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Synthesis and biological evaluation of 4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate derivatives as potent anti-inflammatory and selective COX-2 inhibitors

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ABSTRACT

Twelve new 4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate derivatives have been synthesized and anti-inflammatory and cyclooxygenase (COX-1 and COX-2) inhibitory activities have been evaluated. Structures of these compounds were established by IR, ¹H NMR, Mass, and Elemental microanalyses data. These compounds also exhibited significant anti-inflammatory activity, which is comparable to that of celecoxib in the carrageenan-induced rat paw edema method. The selected compounds were evaluated for their preliminary in vitro cyclooxygenase inhibitory activity against COX-2 and COX-1 enzymes. The compounds tested showed selective inhibitory activity toward COX-2 (72-5%) over COX-1 (3.4%), amongst them compounds 3c and 3i showed appreciable COX-2 selective inhibitory activity.

Key words: 2-hydroxyphenyl acetate, NSAIDs, cyclooxygenase-2 inhibitors, anti-inflammatory, rat paw edema assay.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) still remain among the most extensively used drugs worldwide and have been used in the treatment of inflammatory conditions like rheumatoid arthritis, osteoarthritis, orthopedic injuries, post-operative pain, etc. [1,2]. However, the use of conventional NSAIDs have been restricted due to their adverse effect especially gastrointestinal toxicity and renal insufficiency [3,4]. A major discovery in the search of novel anti-inflammatory agents without deleterious side effects exhibited by the conventional NSAIDs came from the identification of two different isoforms of the cyclooxygenase (COX) enzyme known as COX-1 and COX-2. Cyclooxygenase (COX) or prostaglandin endoperoxide synthase (PGHS) catalyzes the first step in the biosynthesis of the prosta- glandins (PGs) from the substrate arachidonic acid (AA) [1]. COX enzyme possesses two distinct catalytic activities: (1) cyclo- oxygenase activity that catalyzes the oxidation of AA to produce hydroperoxyendoperoxide (PGG₂) and (2) peroxidase activity that reduces the hydroperoxide PGG₂ to the hydroxyendoperoxide (PGH₂). The PGH₂ is transformed by a range of enzymic and nonenzymic mechanisms into the primary prostanoids. In addition, arachidonic acid is a substrate for a variety of additional oxidative enzymes such as lipoxygenase, which generates biologically active lipids: hydroperoxyeicosatetraenoic acid (HPETE), hydroxyeico- satetraenoic acid (HETE), and leukotrienes (LTA₄, LTB₄, LTC₄, and LTE₄). The cyclooxygenase (COX) enzymes, were identified as the molecular targets of all nonsteroidal anti-inflammatory drugs (NSAIDs) [2e4]. COX-1 is the constitutive isoform and is mainly responsible for the synthesis of cytoprotective PGs

in gastrointestinal (GI) tract whereas COX-2 is inducible and plays a major role in PG biosynthesis in inflammatory cells [5e7]. It is believed that the inhibition of COX-1 causes unfavorable GI side effects [8]. Therefore, development of novel compounds having anti-inflammatory activity with an improved safety profile is still a necessity. Literature survey revealed that many acetyl salicylic derivatives [9] have found their clinical application as NSAIDs. Salicylates are the class of compounds that are widely valued for their pain killing, antipyretic and anti-inflammatory properties. The most commonly known and used salicylates are salicylic acid (also called 2-hydroxybenzoic acid), aspirin (acetylsalicylic acid -ASA) and sodium salicylates. They are used extensively for the relief of headache, inflammation, arthritis pain, and some are employed in the treatment of heart attacks and strokes in the elderly. Their mode of action is the inhibition of the synthesis of prostaglandin and its derivatives that cause inflammation, pain, rise in temperature and related. Recently, salicylic acid has been used primarily as an intermediate in the production of agrochemicals, dyes and colorants products. Salicylate toxicity and poisoning are rare in recommended doses; however, salicylate poisoning and its side effects are prominent problem in developing countries where they are used as antipyretic in the management of infectious malaria, both in children and in elderly people. Meanwhile, there are development and introduction of new analgesic, antipyretic and anti-inflammatory agents that compete with aspirin. This has made chemists to search for a better tolerable drug which are devoid of toxic and side effects of aspirin has been shown in the CNS, respiratory, gastro-intestinal tract, hepatic, metabolic and coagulation systems of the body. This work is the first stage in evaluating the various biological activities produced by twelve derivatives of salicylic acid synthesized in our laboratories. These compounds are tested to examine their potency, efficacy and cytotoxicity with a view of developing a compound having lower toxicity and less side effects. Researchers have recently focused on selective COX-2 inhibitors which are believed to reduce inflammation without influencing normal physiologic functions of COX-1. Figure 1 and Figure 2.

FIGURE 1: Selective cox-2 inhibitors

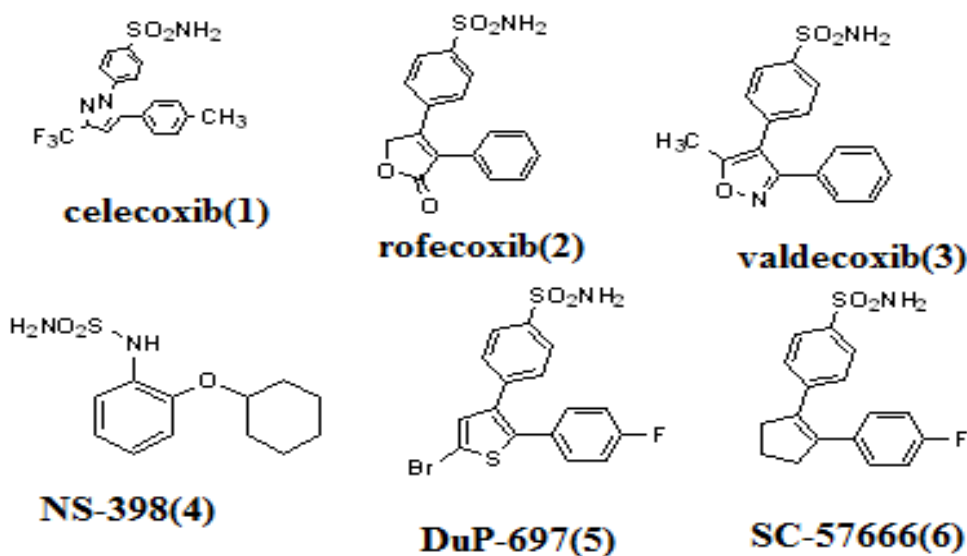
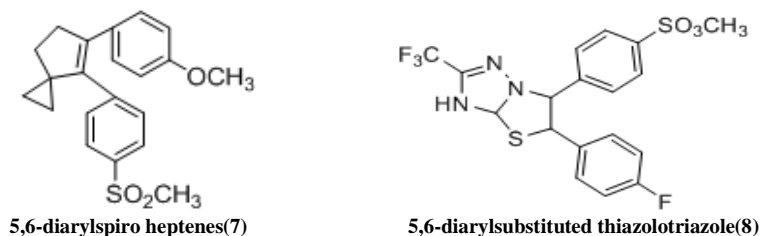
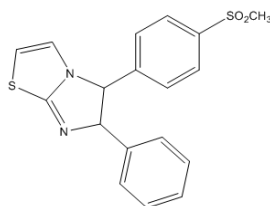
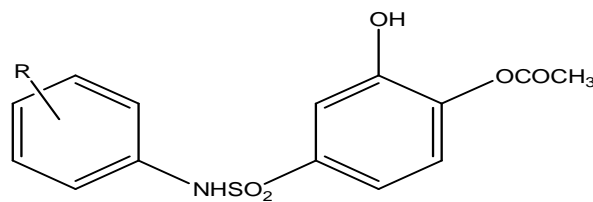


FIGURE 2: Recently reported selective cox-2 inhibitors





5,6-diarylimidazo[2,1-b]thiazole(9)



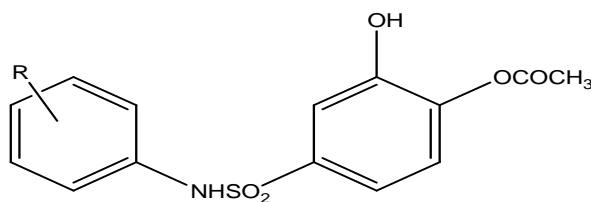
4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate derivatives(10)

Motivated by the aforesaid findings, and pursuing our studies on acetyl salicylate moiety, we were designed to synthesize a new series of 5-(N substituted phenyl sulfamoyl) acetyl salicylic acid derivatives and tested them as COXs inhibitors.

MATERIALS AND METHODS

Melting points were determined with a Reichert–Jung hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550-FT spectrometer. ¹H NMR (400 MHz) spectra were measured on a Varian Unity plus 400 spectrometer in CDCl₃ or DMSO-d₆ with TMS as the internal standard, where J (coupling constant) values are estimated in Hertz. Spin multiples are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra were obtained with a Finnigan Mat TSQ-70 spectrometer. Elemental microanalyses were carried out with a Perkin-Elmer 240-C apparatus and were within ±0.4% of the theoretical values for C, H, and N. All solvents and reagents were purchased from the Fluka, Aldrich or Merck Chemical Company. Albino rats, used in the anti-inflammatory screens, and experiments were carried out using protocols approved by the Ethics Committee of SardarBhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun, India.

Table 1 :Lead structure of 2, 5-diphenyl-1,3,4-oxadiazole derivatives:



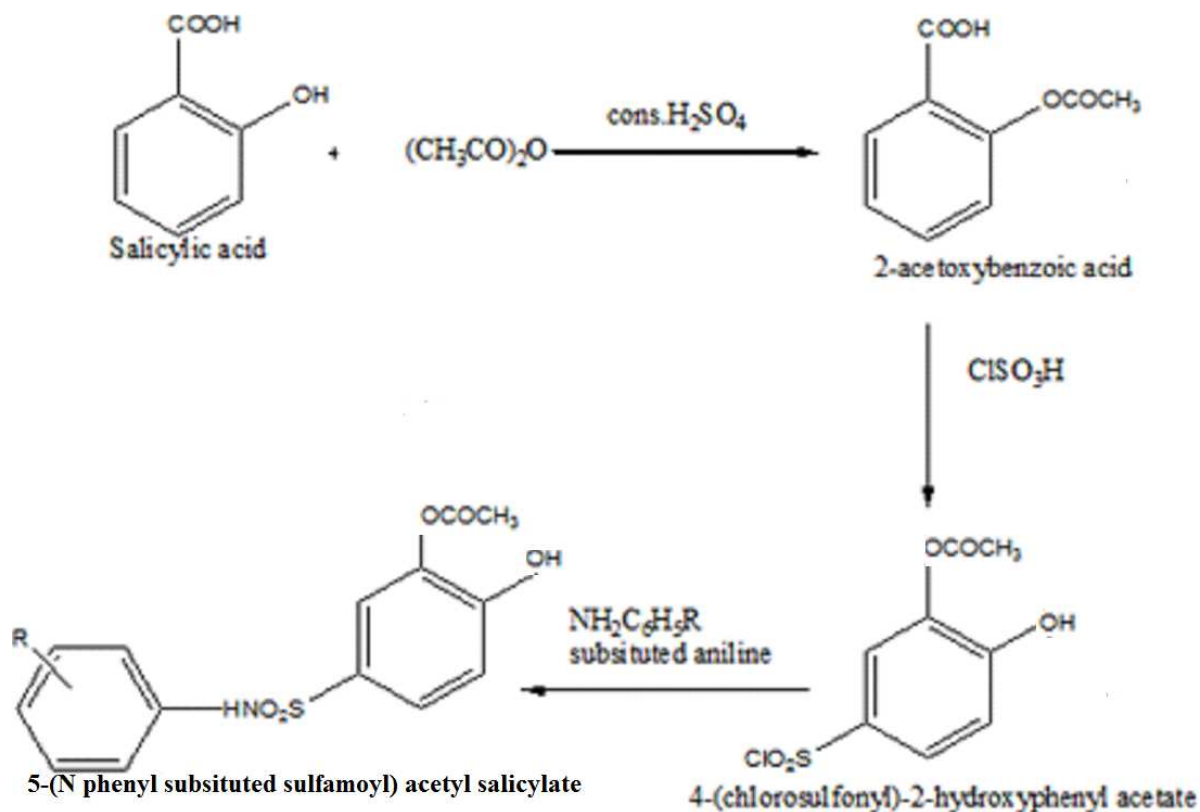
compound	R
4-(phenylsulfamoyl)-2-hydroxyphenyl acetate (3a)	H
4-(2-fluorophenylsulfamoyl)-2-hydroxyphenyl acetate (3b)	2-F
4-(3-hydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3c):	3-OH
4-(2-chlorophenylsulfamoyl)-2-hydroxyphenyl acetate (3d)	2-Cl
4-(3-fluorophenylsulfamoyl)-2-hydroxyphenyl acetate (3e)	3-F
4-(4-aminophenylsulfamoyl)-2-hydroxyphenyl acetate (3f)	4-NH ₂
4-(4-hydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3g)	2-OH
4-(4-acetoxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3h)	4-COOH
4-(2-hydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3i)	4-OH
4-(2,3-dihydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3j)	2,3-dihydroxy

Chemistry

General procedure for the preparation of 5-(N substituted phenyl sulfamoyl) acetyl salicylic acid derivatives(3a–j)

6gm of salicylic acid, 8.5ml of acetic anhydride and 1-2 ml of Con. sulphuric acid was refluxed under anhydrous conditions for 1 hours. The reaction was monitored by TLC, using chloroform and methanol (95:5) as a solvent, crude product washed with cold water and dried. acetylsalicylate 14.0ml (0.1moles) was placed with 58.26 ml (0.5moles) of chlorosulfonic acid at 12-15 °C. Temperature is maintained at approximately 15 °C, therefore large volume of HCl are evolved and then reflux the mixture to 60 °C for 3 hrs. The solid sulphonyl chloride which separates is collected and washed with water. 4.20gm (0.0168 moles) of 2- substituted- 5-chlorosulphonyl intermediate 2 is added with stirring during about 5 minutes to 3.31ml (0.07moles) amine derivatives containing the mixture is allowed to heat up to 80-90°C on molten condition on mechanical stirrer and then mixture is shaken

vigorously., 10 ml of the NaOH solution is added carefully with stirring at 10 minutes time interval. The liquid phase of the final mixture should be alkaline. The reaction is completed by heating the mixture on a steam bath for 1 hour with vigorous mechanical stirring. The mixture was poured into ice (20g) and extracted with chloroform. (2 x 25ml) The organic layers were collected and washed with brine (2 x 10ml) dried sodium sulfate and filtered and concentrated under vacuum.purification by flash chromatography,eluting with CH₃CL/MeOH (20:1) and crystallisation from suitable solvent gave 3a-j.scheme 1



Scheme 1: outline of synthesis

4-(phenylsulfamoyl)-2-hydroxyphenyl acetate (3a) : Yield 67%; mp236 C (n- butanol); IR (KBr): 1278, 1151 (SO₂) cm⁻¹; ¹H NMR(CDCl₃,300Hz) 2. 24(s,3H,-CH₃),4.45(m,1H,-NH)5.67(s,1H,-OH),6.26(m,2H,-CH),7.16(m,6H,-CH) ESIMS m/z 374(M¹ + 1), Anal Calcd for C₁₇H₁₅N₃O₃S₂ : C, 54.67; H, 4.05; N, 11.25; O, 12.85; S, 17.17, Found: C, 54.77; H, 4.15; N, 11.32

4-(2-fluorophenylsulfamoyl)-2-hydroxyphenyl acetate (3b): 4-(2-fluorophenylsulfamoyl)-2-hydroxyphenyl acetate(3b): Yield 76%; mp 236 C (n- butanol); IR (KBr): 1278, 1151 (SO₂) cm⁻¹; ¹H NMR (CDCl₃,300Hz) 2.12(s,3H,-CH₃),4.23(m,1H,-NH)5.35(s,1H,-OH),6.36(m,2H,-CH),7.11(m,6H,-CH), ESIMS m/z 325 (M¹ + 1), Anal Calcd for C₁₄H₁₂FNO₅S : C, 51.69; H, 3.72; F, 5.84; N, 4.31; O, 24.59; S, 9.86 found C, 50.02; H, 3.21; F, 5.12; N, 4.78; O, 24.11; S, 9.01

4-(3-hydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3c):Yield 56%; mp 357 C (n- butanol); IR (KBr): 1278, 1151 (SO₂) cm⁻¹; ¹H NMR (CDCl₃,300Hz) 2.02(s,3H,-CH₃),4.23(m,1H,-NH)5.35(s,2H,-OH),6.12(m,2H,-CH),7.34(m,6H,-CH), ESIMS m/z 323 (M¹ + 1), Anal Calcd for C₁₄H₁₃NO₆S C, 52.01; H, 4.05; N, 4.33; O, 29.69; S, 9.92 found: C, 51.98; H, 4.01; N, 4.03; O, 29.03; S, 9.12

4-(2chlorophenylsulfamoyl)-2-hydroxyphenyl acetate (3d): Yield 46%; mp337° C (n- butanol); IR (KBr): 1278, 1151 (SO₂) cm⁻¹; ¹H NMR(CDCl₃,300Hz) 2.13(s,3H,CH₃),4.21(m,1H,-NH)5.04(s,2H,-OH),6.32(m,2H,-

CH), 7.64(m, 6H, -CH) ESIMS m/z 341 ($M^1 + 1$), Anal Calcd for $C_{14}H_{12}ClNO_5S$: C, 49.20; H, 3.54; Cl, 10.37; N, 4.10; O, 23.41; S, 9.38 Found: C, 50.12; H, 3.12; Cl, 10.23; N, 4.01; O, 23.12; S, 9.01

4-3-fluorophenylsulfamoyl)-2-hydroxyphenyl acetate (3e): Yield 76%; mp 278° C (n- butanol); IR (KBr): 1278, 1151 (SO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 300Hz) 2.03(s, 3H, -CH₃), 4.13(m, 1H, -NH), 5.05(s, 1H, -OH), 6.16(m, 2H, -CH), 7.16(m, 6H, -CH), ESIMS m/z 325 ($M^1 + 1$), Anal Calcd for $C_{14}H_{12}FNO_5S$: C, 51.69; H, 3.72; F, 5.84; N, 4.31; O, 24.59; S, 9.86 found C, 50.02; H, 3.56; F, 5.42; N, 4.78; O, 24.35; S, 9.34

4-(4-aminophenylsulfamoyl)-2-hydroxyphenyl acetate (3f): Yield 58%; mp 328° C (n- butanol); IR (KBr): 1278, 1151 (SO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 300Hz) 2.03 (s, 3H, CH₃), 4.13(m, 1H, -NH), 5.05(s, 1H, -OH), 6.16(m, 2H, -CH), 7.16(m, 6H, -CH), ESIMS m/z 322 ($M^1 + 1$), Anal Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.17; H, 4.38; N, 8.69; O, 24.82; S, 9.95, Found: C, 52.12; H, 4.10; N, 8.12; O, 24.02; S, 9.01

4-(4-hydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3g): Yield 62%; mp 212° C (n- butanol); IR (KBr): 1278, 1151 (SO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 300Hz) 2.14 (s, 3H, -CH₃), 4.15(m, 1H, -NH), 5.15(s, 2H, -OH), 6.32(m, 2H, -CH), 7.69(m, 6H, -CH), ESIMS m/z 374 ($M^1 + 1$), Anal Calcd for $C_{14}H_{13}NO_6S$: C, 52.01; H, 4.05; N, 4.33; O, 29.69; S, 9.92 Found C, 51.34; H, 4.01; N, 4.01; O, 29.01; S, 9.02

4-(4-acetoxy phenylsulfamoyl)-2-hydroxyphenyl acetate (3h): Yield 67%; mp 348° C (n- butanol); IR (KBr): 1278, 1151 (SO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 300Hz) 2.34 (s, 3H, -CH₃), 4.45(m, 1H, -NH), 5.01(s, 2H, -OH), 6.42(m, 2H, -CH), 7.64(m, 6H, -CH), ESIMS m/z 374 ($M^1 + 1$), Anal Calcd for $C_{16}H_{15}NO_7S$: C, 52.60; H, 4.14; N, 3.83; O, 30.65; S, 8.78 Found: C, 51.50; H, 4.04; N, 3.13; O, 30.01; S, 7.90

4-(2-hydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3i): Yield 47%; mp 345° C (n- butanol); IR (KBr): 1278, 1151 (SO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 300Hz) 2.34 (s, 3H, -CH₃), 4.45(m, 1H, -NH), 5.01(s, 2H, -OH), 6.42(m, 2H, -CH), 7.64(m, 6H, -CH) ESIMS m/z 323 ($M^1 + 1$), Anal Calcd for $C_{14}H_{13}NO_6S$: C, 52.01; H, 4.05; N, 4.33; O, 29.69; S, 9.92, Found: C, 52.09; H, 3.65; N, 4.12; O, 29.69; S, 9.42

4-(2,3-dihydroxyphenylsulfamoyl)-2-hydroxyphenyl acetate (3j): Yield 43%; mp 324° C (n- butanol); IR (KBr): 1278, 1151 (SO_2) cm^{-1} ; 1H NMR ($CDCl_3$, 300Hz) 2.0 (m, 2H, amine), 2.01(s, 3H, -CH₃), 4.45(m, 1H, -NH), 5.01(s, 3H, -OH), 6.23(m, 2H, -CH), 7.14(m, 6H, -CH), ESIMS m/z 322 ($M^1 + 1$), Anal Calcd for $C_{17}H_{15}N_3O_3S_2$: C, 54.67; H, 4.05; N, 11.25; O, 12.85; S, 17.17, Found: C, 54.77; H, 4.15; N, 11.32

RESULTS AND DISCUSSION

In vivo anti-inflammatory activity.

The preliminary in vivo anti-inflammatory activity was evaluated using carrageenan- induced rat paw edema assay model of inflammation by adopting the method of Winter et al.[36] for the selected compounds listed in Table 2. Male albino rats (170–220 g) were fasted with free access to water at least 12 h prior to experiments and divided randomly into nine groups of six each. Control group received 1 mL of vehicle (0.5% methyl cellulose and 0.025% Tween 20), standard group received 10 mg/kg of celecoxib, and test groups received 10 mg/kg of synthesized compounds. The rats were dosed orally, 1 h later, a subplantar injection of 0.05 mL of 1% solution of carrageenan in 0.9% sterile solution was administered to the left hind foot pad of each animal. The paw edema volume was measured with a digital plethysmometer (Ugo-Basile, Italy) at 0, 2, 4 h after carrageenan injection. Paw edema volume was compared with vehicle control group and percent reduction was calculated as $1 - (\text{edema volume in the drug treated group} / \text{edema volume in the control group}) \times 100$

In vitro cyclooxygenase inhibition studies.

The selected compounds listed in Table 3 were tested for their ability to inhibit in vitro COX-1 and COX-2 using a colorimetric COX (ovine) inhibitor screening kit (Catalog No. 760 111, Cayman Chemicals Inc., Ann Arbor, MI, USA) using the previously established method.[37]

Table2: % inhibition of different compounds

S. No	compound	No. of animals used.	Average Body Weight (gms)	Dose (mg/kg)	Mean Paw Swelling±S.D	Inhibition %
1.	Control	5	264	50	0.286±0.052	-----
2.	Ibuprofen	5	230	50	0.066±0.017	76.63%
3.	Compound 3a	5	200	50	0.087±0.027	68.23%
4.	Compound3b	5	268	50	0.097±0.017	67.43%
5.	Compound 3c	5	224	50	0.074±0.036	72.42%
6.	Compound 3d	5	212	50	0.103±0.033	65.64%
7.	Compound 3e	5	270	50	0.101±0.024	65%
8.	Compound3f	5	220	50	0.083±0.026	71.63%
9.	Compound3g	5	256	50	0.088±0.015	68.23%
10.	Compound3h	5	245	50	0.111±0.033	61.1%
11.	Compound3i	5	237	50	0.053±0.016	79.4%

Table 3: In vitro inhibition of purified COX-2 by 2,5-diphenyl-1,3,4-oxadiazole derivatives

s.no	COX-2 inhibition (%) ^a	COX-1 inhibition (%) ^a
3a	5.23± 8.23	nt ^c
3b	42.82± 3.34	nt
3c	71.24±1.34	3.46 ± 8.03 (10 mM) 18.27±7.05 (100 mM)
3d	47.61± 2.37	nt
3e	27.55±2.30	nt
3f	34.76± 5.28	nt
3g	35.60± 2.31	nt
3h	48.19± 5.31	nt
3i	79.13± 1.31	3.34±7.01 (10 mM) 17.25 ±8.02 (100 mM)
indomethacin	90.44±0.24	72.89±6.31
Celecoxib	61.78±2.83	12.66 ±6.66

^aData are indicated as percentage of inhibition at 10 mM_SEM (n 1/44).

^bcelecoxib was assayed at 100 mM and 1 mM for COX-1 and COX-2, respectively.

^cnt: not tested.

The compounds reported herein were tested for their ability to inhibit COX-2 and/or COX-1 using the purified colorimetric COX (ovine) method. The in vitro activity results are reported as a percentage of inhibition of the purified enzymes at 10 mM (Table 2). In this preliminary study towards new potential COX-2 selective compounds as novel drug candidates for inflammatory and related diseases, we have introduced systematic modifications to the 4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate core structure. It is well established 2-hydroxyphenyl acetate derivatives is a good template for anti-inflammatory and selective COX-2 inhibition. Thus, taking into account this structural feature, we planned a structure-activity relationship study using the 4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate core as a template. In particular, we envisaged a series of substitution on the 2 and 5 position aryl ring in order to introduce more flexibility to the template, while keeping the 4-(phenylsulfamoyl)-2-hydroxyphenyl acetate which was required to maintain COX-2 selectivity. Results are shown in Table 2. In general, none of the newly synthesized derivatives proved to be endowed with the desired activity profile at COX-2, as none but two of the compounds (compound 3c and 3i) inhibited at least 50% of the COX-2 isoform during preliminary screening. Compound 3c and 3i are endowed with a 3 and 4 hydroxy on the phenyl ring. We found that chloro, fluoro and acetoxysubstitution with phenyl ring had a low COX-2 activity with respect to the hydroxy analogs. This preliminary results indicated that the presence of hydroxy is important for COX-2 activity and acetoxy on the phenyl ring was less effective. [29,30]. Within the sulfonamide analogs, introduction of smaller substituents on the p-phenyl position, i.e., 3e caused a decrease in the observed COX-2 activity at 10 mM screening.

CONCLUSION

The synthesis of a series 4-(substituted phenylsulfamoyl)-2-hydroxyphenyl acetate derivatives substituted at R₁ and R₂ is described along with their preliminary evaluation as potential COX-2 inhibitors. Most of the compounds show no significant COX-2 inhibitory activity. Only compound 3c and 3j displayed potent and selective COX-2

inhibition. In conclusion, we feel that the preliminary in vitro activity results of this class of compounds may possess potential for design of future molecules with modifications on the aryl substituents inhibit one or more of these enzymes. Further studies are in progress.

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