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Synthesis, molecular docking, and pharmacological evaluation of *N*-(2-(3,5-dimethoxyphenyl)benzoxazole-5-yl)benzamide derivatives as selective COX-2 inhibitors and anti-inflammatory agents

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Abstract

A series of *N*-(2-(3,5-dimethoxyphenyl)benzoxazole-5-yl)benzamide derivatives (**3a–m**) was synthesized and evaluated for their *in vitro* inhibitory activity against COX-1 and COX-2. The compounds with considerable *in vitro* activity (IC_{50} < 1 μM) were evaluated *in vivo* for their anti-inflammatory potential by the carrageenan-induced rat paw edema method. Out of 13 newly synthesized compounds, **3a**, **3b**, **3d**, **3g**, **3j**, and **3k** were found to be the most potent COX-2 inhibitors in the *in vitro* enzymatic assay, with IC_{50} values in the range of 0.06–0.71 μM. The *in vivo* anti-inflammatory activity of these six compounds (**3a**, **3b**, **3d**, **3g**, **3j**, and **3k**) was assessed by the carrageenan-induced rat paw edema method. Compounds **3d** (84.09%), **3g** (79.54%), and **3a** (70.45%) demonstrated significant anti-inflammatory activity compared to the standard drug ibuprofen (65.90%) and were also found to be safer than ibuprofen, by ulcerogenic studies. A docking study was done using the crystal structure of human COX-2, to understand the binding mechanism of these inhibitors to the active site of COX-2.

KEYWORDS
anti-inflammatory activity, COX-1, COX-2, *N*-(3,5-dimethoxphenyl)-benzoxazole, ulcerogenic activity

1 | INTRODUCTION

Inflammation is a local defense reaction to any noxious stimulus that threatens the host to cellular infection and injury. It is characterized by swelling, heat, redness, and pain.[1] Non-steroidal anti-inflammatory (NSAID's) drugs are found to be an important and frequently prescribed group of the therapeutic agents used for the treatment of inflammation and to relieve pain by suppressing cyclooxygenase (COX) enzyme. COX is a protein necessary for prostaglandin synthesis[2] and occurs in two isoforms: COX-1 and COX-2. COX-1, a constitutive isozyme, performs vital functions of gastro and vascular protection. On the contrary, COX-2 is an inducible isozyme responsible for prostaglandin synthesis that triggers inflammatory responses.[3] NSAID's available in the market such as flurbiprofen (A), ibuprofen (B), and indomethacin (C) (Figure 1) show their anti-inflammatory effect through nonselective inhibition of COX. The adverse effects associated with the chronic use of these drugs results in gastrointestinal complications such as stomach erosions,[4–7] silent intestinal ulcerations,[8,9] and kidney problems.[10,11] Many selective COX-2 inhibitors (coxibs) such as celecoxib (D), valdecoxib (E), and rofecoxib (F) (Figure 1) are developed for the treatment of inflammation and have shown to produce lower GI side effects. However, prolonged use of

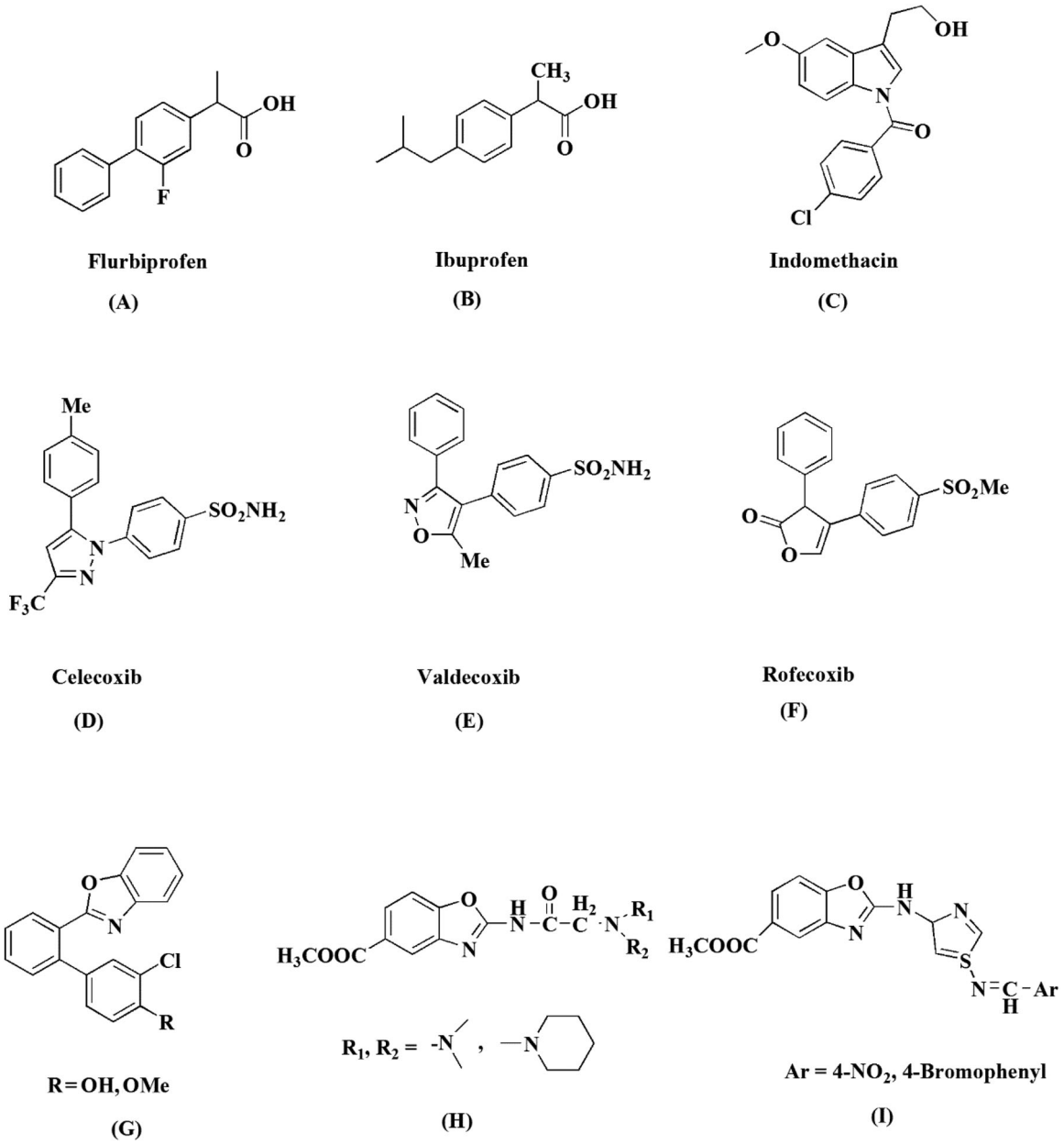


FIGURE 1 Chemical structures of non-selective NSAIDs (A–C), COX-2 selective drugs (D–F), and the reported benzoxazole derivatives (G–I) with COX-2 activity

some coxibs found to possess high incidence of thromboembolic risk in cardiovascular disease patient,[12] due to which valdecoxib (E) and rofecoxib (F) are withdrawn from the market.[13] Therefore, it is imperative to come out with the scaffolds which have the anti-inflammatory effect but reduced side effects and improved gastric safety profile.[14,15]

Development of selective COX-2 inhibitors is a challenge to drug discovery because of the close structural similarity between both the COX isoforms.[16] They both have a hydrophobic tunnel through which the substrate enters the active site of enzyme. The presence of Ile523 in COX-1 makes its binding shorter in comparison to the COX-2 which has Val523 at the same place. This Val523 in COX-2 produces a conformational change in COX-2, thereby forming an additional hydrophobic secondary internal pocket protruding off the primary binding site which is absent in COX-1.[17]

Benzamides and benzoxazole derivatives are known to possess a wide array of biological activities such as anti-inflammatory,[18–23] anti-bacterial,[24–26] antifungal,[26,27] anti-convulsant,[28] and analgesic activity.[23,29,30] The literature data showed that benzamides and benzoxazole moiety (G–I) (Figure 1) can be a potent template for COX-2 inhibitory activity, with GI safety margins.[21,23,31,32] Whereas, 3,5-dimethoxyphenyl moiety is also found to play an important role in anti-inflammatory activity.[33]

Based on the aforementioned findings, in our current study, we combined 3,5-dimethoxyphenyl moiety with benzoxazole and benzamides and reported the synthesis of thirteen novel

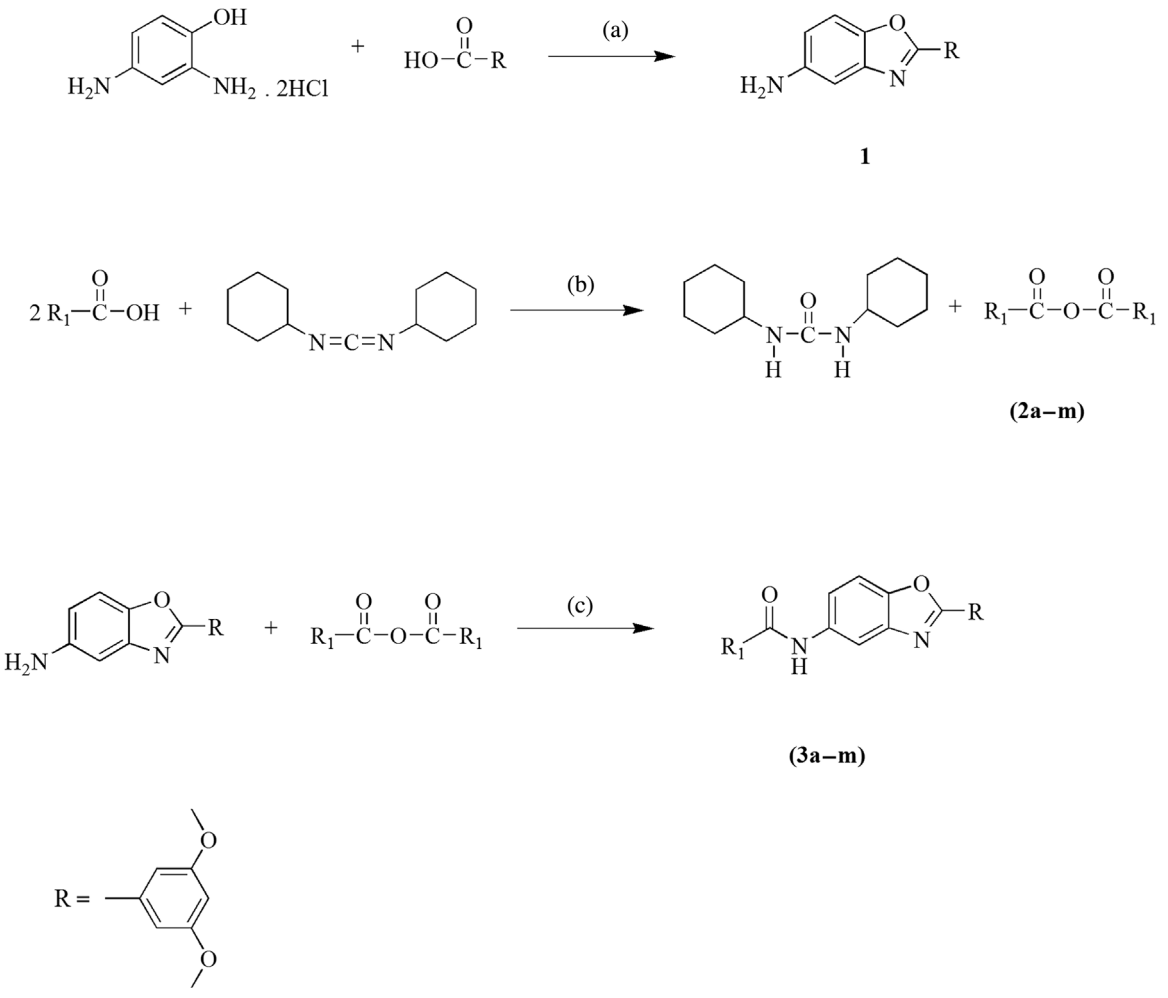
N-(2-(3,5-dimethoxyphenyl)benzoxazole-5-yl)benzamide derivatives and their biological evaluation by *in vitro* COX-1/COX-2 enzyme inhibition assay, *in vivo* anti-inflammatory, and ulcerogenic activity. To confirm their COX-2 binding, we performed molecular docking of newly synthesized molecules in the crystal structure of human COX-2. Computer-aided drug design assists in designing selective and potent inhibitors as well as vaccines. Among others, molecular docking approach is one of the most rational and authentic approaches in the drug design and discovery for studying the molecular interaction of small molecules.[34–36] Besides, ADME analyses were performed to evaluate their suitability as active drug molecules.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

N-(2-(3,5-Dimethoxyphenyl)-benzoxazole-5-yl)benzamides derivatives (**3a–m**) were synthesized as outlined in synthetic Scheme 1. The compound 2-(3,5-dimethoxyphenyl)-benzoxazol-5-amine (**1**) was prepared by the reaction of 2,4-diaminophenol dihydrochloride with 3,5-dimethoxybenzoic acid followed by cyclization in presence of polyphosphoric acid (PPA). Different substituted acid were further reacted with dicyclohexylcarodiimide (DCC) to form their respective anhydrides (**2a–m**). Finally, the title compound was prepared by the nucleophilic attack of benzoxazole amine with their respective anhydride in presence of glacial acetic acid and Zn dust in variable yield (35–82%) (**3a–m**).

The progress of the reaction was checked by TLC. Structures of prepared analogs were confirmed by elemental analysis, FTIR, ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and mass spectrometry. The spectral data obtained were in full agreement with the proposed structures. The IR spectroscopic data of benzoxazole derivatives showed absorption bands between 1600 and 1690 cm^{-1} (—NH—CO—) and 3280–3355 cm^{-1} (—NH) indicating the synthesis of the compounds. ^{1}H NMR spectra of the desired compounds revealed the signals of methyl/ethyl, methoxy/dimethoxy,



SCHEME 1 Synthetic scheme of the title compounds (**3a–m**). Reagents and conditions: (a) PPA, 5–6 h, 80–95°C; (b) dichloromethane; (c) Zn dust, glacial acetic acid, dichloromethane, 4–5 h. R1: **3a** = phenyl; **3b** = 4-chlorophenyl; **3c** = 3-chlorophenyl; **3d** = 2-chlorophenyl; **3e** = 4-methylphenyl; **3f** = 3-methylphenyl; **3g** = 2-methylphenyl; **3h** = 4-ethylphenyl; **3i** = 3,4-dimethoxyphenyl; **3j** = 4-nitrophenyl; **3k** = 2-chloro-4-nitrophenyl; **3l** = 3-nitrophenyl; **3m** = 4-methoxyphenyl

and aromatic protons of benzoxazole ring. Coupling constants (*J*) are given in Hz and spin multiples are given as s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet), and br (broad). The singlet around 3.77–3.99 δ ppm revealed the presence of dimethoxy group and other aromatic protons appeared within the range 6.09–8.07 δ ppm. The NH protons were observed as D_2O exchangeable protons. While the peaks in ^{13}C NMR spectra also confirmed the synthesis of target compounds (**3a–m**). Mass spectra of compounds **3a–m** showed molecular ion peaks at an *m/z* corresponding to their molecular formula. The elemental analysis data were within ±0.5% of the theoretical values.

2.2 | Biological evaluation

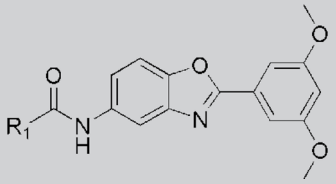
2.2.1 | *In vitro* cyclooxygenase (COX-1 and COX-2) inhibition assay

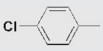
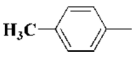
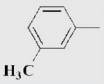
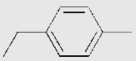
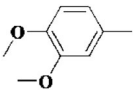
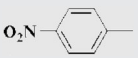
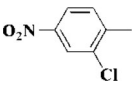
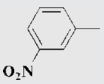
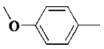
The inhibitory activity of synthesized compounds **3a–m** was evaluated against ovine COX-1 and human recombinant COX-2 using enzyme immunoassay (EIA) kit (Supplementary Figure S1) and the IC_{50} (μM) values were determined (Table 1). The IC_{50} values of celecoxib for COX-1 and COX-2 were observed as 6.20 and 0.15 μM, respectively. The result of the *in vitro* COX-1 and COX-2 inhibitory studies revealed that all the compounds selectively and potentially inhibit COX-2 (IC_{50} = 0.06–22.24 μM range) over COX-1 (IC_{50} = 2.32–35.84 μM range). Further, the selectivity index (SI) was found to be in the range of 1.61–38.66. The results showed that the compounds **3a** (COX-1/COX-2 = 2.44:0.10), **3b** (COX-1/COX−2 = 5.73:0.28), **3d** (COX-1/COX-2 = 2.32:0.06), **3g** (COX-1/COX-2 = 4.68:0.30), **3j** (COX-1/COX−2 = 7.39:0.32), and **3k** (COX-1/COX-2 = 9.42:0.71) were found to be more potent inhibitors of COX-2 in comparison to COX-1 among the synthesized compounds (Figure 2). Compound **3d** was found to be most potent inhibitor of the series with IC_{50} = 0.06 μM (2.50-fold higher) as compared to celecoxib (IC_{50} = 0.15 μM). These six most active COX-2 inhibitors (**3a**, **3b**, **3d**, **3g**, **3j**, and **3k**), IC_{50} < 1 μM, were further evaluated for *in vivo* anti-inflammatory activity.

2.2.2 | *In vivo* anti-inflammatory activity

Anti-inflammatory activity of the selected compounds (**3a**, **3b**, **3d**, **3g**, **3j**, and **3k**) was assessed by the carrageenan-induced rat paw edema method (Table 2). Out of the six compounds, **3a**, **3d**, and **3g** demonstrated more anti-inflammatory activity than standard drug ibuprofen (65.90%). Compound with 2-chlorophenyl (**3d**) emerged as the most promising analog of the series with percentage inhibition of 84.09%. The compounds with 4-ethylphenyl (**3g**) and unsubstituted phenyl (**3a**) also showed remarkable protection against inflammation with percent inhibition of 79.54 and 70.45%, respectively. Whereas compounds with 2-chloro-4-nitro (**3k**), 4-chlorophenyl (**3b**), and 4-nitrophenyl (**3j**) exhibited percent inhibition of paw edema equivalent or near to standard ibuprofen. However, more studies are required to confirm the anti-inflammatory activity of the synthesized compounds.

TABLE 1 *In vitro* COX-1 and COX-2 inhibition and COX-2 selectivity index (SI) data (**3a–m**)



Compound	IC_{50} (μM)[a] R_1	COX-1	COX-2	SI[b]
3a		2.44	0.10	24.40
3b		5.73	0.28	20.46
3c		10.61	2.48	4.27
3d		2.32	0.06	38.66
3e		5.15	1.40	3.67
3f		14.61	3.25	4.49
3g		4.68	0.30	15.6
3h		23.13	14.53	1.59
3i		35.84	22.24	1.61
3j		7.39	0.32	23.09
3k		9.42	0.71	13.26
3l		18.58	8.30	2.23
3m		16.64	4.72	3.52
Celecoxib	–	6.20	0.15	41.33
Ibuprofen	–	1.42	1.08	1.31

[a]IC_{50} value is the concentration of the compound required to produce 50% of inhibition of COX-1 and COX-2, respectively, using enzyme immunoassay kit (catalogue no. 560131, Cayman Chemicals, Inc., Ann Arbor, MI, USA).
[b]*In vitro* COX-2 selectivity index (SI): (COX-1 IC_{50}/COX-2 IC_{50}).

2.2.3 | Acute ulcerogenic activity

Analogs **3a**, **3d**, and **3g** possessing *in vivo* anti-inflammatory activity greater than standard drug ibuprofen were further screened for their ulcerogenic activity. The results (Table 3) (Supplementary Figure S2) showed that the tested compound showed better GI safety profile

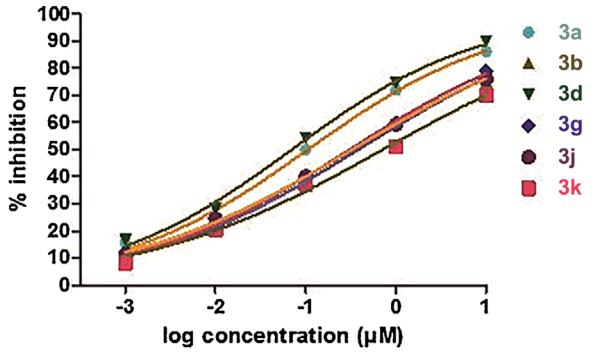


FIGURE 2 *In vitro* percentage inhibition of COX-2 versus log concentration curve of most potent compounds (**3a**, **3b**, **3d**, **3g**, **3j**, and **3k**)

with severity index ranging from 1.00 to 1.90, in comparison to standard drug ibuprofen (2.20 ± 0.44). Most potent compound (**3d**) showed severity index of 1.00 ± 0.50 which was very low in comparison to the standard drug. Hence, these compounds may ascertain to have better safety margin on gastric mucosa than ibuprofen.

2.2.4 | Acute toxicity study

A dose of 2000 and 200 mg/kg resulted in death of animals under test and dose of 20 mg/kg was found to be safe as no mortality and behavioral changes were observed.

2.3 | Computational studies

2.3.1 | Docking studies

The docking study was performed using resolved crystal structure of human COX-2 (PDB ID: 5F19). The results showed that among all the docked molecules, hydrogen bonds with Arg120 and π–π interaction with Tyr355 is conserved with COX-2 active site (Table 4). Compounds **3d**, **3a**, and **3g** showed the most promising *in vitro*, *in vivo*, ulcerogenic potential, and docking score among all the compounds. In addition, the hydrophobic cloud was contributed by Val89, Leu93, Val116, Val349, Leu352, Leu359, Leu384, Tyr385, Trp387, Phe518, Val523, Ala527, and Leu531 as shown in Figure 3. The benzoxazole moiety found to play remarkable role in capturing H-bond with Arg120 (with *N*-atom of benzoxazole ring) and π–π interaction with both aromatic rings of benzoxazole moiety. Apart from above-mentioned residues, some other residues (Tyr385–**3k**; Ser530–**3k**, **3j**; Met522–**3j**) were also found to be involved in interaction and those compounds were found to show moderate *in vivo* and *in vitro* activities. The docking score showed that unsubstituted phenyl ring (**3a**) and *ortho*-substituted phenyl ring (**3d** and **3g**) leads to increase in activity. The compounds with electron withdrawing group at *para* position of phenyl ring (**3b**, **3j**, and **3k**) showed moderate activity whereas electron donating group at *para* position (**3h** and **3i**) leads to considerable decrease in activity. All the compounds showed comparable docking score to celecoxib. The celecoxib possessed van der Waals interactions with amino acid Val349, Leu384, Trp387, Leu352, Tyr385, Phe518, Val523, and Ala527 and hydrogen bond with Gln192, Ser353, Arg513, and Phe518 (Figure 3e). The non-selective inhibitor ibuprofen showed no H-bond with COX-2 but salt bridge with Arg120 (Figure 3d).

2.3.2 | Absorption, distribution, metabolism, and excretion (ADME) study

The ADME parameters for all synthesized ligands were calculated using Qikprop 4.0 (Table 5). Assessment of ADME properties is imperative because they exclude weak or toxic molecule at an early stage of drug discovery and development process. The desirable ADME properties of these compounds make them promising candidates as COX-2 inhibitors.

TABLE 2 *In vivo* anti-inflammatory activity of the most potent compounds using carrageenan-induced rat paw edema method

	Paw edema volume (mL)			
Compound	**0 h**	**3 h**	**Increase in paw edema (mL) (mean ± SEM)[a]**	**% Inhibition[b]**
3a	0.67	0.80	0.13 ± 0.009	70.45
3b	0.69	0.85	0.16 ± 0.024	63.63
3d	0.73	0.80	0.07 ± 0.016	84.09
3g	0.69	0.78	0.09 ± 0.008	79.54
3j	0.67	0.83	0.16 ± 0.024	63.63
3k	0.66	0.81	0.15 ± 0.14	65.90
Control	0.7	1.14	0.44 ± 0.048	–
Ibuprofen	0.65	0.8	0.15 ± 0.022	65.90

–, not applicable. *p*-Values were compared with control group (3 h after inducing edema) (Tukey's test). Number of animals (rats) in each group = 5.
[a]Values are determined after 3 h and are expressed as mean ± SEM.
[b]$p < 0.05$ (significant difference).

TABLE 3 Ulcerogenic activity of the most active compounds in rat model

Compound	Ulcerogenic activity[a] (severity index)[b] (mean ± SD)
3a (60 mg/kg)	1.30 ± 0.45
3d (60 mg/kg)	1.00 ± 0.50
3g (60 mg/kg)	1.90 ± 0.42
Ibuprofen (60 mg/kg)	2.20 ± 0.44
Control (normal saline)	–

[a]Number of animals in each group = 5.
[b]$p < 0.05$ (significant difference).

3 | CONCLUSIONS

In summary, we have reported a simple and efficient method for the synthesis of *N*-(2-(3,5-dimethoxyphenyl)benzoxazole-5-yl)benzamide derivatives (**3a–m**) with good yield. All the prepared analogs were screened for their *in vitro* activity and selected compounds for *in vivo* activity. All compounds exhibited *in vitro* selective inhibition of COX-2 than COX-1. Among the series of newly synthesized compounds, **3a**, **3d**, and **3g** were found to have significant anti-inflammatory and less ulcerogenic activity than ibuprofen. The overall study concludes compound **3d** as the most potent compound of the series with improved gastric safety profile. The *in silico* studies also suggest the similar binding and activity profile of the compounds as observed by the *in vitro* and *in vivo* activities. The compounds **3a**, **3d**, and **3g** can further be explored for development of more safer and active anti-inflammatory agents.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

The chemical and solvents used were purchased from Merck Co. and Sigma by commercial vendors and used in the experiments without purification. COX (ovine/human) inhibitor screening assay kits (catalog no. 560131) were procured from Cayman Chemicals Inc., Ann Arbor, MI, USA. The progress of the chemical reaction was monitored by thin layer chromatography (TLC) on pre-coated plates and compounds were purified using column chromatography on silica gel (100–200 mesh). Iodine vapors were used for detection of spots on TLC plates. The melting points of the synthesized compounds were determined on LAB-India MR-VIS visual melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Bruker Optics spectrophotometer. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on Bruker, Advance DPX-300 spectrometer. Tetramethylsilane (TMS) was used as internal standard and chemical shifts (δ) were determined in parts per million (ppm). Mass spectra (ESI-MS) were recorded on API 2000 LCMS/MS Applied Biosystems. Elemental analyses were carried out on Flash 2000 organic elemental analyzer.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | Synthesis of 2-(3,5-dimethoxyphenyl)-benzoxazol-5-amine (1)

2-(3,5-Dimethoxyphenyl)benzoxazol-5-amine (**1**) was prepared by heating equimolar mixture of 2,4-diaminophenol dihydrochloride (1 mmol) and 3,5-dimethoxybenzoic acid (1 mmol) in presence of cyclizing agent polyphosphoric acid (PPA) (24 g). The mixture was heated at 80–95°C for 5–6 h. After the completion of reaction (monitored by TLC), mixture was cooled to room temperature and poured into ice cold water, neutralized with an excess of 10 N NaOH solution, and extracted with toluene, dried over anhydrous sodium sulfate, and evaporated under vacuum. After evaporation, the product obtained was boiled in charcoal and recrystallized from ethanol to give pure compound (**1**).

Yield: 84%. m.p.: 190–192°C. ATR-FTIR (cm^{-1}): 3325.2 (NH_2), 2825.8 (-CH-), 1682.3, 1452 (aromatic CC), 1600.20 (-NH_2), 1200.5 (C-N), 1111.2 (C-O), 720.32 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H, 2 × -OCH_3), 4.21 (s, 2H, -NH_2), 6.22 (s, 2H, Hd'), 6.45 (s, 1H, H4 of benzoxazole), 6.46 (d, 1H, J = 6 Hz, H6 of benzoxazole), 6.64 (s, 2H, Hb', Hf'), 7.02 (d, 1H, J = 6 Hz, H7 of benzoxazole). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.20, 60.12, 101.45, 104.32, 107.11, 111.42, 128.54, 141.25, 144.62, 163.34. (+) ESI-MS (*m/z*): 271.2 $[M+H]^+$. Anal. calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.67; H, 5.21; N, 10.35.

4.1.3 | General procedure for the synthesis of anhydrides 2a–m

To 50 mL of methylene chloride (DCM), substituted acid derivative (0.02 mol) and dicyclohexylcarbodiimide (DCC) (0.01 mol) were added and stirred at room temperature for 3–4 h. After then the solvent was separated (**2a–m**), the reaction mixture was filtered to remove precipitate of dicyclohexylurea and the filtrate was evaporated to get the oily product (**2a–m**).[37]

Benzoic anhydride (2a)

Yield: 72%. m.p.: 44–46°C. ATR-FTIR (cm^{-1}): 3064.2 (-CH- aromatic), 1789.12, 1711.10 (C═O), 1607.12, 1472.2 (C═C), 732.20 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.49 (m, 4H, Ar-H), 7.68 (d, J = 7.5 Hz, Ar-H), 8.13 (d, 4H, J =7.5 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.80, 134.52, 162.40. (+) ESI-MS (*m/z*): 227.5 $[M+H]^+$. Anal. calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.35; H, 4.47.

4-Chlorobenzoic anhydride (2b)

Yield: 84%. m.p.: 182–184°C. ATR-FTIR (cm^{-1}): 3020.42 (-CH-aromatic), 1800.18, 1722.20 (C═O), 1600.24, 1478.6 (C═C), 784.20 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.41 (t, J = 7.2 Hz, 2H, Ar-H), 7.62 (d, 2H, J = 8.4 Hz, Ar-H), 8.02 (d, 4H,

TABLE 4 Glide score (kcal/mol), type of interactions, and interacting residues of the COX-2 protein with synthesized compounds

		Type of interactions						
		Hydrogen bonds			π-Interactions			
Comp.	Glide score (kcal/mol)	Atom of ligand	Amino acids	Dist (Å)	Type	Ring/group	Amino acids	Dist (Å)
3a	−10.78	N	Arg120	2.23	π-Stacking	Benzoxazole	Tyr355	5.05
		N	Arg120	1.69			Tyr355	5.23
3b	−10.00	N	Arg120	2.22	π-Stacking	Benzoxazole	Tyr355	5.16
		N	Arg120	1.7			Tyr355	5.33
3c	−9.83	N	Arg120	2.16	π-Stacking	Benzoxazole	Tyr355	5.09
		N	Arg120	1.73			Tyr355	5.32
3d	−11.11	N	Arg120	2.16	π-Stacking	Benzoxazole	Tyr355	5.04
		N	Arg120	1.63			Tyr355	5.21
3e	−9.75	N	Arg120	2.26	π-Stacking	Benzoxazole	Tyr355	5.04
		N	Arg120	2.72			Tyr355	5.72
3f	−9.81	N	Arg120	2.22	π-Stacking	Benzoxazole	Tyr355	5.06
		N	Arg120	2.7			Tyr355	5.26
3g	−10.52	N	Arg120	2.19	π-Stacking	Benzoxazole	Tyr355	5.02
		N	Arg120	1.72			Tyr355	5.21
3h	−8.62	N	Arg120	2.18	π-Stacking	Benzoxazole	Tyr355	5.39
		N	Arg120	2.72			Tyr355	5.26
3i	−8.38	−*CO−	Arg120	2.55	π-Stacking	Benzoxazole	Tyr355	5.29
3j	−9.75	N	Arg120	2.24	π-Stacking	Benzoxazole		
		N	Arg120	2.69			Tyr355	5.35
		NO_2	Met522	2.72			Tyr355	5.21
		NO_2	Ser530	3.02				
3k	−9.79	N	Arg120	2.16	π-Stacking	Benzoxazole		
		N	Arg120	2.73			Tyr355	5.3
		NO_2	Tyr385	3.62				
		NO_2	Ser530	2.65				
3l	−9.67	N	Arg120	2.17	π-Stacking	Benzoxazole	Tyr355	5.31
		N	Arg120	2.73			Tyr355	5.05
3m	−9.62	N	Arg120	2.22	π-Stacking	Benzoxazole	Tyr355	5.19
		N	Arg120	2.71				
Ibuprofen	−6.97		–	–	Salt bridge	COOH	Arg120	3.48
Celecoxib	−10.49	NH_2	Gln192	3.55				
		NH_2	Ser353	2.09				
		SO_2	Arg513	2.80				
		SO_2	Phe518	2.69				

J = 8.4 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.31, 130.92, 138.8, 167.20. (+) ESI-MS (m/z): 295.4 $[M+H]^+$. Anal. calcd. for $C_{14}H_8Cl_2O_3$: C, 56.98; H, 2.73. Found: C, 56.99; H, 2.71.

3-Chlorobenzoic anhydride (2c)

Yield: 68%. m.p.: 153–157°C. ATR-FTIR (cm^{-1}): 3015.52 (-CH- aromatic), 1808.12, 1730.40 (CO), 1620.40, 1475.38 (C═C), 790.85 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, 4H, J = 8.4 Hz, Ar-H), 8.02 (d, 2H, J = 6 Hz, Ar-H), 8.14 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.42, 130.12, 130.42, 134.8, 152.70. (+) ESI-MS (m/z): 294.7 $[M+H]^+$. Anal. calcd. for $C_{14}H_8Cl_2O_3$: C, 56.98; H, 2.73. Found: C, 56.97; H, 2.72.

2-Chlorobenzoic anhydride (2d)

Yield: 81%. m.p.: 63–68°C. ATR-FTIR (cm^{-1}): 3010.48 (-CH- aromatic), 1783.26, 1721.11 (C═O), 1618.15, 1472.18 (C═C), 1074.2 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.42 (m, 2H, Ar-H), 7.49–7.54 (m, 4H, Ar-H), 8.02 (d, 2H, J = 7.5 Hz, Ar-H). ^{13}C NMR

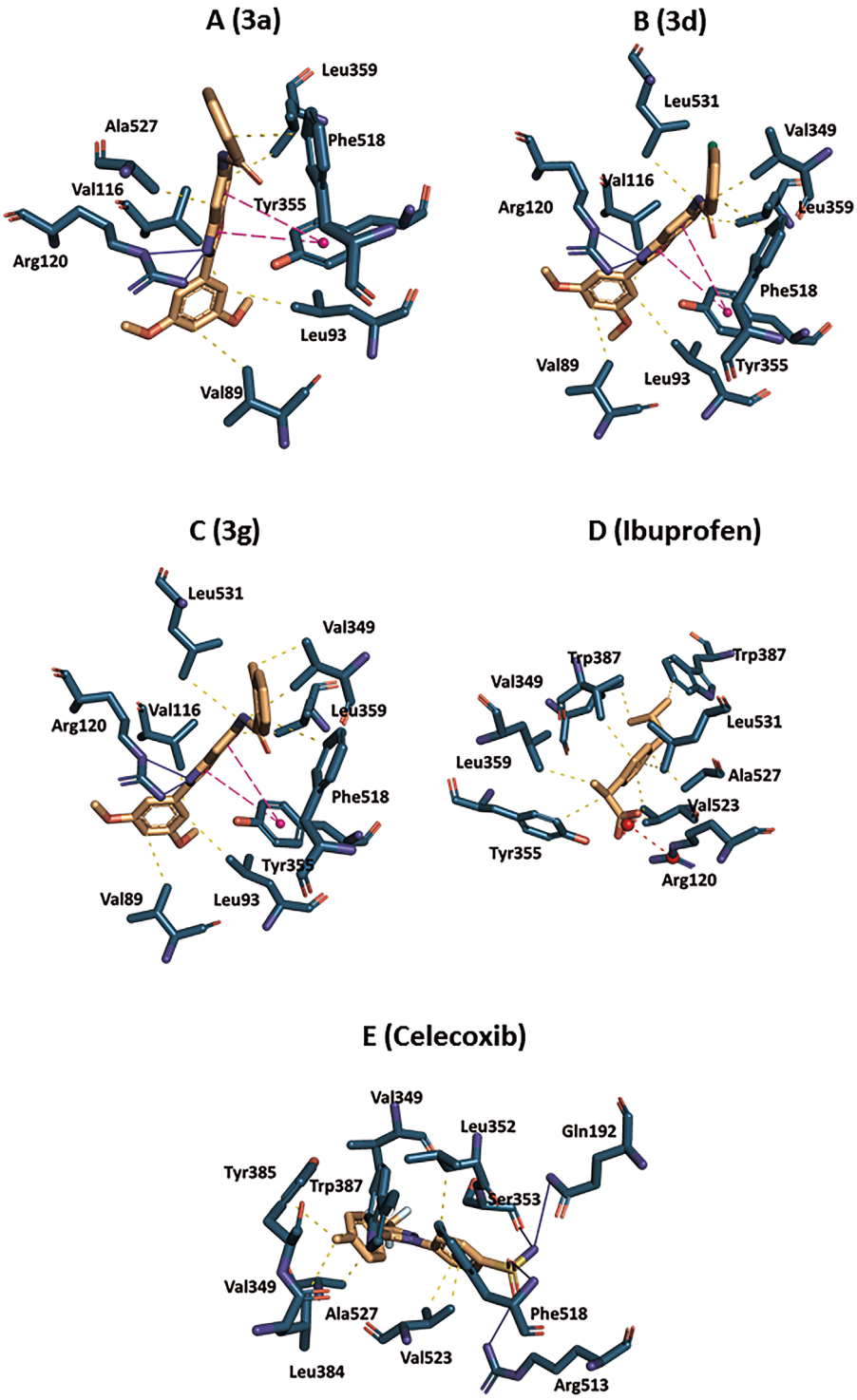


FIGURE 3 Docked pose of compound (A) **3a**, (B) **3d**, (C) **3g**, (D) ibuprofen, (E) celecoxib in the catalytic cavity of COX-2

(75 MHz, $CDCl_3$): δ 126.90, 132.54, 133.60, 134.12, 135.10, 160.28. (+) ESI-MS (*m/z*): 294.2 $[M+H]^+$. Anal. calcd. for $C_{14}H_8Cl_2O_3$: C, 56.98; H, 2.73. Found: C, 56.96; H, 2.74.

4-Methylbenzoic anhydride (2e)

Yield: 59%. m.p.: 79–81°C. ATR-FTIR (cm^{-1}): 3113.25 (-CH- aromatic), 2843.40 (-CH- aliphatic), 1800.12, 1785.10 (C═O), 1625.84, 1480.01 (C═C), 810 (out-of-plane, bend). ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 6H, 2 × -CH_3), 7.32 (d, 4H, *J* = 7.8 Hz, Ar-H), 8.02 (dd, 4H, J_1 = 7.8 Hz, J_2 = 5.1 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 126.4, 129.68, 130.21, 145.54, 162.60. (+) ESI-MS (*m/z*): 255 $[M+H]^+$. Anal. calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.56; H, 5.56.

3-Methylbenzoic anhydride (2f)

Yield: 48%. m.p.: 64–66°C. ATR-FTIR (cm^{-1}): 3010.01 (-CH- aromatic), 2845.84 (-CH- aliphatic), 1810.09, 1795.21 (C═O), 1630.21, 1452.65

TABLE 5 Predicted absorption, distribution, metabolism, and excretion (ADME) properties of synthesized compounds

Comp	#rtvFG	CNS	mol_MW	SASA	FOSA	FISA	donorHB	acceptHB	QPlogPo/w	QPPCaco	QPlogBB	#metab	QPlogKhsa	% Human oral absorption	Rule of five
3a	0	0	374.4	686.2	185.4	64.3	1	6.0	4.2	2433.19	−0.36	3	0.47	100.00	0
3b	0	0	408.8	710.2	185.4	64.2	1	6.0	4.7	2434.04	−0.20	3	0.59	100.00	0
3c	0	0	388.4	718.3	273.5	64.3	1	6.0	4.5	2433.28	−0.38	4	0.63	100.00	0
3d	0	0	408.8	705.5	185.4	56.6	1	6.0	4.7	2873.88	−0.14	3	0.57	100.00	0
3e	0	0	388.4	718.5	273.6	64.3	1	6.0	4.5	2432.88	−0.38	4	0.63	100.00	0
3f	0	0	388.4	718.3	273.5	64.3	1	6.0	4.5	2433.28	−0.38	4	0.63	100.00	0
3g	0	0	388.4	703.7	256.8	49.4	1	6.0	4.6	3368.83	−0.20	4	0.60	100.00	0
3h	0	0	402.4	748.5	315.7	64.3	1	6.0	4.9	2432.91	−0.46	4	0.74	100.00	0
3i	0	0	434.4	767.4	361.8	64.2	1	7.5	4.4	2433.61	−0.52	5	0.49	100.00	0
3j	0	−2	419.3	724.4	185.4	161.3	1	7.0	3.5	292.42	−1.51	4	0.41	91.81	0
3k	0	−2	453.8	743.7	185.4	153.7	1	7.0	4.0	345.20	−1.30	4	0.51	95.95	0
3l	0	−2	419.3	724.1	185.4	161.4	1	7.0	3.5	291.65	−1.51	4	0.41	91.77	0
3m	0	0	404.4	722.1	278.2	64.21	1	6.7	4.3	2437.80	−0.44	4	0.47	100.00	0
Ibuprofen	0	−1	206.2	477.0	278.8	91.23	1	2.0	3.5	342.27	−0.48	2	0.06	92.78	0

Parameters: #rtvFG, number of reactive functional groups. The presence of these groups can lead to false positives in HTS assays and to decomposition, reactivity, or toxicity problems *in vivo* (0–2); CNS, predicted central nervous system activity −2 (inactive) to 2 (active); mol_MW, molecular weight of the molecule; SASA, total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius (300.0–1000.0); FOSA, hydrophobic component of the SASA (saturated carbon and attached hydrogen); FISA, hydrophilic component of the SASA (SASA on N, O, and H on heteroatoms); donorHB, estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution; acceptHB, estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution; QPlogPo/w, predicted octanol/water partition coefficient; QPPCaco, predicted apparent Caco-2 cell permeability in nm/s (<25 poor >500 great); QPlogBB, predicted brain/blood partition coefficient (range or recommended value for 95% of known drug −3 to 1.2); #metab, number of likely metabolic reactions (1–8); QPlogKhsa, prediction of binding to human serum albumin (−1.5 to 15); % human oral absorption, predicted human oral absorption on 0–100% scale (25–80%). The prediction is based on a quantitative multiple linear regression model. This property usually correlates well with human oral absorption, as both measure the same property; rule of five, number of violation of Lipinski's rule of five. Compounds that satisfy these rules are considered drug-like (maximum is 4).

(C═C), 799.20 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H, 2 × -CH_3), 7.32–7.38 (m, 4H, Ar-H), 7.8 (s, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.30, 128.82, 128.88, 131.20, 135.28, 138.80, 162.70. (+) ESI-MS (*m/z*): 255.6 $[M+H]^+$. Anal. calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.57; H, 5.54.

2-Methylbenzoic anhydride (2g)

Yield: 48%. m.p.: 85–87°C. ATR-FTIR (cm^{-1}): 2999.20 (-CH- aromatic), 2680.35 (-CH- aliphatic), 1800.15, 1787.58 (C═O), 1650.61, 1420.46 (C═C), 810.10 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 6H, 2 × -CH_3), 7.25 (d, 4H, *J* = 8.8 Hz, Ar-H), 7.40–7.45 (m, 2H, Ar-H), 7.95 (d, 2H, *J* = 7.7 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.98, 126.16, 127.80, 131.42, 132.30, 133.60, 142.50, 162.98. (+) ESI-MS (*m/z*): 255 $[M+H]^+$. Anal. calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.55; H, 5.56.

4-Ethylbenzoic anhydride (2h)

Yield: 75%. m.p.: 96–98°C. ATR-FTIR (cm^{-1}): 3000.10 (-CH- aromatic), 2590.17 (-CH- aliphatic), 1805.18, 1782.26 (C═O), 1680.12, 1416.30 (C═C), 900 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 6H, *J* = 5.4 Hz, -CH_3), 2.59 (q, 4H, *J* = 7.2 Hz, -CH_2*-CH_3), 7.33 (dd, 4H, J_1 = 3.0 Hz, J_2 = 3.3 Hz, Ar-H), 8.08 (dd, 4H, J_1 = 6.0 Hz, J_2 = 6.0 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.60, 32.42, 127.51, 127.78, 144.18, 152.86. (+) ESI-MS (*m/z*): 283.6 $[M+H]^+$. Anal. calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.58; H, 6.44.

3,4-Dimethoxybenzoic anhydride (2i)

Yield: 67%. m.p.: 122–124°C. ATR-FTIR (cm^{-1}): 3010.42 (-CH- aromatic), 2581.10 (-CH- aliphatic), 1800.12, 1780.56 (C═O), 1672.10, 1410.26 (C═C), 810 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 12H, 4 × -OCH_3), 6.65 (s, 2H, Ar-H), 7.20 (s, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.90, 105.6, 106.88, 132.30, 152.79, 161.45, 161.80. (+) ESI-MS (*m/z*): 347 $[M+H]^+$. Anal. calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.43; H, 5.22.

4-Nitrobenzoic anhydride (2j)

Yield: 74%. m.p.: 92–94°C. ATR-FTIR (cm^{-1}): 2989.81 (-CH- aromatic), 2780.11 (-CH- aliphatic), 1810.14, 1784.46 (C═O), 1676.71, 1408.52 (C═C), 1535.52, 1398.4 (Ar-NO_2), 790 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 4H, Ar-H), 8.40 (d, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 121.01, 131.20, 136.46, 152.75, 153.68 (+) ESI-MS (*m/z*): 317.5 $[M+H]^+$. Anal. calcd. for $C_{14}H_8N_2O_7$: C, 53.17; H, 2.55. Found: C, 53.19; H, 2.56.

2-Chloro-4-nitrobenzoic anhydride (2k)

Yield: 74%. m.p.: 103–105°C. ATR-FTIR (cm^{-1}): 3312.6 (-CH- aromatic), 2910.58 (-CH- aliphatic), 1800.26, 1775.48 (C═O), 1629.4, 1530.2 (C═C), 1532.6 (Ar-NO_2), 1472.2 (-CH bend), 1168.28 (Ar-Cl), 1112.40 (C-O), 790.2 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, 2H, *J* = 3 Hz, Ar-H), 8.36 (d, 2H, *J* = 6.9 Hz, Ar-H), 8.41 (d, 2H, *J* = 5.4 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ

119.12, 123.9, 132.62, 136.08, 137.18, 152.70, 155.06. (+) ESI-MS (*m/z*): 384.2 $[M+H]^+$. Anal. calcd. for $C_{14}H_6Cl_2N_2O_7$: C, 43.66; H, 1.57. Found: C, 43.67; H, 1.54.

3-Nitrobenzoic anhydride (2l)

Yield: 58%; m.p.: 162–164°C. ATR-FTIR (cm^{-1}): 3300.74 (-CH- aromatic), 2928.49 (-CH- aliphatic), 1799.52, 1756.64 (C═O), 1626.2, 1530.4 (C═C), 1539.80, 1376.8 (Ar-NO_2), 790.68 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (t, 2H, *J* = 6.4 Hz, Ar-H), 8.52 (d, 2H, *J* = 3 Hz, Ar-H), 9.08 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.12, 123.9, 132.62, 136.08, 137.18, 152.70, 155.06. (+) ESI-MS (*m/z*): 317.8 $[M+H]^+$. Anal. calcd. for $C_{14}H_8N_2O_7$: C, 53.17; H, 2.55. Found: C, 53.16; H, 2.56.

4-Methoxybenzoic anhydride (2m)

Yield: 66%; m.p.: 88–90°C. ATR-FTIR (cm^{-1}): 3012.16 (-CH- aromatic), 2959.62 (-CH- aliphatic), 1801.60, 1782.10 (C═O), 1618.28, 1515.80 (C═C), 840 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): 3.98 (s, 6H, 2 × -OCH_3), 6.96 (d, 4H, *J* = 7.4 Hz, Ar-H), 8.08 (d, 4H, *J* = 7.4 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.62, 114.28, 121.34, 132.68, 162.36, 164.92. (+) ESI-MS (*m/z*): 287.3 $[M+H]^+$. Anal. calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.12; H, 4.94.

4.1.4 | General procedure for the synthesis of *N*-(2-(3,5-dimethoxyphenyl)benzoxazole-5-yl)-substituted benzamides 3a–m

A mixture of benzoxazolamine (**1**) (0.012 mol), respective anhydride **2a–m** (0.01 mol), zinc dust (0.010 g), in glacial acetic acid and DCM (15 mL) was refluxed for 4–5 h at room temperature. After completion of the reaction, mixture was poured into ice cold water and precipitate obtained was further collected and recrystallized with ethanol to give the pure compound **3a–m**.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)benzamide (3a)

Yield: 72%. m.p.: 115–117°C. ATR-FTIR (cm^{-1}): 3285.6 (NH), 2920.6 (-CH), 1680 (-CONH-), 1620.42, 1468 (aromatic C═C), 1208.2 (C-N), 1110 (C-O), 732.4 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 6H, 2 × -OCH_3), 6.11 (s, 1H, Hd'), 6.50 (s, 2H, Hb', Hf'), 6.80 (d, 1H, *J* = 6.9 Hz, H7 of benzoxazole), 7.36–7.44 (m, 4H, Hc, Hd, He, H4 of benzoxazole), 7.72 (dd, 3H, J_1 = 6 Hz, J_2 = 6 Hz, H6 of benzoxazole merge with Hb, Hf), 8.01 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.32, 59.03, 101.26, 104.65, 104.82, 110.55, 111.85, 118.33, 127.27, 127.32, 130.39, 130.65, 131.77, 134.57, 141.22, 142.65, 162.82, 163.94, 164.65. (+) ESI-MS (*m/z*): 375.2 $[M+H]^+$. Anal. calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.57; H, 4.84; N, 7.45.

4-Chloro-*N*-(2-(3,5-dimethoxyphenyl)benzoxazol-5-yl)-benzamide (3b)

Yield: 82%. m.p.:104–106°C. ATR-FTIR (cm^{-1}): 3284.4 (NH), 2920.2 (-CH), 1672 (-CONH-), 1628.40, 1464 (aromatic C═C), 1220.2 (C-N), 1152.20 (Ar-Cl), 1114 (C-O), 736.2 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 6.09 (s, 1H, Hd'), 6.69 (s, 2H, Hb', Hf'), 7.02 (s, 1H, H7 of benzoxazole), 7.26 (d, 1H, *J* = 3.0 Hz, Hc), 7.36–7.43 (m, 2H, He, H6 of benzoxazole), 7.46–7.57 (m, 3H, Hb, Hf), 7.82 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.44, 56.72, 100.62, 104.24, 104.49, 106.72, 111.05, 112.62, 128.50, 128.92, 130.12, 130.32, 132.84, 135.52, 138.46, 141.28, 145.78, 162.86, 163.92, 164.62. (+) ESI-MS (*m/z*): 409.1 $[M+H]^+$. Anal. calcd. for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.60; H, 4.18; N, 6.83.

3-Chloro-*N*-(2-(3,5-dimethoxyphenyl)benzoxazol-5-yl)-benzamide (3c)

Yield: 76%. m.p.: 96–98°C. ATR-FTIR (cm^{-1}): 3302.8 (NH), 2916.4 (-CH), 1662.9 (-CONH-), 1628.64, 1484.60 (aromatic C═C), 1482.15 (-CH), 1210.2 (C-N), 1162.20 (Ar-Cl), 1050.23 (C-O), 800.91 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.42 (s, 1H, Hd'), 6.61 (s, 2H, Hb', Hf'), 7.09 (d, 1H, *J* = 12 Hz, H7 of benzoxazole), 7.34–7.44 (m, 2H, He, Hd), 7.59 (dd, 3H, J_1 = 6.3 Hz, J_2 = 7.2 Hz, Hf, H4, H6 of benzoxazole), 7.98 (s, 1H, Hb), 8.09 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.24, 57.62, 101.06, 104.26, 104.66, 106.84, 111.06, 112.68, 125.46, 128.64, 130.67, 132.87, 135.14, 135.92, 141.90, 145.74, 162.50, 163.10, 164.70. (+) ESI-MS (*m/z*): 409.5 $[M+H]^+$. Anal. calcd. for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.64; H, 4.20; N, 6.84.

2-Chloro-*N*-(2-(3,5-dimethoxyphenyl)benzoxazol-5-yl)-benzamide (3d)

Yield: 71%. m.p.: 91–93°C. ATR-FTIR (cm^{-1}): 3327.44 (NH), 2909.8 (-CH stretching), 1662.4 (-CONH-), 1625.12, 1524.45 (aromatic C═C), 1480.19 (-CH bend), 1210.2 (C-N), 1162.50 (Ar-Cl), 1110.62 (C-O), 800.52 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 6H, 2 × -OCH_3), 6.69 (s, 1H, Hd'), 7.02 (s, 2H, Hb', Hf'), 7.36 (d, 1H, *J* = 6 Hz, H7 of benzoxazole), 7.47 (t, 3H, *J* = 8.1 Hz, He, Hd), 8.01 (d, 2H, *J* = 6 Hz, H4, H6 of benzoxazole), 8.13 (d, 1H, *J* = 9 Hz, Hf), 8.29 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.36, 61.05, 100.87, 104.59, 104.83, 110.28, 127.70, 128.45, 130.09, 132.95, 133.69, 136.91, 141.28, 142.67, 162.77, 162.94, 165.28. (+) ESI-MS (*m/z*): 409.4 $[M+H]^+$. Anal. calcd. for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.62; H, 4.20; N, 6.84.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)-4-methylbenzamide (3e)

Yield: 56%. m.p.: 150–151°C. ATR-FTIR (cm^{-1}): 3326.42 (NH), 2992.64 (-CH stretching), 1680.46 (-CONH-), 1630.12, 1474.20 (C═C), 1458.42 (-CH bend), 1100.14 (C-O), 732.42 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 1H, -CH_3), 3.84 (s, 3H, -OCH_3), 3.87 (s, 3H, -OCH_3), 6.45 (s, 1H, Hd'), 7.70 (s, 1H, Hb'), 7.20 (s, 1H, Hf'), 7.41 (d, 2H, *J* = 2.4 Hz, Hc, Hd), 7.67 (dd, 2H, J_1 = 5.1 Hz, J_2 = 5.1 Hz, H6, H7 of benzoxazole), 7.82 (s, 2H, H4 of benzoxazole merge with -NH), 8.01 (d, 2H, *J* = 3.9 Hz, Hb, Hf). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.58, 56.38, 58.46, 100.66, 104.82, 105.01, 106.92, 111.05, 112.90, 127.82, 127.98, 128.40, 130.12, 131.40, 136.14, 141.18, 141.50, 145.78, 162.38, 12.89, 163.08, 164.80. (+) ESI-MS

(*m/z*): 389 $[M+H]^+$. Anal. calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.10; H, 5.18; N, 7.20.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)-3-methylbenzamide (3f)

Yield: 51%. m.p.: 142–144°C. ATR-FTIR (cm^{-1}): 3324.26 (NH), 2996.84 (-CH stretching), 1682.60 (-CONH-), 1636.20, 1475.20 (C═C), 1460.82 (-CH bend), 1110.28 (C-O), 810.24 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 1H, -CH3), 3.89 (s, 6H, 2 × -OCH3), 6.26 (s, 1H, Hd'), 6.63 (s, 1H, Hb'), 7.02 (s, 1H, Hf'), 7.27 (d, 1H, *J* = 22.8 Hz, H7 of benzoxazole), 7.45 (t, 1H, *J* = 8.1 Hz, He),7.63 (d, 1H, *J* = 8.4 Hz, H6 of benzoxazole), 7.79 (s, 2H, Hb, H4 of benzoxazole), 8.07 (d, 1H, *J* = 18.9 Hz, Hf), 8.20 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.42, 56.23, 57.18, 100.80, 104.14, 104.62, 106.34, 111.12, 112.67, 125.12, 127.58, 128.90, 132.57, 134.22, 135.10, 138.59, 142.15, 146.20, 162.50, 162.81, 163.12, 164.50. (+) ESI-MS (*m/z*): 389.6 $[M+H]^+$. Anal. calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.11; H, 5.21; N, 7.22.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)-2-methylbenzamide (3g)

Yield: 36%. m.p.: 130–132°C. ATR-FTIR (cm^{-1}): 3320.52 (NH), 2985.62 (-CH stretching), 1680.60 (-CONH-), 1624.26, 1476.28 (C═C), 1450.22 (-CH bend), 1108.06 (C-O), 800.26 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, -CH_3), 3.93 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 6.63 (s, 1H, Hd'), 7.02 (s, 2H, Hb', Hf'), 7.20 (d, 2H, *J* = 4.2 Hz, Hc and H7 of benzoxazole), 7.27 (t, 2H, *J* = 4.2 Hz, He, Hd), 7.64 (d, 1H, *J* = 4.2 Hz, H6 of benzoxazole), 7.78 (s, 1H, H4 of benzoxazole), 7.91 (d, 1H, *J* = 4.8 Hz, Hf), 8.09 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.12, 56.20, 57.36, 100.90, 104.42, 104.84, 106.83, 110.72, 112.55, 126.17, 127.65, 128.24, 129.71, 132.43, 135.17, 135.54, 138.02, 142.20, 146.19, 162.18, 163.23, 163.67, 164.20. (+) ESI-MS (*m/z*): 389.8 $[M+H]^+$. Anal. calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.11; H, 5.21; N, 7.22.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)-4-ethylbenzamide (3h)

Yield: 49%. m.p.: 122–124°C. ATR-FTIR (cm^{-1}): 3310.48 (NH), 2898.16 (-CH stretching), 1690.26 (-CONH-), 1652.22, 1472.52 (C═C), 1462.74 (-CH bend), 1106.28 (C-O), 790.82 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): 1.76 (t, 3H, *J* = 10.5 Hz, -CH_3), 2.65 (q, 2H, *J* = 7.5 Hz, -CH_2-), 3.77 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 6.56 (s, 1H, Hd'), 6.95 (s, 2H, Hb', Hf'), 7.33 (d, 1H, *J* = 1.8 Hz, H7 of benzoxazole), 7.41 (d, 2H, *J* = 7.8 Hz, Hc, He), 7.49 (d, 1H, *J* = 7.8 Hz, H4 of benzoxazole), 7.59 (d, 1H, *J* = 4.8 Hz, H6 of benzoxazole), 7.70 (d, 1H, *J* = 6.0 Hz, Hb), 7.96 (d, 1H, *J* = 7.8 Hz, Hf), 8.18 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.72, 32.49, 56.38, 57.18, 100.29, 104.19, 104.64, 107.18, 111.20, 112.62, 127.49, 127.98, 132.20, 136.20, 142.10, 142.62, 143.20, 146.20, 162.9, 163.20, 163.62, 164.65. (+) ESI-MS (*m/z*): 403.2 $[M+H]^+$. Anal. calcd. for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.62; H, 5.53; N, 6.97.

3,4-Dimethoxy-*N*-(2-(3,5-dimethoxyphenyl)benzoxazol-5-yl)-benzamide (3i)

Yield: 62%. m.p.: 114–116°C. ATR-FTIR (cm^{-1}): 3355.42 (NH), 2950.11 (-CH stretching), 1660.04 (-CONH-), 1610.11, 1465.10 (C═C), 1464.52 (-CH bend), 1110.32 (C-O), 800.60 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): 3.83 (s, 3H, -OCH_3), 3.94 (s, 9H, 3 × -OCH_3), 6.18 (s, 1H, Hd), 6.63 (s, 2H, Hd), 6.63 (s, 2H, Hb', Hf'), 6.92 (d, 1H, *J* = 8.4 Hz, He), 7.35 (d, 1H, *J* = 4.8 Hz, Hf), 7.78 (d, 2H, *J* = 8.4 Hz, H4, H6 of benzoxazole), 8.06 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.20, 56.32, 57.42, 57.64, 100.80, 104.20, 104.82, 108.20, 110.82, 112.60, 116.52, 121.20, 128.14, 128.56, 136.02, 142.22, 146.14, 150.12, 153.60, 163.20, 163.51, 164.85. (+) ESI-MS (*m/z*): 435 $[M+H]^+$. Anal. calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.36; H, 5.09; N, 6.46.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)-4-nitrobenzamide (3j)

Yield: 57%; m.p.: 149–151°C. ATR-FTIR (cm^{-1}): 3280.20 (NH), 2930.6 (-CH stretching), 1664.6 (-CONH-), 1626.2, 1530.4 (C═C), 1535.52, 1398.4 (Ar-NO_2), 1489.6 (-CH bend), 1012.32 (C-O), 810.32 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 6.11 (s, 1H, Hd'), 6.65 (s, 2H, Hb', Hf'), 7.40 (d, 1H, *J* = 2.1 Hz, H7 of benzoxazole), 7.60 (s/d, 2H, *J* = 1.8 Hz, H4, H6 of benzoxazole), 7.72 (d, 1H, *J* = 7.8 Hz, Hb), 7.93 (s, 1H, -NH), 8.09 (d, 1H, *J* = 7.8 Hz, Hf), 8.28 (d, 1H, *J* = 3.3 Hz, Hc), 8.32–8.35 (d, 1H, *J* = 9 Hz, He). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.24, 56.69, 103.85, 104.12, 106.24, 110.01, 112.28, 121.26, 128.41, 128.95, 135.16, 140.34, 141.79, 145.60, 151.96, 162.19, 162.48, 164.62. (+) ESI-MS (*m/z*): 420 $[M+H]^+$. Anal. calcd. for $C_{22}H_{17}N_3O_6$: C, 63.01; H, 4.09; N, 10.02. Found: C, 63.02; H, 4.13; N, 10.03.

2-Chloro-*N*-(2-(3,5-dimethoxyphenyl)benzoxazol-5-yl)-4-nitrobenzamide (3k)

Yield: 35%; m.p.: 115–117°C. ATR-FTIR (cm^{-1}): 3308.2 (NH), 2910.4 (-CH stretching), 1672.2 (-CONH-), 1629.4, 1530.2 (C═C), 1532.6 (Ar-NO_2), 1472.2 (-CH bend), 1168.28 (Ar-Cl), 1112.40 (C-O), 790.2 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 6.61 (s, 1H, Hd'), 6.99 (s, 2H, Hb', Hf'), 7.38 (d, 1H, *J* = 1.2 Hz, H7 of benzoxazole), 7.64 (s/d, 2H, *J* = 6.6 Hz, H4, H6 of benzoxazole), 8.04 (s, 1H, -NH), 8.17 (d, 1H, *J* = 1.8 Hz, Hf), 8.25 (d, 1H, *J* = 1.8 Hz, He), 8.41 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.89, 55.92, 100.44, 103.61, 103.63, 106.21, 110.60, 112.48, 119.39, 124.88, 128.33, 139.36, 133.21, 135.11, 138.46, 141.71, 145.68, 153.21, 162.22, 162.23, 162.41, 164.80. (+) ESI-MS (*m/z*): 454.2 $[M+H]^+$. Anal. calcd. for $C_{22}H_{16}ClN_3O_6$: C, 58.22; H, 3.55; N, 9.26. Found: C, 58.23; H, 3.57; N, 9.27.

N-(2-(3,5-Dimethoxyphenyl)benzoxazol-5-yl)-3-nitrobenzamide (3l)

Yield: 46%; m.p.: 132–134°C. ATR-FTIR (cm^{-1}): 3280.20 (NH), 2930.6 (-CH stretching), 1664.6 (-CONH-), 1626.2, 1530.4 (C═C), 1535.52, 1398.4 (Ar-NO_2), 1489.6 (-CH bend), 1012.32 (C-O) 810.32 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 6H, 2 × -OCH_3),

6.65 (s, 1H, Hd), 7.40 (d, 1H, *J* = 1.5 Hz, H7 of benzoxazole), 7.73 (m, 3H, H4, H6 of benzoxazole merge with He), 8.00 (s, 1H, -NH), 8.32 (dd, 2H, J_1 = 8.4 Hz, J_2 = 2.1 Hz, Hf, Hd), 8.84 (s, 1H, Hb). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.20, 57.12, 104.23, 104.84, 106.20, 110.86, 112.42, 122.48, 124.59, 128.21, 133.40, 135.18, 135.75, 141.72, 145.55, 148.47, 162.70, 163.14, 164.46; (+) ESI-MS (*m/z*): 420.5 $[M+H]^+$. Anal. calcd. for $C_{22}H_{17}N_3O_6$: C, 63.01; H, 4.09; N, 10.02. Found: C, 63.00; H, 4.11; N, 10.04.

4-Methoxy-*N*-(2-(3,5-dimethoxyphenyl)benzoxazol-5-yl)-benzamide (3m)

Yield: 54%. m.p.: 140–142°C. ATR-FTIR (cm^{-1}): 3304.26 (NH), 2890.12 (-CH stretching), 1690.26 (-CONH-), 1638.42, 1479.18 (C═C), 1473.12 (-CH bend), 1109.30 (C-O), 820.20 (out-of-plane, bend). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3H, $-OCH_3$), 3.89 (s, 9H, 3 × $-OCH_3$), 6.36 (s, 1H, Hd'), 6.63 (s, 2H, Hb', Hf'), 7.02 (d, 2H, *J* = 2.1 Hz, Hc, He), 7.40 (d, 1H, *J* = 1.5 Hz, H7 of benzoxazole), 7.64 (d, 2H, *J* = 1.8 Hz, H4, H6 of benzoxazole), 7.89 (d, 2H, *J* = 8.7 Hz, Hb, Hf), 8.03 (s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.69, 57.12, 101.25, 104.60, 104.99, 111.02, 112.58, 114.41, 114.87, 126.52, 128.27, 129.40, 130.04, 135.21, 141.77, 145.69, 162.14, 162.72, 164.12, 164.84. (+) ESI-MS (*m/z*): 405 $[M+H]^+$. Anal. calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.30; H, 4.97; N, 6.94.

4.2 | Biological evaluation

4.2.1 | *In vitro* cyclooxygenase inhibition assay

The *in vitro* inhibition of newly synthesized compounds against COX-1 and COX-2 enzyme was determined using COX (ovine/human) inhibitor screening assay kit (catalog no. 560131). This assay was performed as per the reported literature procedures and manufacturer's assay instructions.[38] The kit is based on the principle of enzyme immunoassay which directly measures $PGF_{2\alpha}$ from PGH_2 produced by reduction with stannous chloride. At the end, the product of enzymatic reaction produces distinct yellow color which absorbs strongly at 412–415 nm. The intensity of the color was determined spectrophotometrically (Bio-Rad ELISA), which is proportional to the amount of PG tracer bound to the well and is inversely proportional to the quantity of free PG's present in the well during incubation. The inhibitory efficacy of novel derivatives was calculated by comparison with various control incubations. The efficiencies of the test compounds that causes 50% inhibition of COX-2 was calculated as IC_{50} from the log concentration versus % inhibition curve.

4.2.2 | *In vivo* activity

Anti-inflammatory activity

The anti-inflammatory activity of the synthesized compounds was evaluated on Wistar albino rat by carrageenan-induced rat paw edema as described by Winter et al.[39] Albino rats weighing 200–250 g were used in the study. The animals were procured from Animal House Center and were divided and housed in different cages at 25–28°C, under well-maintained hygienic and environmental conditions with relative humidity of 50–65%, under 12 h light and dark cycles. All animals were acclimatized for a week before use. The food was withdrawn on the day before the experiment but free access to water was given. All experimental work was conducted according to ethical guidelines and after receiving the approval from Institutional Animal Ethics Committee (IAEC) via protocol no. IAEC/2015-I/Prot no. 09, 10 and IAEC/2016-I/Prot no. 10, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi. The animals were divided into groups consisting of five rats each. Prepared compounds were administered orally (20 mg/kg b.wt.) and the volume of paw was determined plethysmographically (Ugo-Basyl, Italy). Control group received equivalent volume of normal saline and ibuprofen (20 mg/kg b.wt.) was administered orally to the reference group. Carrageenan (0.1 mL, 1.0% w/v in 0.9% of normal saline) was injected after half an hour into the sub-plantar tissue of the rat's hind paw. Difference in paw volume was measured at hourly interval for 3 h (0–3 h). The mean value of treated group was compared with those of control group and analyzed using statistical methods. The percent inhibition of edema was calculated using the following formula:

$$\% \text{ inhibition} = (1 - (V_s/V_c) \times 100)$$

where V_s is the paw volume in the sample-treated group and V_c is the paw volume in the control group.

Acute ulcerogenic activity

The ulcerogenic activity of the prepared analogs was performed according to the reported procedure of Cioli et al.[40] Each study group consisted of five Wistar albino rats. Ibuprofen was used as reference anti-inflammatory drug. The animals were fasted for 18 h before the administration of the test compound, while water was given continuously. The dose quantity was three times (60 mg/kg) of the administered dose for anti-inflammatory studies (20 mg/kg). The control group received only normal saline. After 6 h of the drug administration the rats were sacrificed, stomach was removed and opened around the greater curvature. Inner lining was washed properly with distilled water followed by normal saline. The mucosal damage was inspected and number of ulcers and severity index was calculated on a scale of 0–3, where 0 = no lesions; 0.5 = redness; 1.0 = spot ulcers; 1.5 = hemorrhagic streaks; 2.0 = ulcers > 3 but ≤5; 3.0 = ulcers > 5.

Acute toxicity study

Acute oral toxicity test was carried out according the Organization for Economic Co-operation and Development (OECD) guideline for testing of chemicals number 423. Female Wistar rats were used in this procedure. They were randomly divided into groups containing three rats each. First group served as a control and was given equivalent volume of normal saline. The selected analogue was taken at a dose of 2000, 200, and 20 mg/kg body weight and was given orally to the remaining groups. All the animals were observed continuously

for first 30 min, periodically during the first 24 h and daily thereafter 14 days for behavioral changes and/or death.

4.3 | Computational studies

4.3.1 | Software

The *in silico* experiments were performed on Fujitsu Linux workstation (Xeon quad-core E3-1220 processor). Docking and ADME analyses were carried out using LigPrep 3.0, Impact 6.3, Glide 6.3, and QikProp 4.0 modules of Maestro 9.8 (Schrödinger, LLC, New York, NY, 2014). The ligand and protein interacting behavior was studied using Protein-ligand profiler server.[41] The highly resolved coordinates of human COX-2 were retrieved from RCSB data bank (PDBID-5F19, resolution-2.04 Å).

4.3.2 | Docking study

The crystal structure of human COX-2 (PDB ID: 5F19) was used for molecular docking studies. There are nine *Homo sapiens* COX-2 structures available in RCSB PDB. Among these structures, 5F19 has highest resolution of 2.04 Å and therefore was considered in this study. This structure is aspirin-acetylated human COX-2 in which Ser530 was acetylated.[42] So we mutated this acetylated Ser530 to serine. This protein structure was prepared using Protein Preparation Wizard (Impact 6.3, Schrodinger)[43] as previously described.[44,45] In brief, the structure was processed for addition of hydrogen atoms, formal charges treatment, and assignment of correct bond orders. Structures of the molecules were sketched and prepared using LigPrep 3.0 with Epik 2.8 and tautomeric state and protonation states were expanded at 7.0 ± 2.0 pH units. The OPLS 2005 force field was used for both molecules and protein minimization. The Glide grid was generated by specifying the centroid of the residues His90, Thr94, Arg120, Gln192, Tyr348, Val349, Leu352, Ser353, Gly354, Tyr355, Leu359, Phe381, Leu384, Tyr385, Trp387, Arg513, Ala516, Ile517, Phe518, Gly519, Met522, Val523, Gly526, Ala527, Ser530, and Leu531. Prepared and minimized small molecules were docked into the minimized protein structure using Glide 6.3 XP docking. The 3D complex structures of all molecules were analyzed for Glide score H-bonding, salt bridge, π–π and π–cation interactions.

4.3.3 | ADME study

The ADME properties are imperative to decide the role of a new molecule in drug development process and so are considered as crucial for rational drug design. The lack of best fit ADME parameters of a molecule leads to its denunciation in the progressive stages of drug development process. All the newly synthesized small molecules were analyzed for ADME parameters by QikProp 4.0. The module provides the vision into vital properties of a molecule which decides its safe and druggable behavior like molecular weight, molecular volume, no. of H-bond donors and acceptors, polar surface area, predicted octanol/water partition coefficient and violations related to Lipinski's "Rule of 5."[46]

4.4 | Statistical analysis

Experimental data are expressed as mean. Statistical difference between the treated and control group was evaluated by one way analysis of variance (ANOVA) followed by Tukey's test as a post ANOVA (GraphPad Prism 5, San Diego, USA) to determine the statistical significance. p-Value <0.05 was considered statistically significant.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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REFERENCES

[1] L. L. Thomas, D. A. Williams, *Foye's Principles of Medicinal Chemistry*, 7th ed., Vol. 53, Lippincott William and Wilkins, North America **2013**, p. 987.
[2] S. A. Khan, S. M. Imam, A. Ahmad, S. H. Basha, A. Husain, *J. Saudi Chem. Soc*. **2017**, 469.
[3] N. Zidar, K. Odar, D. Glavac, M. Jaerse, T. Zupanc, D. Stajer, *J. Cell. Mol. Med*. **2009**, *13*, 3755.
[4] C. Bombardier, *Am. J. Cardiol*. **2002**, *89*, 3.
[5] S. Fiorucci, E. Distrutti, *Curr. Med. Chem*. **2011**, *18*, 3494.
[6] B. Cryer, *Am. J. Gastroenterol*. **2005**, *10*, 1694.
[7] M. Lazzaroni, P. G. Bianchi, *Pharmacol. Ther*. **2004**, *20*, 48.
[8] A. D. Capua, C. Sticozzi, S. Brogi, M. Brindisi, A. Cappelli, L. Sautebin, A. Rossi, S. Pace, C. Ghelardini, L. D. C. Mannelli, C. Valacchi, G. Giorgi, A. Giordani, G. Poce, M. Biava, M. Anzini, *Eur. J. Med. Chem*. **2016**, *109*, 99.
[9] D. Adebayo, I. Bjarnason, *Postgrad. Med. J*. **2006**, *82*, 186.
[10] V. Schneider, L. E. Levesque, B. Zhang, T. Hutchinson, J. M. Brophy, *Am. J. Epidemiol*. **2006**, *164*, 881.
[11] G. Mounier, C. Guy, F. Berthoux, M. N. Beyens, M. Ratrema, M. Ollagnier, *Therapie*. **2006**, *61*, 255.
[12] S. Baytas, N. N. T. Dural, Y. S. Ozkan, H. B. Simsek, T. Gursel, S. Unlu, *Turk. J. Chem*. **2012**, *36*, 367–382.
[13] D. Dogne, C. T. Supuran, D. Pratico, *J. Med. Chem*. **2005**, *48*, 2251.

[14] R. A. K. Abdellatif, E. K. A. Abdelall, W. A. A. Fadaly, G. M. Kamel, *Bioorg. Med. Chem. Lett*. **2006**, *26*, 406.
[15] S. S. R. Alsayed, H. A. H. Elshemy, M. A. Abdelgawad, M. S. A. Latif, *Bioorg. Chem*. **2017**, *17*, 173.
[16] C. K. Khatri, K. S. Indalkar, C. R. Patil, S. N. Goyal, G. N. Chaturbhuj, *Bioorg. Med. Chem. Lett*. **2017**, *27*, 1721.
[17] N. M. Raghvendra, A. Jyothsna, A. V. Rao, C. V. S. Subrahmanyam, *Bioorg. Med. Chem. Lett*. **2012**, *22*, 820.
[18] H. G. Pilli, F. Ozkanli, C. Safak, H. Erdogan, S. Unlu, B. Gumusel, R. Demirdamar, *Die Pharmazie* **1994**, *49*, 63.
[19] R. Paramashivappa, P. P. Kumar, P. V. S. Rao, A. S. Rao, *Bioorg. Med. Lett*. **2003**, *13*, 657.
[20] S. M. Sondi, N. Singh, A. Kumar, O. Lozach, L. Meijer, *Bioorg. Med. Chem*. **2006**, *14*, 5850.
[21] S. Ampati, J. V. Vidyasagar, K. Swathi, M. Sarangapani, *J. Chem. Pharm. Res*. **2010**, *2*, 213.
[22] A. K. Chakraborti, K. Seth, S. K. Garg, R. Kumar, P. Purohit, V. S. Meena, R. Goyal, U. C. Banerjee, *Med. Chem. Lett*. **2014**, *5*, 512.
[23] M. Asif, *Mod. Chem. Appl*. **2016**, *4*, 1.
[24] E. A. Sener, O. T. Arpaci, I. Yalcin, N. Altanlar, *Farmaco* **2002**, *57*, 771.
[25] O. I. Yildiz, G. B. Tekiner, I. Yalcin, O. A. Temiz, A. E. Sener, N. Altanlar, *Arch. Pharm*. **2004**, *337*, 402.
[26] A. Fatima, R. Kulkarni, B. Mantipragada, *Med. Chem*. **2015**, *5*, 521.
[27] H. Gadegoni, S. Manda, S. Rangu, *J. Korean Chem. Soc*. **2013**, *57*, 221.
[28] B. J. Kim, J. Kim, Y. K. Kim, S. Y. Choi, H. P. Y. Choo, *Bull. Korean Chem. Soc*. **2010**, *31*, 1270.
[29] N. Siddiqui, M. Sarafaroz, M. Alam, W. Ahsan, *Acta Polo. Pharm. Drug Res*. **2008**, *65*, 449.
[30] V. A. Chatpalliwar, J. S. Jadhav, S. C. Khadse, R. R. Patil, *Ind. J. Heterocycl. Chem*. **2008**, *17*, 343.
[31] C. Safak, H. Erdogan, E. Palaska, R. Sunal, S. Duru, *J. Med. Chem*. **1992**, *135*, 1296.
[32] K. Seth, S. K. Garg, R. Kumar, P. Purohit, V. S. Meena, R. Goyal, U. C. Banerjee, A. K. Chakraborti, *ACS. Med. Chem. Lett*. **2014**, *5*, 512.
[33] J. W. Jeong, I. W. Choi, G. K. Jo, J. Kim, H. Su, C. H. Ryu, W. J. Kim, K. Y. Park, Y. H. Choi, *J. Med. Food* **2015**, *18*, 1.
[34] H. Kumar, A. Shah, M. E. Sobhia, *J. Mol. Model*. **2012**, *18*, 1791.
[35] H. Kumar, R. Kumar, B. K. Grewal, M. E. Sobhia, *Chem. Biol. Drug Des*. **2016**, *78*, 283.
[36] H. Kumar, F. Frischknecht, G. R. Mair, J. Gomes, *Infect. Genet. Evol*. **2015**, *36*, 72.
[37] A. M. H. Shkair, A. K. Shakya, N. M. Raghvendra, R. R. Naik, *Med. Chem*. **2016**, *12*, 90.
[38] S. Consalvi, S. Alfonso, A. D. Capua, G. Poce, A. Pirolli, M. Sabatino, R. Ragno, M. Anzini, S. Sartini, C. L. Motta, L. D. C. Mannelli, C. Ghelardini, M. Biava, *Bioorg. Med. Chem. Lett*. **2015**, *23*, 810.
[39] C. A. Winter, E. A. Risley, G. W. Nuss, *Proc. Soc. Exp. Boil*. **1962**, *111*, 544.
[40] V. Cioli, S. Putzolu, V. Rossi, P. S. Barcellona, C. Corradino, *Toxicol. Appl. Pharmacol*. **1979**, *50*, 283.
[41] S. Salentin, S. Schreiber, V. J. Haupt, M. F. Adasme, M. Schroeder, *Nucl. Acids Res*. **2015**, *43*, 443.
[42] A. A. Bekhit, A. M. Farghaly, R. M. Shafik, M. M. A. Elsemary, M. S. E. Shoukrofy, A. E. A. Bekhit, T. M. Ibrahim, *Future Med. Chem*. **2017**, 881.
[43] Maestro (v9.8), New York: Schrodinger, LLC **2014**.
[44] V. Sharma, H. Kumar, S. Wakode, *RSC Adv*. **2016**, *6*, 75805.
[45] V. Sharma, S. Wakode, *J. Biomol. Struct. Dyn*. **2017**, *35*, 1339.
[46] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev*. **1997**, *23*, 4.

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