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Design, Synthesis and Biological Evaluation of 2 (((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio)benzo[d]oxazoles: New Antiinflammatory and Antioxidant Agents

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The oxadiazole linked benzoxazoles derivatives were designed using scaffold hopping approach and their molecular level interactions with both isoforms of cyclooxygenases, Cyclo OXygenase-1 (**COX-1**) and CycloOXygenase-2 (**COX-2**), were carried out using docking protocols. Mini library of oxadiazole linked benzoxazoles derivatives were synthesized and tested for their COX inhibitory activity by *in vitro* enzyme assay. The results indicated that compound 2-(((5-(2,4-dichlorophenyl)-1,2,4-oxadiazol-3-yl)methyl)thio)benzo[d]oxazole **(5 h)**, 2-(((5-(4-nitrophenyl)-1,2,4-oxadiazol-3-yl)methyl)thio)benzo[d]oxazole **(5 j)** and 2-(((5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl) methyl)thio)benzo[d]oxazole **(5 k)** selectively inhibited COX-2 enzyme. The compound **5 j** exhibited strong selective COX-2 inhibition (IC_{50} = 4.83 μM) followed by compound **5 h** (IC_{50} = 5.10 μM) and **5 k** (IC_{50} = 6.70 μM). The *in vivo* anti-inflammatory activity of compound **5 j** was found to have better efficiency than the standard drug **Ibuprofen** at both 3 h and 5 h intervals. The significant molecular level interactions with respect to position of benzoxazole, 1,2,4-oxadiazole and substituted aryl groups in both **COX-1** and **COX-2** active sites were discussed. Subsequently, 2,2-diphenyl-2-picrylhydrazyl **(DPPH)** anti-oxidant activity was also checked for all the compounds and the compound **5 j** was found to be good anti-oxidant among the series with an IC_{50} of 34.5 μM.

Introduction

Inflammation is body's natural defence mechanism in response to the injury and infection. The uncontrolled inflammatory cascades are responsible for various diseases including rheumatoid (RA), osteoarthritis (OA), inflammatory bowel disease, diabetic neuropathy, inflammation mediated by tumour initiation and progression etc.[1–3] The non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used drugs to alleviate pain and inflammation. The NSAIDs exert their anti-inflammatory action by inhibiting cyclooxygenase (COX) enzymes and they are of two types i.e., COX-1 and COX-2. The COX-1 enzyme, produced by kidney and gastrointestinal tract (GIT) is constitutive, while COX-2 enzyme is inducible and expressed at the site of injury.[4–7] Many of the traditional NSAIDs, such as aspirin, naproxen, ibuprofen and diclofenac are non-selective COX inhibitors which exert notorious side effects, which include GI toxicity, nephrotoxicity and blood thinning properties.[8,9] Therefore preferential inhibition of COX-2 over the COX-1 would be beneficial for the better treatment of inflammation. This led to the development of COX-2 inhibitors, generally known as coxibs, as another important class of NSAIDs.[10] The COX-2 inhibitors, recently celecoxib and valdecoxib were withdrawn from the market due to their severe cardiovascular side effects.[11] Thus the development of novel anti-inflammatory scaffolds with selective COX-2 inhibition is today's need. The potentials of COX-2 inhibitors in cancer therapy, diabetes, kidney dysfunction further proven the importance of concurrent research.[3,12–13]

Benzoxazoles are an important class of bicyclic ring system with multiple biological applications. The bicyclic benzoxazole ring system was well established anti-inflammatory agent that is present in Flunoxaprofen, Benoxaprofen and PF-469327 (**I**, **II**).[14–16] PF-469327, a potential *m*PGES-1 inhibitor is in clinical developmental phase, while Benoxaprofen was withdrawn from the market due to hepatotoxicity, as the drugs have carboxylic function and form a reactive acyl glucuronides.[17,18] The further clinical application of Flunoxaprofen has also been stopped, although the drug is less toxic than Benoxaprofen. We reported herein, the design of the novel benzoxazole analogues as selective COX-2 inhibitors by scaffold-hopping approach.[18] The rationale design of the benzoxazole scaffold is given in **Figure 1**. Paramashivappa *et al.*, reported 2-[(2-methoxy-6-pentadecylphenyl)-methyl]-thio]benzoxazole (**III**) as selective COX-2 inhibitor (IC_{50} = 2.77 μM) that contain benzoxazole nucleus linked through the methylthio (-SCH_2-) linkage to

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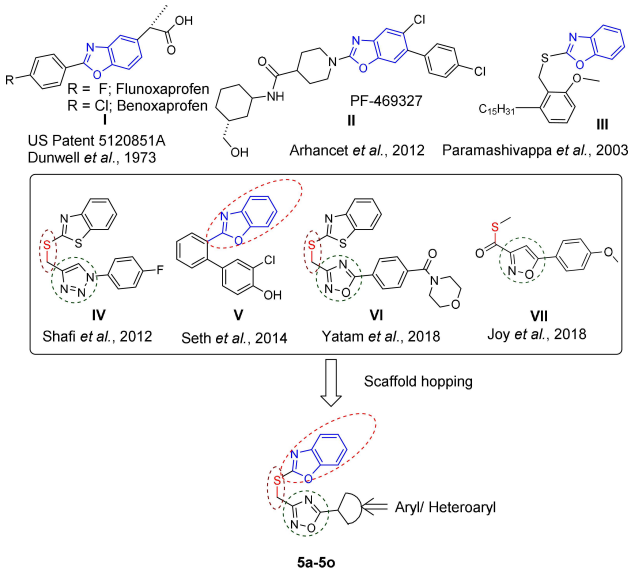


Figure 1. Design of scaffold for selective COX-2 inhibition through the scaffold-hopping approach.

aryl function.[19] Shafi *et al.*, reported, 2-((1-(4-Fluorophenyl)-1H-1,2,3-triazol-4-yl)methylthio)benzothiazole (**IV**) selective COX-2 inhibitor (COX-2/COX-1 = 0.44) in which benzthiazole nucleus was attached to aryl linked triazole through the methylthio (-SCH_2-) linkage.[20] Similarly Seth *et al.*, reported, 2′-benzoxazol-2-yl-3-chlorobiphenyl-4-ol, selective COX-2 inhibitor (IC_{50} = 0.41 ± 0.02 μM) (**V**).[21] Earlier our research group reported the (4-(3-((benzo[d]thiazol-2-ylthio)methyl)-1,2,4-oxadiazol-5-yl)phenyl) (morpholino)methanone (**VI**) as selective COX-2 inhibitor (IC_{50} = 5.0 μM).[22] The molecular dynamic studies of potent, selective COX-2 inhibitors proved S-methylated isoxazoles as essential scaffold for anti-inflammatory area (**VII**).[23] In the present investigation the benzoxazole linked oxadiazole analogues showed enhanced docking scores with more COX-2 selectivity than the reported benzothiazoles.[22] The comparative docking scores of some of the similar compounds are shown in **Table 1S** (Supplementary information).

Results and discussion

Rationale design and molecular docking studies

The benzoxazoles were reported to have good anti-inflammatory activity by targeting COX-2 isoenzyme.[19–21] The, 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)this)benzo[*d*]oxazoles (**5a-5o**) reported herein in this paper was designed by scaffold hopping approach (**Figure 1**). The benzoxazole analogs were docked in the therapeutic functional sites of COX-1 (Flurbiprofen (PDB: 1CQE)) and COX-2 (Mefenamic acid (PDB: 5IKR) active sites, and the docking scores are provided in **Table 1**. The newly designed benzoxazoles (**5a-o**) were found to be accommodated in both COX imperative sites. With respect to COX-2 docking experiment, three diverse types of binding orientations were observed. Accordingly, the compound **5j**, **5m**, **5k**, **5l**, **5g**, **5e**, **5c**, **5n** and **5f** (**Figure 2a**) (indicated with light pink stick residues) were depicted to have ideal alignments within the COX-2 site, the benzoxazole ring displayed π-π connections with Tyr355 and the N atom of benzoxazole depicted hydrogen bond with the guanidine of Arg120. Consecutively, the oxadiazole nucleus subsidized the π-cation interface with Arg120. Though, the binding positioning of **5h**, **5a**, **5d**, **5i**, **5b** and **5o** (**Figure 2b**) (indicated with light blue stick residues) at the COX-2 site is observed as inverse but, the π-π and hydrogen bond interactions of oxadiazole nucleus with Arg120 and Tyr355 might stabilize them well in the cavity. The heteroaryl ring displayed π-cation interactions with Aryl 120. Whereas the most of the newly designed analogs exhibited monopoly type of interactions with the COX-1 imperative site (**Figure 3a**). The oxadiazole nucleus found to have a good π-π

Table 1. The docking score of the 2-(((5-aryl1,2,4-oxadiazol-3-yl)methyl)thio)benzo[*d*]-oxazoles (**5a-5o**).

Ligand	COX-1		COX-2	
	Dock score	MMGBSA dG Bind	Dock score	MMGBSA dG Bind
5a	-7.911	-63.63	-8.044	-77.99
5b	-9.091	-64.81	-7.664	-76.30
5c	-7.386	-65.11	-8.832	-65.35
5d	-7.454	-71.45	-8.033	-80.05
5e	-8.205	-78.79	-8.960	-83.84
5f	-8.219	-75.97	-7.632	-80.30
5g	-7.606	-69.90	-8.976	-69.00
5h	-7.889	-75.24	-8.324	-82.68
5i	-7.637	-71.01	-7.808	-77.87
5j	-7.999	-73.80	-9.393	-75.94
5k	-7.871	-68.82	-9.223	-69.18
5l	-8.471	-85.45	-9.116	-91.28
5m	-8.007	-71.00	-9.240	-74.99
5n	-7.184	-66.26	-8.449	-74.00
5o	-6.701	-64.97	-7.513	-75.95
MFA	-7.902	-63.63	-9.576	-57.36
FBP	-12.090	-54.91	-8.108	-22.90

MFA-Mefanamic acid; FBP-Flurbiprofen

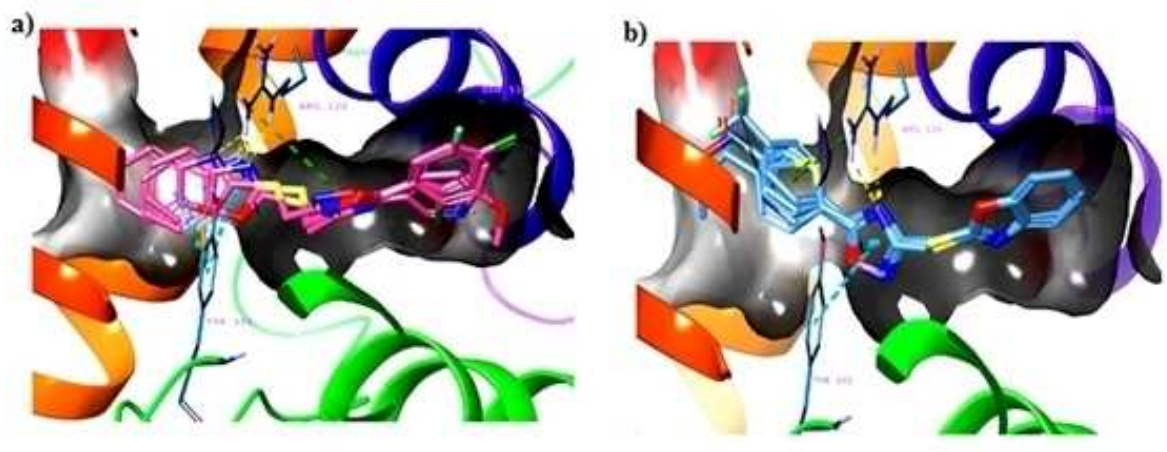


Figure 2. a) SET-1 compounds interactions with COX-2 active site residues; **b)** SET-2 compounds interactions with COX-2 active site residues

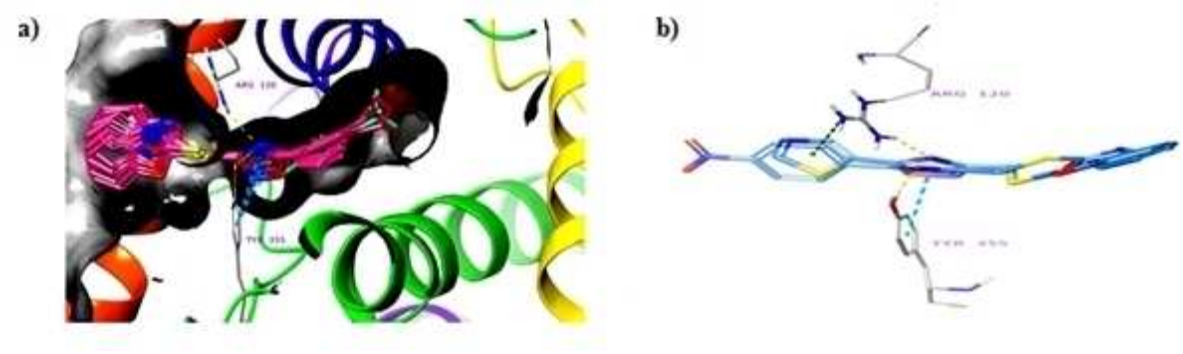
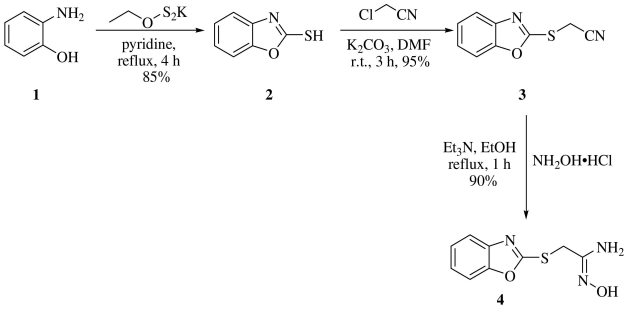


Figure 3. a) SET-1 compounds interactions with COX-1 active site residues; **b)** Compound **5a** and **5o** interactions with COX-1 active site residues

network with Tyr355 along with side chain hydrogen bond (indicated with light pink stick residues) except compound **5a** and **5o**. The **5a** and **5o** have shown opposite binding pattern at the COX-1 site and π-π, π-cation and hydrogen bond with Arg120 and Tyr355 (**Figure 3b**) (indicated with light blue stick residues). We have clearly observed the predominant binding abilities of newly designed compounds at the COX-2 active site than COX-1. The oxadiazole might play a significant role in the COX-2 selectivity because it has displayed fundamental interactions with COX-2 active site residues irrespective of its binding position, whereas the less extent of interaction network of benzoxazoles with COX-1 site might not rendered them towards it.



Scheme 1. Synthetic protocol of 2-(1,3-benzoxazol-2-ylsulfanyl)-*N*′-hydroxyethanimidamide.

Chemistry

To pursue our objective, we initially prepared the starting material, 2-(1,3-benzoxazol-2-ylsulfanyl)-*N*′-hydroxyethanimidamide (**4**) from commercially available 2-aminophenol (**1**)(**Scheme 1**). This precursor **1** was treated with potassium ethyl xanthate in presence of pyridine to afford intermediate benzo [*d*]oxazole-2-thiol (**2**) in 85% yield.[24] Further the compound, **2** was treated with chloroacetonitrile and K_2CO_3 as base in DMF produced, (1,3-benzoxazol-2-ylsulfanyl)acetonitrile (**3**) in excellent yield.[25] Next, desired starting compound **4** was achieved from compound **3** using hydroxylamine hydrochloride and triethylamine in presence of ethanol in 90% yield. After synthesizing precursor **4**, we focused our attention on synthesis of 2-mercapto benzoxazole linked 1,2,4 oxadiazole derivatives (**5a to 5o**). In this regard, we examined the reaction with a variety of both electron-withdrawing and electron-donating substituents at different aromatic positions of carboxylic acid.

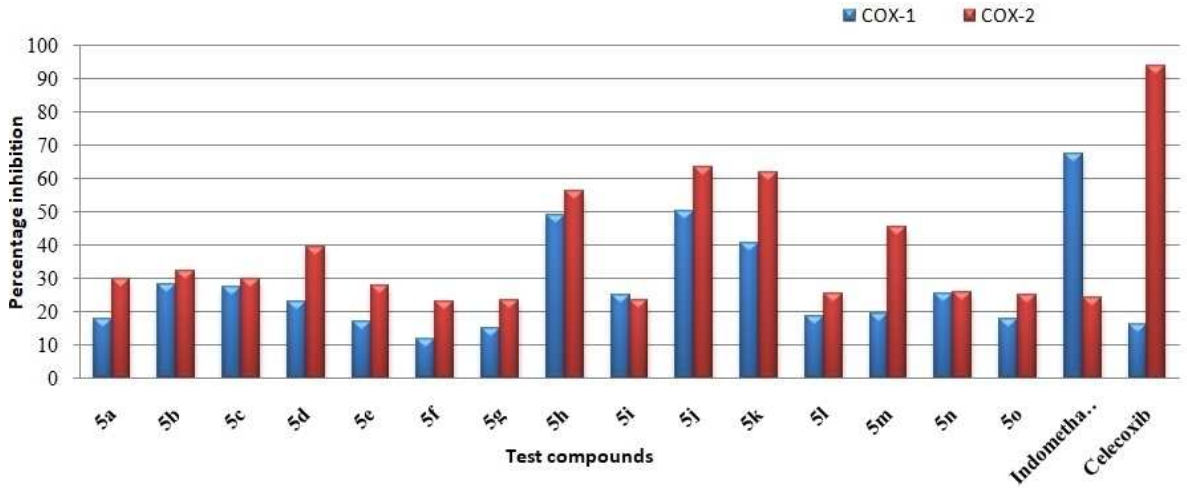
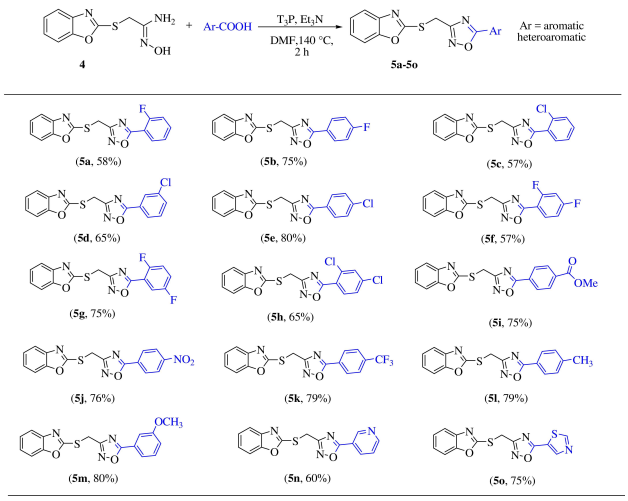


Figure 4. *In vitro* COXs inhibitory activity and selectivity of 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio)benzo[*d*]oxazoles (**5 a-5 o**).

Both electron-withdrawing and donating groups were well tolerated irrespective of the nature of the substituent of the carboxylic acid produced the corresponding products with moderate to good yields. To diversify the present methodology, heteroaromatic substrates were used to realize the expected derivatives 2-mercapto benzoxazole linked 1,2,4 oxadiazole derivatives in moderate yields (**5 n** and **5 o**) (**Scheme 2**). The



Scheme 2. Synthetic protocol of 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio) benzo[*d*]oxazoles (**5 a-5 o**).

percentage yields of the title compounds ranging from 57 to 80% after recrystallization. All the benzoxazoles were further characterized by infrared (IR), nuclear magnetic resonance (^{1}H NMR &^{13}C NMR) and mass spectral studies.

In vitro COX-1 and COX-2 inhibitory activity

The 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio)benzo[*d*]oxazoles (**5 a-5 o**) were evaluated for their *in vitro* COXs inhibitory activity using standard protocol described by Copeland *et al.*, 1994.[26] The title compounds (**5 a-5 o**) were evaluated at 10 μM drug concentrations and the percent inhibitions were recorded. The *in vitro* COXs inhibitory activity and selectivity is given in **Table 2** and **Figure 5**. The compounds **5 h**, **5 j**, **5 k** and **5 m**

Table 2. *In vitro* COX-1 and COX-2 assay of 2-(((5-aryl-1,2,4-oxadiazol-3-yl) methyl)thio)-benzo[*d*]oxazoles (**5 a-5 o**)

Test Compound	Percentage of COX Inhibition at 10 (μM)		Selectivity COX-1/ COX-2	COX Inhibition (IC_{50} μM)	
	COX-1	COX-2		COX-1	COX-2
5a	17.81	29.8	0.60	NT	NT
5b	28.20	32.29	0.87	NT	NT
5c	27.76	29.97	0.92	NT	NT
5d	23.02	39.6	0.59	NT	NT
5e	17.23	27.96	0.61	NT	NT
5f	11.81	23.32	0.50	NT	NT
5 g	15.07	23.51	0.64	NT	NT
5 h	49.01	56.54	0.86	NT	5.10
5i	25.21	23.63	1.06	NT	NT
5j	50.19	63.67	0.78	NT	4.83
5k	40.83	61.89	0.65	NT	6.70
5 l	18.86	25.6	0.73	NT	NT
5 m	19.54	45.65	0.42	NT	NT
5n	25.59	25.85	0.98	NT	NT
5o	17.86	25.24	0.70	NT	NT
Indomethacin	67.40	24.23	2.78	0.21	13
Celecoxib	16.2	94.11	0.17	31	0.34

showed significant COX-2 inhibitory activity at 10 μM concentrations with percent inhibition of 56.54, 63.67, 61.89, and 45.65 respectively. The selectivity ratio (COX-1/COX-2) of compound, **5 h** (0.86) was found to be maximum, followed by compounds,

5j (0.78) and **5k** (0.65). The study was further extended to examine the concentration-activity responses at different concentrations to determine the IC_{50} values for COX-1 and COX-2 and of compounds exhibiting potent COX inhibition. Indomethacin (COX-1 inhibitor), Celecoxib (selective COX-2 inhibitor) were used as a positive controls in the study (**Table 2**). For calculation of the IC_{50} (μM) values, compounds were tested at five different concentrations (5–50 μM). The selectivity ratio (SR values) was defined as % of inhibition of COX-1 / % of inhibition of COX-2. In the assay system, the IC_{50} values of celecoxib on COX-1 and COX-2 were found to be 31 and 0.34 μM, respectively, indicating that celecoxib is a selective COX-2 inhibitor. All compounds exhibited moderate to strong inhibitory effects on COX-1 and COX-2 activity (> 50%). The benzoxazoles, (**5h**, **5j**, **5k**) were found to be most potent against COX (>50% inhibition) and were found to be selective COX-2 inhibitor with an IC_{50} of 5.10, 4.83 and 6.70 μM respectively. Since benzoxazoles, **5h**, **5j** and **5k** were found to be selective COX-2 inhibitors, many of the unwanted adverse effect related to COX-1 inhibition can be prevailed over easily. The structure activity relationship was established with the COXs inhibitory data (IC_{50} in μM) indicates that the aryl group with 4-nitro substitution (**5j**) shows maximum *in vitro* COX inhibitory activity followed by aryl group with 2,4-dichloro (**5h**) and 4-trifluoromethyl (**5k**) substitution.

In vivo anti-inflammatory activity

The activities of benzoxazole analogs were confirmed as COX inhibitors by *in vitro* COX enzyme assay. The most active and COX-2 selective inhibitors (**5k**, **5j** and **5h)** were put forward for *in vivo* anti-inflammatory activity. The *in vivo* studies were evaluated by carrageen induced paw edema analysis as per the reported method (Winter *et al.*, 1962).[27] The *in vivo* anti-inflammatory activity of 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio) benzo[*d*]oxazoles, **5h**, **5j** and **5k** were carefully analysed after oral administration of precise amount (10 mg/kg^{-1}/ body weight) of the specified compounds (**Table 3**). The 3 h and 5 h intervals were set for the monitoring of anti-inflammatory responses, followed by induction of inflammation. The benzoxazole, **5j** and **5h** showed better *in vivo* anti-inflammatory activity than the standard drug Ibuprofen at both 3 h and 5 h time intervals. The compound **5k** displayed comparable anti-inflammatory response with respect to ibuprofen. The major anti-inflammatory profile was observed when *para* nitro functional group presents on the compound (**5j**). The dihalogenated derivative (**5h**) yielded slightly lower profile than **5j** but they both displayed escalating response in 5 h period. Whereas, the presence of *para* trifluromethyl group on **5k** rendered the activity, but the *in vivo* profile was not displayed as the other two active derivatives. However, all the tested compounds significantly exhibited rising anti-inflammatory response second interval and this is observed to be opposite with standard drug ibuprofen. Therefore, the obtained results were in agreement with the *in vitro* assay data.

Table 3. *In vivo* anti-inflammatory activity of some selective 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio)-benzo[*d*]oxazoles.

S. No	Compound	Change in Paw edema volume (ml) after drug treatment		Anti-inflammatory activity % of inhibition	
		3 h	5 h	3 h	5 h
1	Control	0.84 ± 0.168	0.83 ± 0.120	–	–
2	**5h**	0.39 ± 0.069	0.41 ± 0.040	77.4	76.3
3	**5j**	0.15 ± 0.066	0.16 ± 0.067	80.6	85.2
4	**5k**	0.41 ± 0.045	0.42 ± 0.055	65.4	68.9
5	Ibuprofen	0.25 ± 0.135	0.35 ± 0.155	73.3	64.4

DPPH antioxidant activity

All the benzoxazoles (**5a–5o**) were evaluated for the free radical scavenging activity as per the well-known reported method (Burits and Bucar, 2000).[28] The method was based on the theory, that the antioxidant reacts with 2,2-diphenyl-2-picrylhydrazyl (DPPH) and convert it to α,α-diphenyl-β-picryl hydrazine. The antioxidant activity of benzoxazoles was calculated as percent inhibition at 100 μM drug concentration and ascorbic acid was taken as standard drug. The benzoxazoles, **5b**, **5i**, **5j** and **5k** showed promising antioxidant activity with percent inhibition of 78.14, 67.90, 73.60 and 60.72, and remaining benzoxazoles showed less antioxidant activity with percent inhibition < 28.97 at 100 μM. Further IC_{50} was calculated for the benoxazoles having significant antioxidant activity at 100 μM. Among all, the benzoxazoles, **5j** (IC_{50} = 34.5 μM) was found to be potent anti-oxidant agents followed by benzoxazole, 5b (IC_{50} = 40.1 μM). The IC_{50} of benzoxazoles, **5k** and **5i** were found to be 56.0 and 60.7 μM respectively. The drug Ascorbic acid showed 90.02 percent inhibition at 100 μM and its IC_{50} was calculated as 20.9 μM. The antioxidant activity of benzoxazoles is given in **Table 4**. The benzoxazoles containing 4-nitro

Table 4. DPPH antioxidant assay of 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl) thio)-benzo[*d*]oxazoles (**5a-5o**).

S. No	Test Compounds	% of Inhibition at 100 (μM)	IC_{50} (μM)
1.	**5a**	25.84	NT
2.	**5b**	78.14	40.1
3.	**5c**	25.55	NT
4.	**5d**	20.33	NT
5.	**5e**	15.34	NT
6.	**5f**	26.66	NT
7.	**5g**	15.45	NT
8.	**5h**	19.47	NT
9.	**5i**	67.90	60.7
10.	**5j**	73.60	34.5
11.	**5k**	60.72	56.0
12.	**5l**	18.11	NT
13.	**5m**	28.97	NT
14.	**5n**	27.81	NT
15.	**5o**	17.45	NT
16.	**Ascorbic acid**	90.02	20.9

substitution (**5 j**) and 4-fluoro (**5 b**) on the terminal aryl ring showed maximum antioxidant activity followed by 4-trifluoromethyl substitutions (**5 k**) and 4-methylcarboxylate (**5 i**). The presence of 4-nitro group in the benzoxazole scaffold was found to be promising for the DPPH anti-oxidant activity.

Conclusions

A series of fifteen, 2-(((5-aryl-1,2,4-oxadiazol-3-yl)methyl)thio) benzo[*d*]oxazoles (**5 a-o**) were synthesized in satisfactory yield. The scaffold hoping approach design was applied to design the benzoxazoles and further molecular docking studies were carried out for imperative alignment of benzoxazoles at the Flurbiprofen (PDB: 1CQE) and Mefenamic acid (PDB: 5IKR) therapeutic functional sites. All these benzoxazoles were tested for *in vitro* COX-2 inhibitory activity. Some of the benzoxazoles, **5 h**, **5 j** and **5 k** were found to be selective COX-2 inhibitors and showed promising *in vivo* anti-inflammatory activity. Since none of these benzoxazoles exhibited COX-1 inhibition and hence many of the side effects usually observed with available NSAIDs related to COX-1 inhibition, can be avoided. Subsequently the benzoxazoles were tested for DPPH anti-oxidant activity. The benzoxazole, **5 j** was found to be potent antioxidant agent among the series. The biological potential of benzoxazoles reported in this paper validate the application of scaffold hoping approach design and we think, this study would be considered as a valuable starting point for further lead optimization to find more potent anti-inflammatory agents with improved pharmacokinetic and pharmacodynamic properties.

Supporting Information Summary

Supporting information files include the synthetic procedure for benzoxazole based 1,2,4-oxadiazole analogues, *In Vitro* assay against COX-1 and COX-2 enzymes, DPPH antioxidant assay and molecular docking studies on 3D structures of COX-1 and COX-2 enzymes. IR, ^{1}H NMR, ^{13}C NMR, and Mass spectra data of synthesized compounds were also added.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Anti-inflammatory agents · Antioxidant · Benzoxazole · COX Inhibition · DPPH Inhibition

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