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ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 8626–8634
Bioorganic & Medicinal Chemistry

Identification of 2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethyl-pyrazol-1-yl]-*N*-propionylbenzenesulfonamide sodium as a potential COX-2 inhibitor for oral and parenteral administration☆

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Received 20 July 2006; revised 16 August 2006; accepted 17 August 2006
Available online 1 September 2006

Abstract—Synthesis of prodrugs of orally active COX-2 inhibitor **3** involving sulfamoyl (SO_2NH_2) and hydroxymethyl (CH_2OH) groups, and their biological evaluation are described. Of these prodrugs, the *N*-propionyl sulfonamide sodium **3k** was found to be much superior to the parent compound **3** and other marketed COX-2 inhibitors in carrageenan induced rat paw edema model of inflammation due to highly elevated drug levels in systemic circulation. This prodrug has a potential both for oral as well as parenteral administration due to impressive analgesic activity, antipyretic potency, and extraordinary water solubility.

1. Introduction

Prostaglandin (PG) synthase (cyclooxygenase) is a key enzyme involved in inflammatory process. Recently, its two isoforms (COX-1 and COX-2) with entirely different roles have been identified.[1] The COX-1, a constitutive enzyme, mainly expressed in gastrointestinal (GI) tract, is responsible for the cytoprotection and platelet aggregation.[2] So, its inhibition for a long time causes gastrointestinal toxicity such as ulceration, bleeding, and perforation.[3] The COX-2, in contrast, is induced by pro-inflammatory cytokines viz. tumor necrosis factor-α (TNF-α), interleukins, mitogens, and endotoxins at the time of injury, and produces PGs for inflammatory cells (monocytes and macrophages) to cause inflammation, pain, and fever.[4] The conventional non-steroidal anti-inflammatory drugs (NSAIDs), thus being non-selective inhibitors of these two enzymes, exhibit anti-inflammatory activity along with GI toxicity on extended treatment.[5] Hence, the selective inhibition of the COX-2 enzyme, sparing COX-1, emerged as a new concept in treating chronic inflammation. Many drugs viz. celecoxib **7**,[6] rofecoxib **1**,[7] valdecoxib **5**,[8] and etoricoxib **2**[9] were launched as a proof of concept for the treatment of rheumatoid and osteoarthritis, claiming minimal GI damage (Figs. 1 and 2). The recent use of COX-2 inhibitors in cancer[10] and Alzheimer's disease,[11] and the discovery of its third form (COX-3),[12] have also put forth more challenges and opportunities in this area. However, a mild cardiac toxicity associated with COX-2 inhibitors has raised a cautionary flag on this research.[13] Hence, there remains a demand for more efficacious and safer COX-2 inhibitors with higher patient acceptability to completely abandon the use of steroidal and narcotic drugs.

Several vicinal diaryl carbocycles and heterocycles have been identified as COX-2 inhibitors[14] following the molecular recognition model proposed by Kurumbail in 1996.[15] In our own effort of modifying celecoxib-scaffold, we introduced a hydroxymethyl group in its sulfamoyl (SO_2NH_2)–phenyl ring and could identify many

Keywords: Prodrugs; COX-2 inhibitors; 1,5-Diarylpyrazoles; Oral administration; Parenteral administration.
☆DRL Publication No. 267-A. A part of this communication was presented as poster (No. 244, Med. Chem.) in the 225th ACS Meeting, New Orleans, USA.
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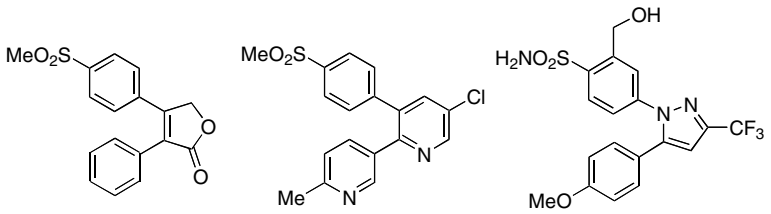
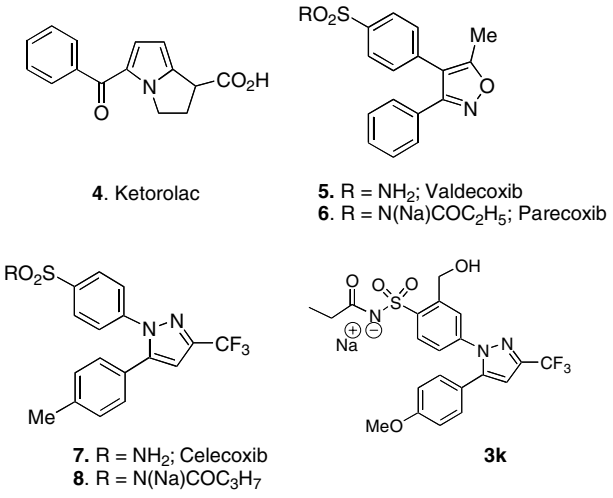
doi:10.1016/j.bmc.2006.08.024



1. Rofecoxib 2. Etoricoxib 3. DRF-4367

Figure 1. COX-2 inhibitors.



4. Ketorolac

5. R = NH_2; Valdecoxib
6. R = $N(Na)COC_2H_5$; Parecoxib

7. R = NH_2; Celecoxib
8. R = $N(Na)COC_3H_7$

3k

Figure 2. Injectable anti-inflammatory agents.

potent COX-2 inhibitors.[16] This series, on further optimization, led to the discovery of a more efficacious compound **3** than celecoxib **7** based on the data obtained from various animal models of acute and chronic inflammation.[17] Due to significantly improved pharmacokinetic profile over celecoxib, this new chemical entity was identified as a potential candidate for oral administration.

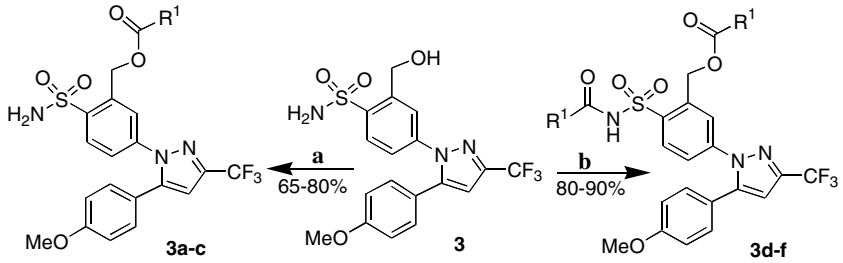
Generally, the patients undergoing surgery, require injectable analgesics for a rapid relief from unbearable pain. Despite many orally effective COX-2 inhibitors in clinic, until recently, this acute pain was managed by ketorolac (Fig. 2),[18] a non-selective cyclooxygenase inhibitor because of modest aqueous solubility of the available COX-2 inhibitors. Parecoxib sodium **6**,[19] a prodrug of valdecoxib **5** (Fig. 2),[8] has recently been introduced for parenteral administration and is claimed to cause minimal GI irritation. Following a similar approach, recently, we could improve the potency of a few poorly active (in vivo) COX-2 inhibitors (in vitro) obtained from the new 1,5-diarylpyrazole class.[20] In this report, we discuss our attempt to further improve the in vivo potency, pharmacokinetic properties, and aqueous solubility of the lead drug candidate **3** of the series through a prodrug approach derivatizing its hydroxymethyl (CH_2OH) as well as sulfonamide (SO_2NH_2) groups. One of its prodrugs **3k** was identified as a highly potent COX-2 inhibitor suitable for oral as well as parenteral administration.

2. Chemistry

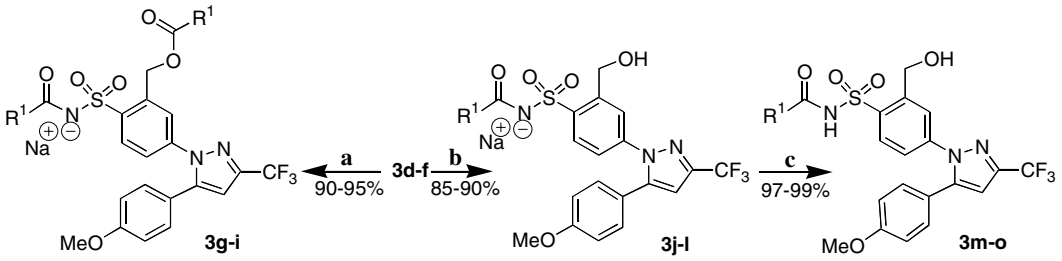
The parent diarylpyrazole **3**, required for the synthesis of prodrugs, was prepared by the reported procedures.[16,17,21] Conversion of this bifunctional compound to its *N*-acyl, *O*-acyl, *N*,*O*-diacyl derivatives, and their sodium salts is depicted in Schemes 1 and 2.[20] While mono *O*-acyl derivatives **3a**–**c** were synthesized in 65–80% yield by pyridine-catalyzed chemoselective acylation of the hydroxymethyl group using acid anhydride in presence of corresponding acid at room temperature, the *N*,*O*-diacyl derivatives **3d**–**f** were prepared in 80–90% yield by triethylamine-catalyzed exhaustive acylation using acid anhydride under heating condition (Scheme 1). In both the transformations, the CH_2 protons shifted from ~5.0 ppm (in drug) to ~5.5 ppm (in prodrugs). The structure of O-acylated products, prepared from chemoselective acylation, was confirmed by the X-ray diffraction studies of one of the analogues **3b** (Fig. 3).[22] The *N*,*O*-diacyl sodium salts **3g**–**i** were prepared in 90–95% yield from the corresponding diacyl derivatives **3d**–**f** using 0.95 equiv of aqueous NaOH (50%) in toluene (Scheme 2). Toluene was found to be the most suitable solvent in this reaction to suppress the ionization of NaOH which could otherwise cause unwanted hydrolysis of the ester. The mono *N*-acylated sodium salts **3j**–**l** were prepared in 85–90% yield by the chemoselective hydrolysis of the *N*,*O*-diacylated derivatives **3d**–**f** using 1.9 equiv of $NaHCO_3$ in methanol at 0–25 °C. Methanol was found to be a suitable solvent for this transformation which avoided the formation of a mixture of mono- and diacylated salts. The *N*-acylated sulfonamides **3m**–**o** were generated in quantitative yield from *N*-acylated sodium salts **3j**–**l** by treating with dilute HCl. The salts were identified by the absence of sulfonamide protons in ^1H NMR and by abnormally high melting points.

3. Biology

The parent compound **3** and its prodrugs **3a**–**o** were screened against human recombinant COX-2 enzyme (expressed in sf-9 cells, infected with baculovirus) and against COX-1 (obtained from microsomal fraction of Ram Seminal Vesicles) at different concentrations by TMPD method using celecoxib **7** as internal standard.[23] All the prodrugs, though less potent than the parent compounds in this assay (general observation),[19] were subjected to in vivo screening to assess their anti-inflam-



Scheme 1. Reagents and conditions: (a) $(R_1CO)_2O$, R_1CO_2H, pyridine, rt, 24 h; (b) $(R_1CO)_2O$, TEA, CH_2Cl_2, reflux, 10–12 h.



Scheme 2. Reagents and conditions: (a) aq NaOH (50%), toluene, 0–20 °C, 5–6 h; (b) $NaHCO_3$, MeOH, rt, 5–6 h; (c) 6 N HCl, rt, 0.5 h.

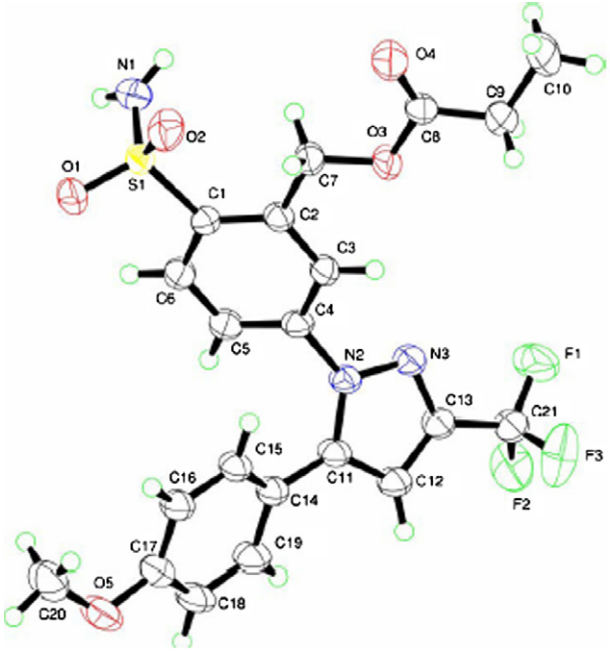


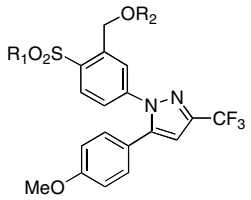
Figure 3. Crystal structure of compound **3b**.

matory activity at an initial dose of 30 mg/kg (po) in carrageenan-induced rat paw edema model.[24] ED_{50}s were calculated only for those prodrugs which reduced the paw swelling by more than 50% at this dose. The prodrugs, exhibiting ED_{50}s better than celecoxib/parecoxib, were subjected to single dose pharmacokinetic studies. Antipyretic[25] and analgesic[26] activities in different animal models, and aqueous solubility were determined for only those prodrugs which could demonstrate a dose dependent effect in carrageenan-induced rat paw edema model.

4. Results and discussion

Compound **3** and its analogues showed better pharmacodynamic and pharmacokinetic profiles than celecoxib which could be attributed to the hydrophilic hydroxymethyl group adjacent to sulfonamide.[17,27] Salts of *N*-acylated sulfonamide of valdecoxib (e.g., parecoxib sodium **6**)[19] and that of celecoxib (**8**)[28] are known to release the parent drug in systemic circulation and show improved efficacy following oral and parenteral administration. The data from in vitro enzyme assay (COX-1/COX-2) and in vivo efficacy from carrageenan-induced rat paw edema model of compound **3**, and its prodrugs are presented in Table 1. The *O*-acetyl and *O*-propionyl derivatives **3a** and **3b** showed a mediocre COX-2 inhibition while *N*-acyl, *N*,*O*-diacyl derivatives, and their sodium salts could hardly exhibit any significant in vitro activity. However, many of them exhibited impressive in vivo activity in the carrageenan-induced rat paw edema model (Table 1). Among *O*-acyl derivatives, the acetyl compound **3a** exhibited ED_{50} similar to celecoxib but the activity decreased through propionyl to butyryl derivatives possibly because of relatively poor rate of hydrolysis of these esters while releasing the parent compound. An almost similar pattern of activity was observed with the *N*,*O*-diacyl derivatives **3d–f**. However, all the sodium salts of these *N*,*O*-diacyl derivatives **3g–i** exhibited impressive in vivo efficacy. Particularly, prodrug **3h** (ED_{50}, 4.8 mg/kg) was found to be the most potent among these. Similarly, among *N*-acyl sodium salts **3j–l**, the *N*-propionyl sulfonamide sodium **3k** exhibited 5-fold better anti-inflammatory potency (ED_{50}, 0.4 mg/kg) than the parent compound **3** (ED_{50}, 1.9 mg/kg) in this model. But, the simple *N*-acyl derivatives **3m–o** showed only modest in vivo activity.

Table 1. In vitro and in vivo activity of compound **3** and its prodrugs



Compound	R^1	R^2	% Inhibition[a]		ED_{50}[c] (mg/kg)
			COX-1	COX-2	
3	NH_2	H	63.25 ± 3.40[b]	0.365 ± 0.082[b]	1.90 ± 0.22
3a	NH_2	$COCH_3$	18	1.700 ± 0.288[b]	7.25 ± 0.58
3b	NH_2	COC_2H_5	100.65 ± 5.45[b]	1.500 ± 0.350[b]	12.12 ± 1.25
3c	NH_2	COC_3H_7	20	45	25[d]
3d	$NHCOCH_3$	$COCH_3$	7	38	15.52 ± 1.65
3e	$NHCOC_2H_5$	COC_2H_5	4	30	15.05 ± 1.15
3f	$NHCOC_3H_7$	COC_3H_7	0	18	31[d]
3g	$N(Na)COCH_3$	$COCH_3$	0	5	7.15 ± 0.28
3h	$N(Na)COC_2H_5$	COC_2H_5	5	35	4.82 ± 0.31
3i	$N(Na)COC_3H_7$	COC_3H_7	0	25	10.04 ± 1.27
3j	$N(Na)COCH_3$	H	2	15	14.34 ± 1.29
3k	$N(Na)COC_2H_5$	H	2	23	0.40 ± 0.06[e]
3l	$N(Na)COC_3H_7$	H	0	19	5.62 ± 0.57
3m	$NHCOCH_3$	H	0	18	16.28 ± 1.35
3n	$NHCOC_2H_5$	H	3	22	22.58 ± 1.95
3o	$NHCOC_3H_7$	H	0	13	10.43 ± 1.38
6	Parecoxib-Na	—	[f]	[f]	98[g]
7	Celecoxib	—	10.75 ± 0.88[b]	0.076 ± 0.002[b]	6.70 ± 0.48
8	CBX-Bu-Na	—	0	2	6.64 ± 0.67

[a] At 10 μM (single determination).
[b] IC_{50} in μM (mean ± SEM, average of three determinations).
[c] Carrageenan-induced rat paw edema model (male Wistar rats). Each value represents the mean ± SEM, experiment in eight animals/group, dosed at 1, 3, 10, and 30 mg/kg, average of three experiments.
[d] % Reduction in paw volume at 30 mg/kg (single determination).
[e] Mean ± SEM, experiment in eight animals/group, dosed at 0.1, 0.3, 1, 3, and 10 mg/kg, average of two experiments.
[f] Not tested.
[g] % Reduction in paw volume at 0.3 mg/kg, see Ref. 19.

The comparative data from single dose oral pharmacokinetic study of compound **3** and its prodrugs, performed in male Wistar rat at 100 mg/kg, are presented in Table 2 and Figure 4. Most of the prodrugs, except *O*-propionyl derivative **3b** and *N*-acetyl sulfonamide sodium **3j**, when dosed, showed enhanced release of drug in plasma when compared to the dosing of parent drug **3**. While *N*,*O*-diacetyl sulfonamide sodium **3g** ($AUC_{0-\infty}$, 140.31 μg h/mL; C_{max}, 14.73 μg/mL) and *N*,*O*-dipropionyl sulfonamide sodium **3h** ($AUC_{0-\infty}$, 220.19 μg h/mL; C_{max}, 18.16 μg/mL) released 2- to 3-fold enhanced concentration of drug, the prodrugs*N*-propionyl sulfonamide sodium **3k** ($AUC_{0-\infty}$, 224.12 μg h/mL; C_{max}, 21.60 μg/mL) and *N*-butyryl sulfonamide sodium **3l** ($AUC_{0-\infty}$, 168.59 μg h/mL; C_{max}, 18.95 μg/mL), respectively, released 4- and 3-fold elevated concentration of drug in blood when compared to the dosing of parent compound **3** ($AUC_{0-\infty}$, 68.51 μg h/mL; C_{max}, 4.08 μg/mL). Presumably, due to this easy biotransformation at physiological condition, the prodrug **3k** exhibited excellent reduction in paw-volume (Table 1). This prodrug also showed a dose proportional drug level in blood ($AUC_{0-\infty}$, 44.81 ± 1.89 μg h/mL and C_{max}, 4.59 ± 1.03 μg/mL at 30 mg/kg) which is an essential requirement for fixing the therapeutic dose during clinical study (Fig. 5). Though most of the prodrugs released improved drug concentration in systemic circulation, it remained unclear why only *N*-propionyl sulfonamide sodium **3k** exhibited better in vivo potency than the parent compound **3**.

Since prodrug **3k** was picked up as the most potent candidate based on above data, its study was advanced to assess its antipyretic[25] and analgesic[26] activities in suitable animal models (Table 3). Though the ED_{50} for antipyretic activity of this prodrug **3k** (6.46 mg/kg) was similar to that of its parent compound **3** (4.68 mg/kg), it was found to be far superior to that of celecoxib **7** (15.68 mg/kg). Similarly, its analgesic activity (ED_{50}, 0.74 mg/kg) was found to be three times better than celecoxib **7** and almost 2-fold better than that of the parent compound **3**. The prodrug **3k** was also found to be six times more efficacious than parecoxib sodium **6** (Lit. data, Table 3).[19]

The preliminary gastrointestinal safety of the prodrug **3k** was compared with those of its parent compound **3**, celecoxib **7** and indomethacin by ^{51}Cr excretion test

Table 2. Single dose oral pharmacokinetic data of compound **3** released from its prodrugs at 100 mg/kg[a]

Drug released from	$AUC_{(0-t)}$ ± SEM[b] (μg h/mL)	$AUC_{(0-\infty)}$ ± SEM[b] (μg h/mL)	C_{max} ± SEM[c] (μg/mL)	T_{max} ± SEM[d] (h)	K_{el} ± SEM[e] (h^{-1})	$t_{1/2}$ ± SEM[f] (h)
3	46.25 ± 8.18	68.51 ± 10.92	4.08 ± 1.08	3.67 ± 0.98	0.08 ± 0.02	9.33 ± 3.05
3b	44.48 ± 1.12	60.22 ± 14.97	4.50 ± 0.35	3.00 ± 0.00	0.05 ± 0.00	13.20 ± 0.83
3g	122.30 ± 19.05	140.31 ± 13.42	14.73 ± 3.56	2.50 ± 0.58	0.10 ± 0.01	6.79 ± 0.54
3h	171.70 ± 38.46	220.19 ± 41.39	18.16 ± 4.85	2.75 ± 1.50	0.07 ± 0.01	10.80 ± 1.73
3j	50.74 ± 15.19	67.31 ± 19.93	8.92 ± 3.62	2.00 ± 1.00	0.15 ± 0.01	4.50 ± 0.30
3k	190.37 ± 8.53	224.12 ± 17.13	21.60 ± 1.11	2.75 ± 0.50	0.08 ± 0.01	9.01 ± 1.20
3l	131.15 ± 23.53	168.59 ± 22.99	18.95 ± 6.61	2.75 ± 0.50	0.14 ± 0.05	4.17 ± 0.56
8	129.20 ± 24.32	132.52 ± 24.12	16.02 ± 1.60	2.50 ± 1.00	0.16 ± 0.03	4.40 ± 0.70

[a] Average of two experiments, each carried out in a group of six animals (male Wistar rats) on single dosing.
[b] Area under curve, the mean ± SEM.
[c] Peak plasma concentration, the mean ± SEM.
[d] Time taken in achieving C_{max}, the mean ± SEM.
[e] Terminal elimination constant, the mean ± SEM.
[f] Terminal half-life, the mean ± SEM.

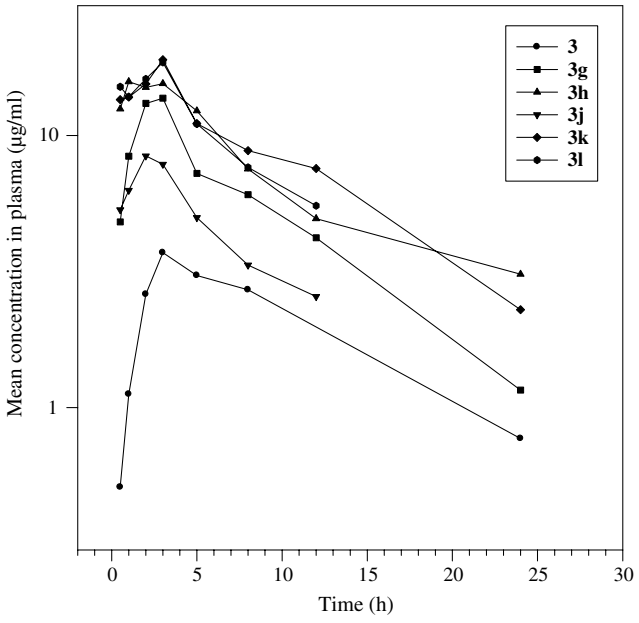


Figure 4. Time versus concentration profile of compound **3** released from its prodrugs in male Wistar rats at 100 mg/kg.

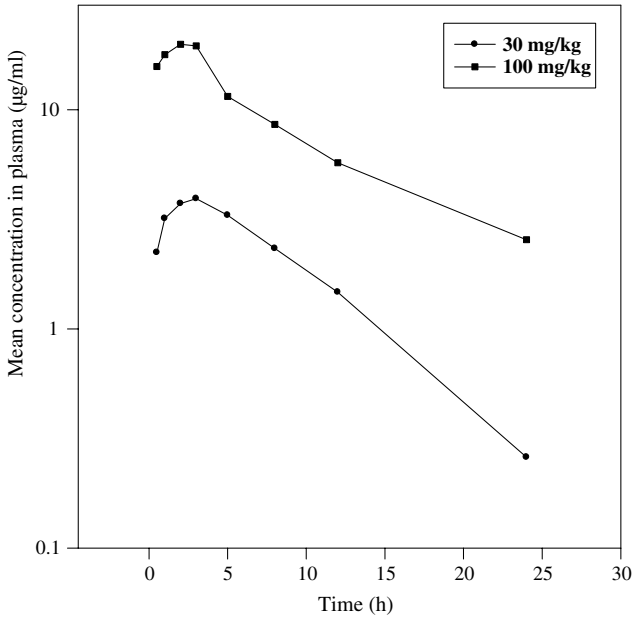


Figure 5. Time versus concentration profile of compound **3** released from prodrug **3k** at 30 and 100 mg/kg in male Wistar rats.

in an acute and chronic model of inflammation at 100 mg/kg. In this study, like parent compound **3**, the safety profile of the prodrug **3k** remained almost same as that of celecoxib **7** (data not tabulated here).[17]

Water solubility is the ultimate criteria for a drug to qualify for parenteral administration. Though most of the *N*-acyl sulfonamide sodium prodrugs were found to be highly soluble in water, the prodrug **3k** exhibited an exceptional aqueous solubility (230 mg/mL at 25 °C), and the solution was stable at room temperature for more than 12 h. With its more than 10-fold superior aqueous solubility compared to those of parecoxib sodium **6** (22 mg/mL)[19] and celecoxib-prodrug **8** (15 mg/mL),[28] it is anticipated that its low volume injection would release a sufficient concentration of drug in plasma on biotransformation to cure patients suffering from severe pain. Thus, based on pharmacodynamic data from different animal models, manifold increased pharmacokinetic profile and exceptional water solubility, the prodrug **3k** has been identified as a potential COX-2 inhibitor both for oral as well as parenteral administration.

Table 3. Comparative in vivo activity of compound **3** and its most active prodrug **3k** in different animal models

Compound	ED_{50}s[a]	
	Pyresis[b]	Hyperalgesia[b]
3	4.68 ± 0.82	1.13 ± 0.06
3k	6.46 ± 0.02	0.74 ± 0.03
7 (Celecoxib)	15.68 ± 0.75	2.11 ± 0.57
6 (Parecoxib-Na)	[c]	5.00[d]

[a] See Section 6.
[b] Each value represents the mean ± SEM of six animals/group (male Wistar rats) dosed at 0.1, 0.3, 1, 3, 10, and 30 mg/kg, average of two experiments.
[c] Not tested.
[d] Data from Ref. 19.

5. Conclusion

In conclusion, we have described herein the synthesis and in vivo activity of various prodrugs of orally active COX-2 inhibitor **3**. One of these prodrugs, the *N*-propionyl sulfonamide sodium **3k**, demonstrated its bioequivalence to compound **3** and exhibited many times improved in vivo efficacy, pharmacokinetic properties, and water solubility. Thus, this prodrug **3k** has been identified as a potential COX-2 inhibitor for oral as well as parenteral administration.

6. Experimental

6.1. Chemistry

Celecoxib, valdecoxib, and the parent compound **3** were prepared according to the literature procedure. Melting points, determined on Buchi-B-540 apparatus, are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR 1650 spectrometer and the ^{1}H NMR and ^{13}C NMR experiments were performed at 200 MHz Varian Gemini 200 spectrometer. Mass spectra were recorded on HP-5989A spectrometer either as direct inlet probe (DIP) or by chemical ionization method using isobutane. Elemental analyses (C, H, N) were performed on Perkin-Elmer 2400 series II CHN-O analyzer. The HPLC purity was determined using 'System 1' consisting column Symmetry C-18 (250 mm) with mobile phase 0.01 M KH_2PO_4/CH_3CN (40:60) and 'System 2' comprising column Intersil ODS 3V (250 mm) with mobile phase H_2O/CH_3CN (50:50), both running at 1.0 mL/min with UV detection at respective wavelengths of maximum absorption. All the analyses were performed in the Analytical Research Division of Discovery Research-Dr. Reddy's Laboratories Ltd.

6.2. Representative synthesis of propionic acid 5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-2-sulfamoyl benzyl ester 3b

2-Hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide **3** (2.0 g, 4.68 mmol) dissolved in propionic acid (10 mL) was sequentially added with pyridine (0.92 g, 11.70 mmol) and propionic anhydride (0.91 g, 7.00 mmol), and stirred at room temperature for 20 h. The reaction mixture was poured on crushed ice, stirred, and extracted with ethyl acetate. The combined organic layer was washed with water, dried (anhyd Na_2SO_4), and evaporated to get a residue which was finally purified by column chromatography using 230–400 mesh silica gel and 30% ethyl acetate–petroleum ether. The concentrated mass was triturated with a minimum quantity of a mixture of ethyl acetate and petroleum ether to afford a colorless solid of the title compound (1.53 g, 68%). Mp 150–152 °C. IR (Nujol) 3395, 2854, 1735, 1461, 1377 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.97 (d, J = 8.6 Hz, 1 H), 7.37 (br s, 2H, D_2O exchangeable), 7.58 (d, J = 8.6 Hz, 1H), 7.42 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 7.00 (d, J = 8.4 Hz, 2H), 5.43 (s, 2H), 3.77 (s, 3H), 2.25 (q, J = 7.2 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 173.2, 160, 145, 142.3 (q, J = 37.4 Hz, 1C), 141.6, 140.7, 135.8, 130.6 (2C), 129.1, 124.3, 124.1, 120.7, 118.8 (q, J = 256.8 Hz, 1C), 114.5 (2C), 106.3, 61.6, 55.4, 26.9, 9.0. MS (DIP Method) 483 $(M)^+$, 464, 426, 409, 403, 347, 318, 273, 149. HPLC (System 1) 99.3%; HPLC (System 2) 98.9%. $C_{21}H_{20}F_3N_3O_5S$ Calcd (%): C, 52.17; H, 4.17; N, 8.69. Found (%): C, 51.95; H, 4.50; N, 8.92.

6.3. Acetic acid 5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-2-sulfamoyl benzyl ester 3a

Mp 170–174 °C. IR (KBr) 3346, 1713, 1559, 1472, 1465 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H), 5.46 (br s, 2H, D_2O exchangeable), 5.35 (s, 2H), 3.84 (s, 3H), 2.03 (s, 3H). MS (CI Method) 470 $(M+H)^+$, 409. HPLC (System 1) 99.4%; HPLC (System 2) 99.5%. $C_{20}H_{18}F_3N_3O_5S$ Calcd (%): C, 51.17; H, 3.86; N, 8.95. Found (%): C, 51.40; H, 3.70; N, 8.83.

6.4. Butyric acid 5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-2-sulfamoyl benzyl ester 3c

Mp 144–146 °C. IR (KBr) 3356, 1707, 1478, 1348 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 1H), 7.65 (br s, 2H, D_2O exchangeable), 7.58 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H), 5.47 (s, 2H), 3.83 (s, 3H), 2.30 (t, J = 7.2 Hz, 2H), 1.64–1.56 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H). MS (DIP Method) 497 $(M)^+$, 409, 347. HPLC (System 1) 98.5%; HPLC (System 2) 98.7%. $C_{22}H_{22}F_3N_3O_5S$ Calcd (%): C, 53.11; H, 4.46; N, 8.45. Found (%): C, 53.10; H, 4.83; N, 8.19.

6.5. Representative synthesis of propionic acid 5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-2-propionylsulfamoyl benzyl ester 3e

2-Hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide **3** (2.0 g, 4.68 mmol) dissolved dichloromethane (30 mL) was added with triethylamine (1.41 g, 14.05 mmol) and stirred at room temperature for 0.5 h. Propionic anhydride (1.52 g, 11.70 mmol) was slowly added to the reaction mixture and refluxed overnight. The reaction mixture was cooled to room temperature, poured over crushed ice, stirred, and extracted with dichloromethane. The combined organic layer was washed with water, dried (anhyd Na_2SO_4), and evaporated to get a residue which was finally purified by column chromatography using 230–400 mesh silica gel and 25% ethyl acetate–petroleum ether. The concentrated mass was triturated with a minimum quantity of a mixture of dichloromethane and petroleum ether to afford a colorless solid of the title compound (1.89 g, 75%). Mp 80–83 °C. IR (KBr) 3250, 2945, 1723, 1612, 1471 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.05 (br s, 1H, D_2O exchangeable), 7.87 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.10 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 5.44 (s, 2H), 3.74 (s, 3H), 2.22 (q, J = 7.8 Hz, 2H), 1.97 (q, J = 7.8 Hz, 2H), 0.92 (t,

J = 7.8 Hz, 3H), 0.80 (t, J = 7.8 Hz, 3H). MS (CI Method) 540 $(M+H)^+$, 483, 426, 409, 403, 347. HPLC (System 1) 98.3%; HPLC (System 2) 98.5%. $C_{24}H_{24}F_3N_3O_6S$ Calcd (%): C, 53.43; H, 4.48; N, 7.79. Found (%): C, 53.38; H, 4.32; N, 8.15.

6.6. Acetic acid 2-acetylsulfamoyl-5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzyl ester 3d

Mp 85–87 °C. IR (KBr) 3438, 1724, 1613, 1472, 1442 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.80 (br s, 1H, D_2O exchangeable), 8.20 (d, J = 8.8 Hz, 1H), 7.63 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2 H), 6.92 (d, J = 8.6 Hz, 2H), 6.72 (s, 1H), 5.48 (s, 2H), 3.84 (s, 3H), 2.08 (s, 6H). MS (CI Method) 512 $(M+H)^+$, 468, 451, 425, 407, 365. HPLC (System 1) 98.9%; HPLC (System 2) 99.0%. $C_{22}H_{20}F_3N_3O_6S$ Calcd (%): C, 51.66; H, 3.94; N, 8.22. Found (%): C, 52.01; H, 3.72; N, 7.85.

6.7. Butyric acid 2-butyrylsulfamoyl-5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzyl ester 3f

Mp 128–130 °C. IR (KBr) 3085, 2960, 1749, 1677, 1471 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.89 (br s, 1H, D_2O exchangeable), 8.20 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 5.50 (s, 2H), 3.83 (s, 3H), 2.32–2.21 (m, 4H), 1.66–1.49 (m, 4H), 0.98–0.84 (m, 6H). MS (CI Method) 568 $(M+H)^+$, 487, 415. HPLC (System 1) 98.8%; HPLC (System 2) 99.3%. $C_{26}H_{28}F_3N_3O_6S$ Calcd (%): C, 55.02; H, 4.97; N, 7.40. Found (%): C, 55.24; H, 5.22; N, 7.76.

6.8. Representative synthesis of sodium salt of propionic acid 5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-2-propionylsulfamoyl benzyl ester 3h

The above prepared compound **3e** (1.5 g, 2.77 mmol) was dissolved in toluene (30 mL) and cooled to 0–5 °C. Aqueous sodium hydroxide [(105 mg, 2.63 mmol), dissolved in 100 μL water] was slowly injected into the reaction mixture and stirred at 5–15 °C for 5 h. The solvent was evaporated under reduced pressure keeping the bath at 15–20 °C. The residue on trituration with a mixture of ethyl acetate and petroleum ether afforded the desired compound **3 h** (1.0 g, 71%). Mp 210–212 °C. IR (KBr) 3443, 2979, 1740, 1613, 1256 cm^{-1}. ^1H NMR (200 MHz, CD_3OD) δ 8.13 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.37 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.89 (s, 1H), 5.63 (s, 2H), 3.85 (s, 3H), 2.31–2.22 (m, 4H), 1.15–1.02 (m, 6H). MS (CI Method) 539 $(M-Na+H)^+$, 483, 465, 426. HPLC (System 1) 97.9%; HPLC (System 2) 98.2%. $C_{24}H_{23}F_3N_3NaO_6S$ Calcd (%): C. 51.34; H, 4.13; N, 7.48. Found (%): C, 51.52; H, 4.31; N, 7.63.

6.9. Sodium salt of acetic acid 2-acetylsulfamoyl-5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzyl ester 3g

Mp 210–212 °C. IR (KBr) 1722, 1622, 1482, 1437 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 8.18 (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 5.46 (s, 2H), 3.90 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H). MS (CI Method) 511 $(M-Na+H)^+$, 468, 451, 425, 407, 365. HPLC (System 1) 97.9%; HPLC (System 2) 98.1%. $C_{22}H_{19}F_3N_3NaO_6S$ Calcd (%): C, 49.53; H, 3.59; N, 7.88. Found (%): C, 49.28; H, 3.92; N, 7.54.

6.10. Sodium salt of butyric acid 2-butyrylsulfamoyl-5-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzyl ester 3i

Mp 195–197 °C. IR (KBr) 3051, 2978, 1751, 1674, 1467 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 8.21 (d, J = 8.6 Hz, 1H), 7.65 (s, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 5.48 (s, 2H), 3.80 (s, 3H), 2.30–2.20 (m, 4H), 1.60–1.50 (m, 4H), 0.96–0.80 (m, 6H). MS (CI Method) 567 $(M-Na+H)^+$, 511, 494, 437. HPLC (System 1) 98.5%; HPLC (System 2) 99.7%. $C_{26}H_{27}F_3N_3NaO_6S$ Calcd (%): C, 52.97; H: 4.62; N, 7.13. Found (%): C, 53.21; H, 5.01; N, 6.87.

6.11. Representative synthesis of sodium salt of 2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-*N*-propionyl benzenesulfonamide 3k

The above prepared compound **3e** (1.5 g, 2.77 mmol) was dissolved in methanol (15 mL) and cooled to 0–5 °C. Solid sodium bicarbonate (0.44 g, 5.27 mmol) was slowly introduced to the reaction mixture and stirring was continued at 15–20 °C for 7 h. The solvent was evaporated under reduced pressure keeping the bath temperature at 15–20 °C. The residue on trituration with diethyl ether afforded a white colored solid of the desired salt **3k** (0.84 g, 60%). Mp 218–220 °C. IR (KBr) 3085, 2960, 1749, 1677, 1471 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 5.50 (br s, 1H, D_2O exchangeable), 5.00 (d, J = 2.8 Hz, 2H), 3.83 (s, 3H), 2.27 (q, J = 7.4 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H). MS (CI Method) 483 $(M-Na+H)^+$, 428. HPLC (System 1) 98.6%; HPLC (System 2) 98.8%. $C_{21}H_{19}F_3N_3NaO_5S$ Calcd (%): C, 49.90; H, 3.79; N, 8.31. Found (%): C, 50.22; H, 4.08; N, 8.10.

6.12. Sodium salt of *N*-acetyl-2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzenesulfonamide 3j

Mp 225–228 °C. IR (KBr) 3459, 1613, 1575, 1471, 1462 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.75 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 7.8 Hz, 2H), 6.93 (s, 1H), 5.25 (br s, 1H, D_2O exchangeable), 4.87 (s, 2H), 3.76 (s, 3H), 1.65 (s, 3H). MS (CI Method) 469 $(M-Na+H)^+$, 427, 346. HPLC (System 1) 96.9%; HPLC (System 2) 97.3%. $C_{20}H_{17}F_3N_3NaO_5S$ Calcd (%): C, 48.88; H, 3.49; N, 8.55. Found (%): C, 49.20; H, 3.72; N, 8.32.

6.13. Sodium salt of *N*-butyryl-2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzenesulfonamide 3l

Mp 255–257 °C. IR (KBr) 3469, 3217, 2964, 1614, 1588, 1470 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.76 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 2.0 & 8.2 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.11 (s, 1H), 7.07 (dd, J = 2.0 & 8.2 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 5.30 (br s, 1H, D_2O exchangeable), 4.89 (d, J = 2.2 Hz, 2H), 3.76 (s, 3H), 1.90 (t, J = 7.0 Hz, 2H), 1.49–1.35 (m, 2H), 0.77 (t, J = 7.2 Hz, 3H). MS (CI Method) 497 $(M-Na+H)^+$, 480, 410, 347, 311, 259. HPLC (System 1) 99.2%; HPLC (System 2) 99.0%. $C_{22}H_{21}F_3N_3NaO_5S$ Calcd (%): C, 50.87; H, 4.07; N, 8.09. Found (%): C, 51.11; H, 4.20; N, 8.14.

6.14. Representative synthesis of 2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl]-*N*-propionyl benzenesulfonamide 3n

The above prepared compound **3k** (0.6 g, 1.18 mmol) was dissolved in water (10 mL) and treated under stirring with 2 N HCl to bring to pH 1–2. After stirring for 0.5 h at room temperature, the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water, dried (anhyd Na_2SO_4), and evaporated to get a residue which on trituration with a mixture of ethyl acetate and petroleum ether afforded a colorless solid of the title compound (0.50 g, 87%). Mp 121–122 °C. IR (KBr) 3421, 1718, 1612, 1472 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.55 (br s, 1H, D_2O exchangeable), 8.02 (d, J = 8.6 Hz, 1H), 7.55 (s, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.70 (s, 1H), 5.50 (br s, 1H, D_2O exchangeable), 5.00 (d, J = 3.0 Hz, 2H), 3.82 (s, 3H), 2.26 (q, J = 7.6 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H). MS (CI Method) 484 $(M+H)^+$, 464, 426, 409, 347, 317. HPLC (System 1) 99.3%; HPLC (System 2) 98.9%. $C_{21}H_{20}F_3N_3O_5S$ Calcd (%): C, 52.17; H, 4.17; N, 8.69. Found (%): C, 51.89; H, 4.40; N, 8.31.

6.15. *N*-Acetyl-2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzenesulfonamide 3m

Mp 127–128 °C. IR (KBr) 3459, 1721, 1575, 1471, 1462 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 8.00 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.60 (br s, 1H, D_2O exchangeable), 7.25 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 6.72 (s, 1H), 5.25 (br s, 1H, D_2O exchangeable), 4.87 (s, 2H), 3.76 (s, 3H), 1.65 (s, 3H). MS (DIP Method) 469 $(M)^+$, 346. HPLC (System 1) 97.9%. $C_{20}H_{18}F_3N_3O_5S$ Calcd (%): C, 51.17; H, 3.86; N, 8.95. Found (%): C, 51.32; H, 4.22; N, 8.87.

6.16. *N*-Butyryl-2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethylpyrazol-1-yl] benzenesulfonamide 3o

Mp 118–120 °C. IR (KBr) 3388, 2975, 1644, 1584, 1462 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (br s, 1 H, D_2O exchangeable), δ 7.75 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.12 (s, 1H), 6.97 (d, J = 8.4 Hz, 2H), 6.86 (s, 1H), 5.32 (br s, 1H, D_2O exchangeable), 4.89 (d, J = 2.2 Hz, 2H), 3.85 (s, 3H), 1.98 (t, J = 7.2 Hz, 2H), 1.50–1.34 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H). MS (CI Method) 498 $(M+H)^+$, 480, 410, 347, 311. HPLC (System 1) 99.5%; HPLC (System 2) 99.7%. $C_{22}H_{22}F_3N_3O_5S$ Calcd (%): C, 53.11; H, 4.46; N, 8.45. Found (%): C, 52.89; H, 4.69; N, 8.29.

6.17. In vitro enzyme assay[23]

Microsomal fraction of ram seminal vesicles was used as a source of COX-1 enzyme and the microsomes from *sf-9* cells infected with baculovirus expressing human COX-2 cDNA were used as a source of COX-2 enzyme in measuring inhibitory activity by TMPD method. The assay mixture (1000 μL) contained 100 μM Tris, pH 8.0, 3 μM EDTA, 15 μM hematin, 150 U enzyme, and 8% DMSO. The mixture was incubated at 25 °C for 15 min before initiation of enzyme reaction in the presence of compound/vehicle. The reaction was initiated by the addition of 100 μM arachidonic acid and 120 μM TMPD, and the velocity of TMPD oxidation over the first 25 s was monitored at 603 nm. The IC_{50} values were calculated using non-linear regression analysis of percent inhibitions.

6.18. In vivo screening. Carrageenan-induced rat paw edema[24]

Male Wistar rats (120–140 g) were fasted for 16 h before starting the experiment. Compounds were suspended in 0.25% CMC and administered orally in a volume of 10 mL/kg. After 2 h of dosing, 50 μL of 1% λ-carrageenan, suspended in saline, was injected into the plantar aponeurosis of the right paw. The paw volume was measured 3 h before and after carrageenan injection using plethysmometer (Ugo-Basile, Italy). The paw edema was compared with the vehicle control group, and the percent inhibition was calculated. ED_{50}s were calculated using linear regression plot.

6.19. Endotoxin-induced pyresis in rats[25]

Male Wistar rats (150–170 g) were fasted for 16 h before starting the experiment, and the baseline rectal temperature was recorded with a flexible temperature probe (YSI series-400) connected to a digital thermometer. At time zero, the rats were intra-peritoneally injected with 0.36 mg/kg of lipopolysaccharide (Sigma Chemical Co., St. Louis, USA), and the rectal temperatures were recorded after 5 and 7 h. The test compounds were administered 5 h after LPS injection to determine their antipyretic potential. The percent reversal of pyrexia was calculated by taking the ratio of the difference in temperature at 5th and 7th h and the baseline of the treated and the control group.

6.20. Carrageenan-induced rat paw hyperalgesia (Randal-Selitto method)[26]

Hyperalgesia was induced in the hind paw of male Wistar rats (150–170 g) by intraplantar injection of carra-

geenan (2 mg/per paw). Test compounds were dosed after 2 h from carrageenan injection. The vocalization response to compression of the carrageenan-injected paw was measured 1 h later by analgesiometer (Ugo-Basile, Italy). For normal response, one group of animals was given intraplantar injection of saline. The percent increase in pain was calculated as difference in threshold in treated versus control group. ED_{50}s were calculated using linear regression plot.

6.21. Single dose oral pharmacokinetic studies

All the studies were carried out in male Wistar rats obtained from the National Institute of Nutrition, Hyderabad, India. The animals (200–225 g) were fasted for 12 h before starting the experiment and had free access to water throughout the experiment. The animals were fed after 3 h from drug administration. The animals were dosed at 100 mg/kg (po) as a 0.25% CMC suspension, and 0.4 mL of blood samples were collected into heparinized microfuge tubes at pre-determined time points from the retro-orbital plexus. An additional study was performed for compound **3 k** at 30 mg/kg. The samples were analyzed by a validated HPLC method after suitable extraction, and plasma concentration versus time profiles were generated for potent compounds along with celecoxib. The pharmacokinetic parameters were calculated by non-compartmental model analysis.

Acknowledgments

The authors are thankful to Dr. K. Anji Reddy for his constant support and encouragement, and to Analytical Research Division, DR-DRL, for spectral analyses.

References and notes

1. Vane, J. R.; Bakhle, Y. S.; Botting, R. M. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 97.
2. Whittle, B. J. R.; Higgs, G. A.; Eakins, K. E.; Moncada, S.; Vane, J. R. *Nature* **1980**, *284*, 271.
3. Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russel, R. I. G. *N. Engl. J. Med.* **1992**, *327*, 749.
4. (a) Xie, W.; Robertson, D. L.; Simmons, D. L. *Drug Dev. Res.* **1992**, *25*, 249; (b) Vane, J. *Nature* **1994**, *367*, 215.
5. Meyer-irchrath, J.; Schror, K. *Curr. Med. Chem.* **2000**, *7*, 1121.
6. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. M.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
7. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Either, D.; Evans, J. F.; Ford- Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O Neil, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vickers, P.; Wong, E.; Xu, L. J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
8. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
9. Sorbera, L. A.; Castaner, R. M.; Silvestre, J.; Castaner, J. *Drugs Future* **2001**, *26*, 346.
10. Vainio, H. *Int. J. Cancer* **2001**, *94*, 613.
11. Pasinetti, G. M. *J. Neurosci. Res.* **1998**, *54*, 1.
12. Chandrasekharan, N. V.; Dai, H.; Roos, K. L.; Evanson, N. K.; Tomsik, J.; Elton, T. S.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 13371.
13. Mukherjee, D.; Nissen, S. E.; Topol, E. J. *J. Am. Med. Assoc.* **2001**, *286*, 954.
14. Dannhardt, G.; Laufer, S. *Curr. Med. Chem.* **2000**, *7*, 1101.
15. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. *Nature* **1996**, *384*, 644.
16. Singh, S. K.; Reddy, P. G.; Rao, K. S.; Lohray, B. B.; Misra, P.; Rajjak, S. A.; Rao, Y. K.; Venkateswarlu, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 499.
17. Singh, S. K.; Saibaba, V.; Rao, K. S.; Rajjak, S. A.; Rao, C. S.; Datla, S. R.; Mamidi, N. V. S. R.; Mullangi, R.; Ravikanth, B.; Rajagopalan, R.; Venkateswarlu, A.; Rao, Y. K. *Org. Biomol. Chem.* **2004**, *2*, 2442.
18. Muchowski, J. M.; Unger, S. H.; Ackrell, J.; Cheung, P.; Cooper, G. F.; Cook, J.; Gallegra, P.; Halpern, O.; Koehler, R.; Kluge, A. F.; Van-Horn, A. R.; Antonio, Y.; Carpio, H.; Franco, F.; Galeazzi, E.; Garcia, I.; Greenhouse, R.; Guzman, A.; Iriarte, J.; Leon, A.; Pena, A.; Perez, V.; Valdez, D.; Ackerman, N.; Ballaron, S. A.; Krishnamurthy, D. V.; Rovito, J. R.; Tomolonis, A. J.; Young, J. M.; Rooks, W. H. *J. Med. Chem.* **1985**, *28*, 1037.
19. Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Kellogg, M. S.; Koboldt, C. M.; Yuan, J.; Zhang, Y. Y.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 1661.
20. Singh, S. K.; Saibaba, V.; Rao, K. S.; Rao, C. S.; Mullangi, R.; Rajagopalan, R.; Rao, Y. K.; Iqbal, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3921.
21. Singh, S. K.; Reddy, M. S.; Shivaramakrishna, S.; Kavitha, D.; Vasudev, R.; Babu, J. M.; Sivalakshmidevi, A.; Rao, Y. K. *Tetrahedron Lett.* **2004**, *45*, 7679.
22. Vyas, K.; Sivalakshmidevi, A.; Singh, S. K.; Rao, Y. K.; Reddy, G. O. *Acta. Cryst.* **2003**, *E59*, 1731.
23. Cromlish, W. A.; Payette, P.; Culp, S. A.; Ouellet, M.; Percival, M. D.; Kennedy, B. P. *Arch. Biochem. Biophy.* **1994**, *314*, 193.
24. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Pro. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
25. Kosersky, D. S.; Dewey, W. L.; Harris, L. S. *Eur. J. Pharmacol.* **1973**, *24*, 1.
26. Hargreaves, K.; Dubner, R.; Brown, F.; Flores, C.; Joris, J. A. *Pain* **1988**, *32*, 77.
27. (a) Mullangi, R.; Mamidi, NVSR.; Jagannath, K.; Singh, S. K.; Rao, K. S.; Rao, Y. K.; Rao, C. S.; Rajagopalan, R.; Srinivas, N. R. *Eur. J. Drug Metabol. Pharmacokinet.* **2003**, *28*, 137; (b) Ravikanth, B.; Mujeeb, S.; Dravid, P. V.; Khan, A. A.; Singh, S. K.; Rao, Y. K.; Mullangi, R.; Srinivas, N. R. *Xenobiotica* **2005**, *35*, 253.
28. Mamidi, NVSR.; Mullangi, R.; Kota, J.; Bhamidipati, R.; Khan, A. A.; Katneni, K.; Datla, S.; Singh, S. K.; Rao, Y. K.; Rao, C. S.; Srinivas, N. R.; Rajagopalan, R. *Biopharm. Drug Dispos.* **2002**, *23*, 273.