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N-Acylated sulfonamide sodium salt: A prodrug of choice for the bifunctional 2-hydroxymethyl-4-(5-phenyl-3-trifluoromethyl-pyrazol-1-yl) benzenesulfonamide class of COX-2 inhibitors☆

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Abstract—Synthesis and biological evaluation of possible prodrugs of COX-2 inhibitors involving sulfonamide and hydroxymethyl groups of 2-hydroxymethyl-4-(5-phenyl-3-trifluoromethyl-pyrazol-1-yl) benzenesulfonamides are described. Out of many options, the sodium salt of *N*-propionyl sulfonamide demonstrated much improved pharmacological profiles and physicochemical properties suitable for oral as well as parenteral administration.

The prostaglandin (PG) synthase (cyclooxygenase), the key enzyme of inflammatory process, exists in two isoforms (COX-1 and COX-2).[1] While COX-1 plays a cytoprotective role,[2] COX-2, induced at the time of injury, causes inflammation, pain, and fever.[3] Thus, conventional non-steroidal anti-inflammatory drugs (NSAIDs), being inhibitors of both, exhibit anti-inflammatory activity along with gastrointestinal (GI) toxicity on extended use.[4] But, the selective COX-2 inhibitors, viz. nimesulide,[5] celecoxib,[6] rofecoxib,[7] valdecoxib[8], and etoricoxib[9], treat the chronic rheumatoid and osteoarthritis without causing GI damage (Fig. 1). A few COX-2 inhibitors have also been studied for the treatment of cancer[10] and Alzheimer's disease.[11] However, a mild cardiac toxicity associated with COX-2 inhibitors (COXIBs) has raised a cautionary flag on this research.[12] So, it is desirable to discover safe, effective, and patient-acceptable COX-2 inhibitors to completely abandon the use of steroidal and narcotic drugs.

Following the structural model of Kurumbail,[13] we chemically modified the safest existing drug celecoxib[6] by introducing a hydroxymethyl group adjacent to its sulfonamide, and the new series showed impressive in vitro and in vivo activity.[14] However, many excellent COX-2 inhibitors of this series could not demonstrate expected in vivo activity. With a view to unveil the potential of these compounds, we conceived the idea to convert them to suitable prodrugs using their amenable sulfonamide (SO_2NH_2) and hydroxymethyl (CH_2OH) groups.

Generally, the surgery patients require injectable analgesics. But, till recently, the drug of choice for this purpose was ketorolac,[15] a non-selective cyclooxygenase inhibitor. This is mainly because of the modest aqueous solubility of existing COX-2 inhibitors. Parecoxib sodium **6**,[16] a prodrug of valdecoxib **5**[8], is the only known COX-2 inhibitor for parenteral administration (Fig. 2). Therefore, with a view to discover a COX-2 inhibitor suitable for oral as well as parenteral administration, we converted the in vitro hits **9**–**15** (which could not exhibit expected in vivo activity) of the series to various possible prodrugs and screened them for anti-inflammatory activity in carrageenan-induced rat paw edema model. A few of them have demonstrated highly improved in vivo efficacy in this preliminary animal

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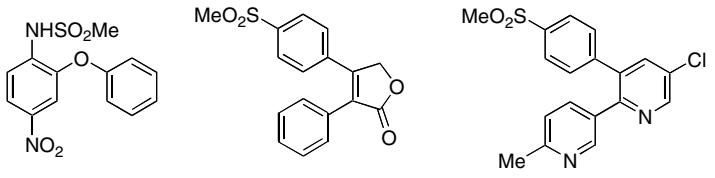
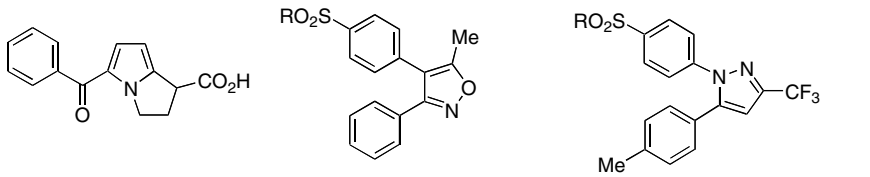


1. Nimesulide **2**. Rofecoxib **3**. Etoricoxib

Figure 1. COX-2 inhibitors.



4. Ketorolac

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

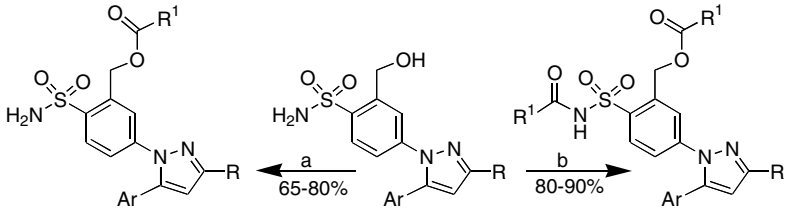
7. R = NH_2; Celecoxib
8. R = $N(Na)COC_3H_7$

Figure 2. Injectable anti-inflammatory agents.

model. Thus, we report here the synthesis and pharmacological activity of these prodrugs.

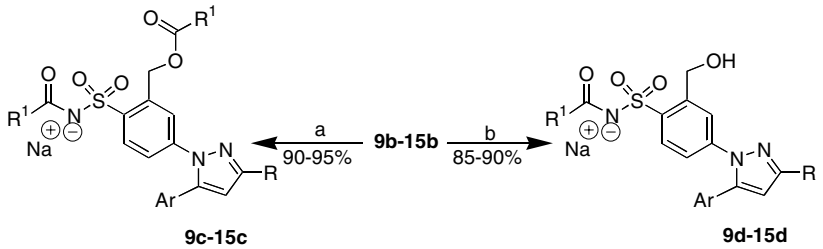
The parent diarylpyrazoles **9**–**15** were prepared by reported methods[14,17] and their conversion to various *N*-acyl, *O*-acyl, *N*,*O*-diacyl derivatives, and their sodium salts is depicted in Schemes 1 and 2. While the mono *O*-acyl derivatives **9a**–**15a** of compounds **9**–**15** were synthesized 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 **9b**–**15b** were prepared in 80–90% yield by triethylamine-catalyzed exhaustive acylation using acid anhydride under heating condition (Scheme 1). The *N*,*O*-diacyl sodium salts **9c**–**15c** were prepared in 90–95% yield from the corresponding diacyl derivatives **9b**–**15b** using 0.95 equiv of aqueous NaOH (50%) in toluene. Toluene was found to be the safest solvent to suppress the ionization of NaOH and check the unwanted hydrolysis of ester functionality. The mono N-acylated sodium salts **9d**–**15d** were prepared in 85–90% yield by the selective hydrolysis of *N*,*O*-diacylated derivatives **9b**–**15b** using 1.9 equiv of $NaHCO_3$ in methanol at 0–25 °C (Scheme 2). The salts were identified by the absence of sulfonamide protons in ^1H NMR, and by their abnormally high melting points.

The compounds were screened in vitro against human recombinant COX-2 enzyme (expressed in sf-9 cells



9a-15a **9-15** **9b-15b**

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.



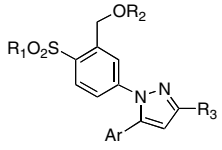
9c-15c **9d-15d**

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

infected with baculovirus) and COX-1 (obtained from microsomal fraction of Ram Seminal Vesicles) at 10 μM by TMPD method using celecoxib **7** as standard.[18] The prodrugs, though found lesser potent than parent compounds in this screen,[16] all of them were subjected to in vivo screening to assess anti-inflammatory activity at 30 mg/kg (po) in carrageenan induced rat paw edema model.[19] ED_{50}s were calculated for those prodrugs which reduced the paw swelling by more than 50% at this dose. Single dose pharmacokinetic studies were performed for potential prodrugs to correlate the observed in vivo effect.

Many compounds of the new series exhibited better pharmacodynamic and pharmacokinetic profiles than celecoxib **7**, possibly due to hydrophilic hydroxymethyl group attached adjacent to sulfonamide.[14b] Salts of N-acylated sulfonamide of valdecoxib (parecoxib sodium **6**)[16] and that of celecoxib (**8**)[20] are known to increase in vivo efficacy on oral/parenteral administration due to much improved drug concentration in systemic circulation. The in vivo efficacy data from carrageenan induced rat paw edema model for the newly prepared prodrugs are presented in Tables 1 and 2. The 4-methylthiophenyl analog **9**, one of the most potent COX-2 inhibitors (IC_{50}, 0.235 μM) of the series which exhibited only 47% reduction in paw volume at 30 mg/kg, and failed to show dose response, was converted into four prodrugs **9a**–**d** (Table 1). Surprisingly, none other than its *O*-propionyl prodrug **9a** (60% at 30 mg/kg) could show better reduction in paw volume. However, this compound failed to respond at lower doses (1, 3, and 10 mg/kg) possibly due to metabolic instability of the 4-methylthiophenyl group. Tremendous improvement was observed in the in vivo activity of prodrugs of 4-bromophenyl analog **10** (IC_{50}, 0.592 μM). While the parent compound showed only 35% reduction in paw volume at 30 mg/kg, its *N*-propionyl sulfonamide sodium **10d** exhibited an ED_{50} of 7.2 mg/kg. Similarly, while its difluoromethyl analog **11** showed only 42% reduction at 30 mg/kg, its *N*,*O*-dipropionyl sulfonamide sodium **11c** exhibited an ED_{50} of 7.9 mg/kg and *N*-propionyl sulfonamide sodium **11d** exhibited an ED_{50} of 5.6 mg/kg. A similar trend was also observed in case

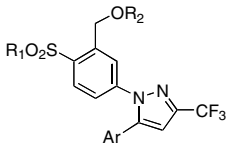
Table 1. In vitro and in vivo activity of 1,5-diarylpyrazoles and their prodrugs in carrageenan induced rat paw edema model

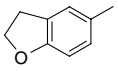
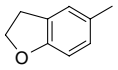
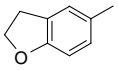
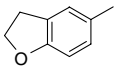
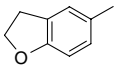
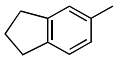
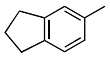
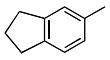
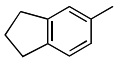
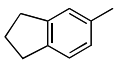


Compound	Ar	R_1	R_2	R_3	% inhibition[a]		ED_{50} (mg/kg)[c]
					COX-1	COX-2	
9	4-SMe-phenyl	NH_2	H	CF_3	59[b]	0.235[b]	47[d]
9a	4-SMe-phenyl	NH_2	COC_2H_5	CF_3	0	40	60[e]
9b	4-SMe-phenyl	$NHCOC_2H_5$	COC_2H_5	CF_3	0	18	38[d]
9c	4-SMe-phenyl	$N(Na)COC_2H_5$	COC_2H_5	CF_3	0	25	40[d]
9d	4-SMe-phenyl	$N(Na)COC_2H_5$	H	CF_3	0	21	36[d]
10	4-Br-phenyl	NH_2	H	CF_3	230[b]	0.592[b]	35[d]
10a	4-Br-phenyl	NH_2	COC_2H_5	CF_3	0	65	17.0
10b	4-Br-phenyl	$NHCOC_2H_5$	COC_2H_5	CF_3	0	25	37[d]
10c	4-Br-phenyl	$N(Na)COC_2H_5$	COC_2H_5	CF_3	0	35	12.5
10d	4-Br-phenyl	$N(Na)COC_2H_5$	H	CF_3	0	23	7.2
11	4-Br-phenyl	NH_2	H	CHF_2	314[b]	0.458[b]	42[d]
11a	4-Br-phenyl	NH_2	COC_2H_5	CHF_2	5	55	40[d]
11b	4-Br-phenyl	$NHCOC_2H_5$	COC_2H_5	CHF_2	1	25	45[d]
11c	4-Br-phenyl	$N(Na)COC_2H_5$	COC_2H_5	CHF_2	0	12	7.9
11d	4-Br-phenyl	$N(Na)COC_2H_5$	H	CHF_2	0	14	5.6
12	3-Me-4-OMe-phenyl	NH_2	H	CF_3	264[b]	0.560[b]	21.7
12a	3-Me-4-OMe-phenyl	NH_2	COC_2H_5	CF_3	12	2.500[b]	10.9
12b	3-Me-4-OMe-phenyl	$NHCOC_2H_5$	COC_2H_5	CF_3	0	10	48[d]
12c	3-Me-4-OMe-phenyl	$N(Na)COC_2H_5$	COC_2H_5	CF_3	0	5	34[d]
12d	3-Me-4-OMe-phenyl	$N(Na)COC_2H_5$	H	CF_3	0	15	6.2
13	3-Me-4-OMe-phenyl	NH_2	H	CHF_2	1000[b]	0.790[b]	18.5
13a	3-Me-4-OMe-phenyl	NH_2	COC_2H_5	CHF_2	0	75	15.0
13b	3-Me-4-OMe-phenyl	$NHCOC_2H_5$	COC_2H_5	CHF_2	0	45	42[d]
13c	3-Me-4-OMe-phenyl	$N(Na)COC_2H_5$	COC_2H_5	CHF_2	0	17	32[d]
13d	3-Me-4-OMe-phenyl	$N(Na)COC_2H_5$	H	CHF_2	0	13	6.3

[a] At 10 μM (single determination).
[b] IC_{50} in μM (means of three determinations).
[c] In six animals/group (male Wistar rats) on oral dosing at 1, 3, 10, and 30 mg/kg (means of three experiments).
[d] % reduction in paw volume at 30 mg/kg (single experiment of six animals/group).
[e] Did not respond at 1, 3 and 10 mg/kg.

Table 2. In vitro and in vivo activity of 1,5-diarylpyrazoles and their prodrugs in carrageenan induced rat paw edema model



Compound	Ar	R_1	R_2	% inhibition[a]		ED_{50} (mg/kg)[c]
				COX-1	COX-2	
14		NH_2	H	36[b]	0.228[b]	22.3
14a		NH_2	COC_2H_5	0	61	8.5
14b		$NHCOC_2H_5$	COC_2H_5	0	2	25[d]
14c		$N(Na)COC_2H_5$	COC_2H_5	0	12	43[d]
14d		$N(Na)COC_2H_5$	H	5	25	7.5
15		NH_2	H	200[b]	0.295[b]	23.5
15a		NH_2	COC_2H_5	0	57	30[d]
15b		$NHCOC_2H_5$	COC_2H_5	0	45	64[e]
15c		$N(Na)COC_2H_5$	COC_2H_5	0	15	41[d]
15d		$N(Na)COC_2H_5$	H	0	22	52[e]
6	Parecoxib-Na	—	—	[f]	[f]	98[g]
7	Celecoxib	—	—	10.75[b]	0.076[b]	6.70
8	CXB-prodrug	—	—	0	2	6.64

[a] At 10 μM (single determination).
[b] IC_{50} in μM (mean of three determinations).
[c] In six animals/group (male Wistar rats) on oral dosing at 1, 3, 10, and 30 mg/kg (means of three experiments).
[d] % reduction in paw volume at 30 mg/kg (single experiment of six animals/group).
[e] Did not respond at 1, 3, and 10 mg/kg.
[f] Not tested.
[g] Reduction in paw volume at 0.3 mg/kg, see Ref. 16.

of 4-methoxy-3-methylphenyl analog **12** (IC_{50}, 0.560 μM; ED_{50}, 21.7 mg/kg) where in vivo potencies of its *O*-propionyl derivative **12a** (ED_{50}, 10.9 mg/kg) and *N*-propionyl sulfonamide sodium **12d** (ED_{50}, 6.2 mg/kg), respectively, improved by 2- and 3-fold. A significant 3-fold improvement was also observed in

Table 3. Single dose oral pharmacokinetic data of prodrugs at 100 mg/kg[a]

Compound	$AUC_{(0-t)}$ (μg h/mL)[b]	$AUC_{(0-\infty)}$ (μg h/mL)[b]	C_{max} (μg/mL)[c]	T_{max} (h)[d]	$t_{1/2}$ (h)[e]
11	238.97 ± 45.42	265.12 ± 40.55	20.78 ± 4.97	2.67 ± 0.58	7.51 ± 1.34
11d	289.32 ± 44.59	321.45 ± 50.21	28.35 ± 5.58	2.85 ± 0.62	7.42 ± 1.25
12	73.69 ± 11.73	111.83 ± 17.87	6.37 ± 0.87	3.50 ± 1.00	6.63 ± 0.67
12d	124.72 ± 18.54	148.75 ± 19.92	9.32 ± 1.20	3.78 ± 0.65	6.82 ± 0.78
13	2.40 ± 0.50	[f]	0.70 ± 0.15	2.25 ± 0.63	[f]
13d	105.85 ± 14.70	114.25 ± 20.14	7.54 ± 2.19	2.82 ± 1.04	5.92 ± 0.54

[a] Average of two experiments, each carried out in a group of six animals (male Wistar rats) on single dosing.
[b] Area under curve.
[c] Peak plasma concentration.
[d] Time taken in achieving C_{max}.
[e] Terminal half-life.
[f] Not determined due to poor and erratic absorption.

the in vivo activity of *N*-propionyl sulfonamide sodium prodrug **13d** (ED_{50}, 6.3 mg/kg) over the parent difluoromethyl analog **13** (IC_{50}, 0.790 μM; ED_{50}, 18.5 mg/kg).

Among the 5-bicyclic substituted derivatives, while the *O*-propionyl prodrug **14a** (ED_{50}, 8.5 mg/kg) and *N*-propionyl sulfonamide sodium prodrug **14d** (ED_{50}, 7.5 mg/kg) of 5-[5-(2,3-dihydrobenzofuranyl)] analog **14** (IC_{50}, 0.228 μM; ED_{50}, 22.3 mg/kg) showed remarkable improvement, none of the prodrugs of 5-indanyl analog **15** (IC_{50}, 0.295 μM; ED_{50}, 23.5 mg/kg) could exhibit improved in vivo efficacy in this model at lower doses.

The oral pharmacokinetic data of compounds **11**, **12**, and **13** and their most active prodrugs are presented in Table 3. Despite excellent pharmacokinetic profile at 100 mg/kg, compound **11** ($AUC_{0-\infty}$, 265.12 μg h/mL; C_{max}, 20.78 μg/mL) did not exhibit expected in vivo activity. However, its *N*-propionyl sulfonamide sodium prodrug **11d** ($AUC_{0-\infty}$, 321.45 μg h/mL; C_{max}, 28.35 μg/mL) showed much improved in vivo activity due to relatively higher drug (released) concentration in plasma. Similarly, compound **12** ($AUC_{0-\infty}$, 111.83 μg h/mL; C_{max}, 6.37 μg/mL) afforded much efficacious prodrug **12d** due to superior absorption and drug concentration in the blood ($AUC_{0-\infty}$, 148.75 μg h/mL; C_{max}, 9.32 μg/mL). But, it was quite surprising to observe the improvement in *N*-propionyl sulfonamide sodium prodrug **13d** ($AUC_{0-\infty}$, 114.25 μg h/mL; C_{max}, 7.54 μg/mL) over its parent compound **13** which was hardly detected in blood due to erratic absorption (C_{max}, 0.70 μg/mL).

While absorption and bioavailability suffice a drug for oral administration, water solubility is an essential requirement for parenteral administration. Though many of these prodrugs showed similar or better in vivo activity than celecoxib and parecoxib, only a few exhibited improved water solubility. Particularly, the prodrugs **11d**–**13d** showed ~5–7 times greater aqueous solubility (150–200 mg/mL at 25 °C) than parecoxib sodium **6** (22 mg/mL)[16] and celecoxib-prodrug **8** (15 mg/mL).[20] Therefore, it was anticipated that a low volume injection of these prodrugs would release high concentration of drug on biotransformation and effectively treat the patient suffering from severe pain.

In conclusion, we have demonstrated herein the conversion of in vivo inactive potent COX-2 inhibitors to potent anti-inflammatory drug candidates through a prodrug approach. The prodrugs *N*-propionyl sulfonamide sodium such as **11d**–**13d** have been identified as potential anti-inflammatory agents for oral as well as parenteral administration. This chemical approach, leading to prodrugs, may be useful in similar situations during many drug discovery and development program.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2006.05.028.

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