Inhibitors with Excellent Pharmacokinetics and Efficacy in Blocking Inflammation

Yanmei Zhang,*[,†] Yican Wang,[†] Chuang He,[†] Xiaorong Liu,[†] Yongzhi Lu,[†] Tingting Chen,[†] Qiong Pan,[†] Jingfang Xiong,[†] Miaoqin She,[†] Zhengchao Tu,*[,†] Xiaochu Qin,[†] Minke Li,[†] Micky D. Tortorella,[†] and John J. Talley*[,‡]

[†]Drug Discovery Pipeline, Guangzhou Institutes of Biomedicine and Health, 190 Kaiyuan Avenue, Science City, Guangzhou 510530, P.R. China

[‡]Euclises Pharmaceuticals, St. Louis, Missouri 63108, United States

Supporting Information



ABSTRACT: In this report, we disclose the design and synthesis of a series of pentafluorosulfanyl (SF_5) benzopyran derivatives as novel COX-2 inhibitors with improved pharmacokinetic and pharmacodynamic properties. The pentafluorosulfanyl compounds showed both potency and selectivity for COX-2 and demonstrated efficacy in several murine models of inflammation and pain. More interestingly, one of the compounds, *R*,*S*-**3a**, revealed exceptional efficacy in the adjuvant induced arthritis (AIA) model, achieving an ED_{50} as low as 0.094 mg/kg. In addition, the pharmacokinetics of compound *R*,*S*-**3a** in rat revealed a half-life in excess of 12 h and plasma drug concentrations well above its IC_{90} for up to 40 h. When *R*,*S*-**3a** was dosed just two times a week in the AIA model, efficacy was still maintained. Overall, drug *R*,*S*-**3a** and other analogues are suitable candidates that merit further investigation for the treatment of inflammation and pain as well as other diseases where COX-2 and PGE_2 play a role in their etiology.

INTRODUCTION

We recently described the use of deuterium to enhance the drug like properties of benzopyran based COX-2 inhibitors.[1] In this report, the application of a pentafluorosulfanyl moiety is explored as a chemical strategy for enhancing both the pharmacokinetic and pharmacodynamic properties of these compounds.

The pentafluorosulfanyl (SF_5) moiety is currently being deployed to improve the physicochemical properties of drug-like molecules.[2,3] It has been shown that the SF_5 moiety can improve the bioavailability and half-life of some drugs[4,5] as well as enhance the chemical and thermal stability of other molecules.[6,7] In addition, the SF_5 moiety has been demonstrated to endow molecules with fluorous behavior, enhanced electron-withdrawing characteristics, increased lipophilicity and larger steric bulk.[8]

Cyclooxygenases (COX) are essential rate-limiting enzymes for the conversion of arachidonic acid to prostaglandins (PGH_2).[9] Various types of prostanoids, such as PGE_2, PGD_2, PGI_2, and TXA_2, metabolized from PGH_2, may contribute to human pathologies if unregulated. For example, PGE_2 is closely associated with inflammation, fever, and pain, whereas PGI_2 is linked to inflammation and vasodilation.[10−15] Thus, inhibition of cyclooxygenases can lower the production of PGH_2 and its downstream metabolites and reduce inflammation.[16] Cyclooxygenases consist of two forms, COX-1 and COX-2. COX-1 is generally constitutively produced in tissues such as the gastrointestinal (GI) tract and blood with a primary role in homeostasis. COX-2 is absent or expressed at low levels in most tissues, however, it becomes significantly upregulated at sites of inflammation.[17−20]

The anti-inflammatory properties of traditional NSAIDs are primarily due to inhibition of COX-2, however, nonselective

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inhibition of COX-1 may result in gastrointestinal damage, bleeding, and ulceration in some patients. Thus, selective COX-2 inhibitors were developed as better NSAIDs and referred to as coxibs.[21−24] However, several of the first- and second-generation coxibs were associated with increased incidences of adverse cardiovascular effects and quickly fell out of favor.[25,26] However, recent studies demonstrated that the risks appear to be drug-dependent rather than class-dependent,[27,28] inspiring renewed interest in the development of what's referred to as third-generation COX-2 inhibitors, coxibs that have unique physicochemical properties with improved safety pharmacological profiles. Benzopyran compounds as selective COX-2 inhibitors have been investigated[29−33] as well as deuterated benzopyran analogues.[1] The deuterated compounds were shown to retain potency and selectivity for COX-2 but possessed improved pharmacokinetics and pharmacodynamics in rodent models of inflammation and pain compared to their nondeuterated congeners. It was also revealed that substitution at the 6-position was optimal for maintaining high potency against COX-2.[34,35]

The pentafluorosulfanyl group (SF_5) is a unique moiety, and when incorporated into compounds, endow molecules with a high dipole moment without increasing molecular polarity resulting in interesting physicochemical properties, including better thermal stability as well as hydrolytic and chemical stability, higher density, and lipophilicity that can lead to better biological activity (Figure 1).[36−42] To some extent, it bears

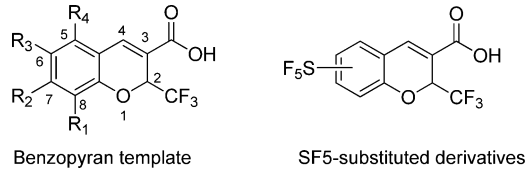


Figure 1. Benzopyran and SF_5-substituted derivatives.

similarity to the trifluoromethyl group but is slightly more electronegative, lipophilic, and appreciably bulkier.[43] These rare properties make the SF_5 moiety suitable for applications in drug development.[44−46]

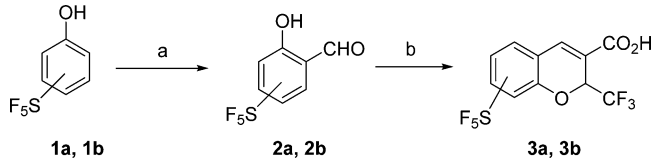
RESULTS

Chemistry. In an effort to develop different selective COX-2 inhibitors, we introduced a SF_5 group on the benzopyran pharmacophore. Although the availability of SF_5 reagents remains limited, new synthetic methods were developed to prepare key intermediates allowing for the synthesis of a series of SF_5-substituted benzopyran derivatives.

The initial synthesis focused on introducing the SF_5 moiety into the 6-position or 7-position. According to published procedures,[1,34] substituted salicylaldehydes **2a**/**2b** were prepared from commercially available *meta* or *para*-(pentafluorosulfanyl)-phenol **1a** and **1b** and then condensed with ethyl 4,4,4-trifluorocrotonate to produce the benzopyran ester. Finally, the ester was hydrolyzed to give *R*,*S*-**3a**, SF_5 at the 6-position or *R*,*S*-**3b**, and SF_5 at the 7-position (Scheme 1). It was observed that *R*,*S*-**3a** was potent in inhibiting COX-2, whereas *R*,*S*-**3b** was much less active (Table 1).

We next turned our attention to the synthesis of 8-bromo 6-substituted SF_5 containing benzopyran derivative **7**. Because of our inability to monobrominate **1a**, we prepared the corresponding anisole derivative **4**, which was readily monobrominated.

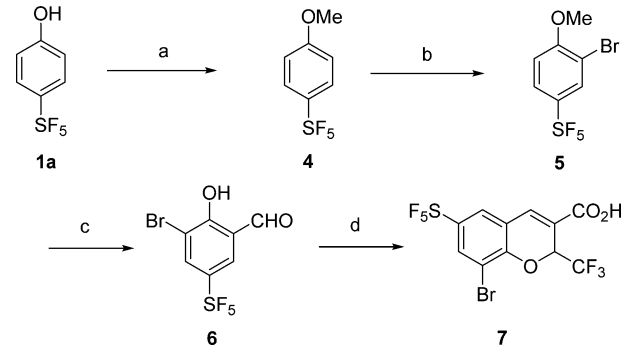
Scheme 1. General Method for the Preparation of Benzopyran Derivatives 3a and 3b[a]



[a]Reagents and conditions: (a) $(CH_2)_6N_4$ (HMTA), CF_3CO_2H (TFA), rt, 1 h; (b) (i) ethyl 4,4,4-trifluorocrotonate, KF, DMSO, 130 °C, 12 h, (ii) NaOH/MeOH/H_2O, rt, 1−2 h. **1a** = 4-(pentafluorosulfanyl)phenol; **1b** = 3-(pentafluorosulfanyl)phenol.

Bromo-substituted anisole (**5**) was then converted to the corresponding phenol by *O*-dealkylation with potassium *n*-octanethiolate and immediately converted to the corresponding salicylaldehyde **6** by treatment with hexamethylenetetramine in trifluoroacetic acid; see Scheme 2. Then **6** was condensed

Scheme 2. Preparation of Target Compound (7)[a]



[a]Reagents and conditions: (a) MeI, K_2CO_3, DMF, 12 h; (b) Br_2, HOAc, 80 °C, 12 h; (c) (i) 1-octanethiol, *tert*-BuOK, DMF, 110 °C, 12 h, (ii) HMTA, TFA, rt, 2 h; (d) (i) ethyl 4,4,4-trifluorocrotonate, KF, DMSO, 130 °C, 12 h, (ii) NaOH/MeOH/H_2O, rt, 1−2 h.

with ethyl 4,4,4-trifluorocrotonate to produce the anticipated benzopyran ester. Finally, the ester was hydrolyzed to give *R*,*S*-**7**. A separate synthetic scheme was developed for the preparation of 6-alkyl substituted intermediates **10a**−**10e** (Scheme 3). Briefly, 2-hydroxy-5-(pentafluorosulfanyl)benzaldehyde (**2a**) was treated with either sodium borohydride (**8a**) or with excess Grignard reagent to produce benzyl alcohol derivatives (**8b**−**8e**). The benzylic hydroxyl was then removed by treatment of **8a**−**8e** with two equivalents of ethyl chloroformate followed by reduction with excess sodium borohydride in THF to afford the 2-alkyl derivatives **9a**−**9e**.[47] The 2-alkyl derivatives **9a**−**9e** were then converted to the corresponding benzaldehydes **10a**−**10b** and thence to benzopyrans (*R*,*S*-**11a**−**11e**), see Scheme 3.

The individual *R* or *S* enantiomers were obtained either by preparative chiral chromatography or by the catalytic asymmetric synthesis shown in Scheme 4.

Cyclooxygenase Assays. The potency of the compounds was determined against human COX-1 (hCOX-1) and human recombinant COX-2 (hCOX-2) enzymes using a substrate-based assay.[34,48−50] Most of the compounds were tested as racemates as separation of the *R*/*S* isomers resulted in lower yields. The IC_{50} values showed that many of the SF_5-substituted molecules were poorly active against COX-1 but very active against COX-2, with the most potent molecules being *R*,*S*-**3a**,

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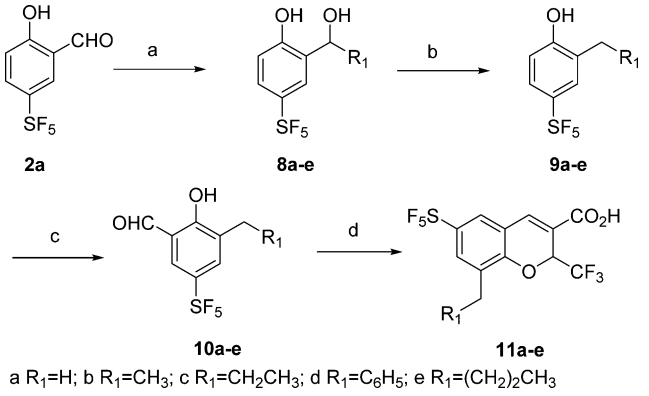
Scheme 3. General Synthesis of Benzopyrans *R,S*-11a−11e[a]



[a]Reagents and conditions: (a) $NaBH_4$, EtOH, reflux, 2 h for R_1 = H, or excess R_1MgBr, THF, 0−25 °C, 12 h; (b) (i) EtOCOCl, Et_3N, DCM, 0−25 °C, 2 h, (ii) $NaBH_4$, EtOH, 0−25 °C, 2 h; (c) HMTA, TFA, 80 °C, 12 h; (d) (i) ethyl 4,4,4-trifluorocrotonate, Et_3N, DMF 80−100 °C, 12−18 h, (ii) NaOH/MeOH/H_2O, rt, 2 h.

S-7, *R,S*-**11a**, and *R,S*-**10c** yielding IC_{50} values of 18, 8 and 26, and 46 nM, respectively (Table 1). On the basis of the structure−activity relationship, it was found that the position of the SF_5 moiety on the aromatic ring is critical for potency as compound *R,S*-**3a** was found to be active against COX-2, whereas *R,S*-**3b**, the same molecule with the SF_5 moiety shifted from position 6 to 7, was much less active. Thus, positioning of the SF_5 moiety was found critical for compound potency against COX-2.

Another interesting observation was that molecule *R*-7 showed some activity against COX-2, although approximately 100 times less active than *S*-7. This is an important finding, as it has previously been shown that the *R*-isomers of benzopyran based COX-2 inhibitors were largely inactive whereas the *S*-isomers were highly active. This suggests that the SF_5 moiety allows the *R*-isomeric form of the compound to bind to the active site of COX-2, albeit weakly.

Serum Protein and the Human Ether-à-go-go-Related Gene (hERG) Binding of Selective Compounds. As long as efficacy is not compromised, it has been suggested that high plasma protein binding may be a desirable property for new coxibs to possess as a way of limiting their off and on target side effects. For example, during vascular inflammation, COX-2 is up-regulated to produce the prostaglandin PGI_2, a vascular vasodilator causing relaxation of veins, large arteries, and arterioles. It is believed that blockade of PGI_2 may be responsible for the increased incidence of heart attack and strokes associated with NSAIDs. Thus, we tested the SF_5 compounds for human plasma protein binding by equilibrium dialysis (Table 2). All the compounds tested showed very high plasma binding, over 99.9% indicating these compounds are tightly bound in the blood and may have diminished off and on target side effects.

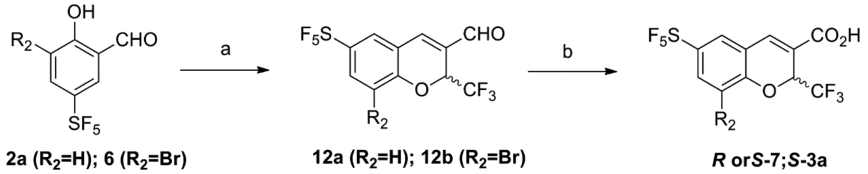
Next we tested selected compounds (*R,S*-**3a**, *S*-**3a**, *R,S*-**11a**, *R,S*-**11b**, *R,S*-**11c**, and *R,S*-**11e**) in the dofetilide binding assay, which is a high-throughput surrogate assay for predicting hERG activity. hERG is a potassium ion channel in cardiac tissues, thus hERG inhibition is an important antitarget that must be avoided during discovery and drug development. All the compounds tested showed no binding up to 50 μM, indicating that this series of compounds will not likely interfere with hERG.

Crystal Structure of *R,S*-3a and Predicted Interaction between *R*-3a or *S*-3a and COX-2. To better understand the structural configuration of this class of chemistry, crystal structure of *R,S*-**3a** was determined (Olex2[S1] was used for structure refinement). The structure has been deposited in the Cambridge Crystallographic Data Centre and assigned to the deposition number CCDC1505776. The crystal of *R,S*-**3a** belongs to space group *P*21/*c* with cell parameters *a* (9.10556), *b* (11.3030), *c* (12.5197), α (90), β (91.1775), and γ (90). There was only one *R,S*-**3a** molecule present in an asymmetric unit. The *R*-**3a** molecule is related to *S*-**3a** through a symmetric center.

To investigate the mechanism of COX-2 inhibited by *R,S*-**3a**, *R,S*-**3a** was fitted into the active site of COX-2 (PDB 4PH9)[S2] using Auto dock Vina[S3] (Figure 2). In accordance with the result of enzyme assay (Table 1), the predicted inhibition activity of *S*-**3a** was apparently higher than *R*-**3a**. The binding affinity energy (BAE) was −10.2 and −8.7 kcal/mol for *S*-**3a** and *R*-**3a**, respectively. We speculate that the subpocket Psel (marked by red circle in Figure 2C,D) that accommodates the $-CF_3$ group is critical for enantioselectivity. Psel prefers to accommodate the $-CF_3$ group of *S*-**3a**, but not that of *R*-**3a**, because it has a deep front side (Figure 2C, marked by a red circle and named Psel-F) and shallow back side (Figure 2D, marked by a red circle and named Psel-R). *S*-**3a** forms three H-bonds with COX-2, and the group $-CF_3$ is accommodated well by Psel-F (Figure 2C). When *R*-**3a** docked to COX-2, one H-bond is lost because its $-CF_3$ group is pushed away by the shallow Psel-R (Figure 2D).

Pharmacokinetic Profile of *R,S*-3a. It has been reported that the SF_5 moiety can enhance the pharmacokinetics of some drugs. *R,S*-**3a** was tested for PK in rats by dosing the compound orally and intravenously at 5 mg/kg (Table 3). The compound demonstrated an excellent PK profile with a half-life of >12 h, a C_{max} of ∼15 mg/L, and 100% bioavailability. Even after 45 h, the rat plasma drug concentration was above the IC_{90} required for COX-2 inhibition as determined in the enzyme assay (Figure 3). Whether this molecule has a longer duration of action in other species remains to be determined. To put this observation into perspective, a structurally similar deuterated

Scheme 4. Catalytic Asymmetric Synthesis of Selected Benzopyrans[a]



[a]Reagents and conditions: (a) 2-nitrobenzoic acid (20 mol %), (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine or (*S*)-2-(diphenyl-((trimethylsilyl)oxy)methyl)pyrrolidine (20 mol %), (*E*)-4,4,4-trifluorobut-2-enal, CH_2Cl_2, rt, 24 h; (b) $KHSO_5$, DMF, rt, 24 h.

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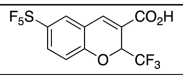
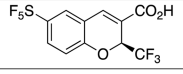
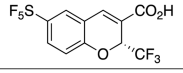
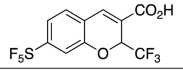
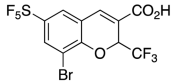
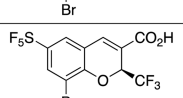
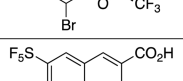
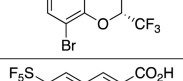
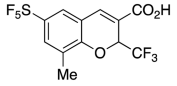
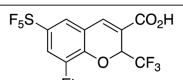
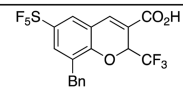
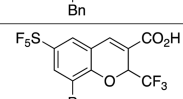
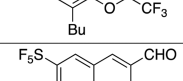
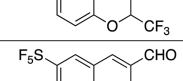
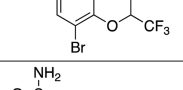
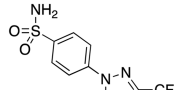
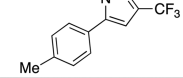
Table 1. SF_5-Substituted Benzopyrans Tested against Human COX-1 and Human COX-2 Enzymes

Compound	(SF #)	Structure	[a]IC_{50} (μM) hCOX-1	hCOX-2
***R,S*-3a**	(SF-1001)		>10	0.018±0.01
***S*-3a**	(SF-1005)		>30	0.010±0.001
***R*-3a**	(SF-1013)		>10	0. 302±0.005
***R,S*-3b**	(SF-1002)		>10	>10
***R,S*-7**	(SF-1012)		>10	0.056±0.005
***S*-7**	(SF-1003)		>10	0.008±0.004
***R*-7**	(SF-1004)		>10	0.34±0.1
***R,S*-11a**	(SF-1006)		>10	0.026±0.003
***R,S*-11b**	(SF-1007)		>10	0.06±0.01
***R,S*-11c**	(SF-1008)		>10	0.046±0.03
***R,S*-11d**	(SF-1011)		>10	>100
***R,S*-11e**	(SF-1009)		>10	0.19±0.01
***R* or *S*-12a**			>10	>10
***R* or *S*-12b**			>10	>10
Celecoxib			>10	0.007±0.002
SC-560			0.053±0.014	>10
DuP-697			>10	0.0331±0.0023

[a]IC_{50} values represent the half-maximal (50%) inhibitory concentration, as determined in triplicate.

Table 2. Human Plasma Protein Binding Was Measured by Rapid Equilibrium Dialysis[a]

compd	conc (μM)	time (h)	mean % nound (n = 3)	SD (%)
chlorpromazine HCl (positive control)	10	5	99.82	0.04
atropine (negative control)	10	5	24.55	0.69
R,S-**3a** (SF-1001)	10	5	99.90	0.07
R,S-**3b** (SF-1002)	10	5	99.94	0.07
S-7 (SF-1003)	10	5	99.91	0.01
R-7 (SF-1004)	10	5	99.95	0.03
S-**3a** (SF-1005)	10	5	99.96	0.01
R,S-**11a** (SF-1006)	10	5	99.95	0.01
R,S-**11e** (SF-1009)	10	5	99.92	0.07

[a]Chlorpromazine HCl and atropine was used as controls, high protein binding versus low protein binding compound, respectively.

benzopyran compound made by our team and published in 2015[1] had a half-life of 4.2 h. Thus, these data suggest that the addition of the SF_5 group may be beneficial for enhancing PK for this single compound, although more SF_5 compounds will have to be tested for PK and in different species before we can make any firm conclusions.

In Vivo Efficacy in Rodent Models of Inflammation and Pain. On the basis of its excellent pharmacokinetics, compound *R,S*-**3a** was selected for in vivo efficacy evaluation in rat models of inflammation and pain. As a comparator compound, celecoxib was chosen as it has extensively been studied in these models.

Air Pouch Model. An air pouch was produced by the subcutaneous injection of sterile air into the back of rats.[55−59] The pouch mimics a synovial cavity providing a localized environment to study an inflammatory response. The rats were then administered either control or compound *R,S*-**3a** orally at various doses. Carrageenan was then injected into the air pouch to produce inflammation. The air pouch was monitored for PGE_2 levels, which is a marker of inflammation, and the efficacy of *R,S*-**3a** was determined. Drug *R,S*-**3a** blocked PGE_2 levels in the pouch in a dose-dependent manner, showing an ED_{50} of ∼0.37 mg/kg, demonstrating that compound *R,S*-**3a** gets to the site of inflammation (Table 4).

Carrageenan Induced Paw Edema. The carrageenan paw edema model was used to detect local inflammation mediated by prostaglandin production.[60−62] Carrageenan was injected into right hind paw of rats. One half-hour before the injection, compound *R,S*-**3a** was orally dosed at different concentrations. Caliper measurements of the paws were taken at baseline (just prior to carrageenan injection) and again between 1 and 4 h postcarrageenan injection. Differences between injected versus noninjected and compound treated versus nontreated paws were determined. Compound *R,S*-**3a** demonstrated concentration-dependent suppression of paw edema, yielding an ED_{50} of ∼4 mg/kg (Table 4).

Thermal Hyperalgesia. Increased sensitivity to pain was assessed in the carrageenan paw edema model as described above.[63−65] One half-hour after oral administration of *R,S*-**3a** at varying doses, carrageenan was injected into right hind paws of the rats, and paw withdrawal thermal latency (PWTL) was

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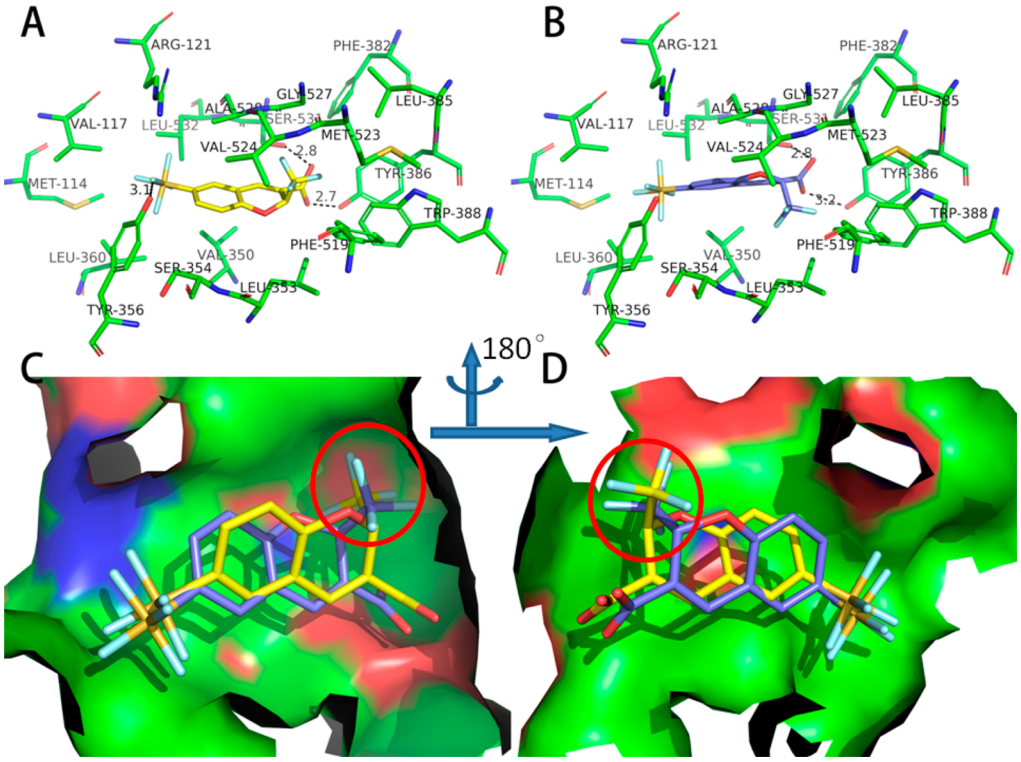

Figure 2. Predicted interaction between *S*-**3a** or *R*-**3a** (Cambridge Crystallographic Data Centre deposition no.: CCDC1505776) and COX-2 (PDB 4PH9). (A,B) Predicted docking pose of *S*-**3a** (yellow sticks) and *R*-**3a** (blue sticks), respectively. Key residues of binding pocket are shown as sticks, and the H-bonds are labeled. (C,D) Surface presentation of binding pocket, (D) is generated by rotating (C) 180° around its vertical axis. This diagram is prepared using Pymol.[54]

Table 3. Rat Pharmacokinetic Profile for Compound *R,S*-3a[a]

administration	PO	IV
rat no.	♂4	♂4
dose level mg/kg	5	5
AUC(0−∞) μg·h/L	414200	364120
$T_{1/2}$ (h)	12.5	17.3
T_{max} (h)	7.75	0.033
C_{max} (μg/L)	15300	31688
V_d	0.341	0.223
F (%)	113.8%	

[a]Compound was dosed both orally (PO) and intravenously (IV).

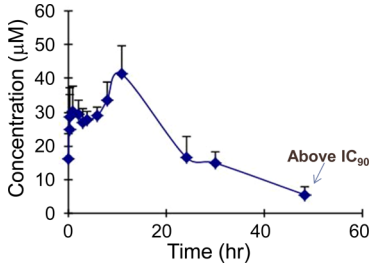

Figure 3. PK profile for compound *R,S*-**3a** in rats. Compound shows a long extended duration in the plasma.

measured before and 3 h post injection using an PL-200 hot plate device. A significant decrease in PWTL was observed in the vehicle group 3 h post injection, indicating increased heat sensitivity, but compound *R,S*-**3a** demonstrated a concentration-dependent reversal of the observed thermal hyperalgesia with an ED_{50} of ∼5.6 mg/kg (Table 4). Almost complete reversal was observed between 10 and 20 mg/kg doses.

Table 4. In Vivo Summary of Compound *R,S*-3a versus Celecoxib in Rat Models of Inflammation and Pain[a]

model	*R,S*-**3a** ED_{50} (mg/kg)[n]	celecoxib ED_{50} (mg/kg)[n]
air pouch	0.37	0.69
paw edema	4.0	2.8
hyperalgesia	2.8	5.0
AIA (*paw edema*)	0.093	1.6
AIA (*arthritis score*)	0.094	0.71
AIA (*movement disorder*)	0.12	9.2

[a]Compounds were dosed at various concentrations to determine the ED_{50} values. [n]ED_{50} values represent the half-maximal (50%) effective dose, as determined in triplicate.

Adjuvant-Induced Arthritis Model (AIA). As an animal model for inflammation and reactive rheumatoid arthritis, AIA is proven to be a valuable model for testing and discovering NSAIDs.[66−68] Each rat (n = 6/dose group) received a subcutaneous injection of adjuvant into the base of the tail. Fourteen days after the injection, only rats that showed significant left hind paw swelling were selected for the study (>95% responded, typically 6 of 6 animals). The rats were then divided into several groups including vehicle and different concentrations of compound *R,S*-**3a**, dosed orally from day 15 to 25. At day 25, the rats were evaluated for disease. In the absence of drug, severe disease progression was observed. However, drug *R,S*-**3a** effectively stopped all disease parameters including paw edema (Figure 4), arthritis, and movement disorder with ED_{50} values of 0.093, 0.094, and 0.12, respectively (Figure 5 and Table 3). Measurement of paw edema was paw volume, arthritis score was based on erythema and swelling of ankles, wrists, and toes (scores ranging from 0 to 16), and

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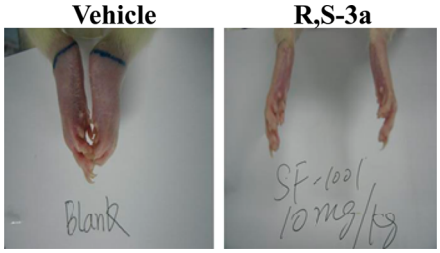

Figure 4. Efficacy of drug *R,S*-**3a** at 10 mg/kg versus vehicle in blocking paw edema in the AIA rat model.

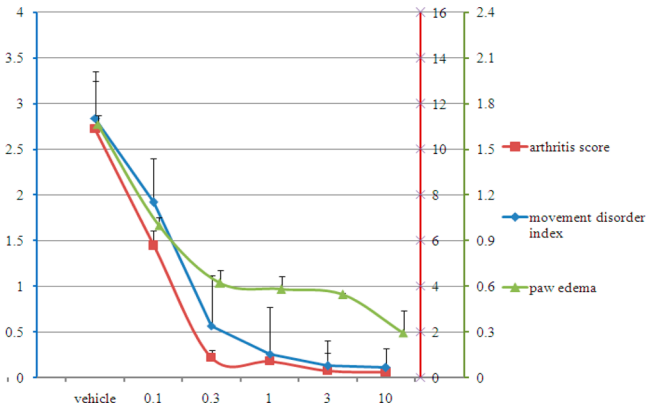

Figure 5. Efficacy of drug *R,S*-**3a** at various doses, vehicle, 0.1, 0.3, 1, 3, and 10 mg/kg (*X*-axis) in blocking paw edema, arthritis, and movement index. Arthritis score is depicted by the red squares, movement disorder index is shown by the blue circles, and paw edema is illustrated by the green triangles.

movement disorder was based on the standard of movement of the animals (scores ranging from 0 to 3).

To determine whether compound *R,S*-**3a** would be effective with less frequent dosing due to its long plasma half-life, the study was repeated, this time dosing at 10 mg/kg every 5 days, starting from day 15 post adjuvant injection and ending on day 25 (two doses as opposed to ten). As hoped, drug *R,S*-**3a** still demonstrated efficacy, again blocking all three disease parameters including paw edema, arthritis, and movement disorder with inhibition scores of 66.9 ± 6.9, 69.6 ± 30.3, and 79.2 ± 40.9, respectively. These data bring up the possibility that drug *R,S*-**3a** may be able to be dosed less frequently.

DISCUSSION AND CONCLUSIONS

A new series of COX-2 inhibitors has been developed by incorporating a pentafluorosulfanyl moiety. Most of compounds were found to be potent and selective for human recombinant COX-2 over COX-1. Moreover, one of the molecules, *R,S*-**3a**, was found to have excellent pharmacokinetics in rodents with a half-life of greater than 12 h. In addition, *R,S*-**3a** proved to be efficacious in multiple models of inflammation and pain, including the rat air pouch, paw edema, hyperalgesia, and adjuvant induced arthritis models. Pronounced efficacy of *R,S*-**3a** was observed in the AIA model, yielding an especially low ED_{50} of 0.094 mg/kg in blocking edema and arthritis disease. This is particularly important, as the AIA system is an industry standard model for predicting human clinical success of new nonsteroidal anti-inflammatory drugs and coxibs. To our knowledge, no other anti-inflammatory drug, either small molecule or protein, has displayed such a low ED_{50}. A representative of this class of SF_5 based drugs may be a good drug candidate for the treatment of inflammation and associated pain as it outperformed celecoxib in all parameters.

Future studies will focus on investigational new drug enabling activities such as large scale manufacturing of compound ***S*-3a** and advanced toxicity studies in rodents and dogs.

EXPERIMENTAL SECTION

General. All commercial chemicals and solvents were obtained from commercial sources and were used without further purification. Solvents were chromatography grade and were used without further purification. Thin layer chromatography (TLC) analysis was performed using Merck silica gel 60 F-254 thin layer plates. LC-MS analyses were performed on the Agilent 1200 HPLC/MCD electrospray mass spectrometer in positive/negative ion mode. The scan range was 100−1000d. High resolution mass spectra were obtained in the ABSciex TOF5600+ MS using electrospray ionization. Preparative reverse phase HPLC was performed on a Shimadzu LC-20AP equipped with a C18 column using a methanol/water gradient. The purity of tested compounds was ≥95% determined by HPLC analysis conducted on the Agilent 1260 system using a reverse phase C18 column with diode array detector unless stated otherwise. Chiral GC-column: Chiralpak OD-H, AS-H, OJ-H, 4.6 mm × 250 mm 5 μm. Specific rotation value were recorded on Autopol IV-T (λ = 589 nm, 50 mm cell, 25 °C). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 or Bruker 400 (at 500 and 125 MHz or 400 and 100 MHz, respectively) and are reported to $CDCl_3$ (δ ^{1}H, 7.26, and ^{13}C, 77.16). ^{19}F NMR (at 471 MHz). Coupling constants (J) are given in Hz.

*2-Hydroxy-5-(pentafluorosulfanyl)benzaldehyde (**2a**).* To a solution of 4-(pentafluorosulfanyl)phenol (2.0 g, 9.1 mmol) in trifluoroacetic acid (TFA) (20 mL) was added hexamethylenetetramine, (HTMA) (1.78 g, 12.7 mmol). The mixture was stirred at 80 °C for 4 h and then cooled to room temperature. To the mixture, H_2O (40 mL) was added and then stirred at room temperature for another 0.5 h. The mixture was then extracted with EtOAc, and the organic layer was washed with saturated $NaHCO_3$, water, and brine. The resulting organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography, yielding the compound as a white solid 1.02 g in 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 9.94 (s, 1H), 7.99 (d, J = 2.7 Hz, 1H), 7.90 (dd, J = 9.2, 2.7 Hz, 1H), 7.02 (d, J = 9.26 Hz, 1H).

*2-Hydroxy-4-(pentafluorosulfanyl)benzaldehyde (**2b**).* The title compound was prepared by the same procedure as **2a** as colorless oil in 40% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.09 (s, 1H), 10.03 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 6.5 Hz, 1H), 7.46 (s, 1H). MS (MM-ES + APCI) m/z: 247.1 $[M - H]^-$.

*R,S-6-(Pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**3a**).* Step 1: A mixture of 2-hydroxy-5-pentafluorosulfanylbenzaldehyde (**2a**) (0.64 g, 2.6 mmol), anhydrous KF (0.30 g, 5.2 mmol), and ethyl 4,4,4-trifluorocrotonate (0.87 g, 5.2 mmol) in anhydrous DMSO (30 mL) was stirred at 130 °C for 5 h. The mixture was cooled to room temperature and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give ethyl 6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2*H*-chromene-3-carboxylate as a yellow solid 0.3 g in 31% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.73 (m, 3H), 7.04 (d, J = 9.2 Hz, 1H), 5.78 (d, J = 6.8 Hz, 1H), 4.34−4.37 (q, J = 7.2 Hz, 2H), 1.35−1.39 (t, J = 7.2 Hz, 3H). This product was used directly in the next step without further purification. Step 2: A solution of ethyl 6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2*H*-chromene-3-carboxylate (0.3 g, 0.75 mmol) was dissolved in (20 mL, MeOH/H_2O = 10/1) and treated with NaOH (0.30 g, 7.5 mmol). The resulting solution was stirred at room temperature overnight. The solution was concentrated to remove the ethanol, acidified to pH = 3, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the target compound as a solid 0.27 g in 100% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.74 (dd, J = 7.8, 2.6 Hz, 1H), 7.68 (d, J = 2.6 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 5.76 (q, J = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.39 (s), 154.52 (s), 147.35−146.75 (m), 134.76 (s),

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130.29 (s), 127.65 (s), 124.48 (t, J = 287.4 Hz), 119.30 (s), 118.92 (s), 116.23 (s), 70.41 (q, J = 32.4 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 84.08 (m, 1F), 63.67 (dd, J = 150.5, 22.1 Hz, 4F), −78.48 (d, J = 6.7 Hz, 3F). HRMS (ESI) calcd for $C_{11}H_5F_8O_3S$ [M − H] 368.9837, found 368.9840. HPLC: 99.438%.

*7-(Pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**3b**).* The title compound was prepared by the same procedure as *R,S*-**3a** as a white solid in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 1H), 5.75 (q, J = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.39 (s), 154.80 (t, J = 17.0 Hz), 152.16 (s), 134.24 (s), 130.43 (s), 124.48 (t, J = 287.4 Hz), 122.43 (s), 120.21 (s), 113.24 (s), 70.20 (q, J = 32.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 82.73 (m, 1F), 62.27 (dd, J = 150.2, 22.0 Hz, 4F), −78.35 (d, J = 6.7 Hz, 3F). HRMS (ESI) calcd for $C_{11}H_5F_8O_3S$ [M − H] 368.9837, found 368.9842. HPLC: 99.443%.

*(S)-6-(Pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (S-**3a**).* A mixture of *S*-**12a** (R_2 = H) (100 mg, 0.28 mmol) and Oxone (209 mg, 0.34 mmol) in DMF (10 mL) was stirred at room temperature overnight. The solution was then diluted with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the title compound 57 mg in 55% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.00 (s, 1H), 7.89 (d, J = 9.0, 1H), 7.23 (d, J = 9.0 Hz, 1H), 6.08 (q, J = 7.0 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.32 (s), 154.47 (s), 146.99 (t, J = 17.2 Hz), 134.73 (s), 130.23 (s), 127.60 (s), 123.28 (q, J = 287.5 Hz), 119.24 (s), 118.83 (s), 116.17 (s), 70.36 (q, J = 32.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 85.46−83.19 (m, 1F), 63.67 (dd, J = 150.5, 22.0 Hz, 4F), −78.48 (d, J = 6.5 Hz, 3F). HRMS (ESI) calcd for $C_{11}H_6F_8O_3S$ [M − H] 368.9837, found 368.9834. HPLC: 98.28%.

*(R)-6-(Pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R-**3a**).* The procedure described for the preparation of *R*-**3a** was used substituting (*R*)-2-(diphenyl((trimethylsilyl)oxy)-methyl)pyrrolidine as the chiral catalyst. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.76 (dd, J = 9.0, 2.6 Hz, 1H), 7.70 (d, J = 2.6 Hz, 1H), 7.09 (dd, J = 9.0, 2.6 Hz, 1H), 5.80 (q, J = 6.6 Hz, 1H). HRMS (ESI) calcd for $C_{11}H_5F_8O_3S$ [M − H] 368.9837, found 369.0002. HPLC: 99.56%.

*1-Methoxy-4-(pentafluorosulfanyl)benzene (**4**).* To a solution of 4-(pentafluorosulfanyl)phenol (5.0 g, 22.7 mmol) and anhydrous K_2CO_3 (9.4 g, 68.1 mmol) in DMF (75 mL) was added iodomethane (3.2 g, 22.7 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight. The mixture was then diluted with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the compound 4.5 g in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.72 (d, J = 7.5 Hz, 2H), 6.92−6.94 (d, J = 7.5 Hz, 2H), 3.87 (s, 3H).

*2-Bromo-1-methoxyphenyl(pentafluorosulfanyl)benzene (**5**).* To a mixture of 1-methoxy-4-(pentafluorosulfanyl)benzene (2.0 g, 8.5 mmol) in AcOH (30 mL) was added Br_2 (6.8 g, 42.7 mmol), and the mixture was stirred at 80 °C overnight. Then solution was diluted with saturated $NaHSO_3$ solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the title compound 1.76 g in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.70−7.73 (d, J = 7.5 Hz, 1H), 6.92−6.94 (d, J = 7.5 Hz, 1H), 3.97 (s, 3H).

*3-Bromo-2-hydroxy-5-(pentafluorosulfanyl)benzaldehyde (**6**).* Step 1: To a solution of *t*-BuOK (1.29 g, 8.6 mmol) in DMF (50 mL) was added 1-octanethiol (1.29 g, 8.6 mmol). The resulting mixture was stirred at room temperature for 10 min, then 1-methoxy-4-(pentafluorosulfanyl)benzene (1.76 g, 5.6 mmol) was added. The resulting mixture was stirred at 110 °C for 1 h. Then the mixture was diluted with H_2O, acidified to pH = 1 and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give 2-bromo-4-(pentafluorosulfanyl)-phenol, 1.41 g in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.64−7.66 (d, J = 7.5 Hz, 1H), 7.06−7.08 (d, J = 7.5 Hz, 1H). Step 2: To a solution of the product of Step 1 (1.4 g, 4.7 mmol) in TFA (20 mL) was added HTMA (0.9 g, 6.6 mmol) portionwise. The mixture was stirred at 80 °C for 8 h and then cooled to room temperature. To the above mixture, H_2O (40 mL) was added and the resulting mixture stirred at room temperature for another 0.5 h. The mixture was then extracted with EtOAc, and the organic layer was washed with saturated $NaHCO_3$, water, and brine. The resulting organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the title compound 0.46 g in 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 1H), 9.93 (s, 1H), 8.19 (s, 1H), 8.00 (s, 1H).

*(R,S)-8-Bromo-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**7**).* The title compound was prepared by the same procedure as *R,S*-**3a** in 60% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ13.69 (s, 1H), 8.28 (q, J = 2.6 Hz, 2H), 8.02 (s, 1H), 6.30 (q, J = 7.0 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.49 (s), 152.11 (s), 147.13 (t, J = 17.9 Hz), 134.81 (s), 133.06 (s), 127.33 (s), 124.70 (t, J = 287.4 Hz), 120.99 (s), 120.20 (s), 109.56 (s), 71.67−71.42 (m). ^{19}F NMR (471 MHz, DMSO-d_6) δ 86.25−85.60 (s, 1F), 65.40−65.07 (dd, J = 151.9, 21.9 Hz, 4F), −77.56 (d, J = 7.0 Hz, 3F). HRMS (ESI) calcd for $C_{11}H_5BrF_8O_3S$ [M− H] 446.8942, found 446.9130. HPLC: 93.84%.

*(S)-8-Bromo-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (S-**7**).* A mixture of *S*-**12b** (R_2 = Br) (104 mg, 0.24 mmol) and Oxone (172 mg, 0.28 mmol) in DMF (10 mL) was stirred at room temperature overnight. The solution was then diluted with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the title compound 72 mg in 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 2.4 Hz, 1H), 7.81 (s, 1H), 7.63 (d, J = 2.4 Hz, 1H), 5.88 (q, J = 6.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.10 (s), 151.61 (s), 147.01 (t, J = 17.9 Hz), 133.94 (s), 132.45 (s), 126.77 (s), 124.46 (t, J = 287.4 Hz), 120.62 (s), 120.22 (s), 109.04 (s), 76.92−67.30 (m). ^{19}F NMR (471 MHz, $CDCl_3$) δ 82.73 (m, 1F), 63.86 (dd, J = 150.8, 22.1 Hz, 4F), −78.58 (d, J = 6.4 Hz, 3F). HRMS (ESI) calcd for $C_{11}H_4BrF_8O_3S$ [M − H] 446.8942, found 446.8957. HPLC: 98.29%.

*(R)-8-Bromo-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R-**7**).* The procedure described for the preparation of *R*-7 was used substituting (*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine as the chiral catalyst. The NMR data was essentially identical to *S*-7. HRMS (ESI) calcd for $C_{11}H_4BrF_8O_3S$ [M − H] 446.8942, found 446.9134. HPLC: 90.91%.

*2-(Hydroxymethyl)-4-(pentafluorosulfanyl)phenol (**8a**).* To a solution of **2a** (0.8 g, 3.2 mmol) in EtOH (15 mL) was added $NaBH_4$ (0.17 g, 4.5 mmol), and then the mixture was refluxed for 2 h. The mixture was then extracted with EtOAc, and the organic layer was washed with brine. The resulting organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the title compound 0.65 g in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 6.92 (d, J = 9.0 Hz, 1H), 4.94 (s, 2H). MS (MM-ES + APCI) m/z: 249.0 $[M - H]^-$.

*2-(1-Hydroxyethyl)-4-(pentafluorosulfanyl)phenol (**8b**).* To a solution of **2a** (0.13 g, 0.5 mmol) in anhydrous THF (6 mL) was added CH_3MgBr (3.0 mL, 3.7 mmol, 1.3 mol/L) dropwise at room temperature. Then the mixture was stirred at room temperature overnight; after that, the mixture was acidified to pH = 3 and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography to give title compound 0.13 g in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.56 (dd, J = 8.9, 2.6 Hz, 1H), 7.38 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 5.12 (q, J = 6.5 Hz, 1H), 1.61 (d, J = 6.6 Hz, 3H). MS (MM-ES + APCI) m/z: 263.0 [M − H].

*2-(1-Hydroxypropyl)-4-(pentafluorosulfanyl)phenol (**8c**).* The title compound was prepared by the same procedure as **8b**, in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.56 (dd, J = 9.0, 2.7 Hz, 1H), 7.34 (d, J = 2.7 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 4.82 (t, J = 13.6 Hz, 1H), 1.89 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).

*2-(Hydroxy(phenyl)methyl)-4-(pentafluorosulfanyl)phenol (**8d**).* The title compound was prepared by the same procedure as **8b** in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.55 (m, 3H), 7.45

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(dd, J = 10.4, 4.8 Hz, 3H), 7.35 (t, J = 7.4 Hz, 2H), 1.26 (s, 1H). MS (MM-ES + APCI) m/z: 325.0 $[M - H]^-$.

*2-(1-Hydroxybutyl)-4-(pentafluorosulfanyl)phenol (**8e**).* The title compound was prepared by the same procedure as **8b** in 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.84 (s, 1H), 3.81 (s, 1H), 1.93−1.66 (m, 2H), 1.56−1.28 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). MS (MM-ES + APCI) m/z: 291.1 $[M - H]^-$.

*2-Methyl-4-(pentafluorosulfanyl)phenol (**9a**).* A solution of 2-(hydroxymethyl)-4-(pentafluorosulfanyl)phenol (170 mg, 0.68 mmol) and trimethylamine (1.50 g, 14.9 mmol) in CH_2Cl_2 (10 mL) was treated with ethyl chloroformate (650 mg, 6.0 mmol) at 0 °C and then allowed to warm to room temperature for 3 h. The solution was concentrated in vacuo and the residue dissolved in ethanol (3 mL) and water (20 mL) and treated with $NaBH_4$ (1.80 g, 39.7 mmol) at 0 °C. The solution was allowed to warm to room temperature overnight and then acidified to pH = 3 with 3 N HCl and then extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4, filtered, and concentrated to give the title compound that was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.46 (dd, J = 8.8, 2.7 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 2.28 (s, 3H). MS (MM-ES + APCI) m/z: 233.0 $[M - H]^-$.

*2-Ethyl-4-(pentafluorosulfanyl)phenol (**9b**).* To a mixture of **8b** (0.13 g, 0.49 mmol) and trimethylamine (TEA) (1.82 g, 18 mmol) in CH_2Cl_2 was added ethyl chloroformate (0.75 g, 6.9 mmol) at 0 °C and then stirred at room temperature for 3 h. After the reaction completed, the mixture was concentrated and dissolved in EtOH (3 mL). To above solution, a solution of $NaBH_4$ (2 g, 55.2 mmol) in H_2O (20 mL) was added at 0 °C. The resulting mixture was then stirred at room temperature overnight. Then the mixture was acidified to pH = 3 and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give title compound, which was used directly in the next step without further purification.

*4-(Pentafluorosulfanyl)-2-propylphenol (**9c**).* The title compound was prepared by the same procedure as **9a** in 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.45 (dd, J = 8.8, 2.7 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 2.61 (t, J = 21.6, 13.7 Hz, 2H), 1.73−1.57 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). MS (MM-ES + APCI) m/z: 261.0 $[M - H]^-$.

*2-Benzyl-4-(pentafluorosulfanyl)phenol (**9d**).* The title compound was prepared by the same procedure as **9a** in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.49 (m, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 6.7 Hz, 3H), 6.82 (d, J = 8.5 Hz, 1H), 4.02 (s, 2H). MS (MM-ES + APCI) m/z: 309.0 $[M - H]^-$.

*2-Butyl-4-(pentafluorosulfanyl)phenol (**9e**).* The title compound was prepared by the same procedure as **7e** in 47% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.71 (s, 1H), 2.70−2.62 (m, 2H), 1.64−1.61 (m, 2H), 1.47−1.36 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). MS (MM-ES + APCI) m/z: 275.1 $[M - H]^-$.

*2-Hydroxy-3-methyl-5-(pentafluorosulfanyl)benzaldehyde (**10a**).* The title compound was prepared by the same procedure as **2a** in 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (s, 1H), 9.91 (s, 1H), 7.83 (s, 1H), 7.76 (s, 1H), 2.33 (s, 3H). MS (MM-ES + APCI) m/z: 261.0 $[M - H]^-$.

*3-Ethyl-2-hydroxy-5-(pentafluorosulfanyl)benzaldehyde (**10b**).* To a solution of **9b** (0.12 g, 0.49 mmol) in TFA (6 mL) was added HTMA (0.20 g, 1.4 mmol) portionwise. The mixture was stirred at 80 °C for 12 h and then cooled to room temperature. To the above mixture was added 3 N HCl (3 mL) and the resulting mixture stirred at room temperature for another 0.5 h. The mixture was then extracted with EtOAc, and the organic layer was washed with saturated $NaHCO_3$, water, and brine. The resulting organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography to give the title compound 40 mg (30% yield for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 9.91 (s, 1H), 7.83 (d, J = 2.7 Hz, 1H), 7.76 (d, J = 2.6 Hz, 1H), 2.75 (q, J = 7.5 Hz, 2H), 1.30−1.22 (m, 3H). MS (MM-ES + APCI) m/z: 275.0 $[M - H]^-$.

*2-Hydroxy-5-(pentafluorosulfanyl)-3-propylbenzaldehyde (**10c**).* The title compound was prepared by the same procedure as **8b** in 25% yield. MS (MM-ES + APCI) m/z: 289.1.0 $[M - H]^-$.

*3-Benzyl-2-hydroxy-5-(pentafluorosulfanyl)benzaldehyde (**10d**).* The title compound was prepared by the same procedure as **9a** in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 9.91 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.37−7.28 (m, 2H), 7.24 (m, 3H), 4.05 (s, 2H). MS (MM-ES + APCI) m/z: 337.0 $[M - H]^-$.

*3-Butyl-2-hydroxy-5-(pentafluorosulfanyl)benzaldehyde (**10e**).* The title compound was prepared by the same procedure as **9a** in 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 9.91 (s, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 2.77−2.67 (m, 2H), 1.66−1.56 (m, 2H), 1.40 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).

*8-Methyl-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**11a**).* The title compound was prepared by the same procedure as *R,S*-**3a** in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.60 (s, 1H), 7.51 (s, 1H), 5.80 (d, J = 6.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.39 (s), 152.50 (s), 146.52 (s), 135.14 (s), 130.80 (s), 126.04 (s), 125.18 (s), 124.47 (t, J = 287.4 Hz), 118.67 (s), 70.37 (d, J = 32.3 Hz), 14.86 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 84.74 (m, 1F), 63.72 (dd, J = 150.5, 21.4 Hz, 4F), −78.78 (d, J = 6.3 Hz, 3F). HRMS (ESI): calcd for $C_{12}H_7F_8O_3S$ $[M - H]$ 382.9994, found 383.0004. HPLC: 95.42%.

*8-Ethyl-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**11b**).* The title compound was prepared by the same procedure as *R,S*-**3a** in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.60 (d, J = 2.5 Hz, 1H), 7.52 (d, J = 2.6 Hz, 1H), 5.80 (q, J = 6.7 Hz, 1H), 2.71 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.20 (s), 152.64 (s), 148.29−146.87 (m), 135.20 (s), 132.64 (s), 130.10 (s), 125.67 (s), 122.78 (t, J = 287.4 Hz), 119.95 (s), 119.53 (s), 71.52−70.60 (m), 22.86 (s), 14.30 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 84.65 (m, 1F), 63.70 (dd, J = 150.4, 22.1 Hz, 4F), −78.55 (d, J = 6.7 Hz, 3F). HRMS (ESI): calcd for $C_{13}H_9F_8O_3S$ $[M - H]$ 397.0150, found 397.0171. HPLC: 98.18%.

*6-(Pentafluorosulfanyl)-8-propyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**11c**).* The title compound was prepared by the same procedure as *R,S*-**3a** in 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.58 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 5.79 (q, J = 6.7 Hz, 1H), 2.65 (m, 2H), 1.64 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.51 (s), 152.33 (s), 146.74 (t, J = 16.6 Hz), 135.19 (s), 130.33 (s), 125.43 (s), 124.57 (t, J = 287.4 Hz), 119.07 (s), 118.79 (s), 70.51 (q, J = 31.8 Hz), 30.75 (s), 22.16 (s), 13.40 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 84.65 (m, 1F), 63.70 (dd, J = 150.5, 21.9 Hz, 4F), −78.54 (d, J = 6.7 Hz, 3F). HRMS (ESI): calcd for $C_{14}H_{11}F_8O_3S$ $[M - H]$ 411.0307, found 411.0309. HPLC: 99.14%.

*8-Benzyl-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**11d**).* The title compound was prepared by the same procedure as *R,S*-**3a** in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.55 (s, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 7.3 Hz, 1H), 7.18 (d, J = 7.2 Hz, 2H), 5.79 (q, J = 6.5 Hz, 1H), 4.08−3.96 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.39 (s), 152.20 (s), 146.75 (t, J = 16.9 Hz), 138.90 (s), 134.91 (s), 130.61 (s), 129.24 (s), 128.48 (s), 126.34 (s), 125.80 (s), 124.77 (t, J = 287.4 Hz), 119.28 (s), 118.89 (s), 70.56 (q, J = 32.3 Hz), 34.15 (s). ^{19}F NMR (471 MHz, $CDCl_3$) δ 84.30 (m, 1F), 63.70 (dd, J = 150.4, 22.2 Hz, 4F), −78.61 (d, J = 6.5 Hz, 3F). HRMS (ESI): calcd for $C_{18}H_{11}F_8O_3S$ $[M - H]$ 459.0307, found 459.0308. HPLC: 99.37%.

*8-Butyl-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic Acid (R,S-**11e**).* The title compound was prepared by the same procedure as *R,S*-**3a** in 90% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.46 (s, 1H), 8.03 (d, J = 2.5 Hz, 1H), 7.99 (d, J = 11.5 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 6.10 (q, J = 7.0 Hz, 1H), 2.74−2.65 (m, 1H), 2.65−2.55 (m, 1H), 1.58−1.45 (m, 2H), 1.34−1.24 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.36 (s), 152.19 (s), 146.56 (d, J = 17.0 Hz), 135.15 (s), 130.49 (s), 130.19 (s), 125.32 (s), 123.33 (t, J = 287.4 Hz), 118.96 (s), 118.58 (s), 70.36 (q, J = 32.2 Hz), 31.02 (s), 28.49 (s), 21.71 (s), 13.58 (s). ^{19}F NMR (471 MHz, DMSO-d_6) δ 88.58−86.89 (m, 1F), 66.35−64.67 (m, 4F), −77.53 (d, J = 7.1 Hz, 3F). HRMS (ESI) calcd for $C_{15}H_{13}F_8O_3S$ $[M - H]$ 425.0463, found 425.0459. HPLC: 92.88%.

*(S)-6-(Pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carbaldehyde (S-**12a**), (R_2 = H).* A mixture of **2a** (100 mg, 0.40 mmol),

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(*E*)-4,4,4-trifluorobut-2-enal (74 mg, 0.60 mmol), (*S*)-2-(diphenyl-(trimethylsilyloxy)methyl) pyrrolidine (20 mg, 0.06 mmol), and 2-nitrobenzoic acid (10 mg, 0.06 mmol) in EtOAc (10 mL) was stirred at room temperature overnight. The solution was then concentrated and purified by column chromatography to give the title compound 113 mg in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.69 (s, 1H), 7.74 (s, 1 H), 7.58 (m, 2 H), 7.08 (d, J = 7.5 Hz, 1H), 5.99 (q, J = 9 Hz, 1H).

*(S)-8-Bromo-6-(pentafluorosulfanyl)-2-(trifluoromethyl)-2H-chromene-3-carbaldehyde (S-**12b**), (R_2 = Br).* A mixture of **6** (R_2 = Br) (100 mg, 0.30 mmol), (*E*)-4,4,4-trifluorobut-2-enal (74 mg, 0.60 mmol), (*S*)-2-(diphenyl(trimethylsilyloxy)methyl) pyrrolidine (20 mg, 0.06 mmol), and 2-nitrobenzoic acid (10 mg, 0.06 mmol) in EtOAc (10 mL) was stirred at room temperature overnight. The solution was then concentrated and purified by column chromatography to give the title compound 106 mg in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.69 (s, 1H), 7.74 (s, 2 H), 7.58 (s, 1 H), 5.99 (m, J = 9 Hz, 1H).

In Vitro COX Enzyme Assay. Compounds were evaluated for COX inhibitory activity in vitro by using Cayman's COX Fluorescent Inhibitor Screening Assay Kit (Cayman Chemical Company, Ann Arbor, MI, USA; item nos. 701070 and 701080). Experiments were performed according to the manufacturer's instruction. Human COX-1 and human recombinant COX-2 enzymes were preincubated with serially diluted test compounds for 15 min at rt, the heme and fluorometric substrates were added and incubated for another 15 min at rt. The reaction was started by the addition of arachidonic acid and allowed to proceed for 2 min. The fluorescence was measured at a 530 nm excitation wavelength and a 595 nm emission wavelength using a microplate reader (Envision, PerkinElmer), and the data were analyzed using Graphpad Prism 5 (Graphpad Software, Inc.).

Fluorescence Polarization hERG Assay. The Inhibition activity of compounds on hERG potassium channel was determined using Predictor hERG Fluorescence Polarization Assay Kit (Life Technologies, Carlsbad, CA, USA). Experiments were performed according to the manufacturer's instructions. In brief, the reactions were carried out in 384-well plates including 10 μL of Predictor hERG membrane and 10 μL of Predictor hERG Tracer Red with appropriate amount of compound or positive control. Reactions were incubated for 2 h at rt and then read on an EnVision Multilabel Reader (PerkinElmer, Inc.) using polarized excitation and emission filters. Data were analyzed using Graphpad Prism 5 (GraphPad Software Inc., San Diego, CA).

Human Plasma Protein Binding. Human plasma protein (Southern Medical University) binding (PPB) of test compounds was measured by rapid equilibrium dialysis device using RED Device Inserts (Thermo Scientific). Reactions were carried out for 5 h, and then the drug concentrations in the sample chamber and buffer chamber were determined by LC/MS (API 3000 three triple quadrupole tandem mass spectrometer AB company) (LC-10ADvp pump (Shimadzu). Using these values, PPB of test compounds were defined using the following equation: PPB rate = [1 − (concentration buffer chamber/concentration plasma chamber)] × 100%.

In Vivo Pharmacodynamics. The assay listed here was performed in accordance with Public Health Service policies, the Animal Welfare Act, and the Laboratory Animal Committee (LAC) of GIBH (Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences) Policy on Humane Care.

Pharmacokinetic Studies. Compounds were dissolved in suitable solvent. Pharmacokinetic properties of SD rats (male) were determined following IV and oral administration. Animals were randomly distributed into two experimental groups (n = 4). The oral groups were given 5 mg/kg of compound by gastric gavage. The other group was dosed by injection into the tail vein (1 mg/kg). After single administration, whole blood samples (100−200 μL) were obtained from the orbital venous plexus at the following time points after dosing: 5, 10, and 30 min and 1, 2, 3, 4, 6, 8, 11, and 24 h (PO); 2, 10, 30 min and 1, 2, 3, 4, 6, 8, 11, and 24 h (IV). Whole blood samples were collected in heparinized tubes. The plasma fraction was immediately separated by centrifugation (8000 rpm, 6 min, 4 °C) and stored at −20 °C until LC-MS analysis. The rats were humanely euthanized by carbon dioxide 24 h after experiment without pain.

Plasma Sample Preparation. The plasma samples were prepared using protein precipitation method. First, 50 μL plasma samples were added to 1.5 mL tube and vortex for 3 min, then 150 μL of acetonitrile containing internal standard were added and vortexed for 5 min, and finally spin tubed in centrifuge at 16000g for 40 min at 4 °C. The standard curve was prepared as follows: The compound was dissolved in DMSO at a concentration of 2 mg/mL and diluted with 50% aq methanol solution to series concentration. Series concentration solution was prepared as plasma sample was.

Liquid Chromatography and Mass Spectrometry Conditions. Chromatographic analyses were performed with a HPLC system consisting of a LC-10ADvp pump (Shimadzu, Japan), MPS3C automatic sampler (Gerstel Auto Sampler, Germany), and API 3000 triple quadrupole tandem mass spectrometer (AB Co., USA). The column used for the separation was a Capcell PAK C18 (2.0 mm × 50 mm, 5 μm). The HPLC mobile phases consisted of water (0.1% form acid) (A) and methanol (0.1% form acid) (B). A gradient program was used for the HPLC separation with 0.3 mL/min. The initial composition was 30% B, increased linearly to 100% B in 1.5 min, and maintained at 100% B for 1.5 min, decreased linearly to 30% B in 0.3 min, then maintained for 0.7 min. The column eluent was directly introduced into electrospray ionization (ESI) interface.

Data Analysis. After centrifugation of plasma samples, 100 μL of the supernatant was transferred to a 96-well plate and analyzed by LC-MS/MS for each individual test compound. The pharmacokinetics parameters were calculated using the pharmacokinetic software DAS.2.0.

Air-Pouch Model of Inflammation. Air pouches were produced by a subcutaneous injection of 20 mL of sterile air into the back area of male Sprague−Dawley rats (Southern Medical University, China) after anesthetization using carbon dioxide. The compounds were administrated orally (10 mL/kg) as a suspension in 0.5% carboxymethyl cellulose at the dose 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg (n = 6) and the vehicle as the control. One day post the air pouch production, 6 mL of 1% carrageenan (Sigma, USA) saline solution was injected into the air cavities to produce an inflammatory reaction 1 h after administration. Then 3 mL of washing solution (9 g/L NaCl, 2 mg/L EDTA, 10 mg/L indomethacin) was injected into the air cavity and shaking. After performing euthanasia to the rats 3 h post the carrageenan injection, 1 mL of exudate washing solution in the air cavity was collected into the EP tube and centrifuged at 8000g for 5 min at 4 °C, the supernatant was collected to analyze the PGE-2 using PGE-2 ELISA kit (R&D Systems, USA). Immediately after collecting the exudates, the gastric mucosa was taken from the stomach and homogenized in washing solution (weight: volume = 1:20), centrifuged at 12000g for 15 min at 4 °C, and the supernatant was collected to determine the PGE-2 using PGE-2 ELISA kit. The EC_{50} was analyzed using the software Grafit 5 (Erithacus Software Ltd., Horley, UK).

Carrageenan Induced Rat Foot Paw Edema. Paw edema was induced by injecting subcutaneously 0.2 mL of 3% λ-carrageenan (Sigma, USA) saline solution into the right hind paw of male Sprague−Dawley rats (Southern Medical University, China) with the weight from 180 to 220 g. The compounds were administrated orally as a suspension in 0.5% carboxymethyl cellulose at the dose 1, 3, 10, 30, 100 mg/kg (n = 6) and the vehicle as the control at the time 0.5 h before immunization. Paw volumes were measured by water displacement with a plethysmometer PV-200 (Chengdu Technology and Market Co., China); immediately after immunization and 3 h post immunization, the percentage of inhibition was calculated by comparing the paw volume increment of treated animals, and the EC_{50} was analyzed using the software Grafit 5 (Erithacus Software Ltd., Horley, UK).

Carrageenan Induced Rat Foot Paw Hyperalgesia. Paw hyperalgesia was induced by injecting subcutaneously 0.2 mL of 3% λ-carrageenan (Sigma, USA) saline solution into the right hind paw of male Sprague−Dawley rats (Southern Medical University, China) with the weight from 180 to 220 g. The compounds were administrated orally as a suspension in 0.5% carboxymethyl cellulose at the dose of 1, 3, 10, 30, and 100 mg/kg (n = 6) and the vehicle as the control at the

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time 0.5 h before immunization. Hyperalgesia was measured as the antinociceptive response to thermal stimuli from a radiant heat source positioned under a Plexiglas floor directly beneath the right hind paw before immunization and 3 h post immunization using the PL-200 thermal stabbing pain equipment (Chengdu Technology and Market Co., Ltd., China), the percentage of inhibition was calculated by comparing the paw withdrawal latency of treated and controlled animals, and the EC_{50} was analyzed using the software Grafit 5 (Erithacus Software Ltd., Horley, UK).

Adjuvant Induced Rat Arthritis. The adjuvant arthritis was induced by injection of 1 mg of heat-killed *Mycobacterium tuberculosis* (Difco, USA) in 0.2 mL of mineral oil (Sigma, USA) into the base of the tail of the male Lewis rat (Charles River, China) with the weight from 170 to 200 g. The volume of the left hind paw was measured using a plethysmometer (Chengdu Technology and Market Co., Ltd., China) on day zero and 14th post adjuvant injection, and the rats on the day 14 having a left hind paw volume of 0.375 mL greater than that on day zero post adjuvant injection were randomly divided into six groups with each containing six animals. Treatment was initiated on day 15 and until day 24 after the immunization. Different dosages of the compound suspended in 0.5% methylcellulose (0.1, 0.3, 1, 3, and 10 mg/kg and vehicle) were administrated by oral gavage one time daily. The left hind paw volume and the clinical score of each rat were examined on day 25 after immunization, and the clinical scoring for each limb ranged from 0 to 4 (0 = no erythema or swelling, 1 = slight erythema or swelling of one of the toes or fingers, 2 = erythema and swelling of more than one toe or finger, 3 = erythema and swelling of the ankle or wrist, 4 = complete erythema and swelling of toes or fingers and ankle or wrist, and inability to bend the ankle or wrist). The percent inhibition was calculated by comparing the paw withdrawal latency of treated animals, and the EC_{50} was analyzed using the software Grafit 5 (Erithacus Software Ltd., Horley, UK).

Crystal Generation for *R,S*-3a and Molecular Docking Analysis. *R,S*-**3a** was dissolved in methanol. Single crystals were prepared by solvent volatilization. Data sets were collected on an Oxford Onyx CCD detector using Cu Kα radiation from a rotating-anode Gemini R Ultra system. The data was reduced using the software CrysAlisPro (Oxford Diffraction Limited), and the structure was determined and refined using Olex2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.6b01484.

HPLC traces, HRMS reports, ^{1}H, ^{13}C, ^{19}F NMRs, and chiral HPLC traces (PDF)

Molecular formula strings (CSV)

■ AUTHOR INFORMATION

Corresponding Authors

*For Y.Z.: phone, 86-20-32015277; E-mail, zhang_yanmei@gibh.ac.cn.

*For Z.T.: phone, 86-186-6569-9676; E-mail, tu_zhengchao@gibh.ac.cn.

*For J.J.T.: phone, 1-314-650-2151; E-mail, jjtalley@euclises.com.

ORCID

Yanmei Zhang: 0000-0002-2300-7390

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

F, oral bioavailability; PK, pharmacokinetics; PD, pharmacodynamics; AUC, area under the curve; T_{max}, time to maximum drug concentration; C_{max}, maximum concentration of drug; MMP, matrix metalloprotease; COX-1, cyclooxygenase 1; COX-2, cyclooxygenase 2

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