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2-(2-Arylphenyl)benzoxazole As a Novel Anti-Inflammatory Scaffold: Synthesis and Biological Evaluation

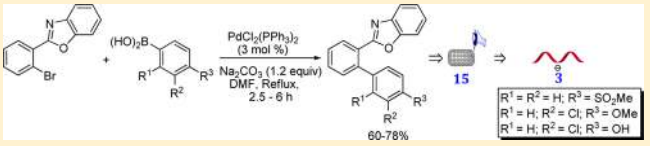
Kapileswar Seth,[†] Sanjeev K. Garg,[†] Raj Kumar,[†] Priyank Purohit,[†] Vachan S. Meena,[‡] Rohit Goyal,[§,∥] Uttam C. Banerjee,[‡] and Asit K. Chakraborti*,[†]

[†]Department of Medicinal Chemistry and [‡]Department of Pharmaceutical Technology (Biotechnology), National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar 160 062 Punjab, India

[§]Indo-Soviet Friendship (ISF) College of Pharmacy, Moga, 142 001 Punjab, India

Supporting Information

ABSTRACT: The 2-(2-arylphenyl)benzoxazole moiety has been found to be a new and selective ligand for the enzyme cyclooxygenase-2 (COX-2). The 2-(2-arylphenyl)benzoxazoles **3a−m** have been synthesized by Suzuki reaction of 2-(2-bromophenyl)benzoxazole. Further synthetic manipulation of **3f** and **3i** led to **3o** and **3n**, respectively. The compounds **3g**, **3n**, and **3o** selectively inhibited COX-2 with selectivity index of **3n** much better than that of the COX-2 selective NSAID celecoxib. The in vivo anti-inflammatory potency of **3g** and **3n** is comparable to that of celecoxib and the nonselective NSAID diclofenac at two different doses, and **3o** showed better potency compared to these clinically used NSAIDs.



KEYWORDS: *2-(2-Arylphenyl)benzoxazoles, novel anti-inflammatory scaffold, 3D QSAR, cyclooxygenase-2 selective, in vivo potency*

Inflammation is the natural defense mechanism of the body to deal with infection and tissue damage. However, uncontrolled inflammatory cascades is responsible for various diseases such as chronic asthma, rheumatoid and osteo-arthritis, multiple sclerosis, inflammatory bowl diseases and psoriasis,[1] diabetic nephropathy,[2] tumor initiation, and malignant progression.[3] Pain is the most prevalent inflammatory symptom needing medical attention with an estimated amount of 105 million of affected people in the US amounting to the financial burden of US$ 100 billion per annum to the health care expenditure.[4] Rheumatoid arthritis (RA) and osteoarthritis (OA) are the sever forms of inflammatory pain with a decade span of the disease shortening the life expectancy.[5,6] The major complication of RA is its association with acceleration of cardiovascular diseases (CVDs).[7] The nonsteroidal anti-inflammatory drugs (NSAIDs) are used worldwide for therapeutic intervention of pain and inflammation. These exert their anti-inflammatory activity by inhibition of cyclo-oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes.[8] The side effects such as gastric ulcer and gastro-intestinal bleeding associated with the traditional NSAIDs (nonselective inhibitors of COX-1 and COX-2) led to the development of selective COX-2 inhibitors as a new class of NSAIDs generally recognized as coxibs.[9] The recent withdrawal of COX-2 selective inhibitors rofecoxib and valdecoxib due to adverse cardiovascular side effects[10] fuelled a debate about the increased cardiovascular risk associated with existing COX-2 inhibitors[11] pressing the need for novel anti-inflammatory scaffold. The additional findings on therapeutic benefit of

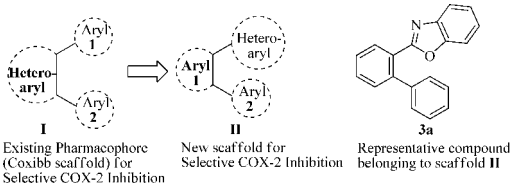
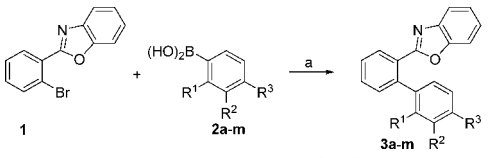


Figure 1. Topological model for selective COX-2 inhibition through scaffold-hopping.

Scheme 1. Synthesis of 3a−m[a]



3a: $R^1 = R^2 = R^3 = H$, 4 h, 65%
3b: $R^1 = R^2 = H$, $R^3 = OCH_3$, 5 h, 68%
3c: $R^1 = H$, $R^2 = R^3 = OCH_3$, 5.5 h, 63%
3d: $R^1 = R^2 = OCH_3$, $R^3 = H$, 6 h, 60%
3e: $R^1 = H$, $R^2 = OC_6H_9$, $R^3 = OCH_3$, 5 h, 61%
3f: $R^1 = R^2 = H$, $R^3 = SCH_3$, 4.5 h, 67%
3g: $R^1 = H$, $R^2 = Cl$, $R^3 = OCH_3$, 3 h, 66%
3h: $R^1 = H$, $R^2 = Cl$, $R^3 = O^iPr$, 4 h, 64%
3i: $R^1 = H$, $R^2 = Cl$, $R^3 = OBn$, 6 h, 65%
3j: $R^1 = R^2 = H$, $R^3 = F$, 2.5 h, 75%
3k: $R^1 = R^2 = H$, $R^3 = CF_3$, 3 h, 78%
3l: $R^1 = R^2 = H$, $R^3 = CHO$, 4 h, 61%
3m: $R^1 = R^2 = H$, $R^3 = CN$, 3.5 h, 75%

[a]Reagents and conditions: (a) $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (1.2 equiv), DMF, reflux, 2.5−6 h.

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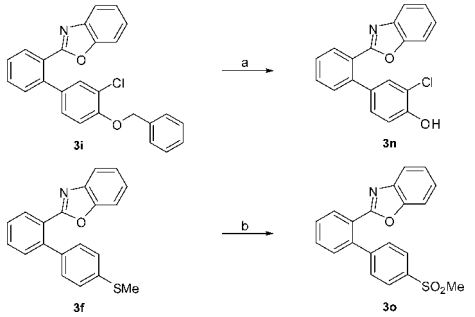
Table 1. In Vitro COX-1 and COX-2 Inhibitory Potency of 2-Benzoxazolyl Biaryls[a]

		% inhibition[b,c]			
entry	compd	COX-1	COX-2	COX-2/COX-1	SI[d]
1	**3a**	23.98 ± 1.41	10.61 ± 1.41	0.44 ± 0.09	
2	**3b**	19.08 ± 2.12	14.85 ± 2.83	0.78 ± 0.24	
3	**3c**	58.23 ± 4.24	86.62 ± 1.41	1.49 ± 0.08	
4	**3d**	74.87 ± 3.54	59.85 ± 2.12	0.80 ± 0.07	
5	**3e**	17.13 ± 4.24	14.85 ± 3.54	0.87 ± 0.01	
6	**3f**	4.07 ± 2.12	43.45 ± 2.12	10.68 ± 6.07	
7	**3g**	6.45 ± 1.41	81.36 ± 2.83	12.61 ± 2.33	
		46.78 ± 0.02[e]	0.67 ± 0.04[e]		69.82 ± 3.71
8	**3h**	2.19 ± 0.71	33.94 ± 3.54	15.50 ± 6.65	
9	**3i**	10.28 ± 2.12	16.97 ± 2.12	1.65 ± 0.55	
10	**3j**	1.65 ± 0.55	8.46 ± 2.12	1.57 ± 0.42	
11	**3k**	3.45 ± 1.41	11.67 ± 3.54	3.38 ± 2.41	
12	**3l**	6.58 ± 2.12	57.95 ± 2.83	8.81 ± 2.43	
13	**3m**	8.46 ± 2.12	40.85 ± 2.83	4.83 ± 1.54	
14	**3n**	7.56 ± 4.24	94.90 ± 4.24	12.55 ± 7.57	
		46.25 ± 0.04[e]	0.41 ± 0.02[e]		112.80 ± 5.62
15	**3o**	10.80 ± 2.12	75.12 ± 2.12	6.96 ± 1.17	
		45.06 ± 0.04[e]	1.34 ± 0.05[e]		33.62 ± 1.21
16	**4**	26.68 ± 2.12	100	3.75 ± 0.30	
		27.25 ± 0.04[e]	0.29 ± 0.02[e]		92.87 ± 6.46

[a]The enzyme inhibition studies were performed using COX inhibitor screening assay kit available commercially (catalog number 560131, Cayman chemical company) as per the manufacturer's protocol (www.caymanchem.com). [b]Results are expressed as means of two determinations ± SD, and deviation from the mean is <10% of the mean value. [c]Calculated at 10 μM concentration of the compound. [d]The COX-2 selectivity index (SI) [IC_{50} (COX-1)/IC_{50} (COX-2)] are expressed as means of two determinations ± SD. [e]The IC_{50} values are expressed as means of two determinations ± SD.

Scheme 2. Synthetic Modification of 3i and 3f to Form 3n and 3o, Respectively[a]



[a]Reagents and conditions: (a) Pd/C (10% ww/w), H_2, 40 psi, EtOH, rt, 4 h, 80%; (b) aq. oxone (3 equiv), 1,4-dioxane, rt, 4 h, 80%.

Table 2. In Vivo Anti-Inflammatory Activity of 3g, 3n, 3o, Celecoxib (4), and Diclofenac (5)

entry	group (mg/kg)	dose (mL)[a]	rat paw volume	% inhibition
1	carrageenan (control)	vehicle treated	0.87 ± 0.20	
2	**3g**	12.5	0.40 ± 0.04[b]	53.85
3	**3g**	25	0.31 ± 0.06[b]	64.42
4	**3n**	12.5	0.28 ± 0.04[b]	68.27
5	**3n**	25	0.15 ± 0.04[b]	82.69
6	**3o**	12.5	0.32 ± 0.04[b]	62.50
7	**3o**	25	0.22 ± 0.05[b]	75.00
8	**4**	12.5	0.34 ± 0.04[b]	60.57
9	**4**	25	0.22 ± 0.05[b]	74.61
10	**5**	12.5	0.28 ± 0.04[b]	67.31
11	**5**	25	0.13 ± 0.03[b]	84.62

[a]Carrageenan induced rat paw edema model, using six animals in each group of Wistar albino rats at 3 h. Results are expressed as mean ± SD and analyzed by two-way ANOVA followed by Tukey's multiple comparison test. [b]$p < 0.05$ vs carrageenan control considered to be statistically significant.

COX-2 inhibition for new therapeutic areas such as diabetes,[2] cancer,[3,12−16] and kidney dysfunction[17] rejuvenate the medicinal chemists to search for novel COX-2 selective anti-inflammatory agents to address the concern over the safe use of currently approved drugs that are associated with poor tolerability, unfavorable side effects, long-term safety, abuse, and inconvenience of use.[18,19] The COX-2 isoenzyme plays a central role in the development of colorectal cancer through acceleration of angiogenesis, increased invasiveness, and antiapoptotic effects.[20] The role of COX-2 in tumor growth and/or metastases has been demonstrated through exhaustive preclinical and clinical data.[21] The ability of COX-2 inhibitors to prevent colorectal cancer has been demonstrated by several in vitro and in vivo clinical studies.[22,23] In view of the mortality associated with many cancers and limited current treatment options using agents such as adriamycin that induces direct cardiovascular damage in several patients, COX-2 remains a very important drug target to treat debilitating diseases such as RA and OA and a preventive measure for colon cancer. However, it is worth mentioning that selective COX-2 inhibitors can also exhibit their anticarcinogenic effects through COX-independent pathway.[24−26] Herein we disclose 2-(2-arylphenyl)benzoxazole as a novel scaffold for selective inhibition of COX-2 and discover three new compounds in this structural class as potential new drug candidates for RA/OA with two of them having anti-inflammatory potential

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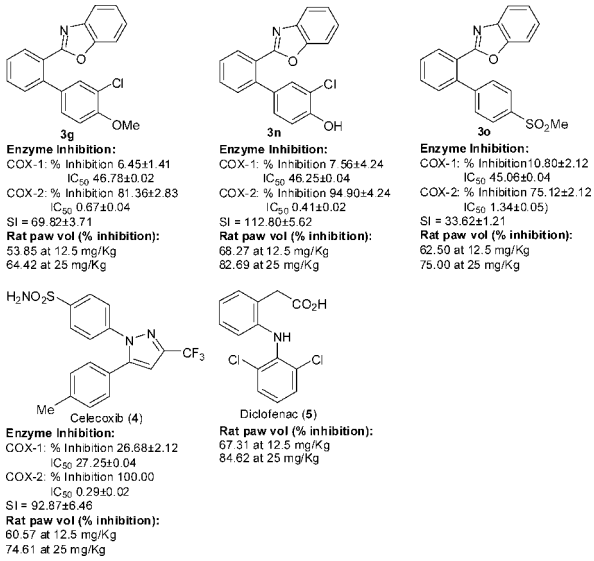

Figure 2. Comparison of the COX enzyme inhibitory activity/selectivity and anti-inflammatory potency of **3g**, **3n**, and **3o** with those of the clinically used NSAIDs **4** and **5**.

comparable to the clinically used diclofenac and celecoxib and the other being better than these therapeutic agents.

Design. Scaffold-hopping[27] has been a popular approach to discover structurally novel potent compounds with improved properties. The current therapeutic regime for RA is dominated by the 1,2-diaryl heterocycle[28] class of COX-2 selective inhibitors such as celecoxib, rofecoxib, valdecoxib, and etoricoxib commonly termed as coxibs generated through scaffold-hopping by heterocycle replacement of the nonselective inhibitor oxaprozin.[29] Thus, the structural modification of nonselective NSAIDs has been a proven strategy to evolve COX-2 selective inhibitors[29] as exemplified by transformation of the (i) nonselective flurbiprofen to its COX-2 selective diethoxy derivative, (ii) indomethacin to the corresponding ester/amide and reverse ester/amide for selective inhibition of COX-2, and (iii) diclofenac to the most highly COX-2 selective agent lumiracoxib. Under the present study we derived a topological model (Figure 1) that contains a central aromatic ring with adjacently disposed heteroaryl and aryl rings. The heteroaryl moiety is represented by benzoxazole (in analogy with the central oxazole ring of the prototype oxaprozin), and the other aryl ring provides scope for diversity generation through incorporation of various substituents/functionalities. The new pharmacophore model was rationalized through computational studies (3D QSAR modeling) that indicated it to be a ligand selective for the COX-2 active site with the ligand−receptor binding interaction energy comparable to that of the COX-2 selective NSAID celecoxib and exhibited docking pose in the COX-2 active site similar to that of celecoxib, rofecoxib, and etoricoxib.[29]

Synthesis. The compounds **3a**−**m** belonging to the scaffold **II** were synthesized in 60−78% yields by Suzuki cross-coupling reaction of 2-(2-bromophenyl)-benzoxazole **1**[30,31] with the arylboronic acids **2a**−**m** bearing various functional groups, e.g., OCH_3, SCH_3, OC_5H_9, O^iPr, OCH_2Ph, CF_3, CHO, CN, and Cl (Scheme 1).

Biological evaluation. The compounds **3a**−**m** were subjected to COX-1 and COX-2 enzyme inhibitory assay (Table 1).

While, in general, all of these inhibited the COX enzymes, **3g** was the most potent and selective inhibitor of COX-2. The analogous *O*-benzylated compound **3i** that exhibited poor enzyme inhibitory potential on conversion to the hydroxyl derivative **3n** (Scheme 2) showed COX-2 inhibitory activity and selectivity exceedingly superior to those of **3i** and better than that of **3g**. The transformation of **3f** to the corresponding methane sulfonate derivative **3o** (Scheme 2) drastically increased the COX-2 inhibitory potency and selectivity.

The in vivo anti-inflammatory activity of **3g**, **3n**, and **3o** was evaluated (Table 2) by carrageenan-induced rat paw edema using Wistar albino rats[32] at two different doses (12.5 and 25 mg/kg).

The anti-inflammatory activity of **3g** and **3o** was found to be comparable to that of the COX-2 selective NSAID **4**, and the traditional (nonselective inhibitor COX-1 and COX-2) NSAID diclofenac **5** and **3n** proved to be more potent than **4** and **5** as anti-inflammatory agent (Figure 2).

The COX-2 selectivity of **3g**, **3n**, and **3o** was rationalized through computational studies (3D QSAR).[29] All of these three novel COX-2 inhibitors were found to be very good ligands of the COX-2 (6COX) active site with docking score comparable to that of celecoxib. The compounds **3g**, **3n**, and **3o** exhibited a V-shaped docking pose similar to that of celecoxib, rofecoxib, and etoricoxib in the COX-2 active site and did not exhibit any significant interaction with the COX-1 (3KK6) active site that justified their COX-2 selectivity.

The other derivatives (**3b**−**o**) were also docked inside the active site of COX-2 , and all were observed to have similar V-shaped docking poses.[29] The in silico (docking) studies support the better activity/selectivity of compounds **3g**, **3n**, and **3o** compared to the other benzoxazole derivatives (**3b**−**o**). The docking scores of **3g**, **3n**, and **3o** are higher than those of the remaining benzoxazoles and showed some distinct interactions with the active site of the COX-2 enzyme.[29] The compound **3g** showed weak interaction of the hydrogen atom of the methoxy group with the carbonyl (C═O) oxygen atom of Gln192. The compound **3n** showed hydrogen bonding interaction through the hydrogen atom of the hydroxyl group with the carbonyl (C═O) oxygen atom of Gln192 (O−H···O═C, Gln192, 3.0 Å). The compound **3o** showed strong hydrogen bonding interaction through the oxygen atom of SO_2Me group with the hydrogen atom of the C═NH of the guanidine moiety of Arg513 (S═O···H−N, Arg512, 2.8 Å). The marketed COX-2 selective drugs, having methyl sulfonyl moieties, e.g., rofecoxib and etoricoxib, were docked into the active site of COX-2, and similar types of interactions were observed. The devoid of the amino acid Arg513 in COX-1 provides the advantage for COX-2 selectivity. However, the corresponding interactions in the cases of **3b**−**o** are weak.

In conclusion, a new pharmacophoric model for selective inhibition of COX-2 has been devised through scaffold-hopping to generate novel compounds for controlling inflammation as potential therapeutic agents for the treatment of RA and OA. The synthesized compounds exhibited COX inhibitory potential, and three of them emerged as selective in vitro COX-2 inhibitors with in vivo anti-inflammatory potency better than that of the standard anti-inflammatory drugs diclofenac and celecoxib. The COX-2 selectivity of the newly generated compounds representing a novel structural scaffold was rationalized through computational studies (3D QSAR) that revealed the various noncovalent interaction with the COX-2 (6COX) active site. The lack of any significant interaction with

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the COX-1 (3KK6) active site and V-shaped docking pose of these three COX-2 inhibitors as well as of celecoxib, rofecoxib, and etoricoxib established their COX-2 selectivity. Thus, the present work unfolds a new chemical class and next generation selective COX-2 inhibitors as anti-inflammatory agents. In view of the adverse side effect of some of the existing COX-2 selective anti-inflammatory drugs that led to the withdrawal of some of them from the market, the present findings of new anti-inflammatory scaffold should help finding more effective therapeutics for the treatment of RA and OA. With the newer clinical indication of NSAIDs with cancer risk reduction in chronic dialysis patients, this new generation of COX-2 selective inhibitors may also provide newer and alternate cancer therapeutics.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data and scanned spectra (^{1}H and ^{13}C NMR, HPLC); 3D QSAR. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(A.K.C.) Tel: 91-(0)-172 2214683. Fax: 91-(0)-172 2214692. E-mail: akchakraborti@niper.ac.in or akchakraborti@rediffmail.com.

Present Address

[‖]Department of Pharmacology, School of Pharmaceutical Sciences, Shoolini University, Solan 173212, HP, India.

Author Contributions

A.K.C. conceived the project, designed the experiments, analyzed the data, and wrote the paper. K.S., S.K.G., R.K., and P.P. performed the synthesis and enzyme assays. V.S.M. and U.C.B. were associated with the enzyme inhibitory studies. R.G. performed the in vivo experiments.

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Notes

The authors declare no competing financial interest.

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