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Green synthesis of therapeutically active 1,3,4-oxadiazoles as antioxidants, selective COX-2 inhibitors and their *in silico* studies

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ABSTRACT

A modest, competent and green synthetic procedure for novel coumarinyl-1,3,4-oxadiazolyl-2-mercaptobenzoxazoles **8i-t** has been reported. Analysis of the docked (PDB ID: 5IKR; A-Chain) poses of the compounds illustrated that they adopt identical conformations to the extremely selective COX-2 inhibitor. The biological outcomes as well as computational study suggested that the compounds originated to have elevated resemblance towards COX-2 enzyme than COX-1. The compounds **8i**, **8l**, **8q**, **8r**, **8s** and **8t** emerged as most potent and selective COX-2 inhibitors in contrast with Mefenamic acid. The selectivity index of **8l**, **8n** and **8r** was respectively found to be 33.95, 20.25 and 24.98 which manifested their high selectivity against COX-2. Interestingly, the compounds which were active as COX-2 inhibitors were also active as antioxidant agents.

Inflammation is a multifarious occurrence concerning humoral and cellular reactions through innumerable inflammatory mediators.[1] A great deal of attentiveness has been attracted by Cyclooxygenase (COX) enzymes as significant targets for drug pioneering due to their crucial role in prostaglandin biosynthesis. Inhibition of COX enzymes is a promising approach for the pharmacological intervention in inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most recurrently stipulated clinical tools due to their superior anti-inflammatory, analgesic and antipyretic effects which employ through the inhibition of COX-1 and COX-2 however, COX-1 is inhibited more vigorously than COX-2. NSAIDs are predominantly used for diminishing pain and inflammation in osteoarthritis, rheumatoid arthritis and arthritis of systemic lupus erythematosus, psoriasis and other seronegative spondyloarthropathies.[2] Nevertheless, their therapeutic benefit is habitually limited by troublesome side effects at the gastrointestinal level (mucosal damage, bleeding). Profound investigation divulged that inhibition of COX-2 is associated with anti-inflammatory and analgesic properties, whereas COX-1 executes a significant role in physiological homeostasis. Subsequently, a new genre of selective COX-2 inhibitors (coxibs) had been evolved.[3] While, the selective COX-2 inhibitors have not exhibited any gastrointestinal side effects, they endure from the drawbacks of cardiovascular complications that preceded to the withdrawal of Rofecoxib (Vioxx) and Valdecoxib (Bextra) from the market in 2004 and 2005, respectively.[4,5]

Heterocycles encompassing five-membered oxadiazole nucleus procure a miscellany of useful biological consequences such as anti-edema, antioxidant and anti-inflammatory activities. 1,3,4-Oxadiazoles exhibit anti-inflammatory activity by virtue of dual mechanism i.e., their enzyme inhibiting properties for both *cyclooxygenase* and *5-lipooxygenase* to bring down gastric ulcer formation.[6–9] During the last decade 686 patent applications concerning to drug discovery program have been filed on oxadiazole scaffold.[3] For the treatment of cancer and cystic fibrosis the valuable privileges of the oxadiazole scaffold such as Zibotentan and Ataluren respectively are enduring clinical trials with respect to the drug discovery.[10] In recent years there has been a massive analysis on the diverse set of oxadiazoles among which several such scaffolds were found to possess an extensive spectrum of pharmacological activities.[11]

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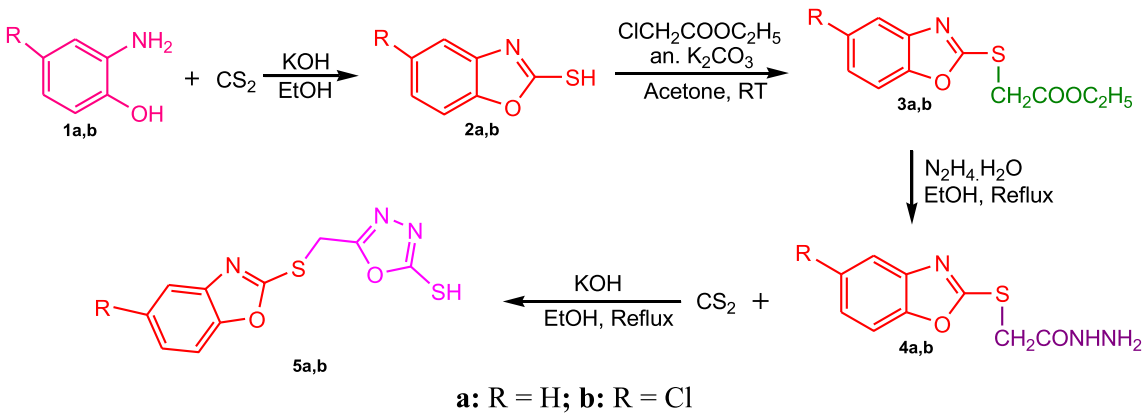
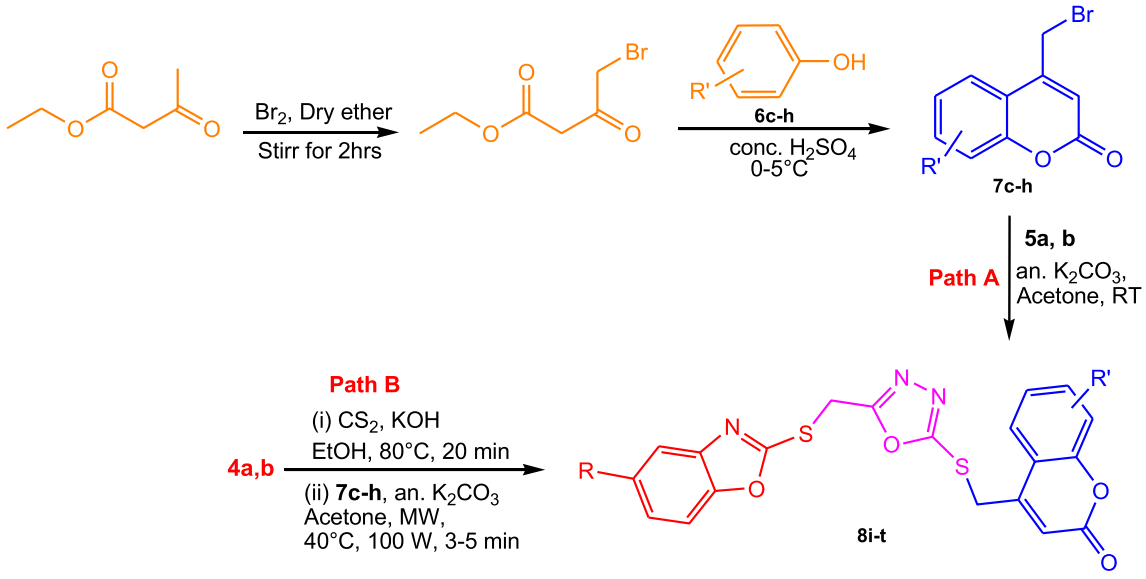


Scheme 1. Synthesis of 1,3,4-oxadiazole intermediates 5a,b.



Scheme 2. Synthetic strategy for the fabrication of compounds **8i-t**.

Reactive oxygen species (ROS) such as superoxide, singlet oxygen, hydroxyl radical and hydrogen peroxide produced under oxidative stress damage the lipids, proteins and DNA, causing serious health problems such as cancer, inflammation, cardiovascular and neurodegenerative disorders.[12] Besides, radical reactions play a considerable role in the evolution of life confining habitual diseases such as cancer, ageing, diabetes, arteriosclerosis and others. Antioxidants are molecules, natural or synthetic, accomplished of interrelating with free radicals and impeding their chain reactions before imperative vital molecules are harmed. Thus, they are lately formulated as the drug candidates to retort these multifarious diseases such as carcinogenesis, inflammation, atherogenesis and ageing in aerobic organisms.[13] Interpretation of these outcomes, it was deemed of concern to incorporate the synthesis of 1,3,4-oxadiazole derivatives, anticipating to seize promising antioxidant activity.

Prior studies have revealed that pharmacophores comprising of benzoxazole moiety have incredible biological activities encompassing anti-inflammatory.[14] Coumarins form an influential genre of compounds, that manifest a range of therapeutic activities including anti-inflammatory and antioxidant.[15,16] A variety of coumarin-coupled derivatives are predicted as controllers of the lipoxygenase and cyclo-oxygenase pathways of arachidonate metabolism.[17–19]

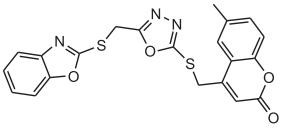
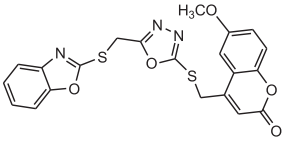
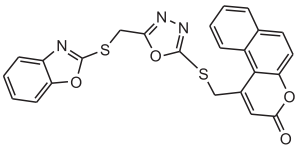
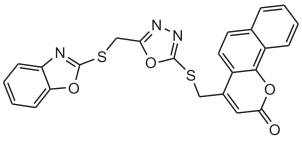
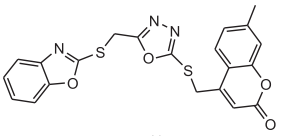
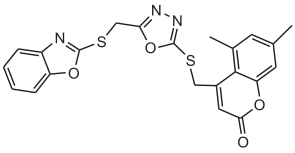
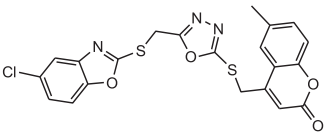
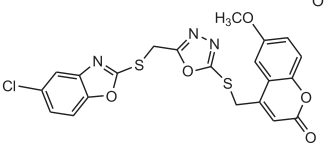
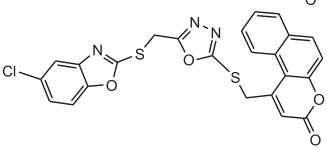
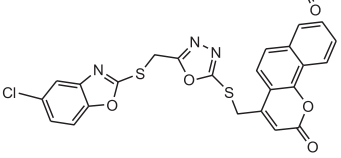
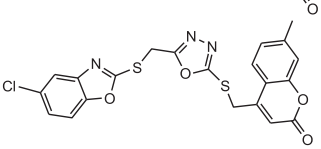
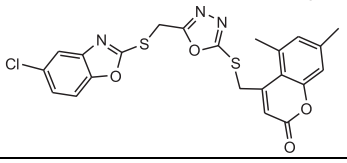
Microwave irradiation (MWI) procedure has been the biggest advantage in the target synthesis due to its direct transfer of heat into the reaction mixture, consequently reducing the reaction times. Often, a few minutes of microwave irradiation is sufficient for a reaction that conventionally requires several hours for accomplishment.[20] Additionally, it provides supremacy such as accelerating the inert transformations, ecologically feasible conditions, higher yields and vigorously encourage the cyclocondensation reaction.[21]

Results and discussion

The starting compounds **4a-b** and the **5a-b** were prepared according to the Scheme 1. The title compounds (**8i-t**) were synthesized by employing conventional (Scheme 2, **Path A**) as well as microwave irradiation technique (Scheme 2, **Path B**). In routine way, the compounds were obtained in a stepwise manner which incorporates the preparation of 2-mercapto benzoxazole from substituted 2-amino phenols. Mercacapto benzoxazole is then esterified by the treatment of ethylchloroacetate followed by the reaction with hydrazine to produce hydrazine carboxamide (acid hydrazide). Intramolecular cyclization of **4a-b** under strong basic conditions with carbon disulfide furnished the key intermediary **5a-b** in good yields (68–70%). Ultimately, the reaction of **5a-b** with proper electrophilic halides yielded the title compounds **8i-t** in admirable yields.

We were interested in exploring the most efficient and user-friendly protocol. Hence, aiming to intensify the yield, we refluxed the reaction

Table 1
Title compounds **8i-t** and the comparison of conventional and microwave methods.

Entry	Structures	Conventional		Microwave	
		Time (hrs)	Yield (%)	Time (min)	Yield (%)
8i		10	72	14	92
8j		11	66	16	85
8k		11	65	15	86
8l		12	68	14	82
8m		11	70	15	87
8n		12	65	15	90
8o		12	67	15	92
8p		12	64	14	78
8q		12	68	14	84
8r		11	63	13	80
8s		10	67	15	88
8t		11	72	15	90

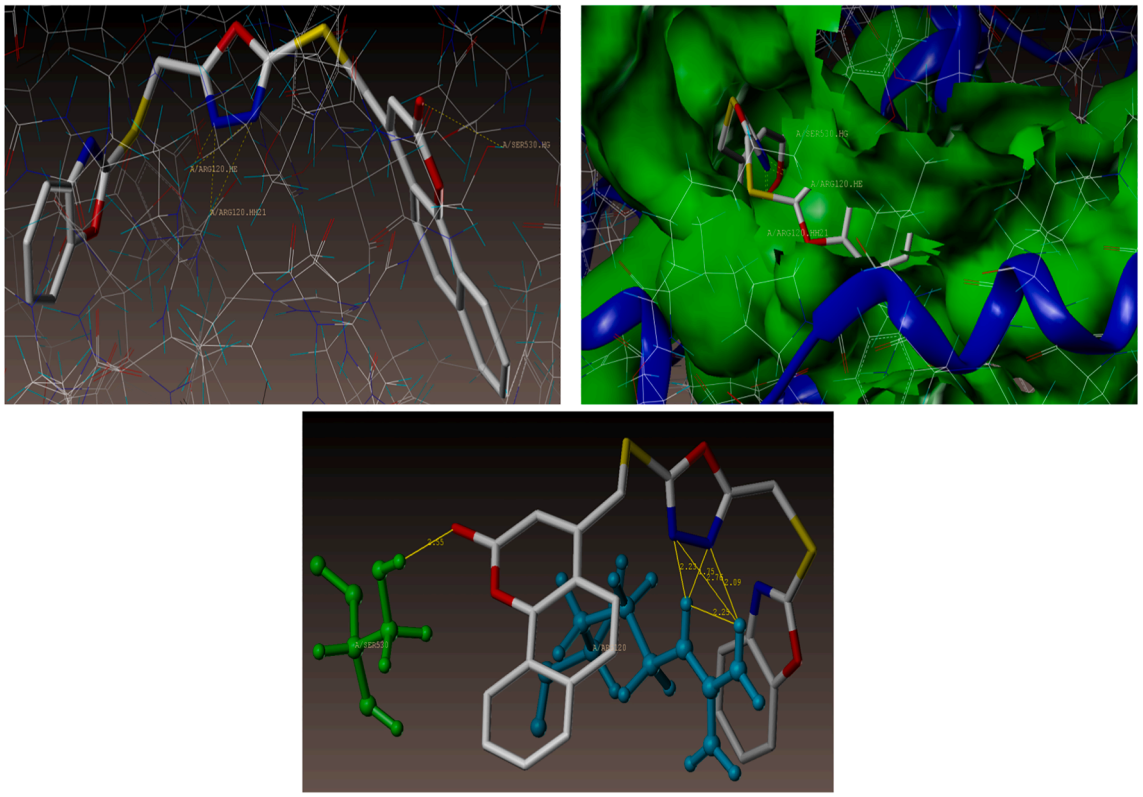


Fig. 1. Interaction of **8l** at the binding site of the enzyme (PDB ID: 5IKR).

mixture of the compounds **5a-b** and **7c-h** which resulted into the reduced reaction time for completion of the reaction. The desired product was obtained in 2–3 h with moderate yield. The diminished reaction time encouraged us to proceed with the microwave synthesis approach where the heat is directly transmitted to the contents of the reaction mixture. Hence, a mixture of the compound **4a-b**, carbon disulphide and potassium hydroxide in ethanol were taken in a sealed glass vial (10 ml) and irradiated under microwave (MW) at 100 W (60 °C) for 10 min. The excess ethanol was distilled off to get **5a-b** and substituted bromomethyl coumarins **7c-h** were added to the same reaction mixture in acetone followed by anhydrous K_2CO_3 and irradiated again at 100 W (40 °C). The desired product was formed with significantly diminished reaction time and enhanced yield. The non-classical reaction (MWI) rates were faster than usual heating conditions (Table 1).

Compounds were docked into the active site of both the human COX-2 enzyme (PDB: 5IKR) and the Ovine COX-1 (PDB code: 4O1Z) as a means to elucidate the relationship between structure of the compounds,

Table 2
Surflex Docking score (kcal/mol) of the derivatives on PDB ID: 5IKR.

Compounds	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	Chem Score[g]
5IKR_Ligand	7.63	−1.16	1.35	−133.442	−47.85	−180.07	−35.73
8l	9.51	−2.17	1.08	−145.411	−64.48	−340.71	−44.11
8t	8.78	−2.41	1.15	−132.381	−69.26	−343.13	−37.54
8n	8.41	−4.47	1.08	−133.934	−79.54	−354.29	−34.83
8s	8.29	−1.95	1.11	−127.883	−58.41	−308.76	−37.43
8p	8.19	−2.53	2.07	−126.404	−73.55	−320.05	−37.30
8m	8.18	−2.01	1.30	−120.642	−63.79	−304.18	−36.14
8i	7.32	−2.41	0.79	−123.160	−59.28	−311.92	−35.20
8j	7.08	−2.00	2.12	−112.385	−95.90	−273.18	−36.47
8r	7.04	−2.14	1.44	−139.314	−94.76	−326.28	−43.39
8o	6.99	−3.33	0.81	−132.495	−37.82	−352.52	−33.80
8k	6.39	−4.03	1.17	−129.691	−75.03	−326.43	−39.35
8q	4.17	−5.04	0.30	−142.887	−49.56	−334.41	−37.44

Negative numbers indicate penetration.

[a] CScore (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.

[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable.

[c] Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.

[d] D-score for charge and van der Waals interactions between the protein and the ligand.

[e] PMF-score indicating the Helmholtz free energies of interactions for protein–ligand atom pairs (Potential of Mean Force, PMF).

[f] G-score showing hydrogen bonding, complex (ligand–protein), and internal (ligand–ligand) energies.

[g] Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.

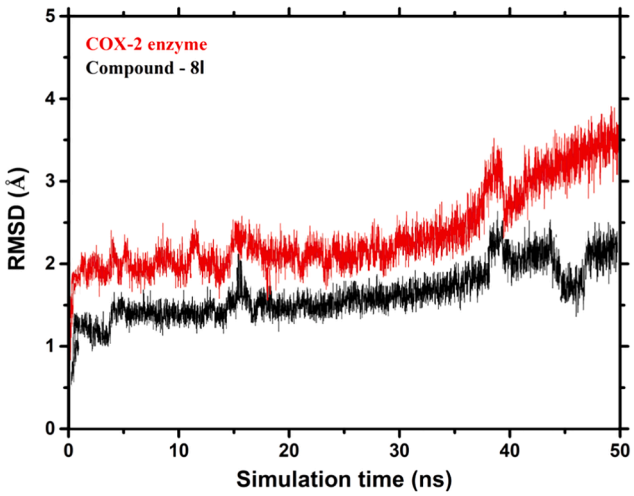


Fig. 2. RMSD of COX-2 enzyme and compound **8l**.

Table 3
COX-1/COX-2 inhibitory activity of the compounds 8i-t.

Compound	COX-1 (IC_{50} μg/mL)	COX-2 (IC_{50} μg/mL)	Selectivity Index
8i	245.93 ± 1.36	19.95 ± 0.91	12.32
8j	104.24 ± 0.86	32.93 ± 1.35	3.16
8k	106.82 ± 1.16	24.59 ± 1.21	4.34
8l	435.26 ± 1.02	12.82 ± 0.98	33.95
8m	87.26 ± 3.52	23.74 ± 1.61	3.67
8n	506.80 ± 2.32	25.02 ± 1.14	20.25
8o	206.13 ± 2.62	54.42 ± 0.86	3.78
8p	576.87 ± 4.16	44.54 ± 2.10	12.95
8q	326.35 ± 1.53	17.70 ± 1.76	18.43
8r	283.58 ± 2.16	11.35 ± 1.52	24.98
8s	145.18 ± 1.08	13.67 ± 2.72	10.62
8t	245.32 ± 0.96	13.23 ± 1.04	18.54
Mefenamic acid	186.34 ± 1.21	25.21 ± 1.16	7.39

COX-1 and COX-2 selectivity and their binding approaches. The compounds were comprised in hydrogen bonding interactions with the hydroxyl group of SER530 which have been reported to play a vital part in the inhibition of COX-2 enzyme.

The biological outcomes were well supported by the consequences of the computational study where the docked compounds were instituted to reinforce the examined inhibitory results. This suggests that the compounds are originated to have elevated resemblance towards COX-2 enzyme than COX-1 thus exhibiting utmost selectivity towards COX-2.

The docking study divulged that compound **8l** acts as good inhibitor of cyclooxygenase 2 enzyme. As portrayed in Fig. 1, compound **8l** fabricated five hydrogen bonding interactions at the dynamic location of the enzyme (PDB ID: 5IKR; A-Chain) out of which nitrogen atom present on the 3rd position of oxadiazole ring frames two bonding interactions with hydrogen atoms of ARG120 (-N—— H-ARG120, 2.09 Å; 1.75 Å), the nitrogen atom present on the 4th position of oxadiazole ring makes two interactions with hydrogen atoms of ARG120 (-N—— H-ARG120, 2.23 Å; 2.76 Å) and oxygen atom present on the 2nd position of chromene ring forms an interaction with hydrogen atom of SER530 (-O—— H-SER530, 2.55 Å).

The consensus score acquired in the range 4.17–9.51 implied that docking study was optimistic and the devised molecules manifested substantial affinity towards 5IKR_ligand. The docked poses revealed that the studied compounds have demonstrated the same kind of interaction with amino acid residue (SER530) as that of 5IKR_ligand. Eventually, we conclude that synthesized molecules preferentially bind to enzyme in comparison to the 5IKR_ligand (Table 2) which substantiates the observed preferential *in vitro* COX-2 inhibition. The interaction of all the

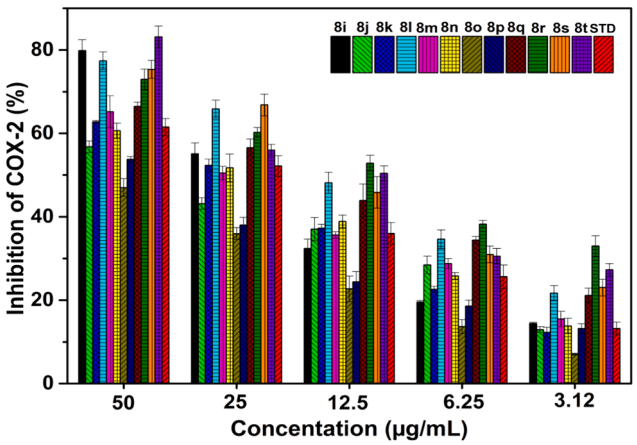


Fig. 3. COX-2 inhibition (%) of compounds 8i-t at different concentrations. *STD- Mefenamic acid.

compounds together, compound **8s** and Mefenamic acid (standard) with the enzyme (PDB ID: 5IKR; A-Chain), hydrophobic and hydrophilic amino acids of the enzyme surrounding the compounds **8l** and **8s** are provided in the supplementary information.

We have executed the computation of Root Mean Square Deviation (RMSD) which appraises resemblance flanked by two superimposed atomic coordinates. The acquired plot of RMSD v/s simulation time of COX-2 enzyme and compound **8l** is embodied in Fig. 2, which suggested that docking study was affirmative and our devised molecules manifested significant affinity towards 5IKR _ligand.

In vitro anti-inflammatory assay

The synthesized molecules were evaluated for *in vitro* COX-1 and COX-2 inhibition. The results obtained in the form of IC_{50} and are tabulated in Table 3. All the compounds were active as COX-1 and COX-2 inhibitors. It is evident from the obtained data that the synthesized compounds are more selective as COX-2 inhibitors than COX-1 in correlation with the docking studies, which revealed the title compounds prompted better uniformity towards COX-2 than COX-1. The compounds possessing halo substituent exhibited the most potent and discerning inhibition of COX-2. The compounds **8i** (methyl at C_6 position of the coumarin), **8l** (benzo at $C_{7,8}$ position of the coumarin), **8q** (Cl at C_5 position of benzoxazole and benzo at $C_{5,6}$ position of the coumarin), **8r** (Cl at C_5 position of benzoxazole and benzo at $C_{7,8}$ position of the coumarin), **8s** (Cl at C_5 position of benzoxazole and methyl at C_7 position of the coumarin) and **8t** (Cl at C_5 position of benzoxazole and methyl at $C_{5,7}$ position of the coumarin) emerged as most potent and selective COX-2 inhibitors with IC_{50} values of 19.95, 12.82, 17.70, 11.35, 13.67 and 13.23 μg/mL respectively (Fig. 3). The selectivity index of **8l**, **8n** and **8r** was found to be 33.95, 20.25 and 24.98 respectively, manifested their high selectivity against COX-2. Overall, this study paves a way for the development of 2,5-substituted 1,3,4-oxadiazoles as potent and selective COX-2 inhibitors.

In vitro anti-oxidant assay

The reactive oxygen species play conclusive role in inflammatory provisions. Oxidative stress is essential for gastrointestinal ulceration. The compounds possessing antioxidant activity besides anti-inflammatory activity may offer a feasible direction to more secure anti-inflammatory agents.[22]

Antioxidants that evince DPPH radical scavenging activity is progressively accepting consideration as they have been reported to encompass interesting anticancer, anti-ageing and anti-inflammatory activities. Accordingly, compounds with antioxidant property could be

Table 4
Antioxidant activity of the compounds 8i-t.

Compounds	IC_{50} (μg/mL)	Correlation coefficient
8i	24.04	0.989
8j	63.09	0.995
8k	45.86	0.986
8l	23.71	0.996
8m	49.87	0.995
8n	33.47	0.978
8o	48.69	0.989
8p	52.85	0.978
8q	26.78	0.990
8r	23.95	0.995
8s	27.73	0.992
8t	26.98	0.996
Ascorbic acid	25.74	0.989

*Correlation is significant at 0.010 level.

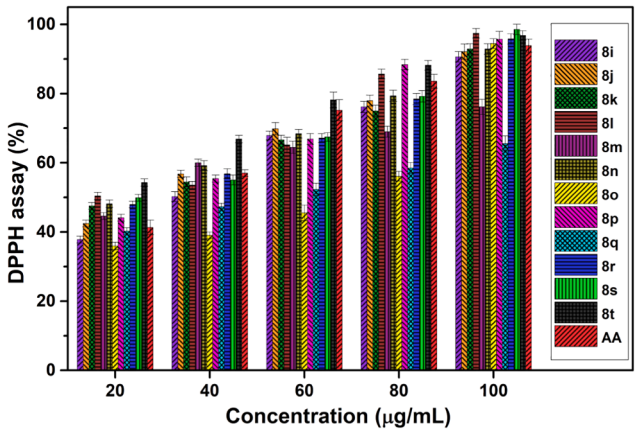


Fig. 4. Radical scavenging (%) of compounds 8i-t at different concentrations. *AA-Ascorbic acid.

anticipated to offer assurance in rheumatoid arthritis and inflammation and to lead to possibly viable drugs. Indeed, numerous non-steroidal anti-inflammatory drugs have been accounted to operate either as inhibitors of free radical fabrication or as radical scavengers.[23] The reducing abilities of the compounds **8i-t** were assessed using DPPH free radical scavenging assay in an iron free system. The scavenging activities of the compounds were determined and compared with standard ascorbic acid. IC_{50} value is an essential parameter to evaluate the potency. The IC_{50} value existing between 10–50, 50–100, and >100 μg/mL signifies strong, moderate and poor antioxidant activity respectively.[24] The obtained radical scavenging activity results as exemplified in Table 4 manifested that compounds **8i**, **8l**, **8q**, **8r**, **8s** and **8t** with the substituents like halogen, alkyl and aryl groups are possessing very good antioxidant activity with IC_{50} values of 24.04, 23.71, 26.78, 23.95, 27.73 and 26.98 μg/mL respectively in comparison to ascorbic acid with an IC_{50} value of 25.74 μg/mL (Fig. 4). Accordingly, we can conclude from the acquired IC_{50} values and correlation coefficient that all the compounds exhibit strong antioxidant activity except **8j** and **8p** with moderate activity.

Anti-inflammatory agents are useful in relieving pain in many conditions, ranging from menstrual and postoperative pain to arthritic pain. In view of this and to wrap up the present work and results, we conclude a modest, proficient and green synthesis of novel coumarinyl-1,3,4-oxadiazolyl-2-mercaptobenzoxazoles **8i-t**. Docking studies exemplified strong binding interactions with enzyme (PDB ID: 5IKR; A-Chain) by means of high C-score values acquired in the range 4.17–9.51. The biological outcomes as well as the computational study revealed that the title compounds have more affinity of inhibition towards COX-2 enzyme than COX-1. The compounds possessing halogen entity showed potent and selective inhibition of COX-2. The compounds **8i**, **8l**, **8q**, **8r**, **8s** and **8t** emerged as most potent and selective COX-2 inhibitors with IC_{50} values of 19.95, 12.82, 17.70, 11.35, 13.67 and 13.23 μg/mL respectively. The selectivity index demonstrated their high selectivity against COX-2. The antioxidant assets of the synthesized compounds were evaluated using the 1,1-diphenyl-2-picrylhydrazyl, DPPH, free radical scavenging assay. The compounds which were active as COX-2 inhibitors were also active as antioxidant agents. Overall the study sets a trend for the advancement of 2,5-substituted-1,3,4-oxadiazoles as latent and selective COX-2 inhibitors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.128112.

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