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Synthesis of substituted fluorobenzimidazoles as inhibitors of 5-lipoxygenase and soluble epoxide hydrolase for anti-inflammatory activity

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Abstract

A new series of 4-((5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-benzoic acids **4a–o** and 2-(5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acids **8a–e** were synthesized, and their inhibitory potencies against soluble epoxide hydrolase (sEH) and 5-lipoxygenase (5-LOX) were investigated. These molecules were designed based on the combination of 5-LOX and sEH pharmacophores, resulting in hybrid analogs with potent sEH and 5-LOX inhibitory activity. Compound **4g** showed remarkable activity with IC_{50} values of less than 1 μM (0.9 μM) against 5-LOX, while compound **4k** displayed promising activity against sEH with $IC_{50} \leq 1$ μM (0.7 μM). These compounds were evaluated for their *in vivo* potential using the carrageenan-induced rat paw edema assay. Based on the obtained results, the structure–activity relationship was established and a correlation between the activities was observed. Compounds **4f**, **4g**, **4k**, **4n**, and **8e** showed potent anti-inflammatory activity and significant inhibition of edema (64.13, 67.39, 66.30, 65.21, and 58.69%, respectively) at a dose of 100 mg/kg, comparable to the standard drug ibuprofen (70.65%) at 3 h.

KEYWORDS
5-lipoxygenase, anti-inflammatory activity, fluorobenzimidazole, rat paw edema, soluble epoxide hydrolase

1 | INTRODUCTION

Lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP 450) epoxygenase are the key enzymes within the arachidonic acid (AA) cascade, where they play vital roles in the synthesis of prostaglandins (PGs), leukotrienes (LTs), and undesirable pro-inflammatory mediators leading to inflammation and pain.[1,2] Various inflammatory diseases are associated with the excessive formation of LTs and PGs. In the past three decades, significant effort has been directed toward the understanding of numerous biological roles of mediators of inflammation and beneficial effects of selective inhibiton of COX, LOX, and soluble epoxide hydrolase (sEH). Among the three isoforms of LOXs, the enzyme primarily responsible for the role in the inflammatory process was found to be 5-lipoxygenase (5-LOX), due to its key role in LTs biosynthesis.[3,4] COX enzymes exist in two isoforms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).[5] In contrast to the constitutive COX-1, the inducible COX-2 is expressed in many tissues and the prostaglandins produced by COX-2 play a major role in inflammatory reactions, and are responsible for the characteristic inflammatory symptoms.[6] The preferential binding of selective inhibitors to the COX-2 enzyme over COX-1 enzyme prevents the side effects associated with the COX-1 inhibition.[7]

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The enzyme sEH is a novel target for pharmacologic therapies of inflammation as it is actively involved in the conversion of EETs (epoxyeicosatrienoic acids) to DHETs (dihydroxyeicosatrienoic acids), and EETs are key anti-inflammatory mediators that are generated by the CYP 450 enzymes by catalyzing the epoxidation of AA.[8] There is recent evidence that when EETs are stabilized by sEH inhibitors, they have dramatically increased anti-inflammatory properties due to the rise in localized endogenous EETs levels.[9,10] Efficacies of selective inhibitors of sEH in acute animal models of inflammatory disease have been demonstrated to produce beneficial effects, as they were found to possess marked anti-inflammatory activity.[11,12] Furthermore, it was demonstrated using a xylene-induced ear edema model in mice that sEH inhibition reduces inflammation *in vivo*.[13] Accordingly, any agent that inhibits sEH is expected to be of considerable therapeutic value for the treatment of conditions associated with local or systemic inflammation. Dual inhibitors able to block equally the COX/LOX, COX/sEH, or LOX/sEH enzymatic pathways offer a better alternate approach in designing a new drug with a superior anti-inflammatory profile with fewer side effects than targeting a single enzyme or pathway inhibition.[14–17] Nimesulide, sorafenib, dCP2PU (1-(3, 4-dichlorophenyl)-3-(4-phenoxyphenyl)urea), t-AUCB (*trans*-4-[4-(3-adamantan-1-ylureido)-cyclohexyloxy]-benzoic acid), t-TUCB (*trans*-4-[4-(3-trifluoromethoxyphenyl-1-ureido)-cyclohexyloxy]-benzoic acid), and RWJ-63556 are some of the aryl ether analogs with potential *in vitro* and *in vivo* anti-inflammatory activity,[18–21] as depicted in Figure 1. Benzimidazole analog **2** inhibits sEH with IC_{50} value of 0.6 μM and compound **3** inhibited 5-LOX and sEH with IC_{50} values of 36 and 3.5 μM, respectively.[22,23] Recently synthesis and structure–activity relationship (SAR) of some halogenated phenyl ether triazole-based compounds as potent dual mPGES-1 and 5-LOX inhibitors were reported, and biological evaluation of selected compounds from the data set has disclosed three new potential anti-inflammatory drugs.[24,25] Benzimidazole scaffolds and their bioisosteres are well known as a privileged scaffold in drug discovery. Benzimidazole analogues have been reported as effective anti-inflammatory agents with COX-2 and 5-LOX inhibiting action.[26–32] Several non-urea derivatives and aminoheterocycles as amide mimics were reported as potent sEH inhibitors, and to our knowledge very few papers have been published on the synthesis and *in vitro* evaluation of benzimidazoles as sEH inhibitors.[33–36]

In light of these observations, and our exploration for new molecules with anti-inflammatory activity that embody these structural characteristics encouraged us to design and synthesize new aryl ether substituted fluorobenzimidazoles for examination as inhibitors of sEH and 5-LOX for anti-inflammatory activity. Current research focuses on the design of multi-target ligands interfering with AA cascade. We chose the strategy of designed multiple ligands (DMLs) involving dual inhibition of 5-LOX and sEH. The main design strategy of DMLs comprises the linking of two selective pharmacophores leading to only one active compound,[37–39] targeting various steps of the AA cascade. Benzimidazole core (central linker) was combined with benzoic acid moiety on one side and aryl ether linkage on the other. The latter is responsible for inhibitory activity on 5-LOX, while the benzoic acid motif is supposed to inhibit sEH. Both the primary and secondary pharmacophore share the common acidic imide linkage present in the bezimidazole ring (Figure 2). While evidence from *in vitro* studies does not prove *in vivo* biological activity, these do provide a rationale and support for the possible use of these novel compounds to suppress inflammation *in vivo*. The approach of dual inhibition of sEH and 5-LOX has been proposed as a more promising initiative for the development of safer drugs in inflammatory disorders. Accordingly, sEH and 5-LOX inhibition was evaluated and furthermore the compounds were screened for anti-inflammatory activity by carrageenan-induced rat paw edema method. Keeping in view the benefits of DMLs, an attempt was made to combine the structural characteristics of some potent sEH and 5-LOX inhibitors. Association of such pharmacophoric groups has led to some novel sEH/5-LOX dual inhibitors with *in vitro* and *in vivo* anti-inflammatory activity.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

As illustrated in Schemes 1 and 2, designed molecules **4a–o** and **8a–e** were prepared via a two-step process involving *S*-alkylation of substituted-2-mercaptobenzimidazoles **1a–o** followed by hydrolysis of the resulting ester. The substituted-2-mercaptobenzimidazoles **1a–o** required for the synthesis of esters **3a–o** were prepared as described in the earlier report.[40] The esters **3a–o** were obtained by *S*-alkylation of substituted-2-mercaptobenzimidazoles **1a–o** with methyl 4-(bromomethyl)benzoate **2** in the presence of potassium carbonate in dry DMF at room temperature. The crude esters **3a–o** so obtained were used for the next step without further purification. Hydrolysis of the ester group in compounds **3a–o** under alkaline condition followed by acidification yielded the desired benzoic acids **4a–o** (Scheme 1).

A similar synthetic protocol was adopted for the synthesis of 2-(6-(substituted)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acids **8a–e** under same conditions as depicted in Scheme 2. The esters **7a–e** obtained by S_N2 reaction of substituted-2-mercaptobenzimidazoles **5a–e** with ethyl-2-bromo-2-methylpropionate **6** were subjected to alkaline hydrolysis to afford the propanoic acids **8a–e**.

The structures of the newly synthesized substituted fluorobenz imidazoles were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. ^{1}H NMR spectral analysis of compounds **4a–o** showed a singlet at 4.59–4.65 ppm, due to the presence of the methylenic —CH_2— proton and another singlet at 12.22–12.98 ppm corresponding to one proton of COOH group. IR spectrum characteristic bands were observed at 3398–3425 cm^{-1} and 2910–2969 cm^{-1}, assignable to stretching vibrations of the NH and benzylic S-CH_2 respectively. While C═O stretching bands of carboxylic acid appeared from 1689 to 1710 cm^{-1}, the OH stretching bands was observed from 3200 to 3300 cm^{-1} in the IR spectra of the compounds **4a–o**. The ^{13}C NMR results showed that the compounds presented the expected carbonyl signal at δ 166–170 ppm and methylene signal at δ 33–35 ppm.

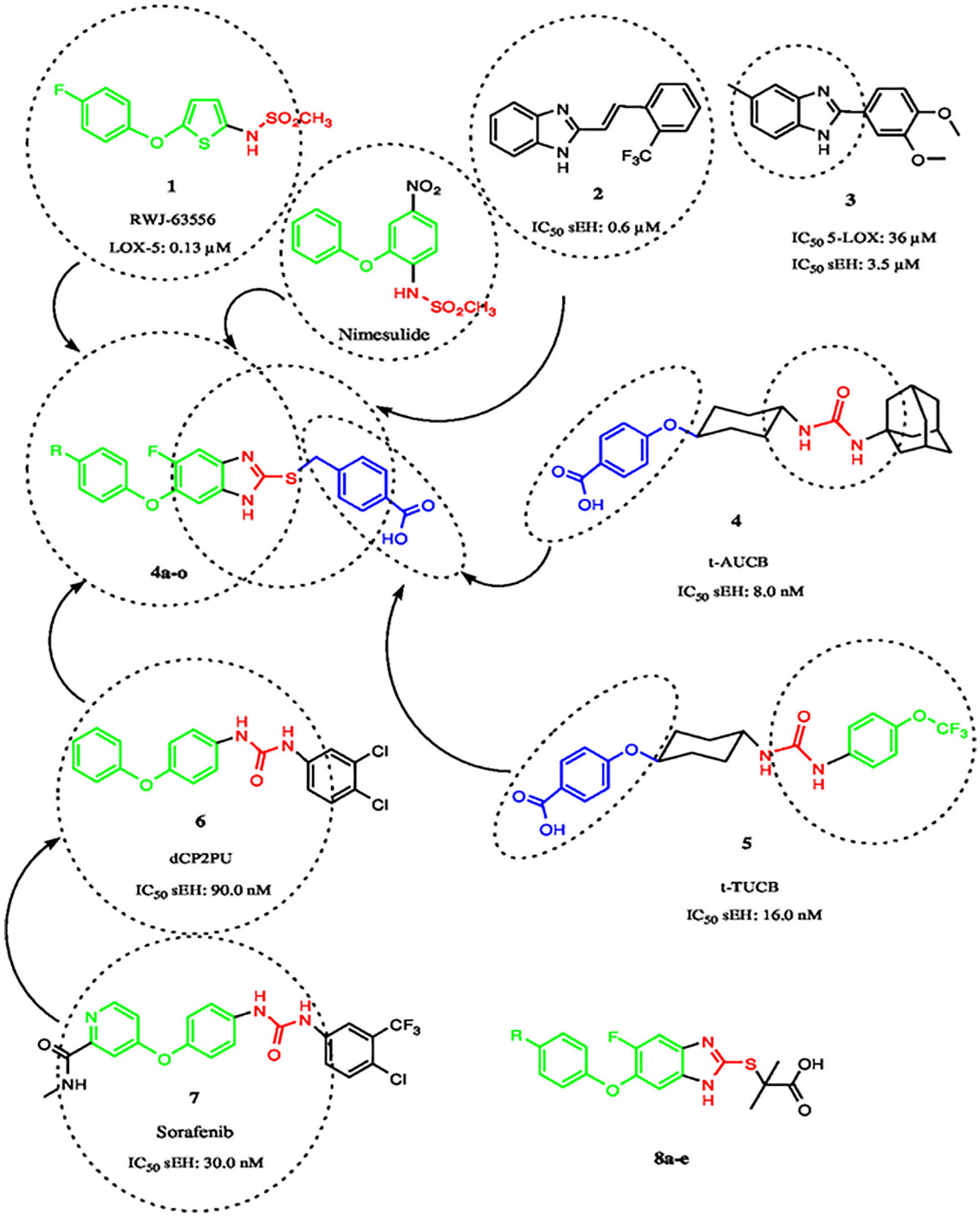


FIGURE 1 Chemical structures of some representative 5-LOX and sEH inhibitors reported in the literature and of the synthesized substituted fluorobenzimidazoles (**4a–o** and **8a–e**) as anti-inflammatory agents

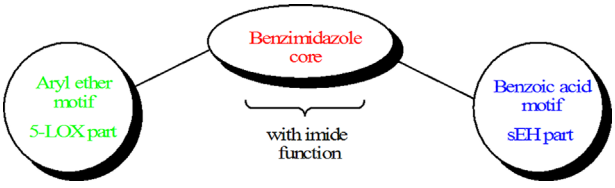
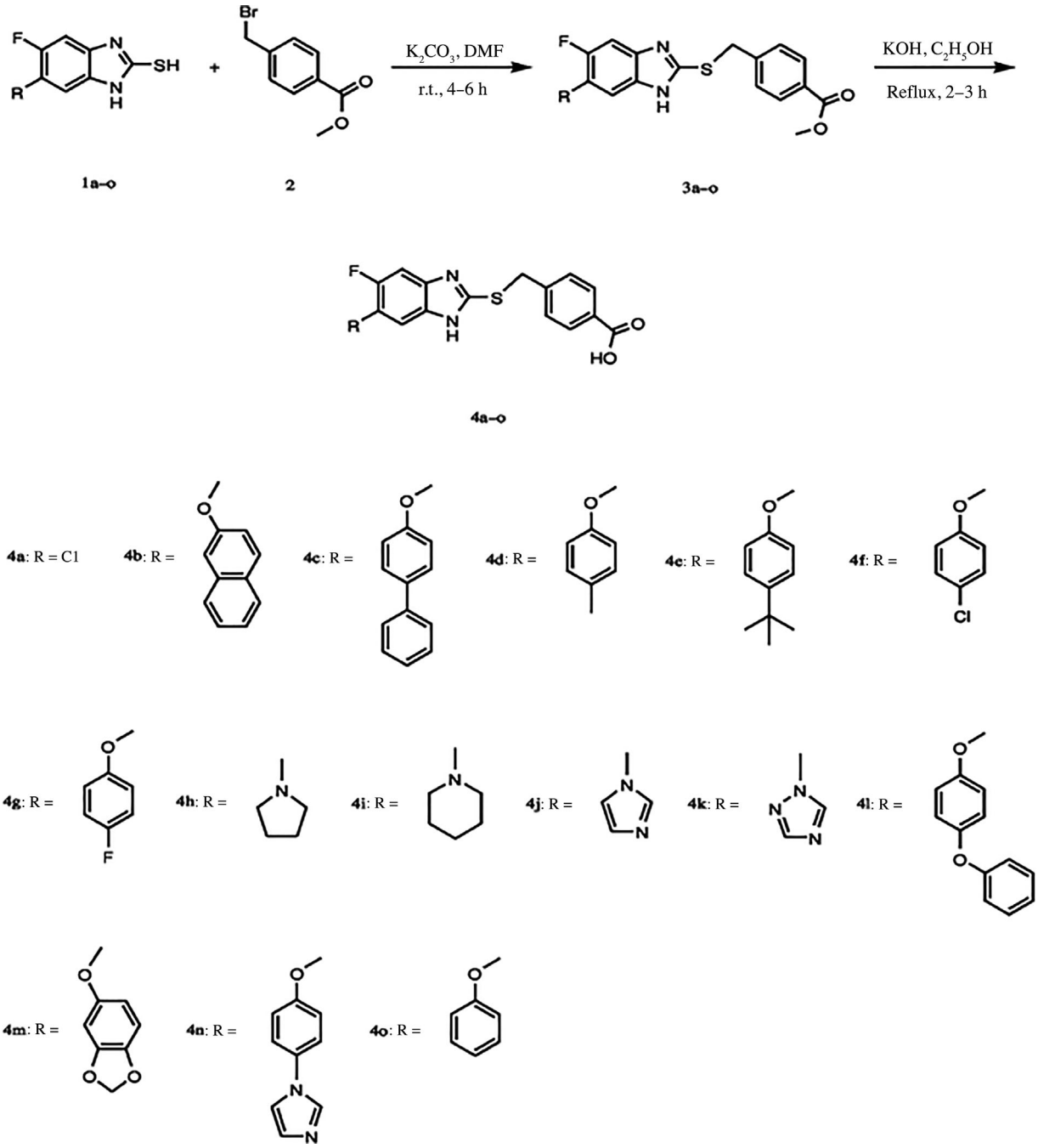


FIGURE 2 5-LOX and sEH dual inhibitor pharmacophore model

On the other hand, IR spectra of compounds with 2-methyl propanoic acid head **8a–e** exhibited the absorption band at around 1700–1735 cm^{-1} (CO stretch) and 3210–3250 cm^{-1} (OH stretch), indicating the presence of carboxyl group. The ^{1}H and ^{13}C NMR spectra further support the presence of acid group. The ^{1}H NMR spectrum displayed COOH proton signal as a singlet at 12.88–13.59 ppm, while carbonyl carbon appeared at δ 169–175 ppm in the



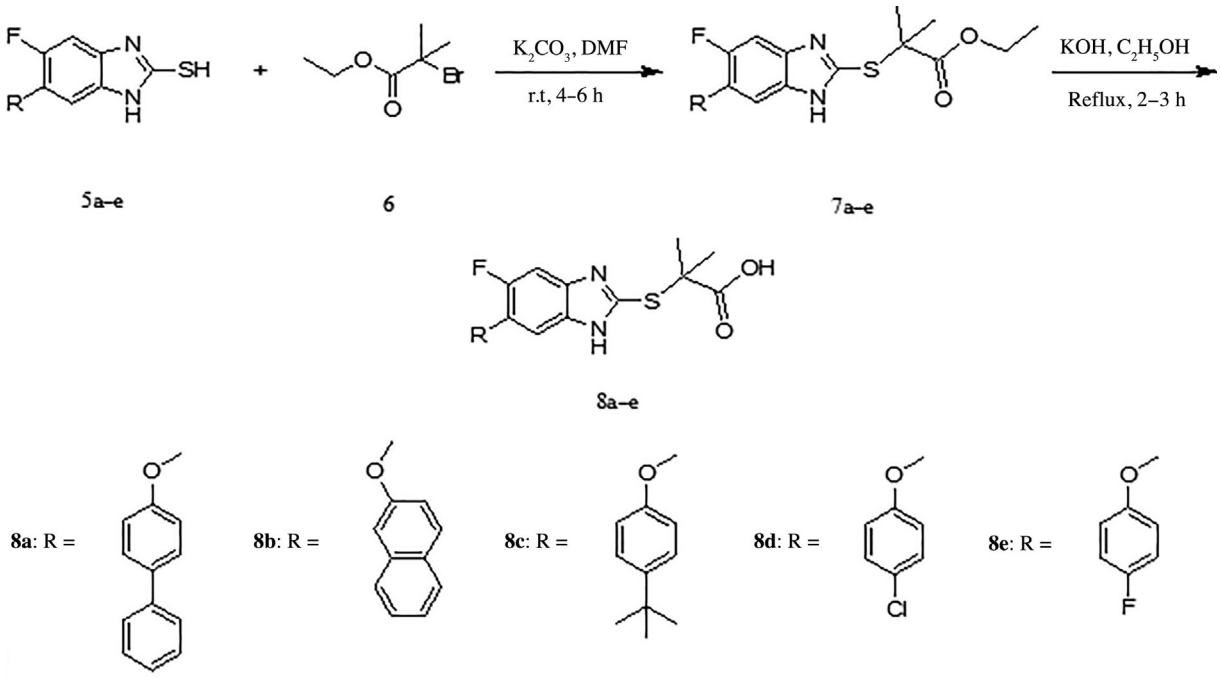
SCHEME 1 Synthesis of compounds **4a–o**

^{13}C NMR spectrum. IR spectra showed bands at 2914–2969 cm^{-1}, attributed to a methyl group. The presence of strong bands at 3406–3425 cm^{-1} was clear indication of NH stretching. The ^{1}H NMR spectrum revealed the presence of signals for methyl groups resonating between δ 1.53 and 1.60 ppm as singlets. In the ^{13}C NMR spectrum, the two carbons of the methyl groups were visible at δ 26–27 ppm, while the quaternary carbon attached to the methyl groups was observed at δ 50–53 ppm. The mass spectra were in agreement with the suggested structures of all the synthesized compounds.

2.2 | Biological evaluation

2.2.1 | *In vitro* soybean lipoxygenase and sEH inhibition

Test compounds and inhibitors were screened for potency *in vitro* against recombinant human sEH and soybean lipoxygenase. The concentration of the test compounds and inhibitors that reduces the enzyme activity by 50% was designated as IC_{50}. The test compounds were assayed for soybean lipoxygenase and sEH inhibitory activity in



SCHEME 2 Synthesis of compounds **8a–e**

triplicates, and the IC_{50} values are reported as the average of the obtained results with at least two points in the linear region of the curve on either side of the IC_{50} (Table 1).

RWJ-63556 which is structurally related to nimesulide and its analogues is an acidic anti-inflammatory drug, and was reported as a potent orally active 5-LOX inhibitor. Acidic nature of RWJ-63556 is attributed to the presence of a sulfonanilide group. As depicted in Figure 3, our strategy was based on incorporating the two key pharmacophores of RWJ-63556 in the benzimidazole ring. Primary pharmacophore in RWJ-63556 is a diaryl ether function, while the secondary pharmacophore is an acidic NH group. We have investigated new molecules designed by retaining these two pharmacophores in the benzimidazole ring for 5-LOX inhibitory activity.

This compound displayed significant anti-inflammatory activity in a canine model of local inflammation, and served as lead compound for the synthesis of compounds **4b–g** and **4l–o**, retaining the 5-LOX pharmacophores present in RWJ-63556. The synthesized compounds **4a–o** were tested for their ability to inhibit 5-LOX. Among the tested compounds, aryl ether analogs **4f** and **4g** with electron withdrawing Cl (IC_{50} = 3 μM) and F (IC_{50} = 0.9 μM) at 4-position of the 6-phenyl ring were found to exhibit significant 5-LOX inhibitory activity. The other aryl ether analogs **4b** (IC_{50} = 27 μM), **4c** (IC_{50} = 10 μM), **4d** (IC_{50} = 17 μM), and **4e** (IC_{50} = 21 μM) also exhibited good, although not the best 5-LOX inhibitory action. It was found that introduction of heterocyclic amines like pyrrolidine **4h** (IC_{50} = 89 μM) and piperidine **4i** (IC_{50} = 77 μM) proved to be detrimental for activity. However, introduction of aromatic azoles like imidazole **4j** (IC_{50} = 32 μM) and triazole **4k** (IC_{50} = 35 μM) exhibited moderate activity. These results illustrated that aryl ether function at 6-position of the benzimidazole ring with electron withdrawing group at 4-position of the aromatic ring was important for 5-LOX inhibitory activity. The *in vitro* 5-LOX inhibitory activity of phenyl ether analog **4o** (IC_{50} = 14 μM) was comparable to the compounds **4c** and **4d** with IC_{50} values of 10 and 17 μM. Compound **4a**, with a chlorine atom at 6-position of the benzimidazole ring, was found to be least active of the series with IC_{50} value of 63 μM.

As discussed in Section 1, there are several excellent lead structures under investigation as sEH inhibitors. An effort toward designing novel synthetic inhibitors of sEH based on reported active lead compounds resulted in a series of fluorobenzimidazoles **4a–o**. Inhibition potency of the described compounds ranges from 0.7 to 100 μM against recombinant human sEH. Compared to the unsubstituted benzimidazole compound **4a** (IC_{50} = 41 μM), the inhibition potencies increased dramatically when 6-chlorine in **4a** was replaced with aryl ethers resulting in compounds **4b** (IC_{50} = 14 μM), **4c** (IC_{50} = 2.7 μM), **4d** (IC_{50} = 12 μM), **4e** (IC_{50} = 10 μM), **4f** (IC_{50} = 7 μM), and **4g** (IC_{50} = 4 μM). Analogues **4f** and **4g** with electron withdrawing Cl and F showed a dramatic increase in potency over other aryl ethers **4b–e**. Likewise, replacement of the 6-chlorine atom in **4a** with aromatic azoles yielded **4j** and **4k** as potent inhibitors of human sEH. Compound **4k** with triazole ring was found to be a potent inhibitor of sEH (IC_{50} = 0.7 μM), with activity better than derivative **4j** (IC_{50} = 1.8 μM) with isosterically replaced imidazole ring. Introduction of pyrrolidine and piperidine ring in the 6-position of the benzimidazole ring, resulted in compounds **4h** (IC_{50} = 77 μM) and **4i** (IC_{50} = 100 μM), with a significant drop in potency compared to the other derivatives. Interestingly, the unsubstituted phenyl ether analog **4o** (IC_{50} = 25 μM) was the least active.

TABLE 1 *In vitro* screening of the synthesized compounds (**4a–o**, **8a**, and **8e**) for 5-LOX and sEH inhibitory activity

Compound[a]	5-LOX inhibitory activity (IC_{50}[d], μM)	sEH inhibitory activity (IC_{50}[d], μM)
4a	63	41
4b	27	14
4c	10	2.7
4d	17	12
4e	21	10
4f	**3**	7
4g	**0.9**	4
4h	89	77
4i	77	100
4j	32	**1.8**
4k	35	**0.7**
4l	45	17
4m	49	19
4n	30	3.1
4o	14	25
8a	19	>100
8e	5	>100
t-AUCB[b]	–	**2 nM**
NDGA[c]	**12.5**	–

[a]Detailed structures are shown in Schemes 1 and 2.
[b]A fluorescent-based assay was performed and *t*-AUCB used as a positive control was found to have an IC_{50} value of 2 nM.[44]
[c]Nordihydroguaiaretic acid (NDGA) was used as positive control for 5-LOX inhibitory activity by UV absorbance-based enzyme assay.
[d]For each compound, the percent inhibition was determined in triplicates. Synthesized compounds and standard drugs in bold - showing significant inhibition.

Having established the role of aryl ether linkage for 5-LOX inhibition and heteroaromatic azole linkage for sEH inhibition at 6-position, hybrid analog **4n** was synthesized. The molecular hybrid **4n** (IC_{50} = 30 μM) with aryl ether linkage at 6-position bearing an imidazole ring at 4-position of the phenyl ring has significantly enhanced the 5-LOX inhibitory activity as compared to diether analog **4l** (IC_{50} = 45 μM) and compound **4m** (IC_{50} = 49 μM) with methylenedioxyphenyl moiety. On the other hand, *N*-phenoxyimidazole substituted compound **4n** (IC_{50} = 3.1 μM) was more active compared to diether **4l** (IC_{50} = 17 μM) and methylenedioxyphenyl containing benzimidazole molecule **4m** (IC_{50} = 19 μM), that are well tolerated with moderate sEH inhibitory activity. The novel hybrid compound **4n** demonstrated an *in vitro* 10-fold increase in potency against sEH relative to 5-LOX inhibition.

In continuation of these studies, and in order to gain more insight on the SAR, compounds with an aliphatic carboxylic head were synthesized and evaluated for *in vitro* anti-inflammatory activity. Among the compounds containing the propanoic acid group, **8a** and **8e** were the selected candidates for *in vitro* anti-inflammatory activity. Replacement of benzoic acid head with aliphatic propanoic acid function resulted in a significant decrease in sEH inhibition (IC_{50} = >100 μM), while the 5-LOX inhibitory activity for the compounds **8a** (IC_{50} = 19 μM) and **8e** (IC_{50} = 5 μM) was retained. Importantly, this observation suggested that aryl ether linkage at 6-position plays an important role in determining the anti-inflammatory activities of these analogs. The study also suggested that the aryl ether linkage is required for 5-LOX inhibiton, while benzoic acid part is essential for the sEH inhibitory activity. We found that the compound with fluorophenyl ether linkage at 6-position **8e** appeared to be the most potent 5-LOX inhibitor among the propanoic acid derivatives synthesized.

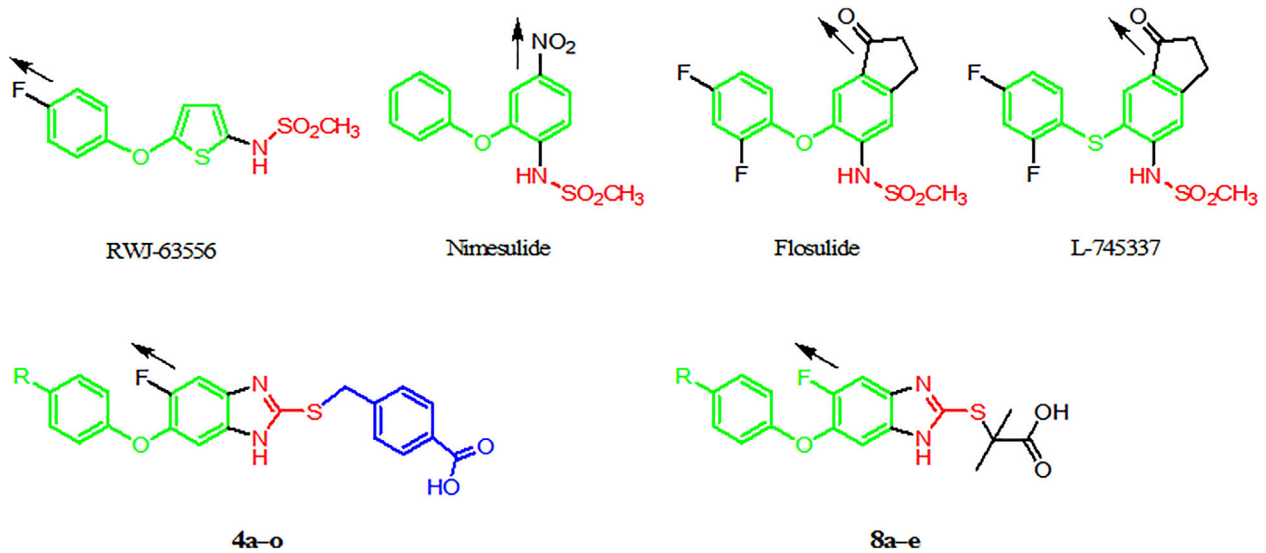


FIGURE 3 Rationale for the design and synthesis of the substituted fluorobenzimidazoles (**4a–o** and **8a–e**) as anti-inflammatory agents, and the importance of an acidic NH group in the representative anti-inflammatory agents and synthesized compounds for 5-LOX inhibitory activity

2.2.2 | *In vivo* inhibition of carrageenan-induced paw edema

All the newly synthesized fluorobenzimidazoles **4a–o** were screened for *in vivo* anti-inflammatory activity by employing carrageenan-induced rat paw edema method and the results are summarized in Tables 2 and 3. Most of the test compounds showed appreciable inhibition of the edema size in comparison with standard drug ibuprofen. The tested compounds showed anti-inflammatory activity ranging from 45.65 to 67.39%, whereas the reference drug ibuprofen showed 70.65% inhibition after 3 h. The *in vivo* anti-inflammatory activity data revealed that the substitution pattern at 6-position of the benzimidazole ring seemed to have different influence on the inhibition of inflammation, i.e., paw edema. The unsubstituted fluorobenzimidazole counterpart **4a** was synthesized to see its effect on activity profile, and was found to have the least inhibitory effect with percent inhibition of 45.65%. Among the aryl ether derivatives, compounds **4b–e** with alkyl or aryl substituents showed good anti-inflammatory activity with a percent inhibition of 52.17, 56.52, 57.60, and 55.43%, respectively. In the ether series, the phenyl ether analog **4o** was least active with 50.00% inhibition. On the other hand, a considerable increase in activity was observed in compounds **4f** and **4g** containing chlorine and fluorine with a percent inhibition of 64.13 and 67.39% comparable to the standard drug ibuprofen. The result shows that an electron-withdrawing group increases the anti-inflammatory activity of the compound. Another feature observed during the study is that the analogues **4j** and **4k** with imidazole and 1,2,4-triazole at C-6 on the phenyl ring of fluorobenzimidazole show better anti-inflammatory properties (59.78 and 66.30%) than the analogues **4h** and **4i** substituted with alicyclic amines (48.91 and 47.82%). Surprisingly, the hybrid analogue **4n** showed 65.21% inhibition comparable to ibuprofen at 3 h. The SAR was not very discernable for compounds **4e** and **4m** that were equipotent with 55.43% inhibition, while compound **4l** with 53.26% inhibition displayed activity similar to **4b** with 52.17% inhibition.

On the other hand, compounds **8a** and **8e** with propanoic acid function were well tolerated and showed good anti-inflammatory activity (53.26 and 58.69%). In this series **8e** emerged as the potent analogue.

SAR study reveals that imidazole and triazole substituted derivatives (**4j** and **4k**), and compounds with F and Cl bearing ether linkage at C-6 on the phenyl ring of fluorobenzimidazole (**4f** and **4g**), were the most active of all the compounds and showed significant inhibitory activity both *in vitro* and *in vivo*. Clear correlation between *in vitro* activity for 5-LOX and sEH inhibition, and *in vivo* activity for inhibition of edema (%) by test compounds, has been established.

TABLE 2 Anti-inflammatory activity of the tested compounds using acute carrageenan-induced paw edema in rats at 100 mg/kg body weight

			Mean paw edema volume in mL ± SEM[a,b]			
Groups	**Treatment**	**Dose (mg/kg) orally**	**1 h**	**2 h**	**3 h**	**4 h**
I	Control	1% CMC[c]	0.34 ± 0.004	0.70 ± 0.006	0.92 ± 0.003	0.95 ± 0.006
II	Ibuprofen	100	0.23 ± 0.009	0.36 ± 0.008	0.27 ± 0.006	0.38 ± 0.003
III	**4a**	100	0.26 ± 0.013	0.47 ± 0.022	0.50 ± 0.011	0.53 ± 0.022
IV	**4b**	100	0.27 ± 0.008	0.45 ± 0.004	0.44 ± 0.006	0.52 ± 0.006
V	**4c**	100	0.24 ± 0.013	0.42 ± 0.006	0.40 ± 0.013	0.58 ± 0.013
VI	**4d**	100	0.30 ± 0.009	0.52 ± 0.022	0.39 ± 0.011	0.45 ± 0.013
VII	**4e**	100	0.30 ± 0.009	0.54 ± 0.011	0.41 ± 0.009	0.43 ± 0.022
VIII	**4f**	100	0.27 ± 0.008	0.48 ± 0.013	0.33 ± 0.008	0.40 ± 0.008
IX	**4g**	100	0.25 ± 0.011	0.40 ± 0.022	0.30 ± 0.022	0.49 ± 0.011
X	**4h**	100	0.23 ± 0.009	0.38 ± 0.011	0.47 ± 0.006	0.50 ± 0.006
XI	**4i**	100	0.28 ± 0.004	0.49 ± 0.006	0.48 ± 0.011	0.52 ± 0.006
XII	**4j**	100	0.29 ± 0.011	0.50 ± 0.005	0.37 ± 0.004	0.55 ± 0.011
XIII	**4k**	100	0.25 ± 0.011	0.42 ± 0.008	0.31 ± 0.010	0.47 ± 0.010
XIV	**4l**	100	0.27 ± 0.008	0.41 ± 0.004	0.43 ± 0.006	0.51 ± 0.006
XV	**4m**	100	0.28 ± 0.004	0.48 ± 0.013	0.41 ± 0.009	0.45 ± 0.013
XVI	**4n**	100	0.24 ± 0.013	0.44 ± 0.003	0.32 ± 0.011	0.48 ± 0.004
XVII	**4o**	100	0.31 ± 0.002	0.53 ± 0.009	0.46 ± 0.007	0.46 ± 0.005
XVIII	**8a**	100	0.25 ± 0.007	0.41 ± 0.003	0.43 ± 0.008	0.57 ± 0.009
XIX	**8e**	100	0.24 ± 0.003	0.40 ± 0.022	0.38 ± 0.006	0.49 ± 0.011

[a]SEM denotes the standard error of the mean.
[b]All data are significantly different from control ($p < 0.001$).
[c]Carboxymethyl cellulose.
Synthesized compounds and standard drugs in bold - showing significant inhibition.

TABLE 3 Inhibition of edema (%) by standard drug and test compounds (**4a–o**, **8a**, and **8e**)

		Inhibition of edema (%)			
Treatment	**Dose (mg/kg) orally**	**1 h**	**2 h**	**3 h**	**4 h**
Ibuprofen	100	32.35	48.57	**70.65**	60.00
4a	100	23.52	32.85	45.65	44.21
4b	100	20.58	35.71	52.17	45.26
4c	100	29.41	40.00	56.52	38.94
4d	100	11.76	25.71	57.60	52.63
4e	100	11.76	22.85	55.43	54.73
4f	100	20.58	31.42	**64.13**	57.89
4g	100	26.47	42.85	**67.39**	48.42
4h	100	32.35	45.71	48.91	47.36
4i	100	17.64	30.00	47.82	45.26
4j	100	14.70	28.57	**59.78**	42.10
4k	100	26.47	40.00	**66.30**	50.52
4l	100	20.58	41.42	53.26	46.31
4m	100	17.64	31.42	55.43	52.63
4n	100	29.41	37.14	**65.21**	49.47
4o	100	08.82	24.28	50.00	51.57
8a	100	26.47	41.42	53.26	40.00
8e	100	29.41	42.85	58.69	48.42

Synthesized compounds and standard drugs in bold - showing significant inhibition.

3 | CONCLUSION

A series of novel 4-((5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)benzoic acids **4a–o** and 2-(5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acids **8a–e** were synthesized and examined for activity against sEH and 5-LOX. The *in vitro* assays undertaken in this study showed that the compounds exhibited moderate to good activity in sEH and 5-LOX inhibition. The benzimidazole scaffold with aryl ether and azole linkage at 6-position has been shown to be effective inhibitor of 5-LOX and sEH, and the inhibition displayed were all in micromolar range. The most active analogue against sEH was **4k**, and compound **4g** emerged as the promising benzimidazole derivative against 5-LOX. From the assays undertaken in this study, it is clear that the incorporation of fluorine into the molecule has had a significant impact on the inhibition of sEH and 5-LOX. However, when compared to the heterocyclic amine substituted derivative, the aryl ether analog reduced the IC_{50} value. The azole substituted compounds emerged as the potent sEH inhibitors, while the aryl ether analogs exhibited moderate to good 5-LOX inhibition. It was interesting that the sEH inhibitory activity of the phenylimidazole hybrid analog **4n** was better than the 5-LOX inhibitory action. A substantial reduction in sEH inhibitory activity was observed in case of substituted fluorobenzimidazoles with propanoic acid head (**8a** and **8e**), leading to the assumption that selective 5-LOX inhibition might be contributing to their anti-inflammatory properties. To rationalize the *in vitro* anti-inflammatory activity, the compounds were further evaluated *in vivo* for their anti-inflammatory activity by the carrageenan-induced rat paw edema assay. In conclusion, the significant inhibition shown by compounds **4f**, **4g**, **4k**, **4n**, and **8e** comparable to the standard drug ibuprofen clearly indicates that these compounds can serve as lead molecules for further development as potent anti-inflammatory agents. Further optimization of the lead compounds for their anti-inflammatory activities is actively underway in our laboratory.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All chemicals were purchased from commercial sources and were used without further purification. Solvents were purified and dried by standard methods. Melting points (uncorrected) were determined in open glass capillaries. The IR spectra were recorded on a Shimadzu-5400 FT-IR spectrometer in KBr pellets and band positions are reported in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR were measured in $CDCl_3$ or DMSO-d_6 on a Bruker Avance-400 MHZ spectrometer. Chemical shifts are expressed in δ (ppm) relative to the internal standard and coupling constants J in Hz. Electrospray ionization mass spectra (ESI-MS) were recorded on a LCMS 3200 triple quad (Q Trap) and LCMS 3000 API SCIEX mass spectrometer. Microanalyses were performed on a Perkin-Elmer 2400 CHN element analyzer. All compounds were within ±0.4% of the theoretical values. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica gel precoated aluminum sheets (60 F_{254}, Merck) and UV light was used for visualization at 254 nm.

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

4.1.2 | General procedure for the synthesis of 4-((5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acids (4a–o)

A mixture of 5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazole-2-thiol **1a–o** (2 mmol), methyl 4-(bromomethyl)benzoate **2** (2 mmol), and K_2CO_3 (4 mmol) in dry DMF (10 mL) was stirred at room temperature for 5 h in a nitrogen-flushed flask (completion of the reaction was monitored by TLC). After completion of reaction, the reaction mixture was treated with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4, and filtered. The organic solvent was evaporated under vacuum to afford the crude esters **3a–o** that were used for the next step without further purification. The ester was subjected to alkaline hydrolysis by refluxing with 50% KOH in ethanol for 3 h. After removal of alcohol under vacuum, water was added to the residue with stirring and acidified with 2 N HCl to pH 4. The precipitated product was separated by filtration at the pump, followed by water wash and dried. The crude residue was purified by recrystallization from ethanol to afford **4a–o**.

4-((6-Chloro-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-benzoic acid (4a)

Pale beige solid; yield 57%; mp 195–197°C; IR (KBr cm^{-1}): 3420 (NH str), 3200 (OH str), 3080 (Ar CH str), 2950 (CH_2 str), 1700 (Ar CO str), 1615 (C═N str), 1500, 1455 (C═C ring str), 1350 (Ar C-N str), 1154 (C-F str), 1020 (C-Cl str); ^{1}H NMR (DMSO-d_6): δ 4.61 (s, 2H, CH_2), 7.53–7.63 (m, 4H, ArH), 7.85–7.86 (d, 2H, ArH), 12.87 (br.s, 2H, NH and COOH); ^{13}C NMR (DMSO-d_6): δ 34.89 (S-CH_2), 99.42, 99.86, 114.20, 115.26, 128.78, 129.40, 139.78, 140.40, 150.85, 161.86 (Ar-C), 166.93 (CO); MS (ESI) *m/z*: 336.1 (M−1). Anal. calcd. for $C_{15}H_{10}ClFN_2O_2S$: C, 53.50; H, 2.99; N, 8.31. Found: C, 53.41; H, 2.92; N, 8.39.

4-((5-Fluoro-6-naphthalen-2-yloxy)-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)benzoic acid (4b)

White solid; yield 63%; mp 177–179°C; IR (KBr cm^{-1}): 3398 (NH str), 3207 (OH str), 3039 (Ar CH str), 2969 (CH_2 str), 1691 (Ar CO str), 1610 (C═N str), 1597, 1577, 1473 (C═C str), 1354 (Ar C-N str), 1225 (Ar-O-Ar, C-O-C str), 1159 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.62 (s, 2H, CH_2), 6.70–6.71 (d, 1H, ArH), 7.32–7.37 (m, 1H, ArH), 7.42 (s, 1H, ArH), 7.53–7.65 (m, 7H, ArH), 7.85–7.91 (m, 2H, ArH), 7.97 (s, 1H, NH), 8.25–8.28 (d, 1H, *J* = 12.0 Hz, ArH), 12.70 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 35.27 (S-CH_2), 109.89, 121.76, 122.89, 125.24, 126.47, 126.61, 127.34, 127.55, 128.23, 129.48, 129.77, 129.97, 130.25, 134.85, 138.97, 143.28, 151.53, 154.22 (Ar-C), 167.46 (CO); MS (ESI) *m/z*: 444.2 (M−1). Anal. calcd. for $C_{25}H_{17}FN_2O_3S$: C, 67.56; H, 3.85; N, 6.30. Found: C, 67.41; H, 3.72; N, 6.25.

4-((6-(4-Phenylphenoxy)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)benzoic acid (4c)

White solid; yield 69%; mp 183–185°C; IR (KBr cm^{-1}): 3400 (NH str), 3220 (OH str), 3090 (Ar CH str), 2965 (CH_2 str), 1703 (Ar CO str), 1605 (C═N str), 1514, 1485, 1473 (C═C ring str), 1352 (Ar C-N str), 1218 (Ar-O-Ar, C-O-C str), 1151 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.61 (s, 2H, CH_2), 6.98–7.01 (d, 2H, *J* = 12.0 Hz, ArH), 7.29–7.63 (m, 11H, ArH), 7.86–7.88 (d, 2H, *J* = 8.0 Hz, ArH), 12.86 (br.s, 2H, NH and COOH); ^{13}C NMR (DMSO-d_6): δ 34.75 (S-CH_2), 116.27, 126.35, 127.00, 128.11, 128.78, 128.84, 129.40, 130.91, 134.62, 137.58, 139.48, 142.14, 143.37, 148.60, 148.87, 149.40, 151.21, 151.78, 157.78 (Ar-C), 167.79 (CO); MS (ESI) *m/z*: 470.1 (M−1). Anal. calcd. for $C_{27}H_{19}FN_2O_3S$: C, 68.93; H, 4.07; N, 5.95. Found: C, 68.79; H, 3.98; N, 5.90.

4-((5-Fluoro-6-(*p*-tolyloxy)-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acid (4d)

White solid; yield 53%; mp 155–157°C; IR (KBr cm^{-1}): 3408 (NH str), 3218 (OH str), 3105, 3050 (Ar CH str), 2916 (CH_2 str), 2865 (CH_3 str), 1700 (Ar CO str), 1608 (C═N str), 1550, 1520, 1430 (CC ring str), 1360 (Ar C-N str), 1218 (Ar-O-Ar, C-O-C str), 1160 (C-F str); ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 6.81–6.83 (d, 2H, *J* = 8.0 Hz, ArH), 7.11–7.13 (d, 2H, *J* = 8.0 Hz, ArH), 7.47–7.53 (m, 4H, ArH), 7.84–7.86 (d, 2H, *J* = 8.0 Hz, ArH), 8.24 (s, 1H, NH), 12.78 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 20.08 (CH_3), 34.78 (S-CH_2), 98.03, 98.93, 103.12, 115.58, 116.08, 128.75, 129.39, 130.12, 131.57, 140.03, 149.30, 150.92, 151.65, 155.83 (Ar-C), 166.03 (CO); MS (ESI) *m/z*: 408.3 (M−1). Anal. calcd. for $C_{22}H_{17}FN_2O_3S$: C, 64.70; H, 4.19; N, 6.85. Found: C, 64.55; H, 4.11; N, 6.75.

4-((6-(4-*tert*-Butylphenoxy)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)benzoic acid (4e)

White solid; yield 61%; mp 166–168°C; IR (KBr cm^{-1}): 3420 (NH str), 3205 (OH str), 3070 (Ar CH str), 2960 (CH_2 str), 2882 (CH_3 str), 1690 (Ar CO str), 1605 (C═N str), 1515, 1475 (C═C ring str), 1350 (Ar C-N str), 1225 (Ar-O-Ar, C-O-C str), 1175 (C-F str); ^{1}H NMR (DMSO-d_6): δ 1.25 (s, 9H, $3CH_3$), 4.61 (s, 2H, CH_2), 6.83–6.93 (d, 2H, ArH), 7.33–7.38 (m, 2H, ArH), 7.41–7.43 (d, 1H, *J* = 8.0 Hz, ArH), 7.46–7.49 (d, 1H, *J* = 12.0 Hz, ArH), 7.54–7.56 (d, 2H, *J* = 8.0 Hz, ArH), 7.85–7.87 (d, 2H, *J* = 8.0 Hz, ArH), 7.90 (s, 1H, NH), 12.64 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 31.23 ($(CH_3)_3$), 33.92 ($C(CH_3)_3$), 34.78 (S-CH_2), 115.64, 116.87, 126.49, 126.81, 127.04, 128.97, 129.27, 129.47, 129.64, 129.75, 138.38, 138.53, 142.73, 143.87, 144.98, 149.46, 150.86, 151.84, 155.68 (Ar-C), 166.96 (CO); MS (ESI) *m/z*: 450.2 (M−1). Anal. calcd. for $C_{25}H_{23}FN_2O_3S$: C, 66.65; H, 5.14; N, 6.21. Found: C, 66.51; H, 5.03; N, 6.14.

4-((6-(4-Chlorophenoxy)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acid (4f)

White solid; yield 64%; mp 159–160°C; IR (KBr cm^{-1}): 3410 (NH str), 3225 (OH str), 3090 (Ar CH str), 2925 (CH_2 str), 1697 (Ar CO str), 1620 (C═N str), 1485, 1473 (C═C ring str), 1354 (Ar C-N str), 1220 (Ar-O-Ar, C-O-C str), 1151 (C-F str), 1080 (C-Cl str); ^{1}H NMR (DMSO-d_6): δ 4.60 (s, 2H, CH_2), 6.42 (m, 2H, ArH), 6.93–6.94 (d, 2H, ArH), 7.35–7.37

(m, 2H, *J* = 8.0 Hz, ArH), 7.51 (s, 2H, ArH), 7.85 (s, 2H, ArH), 8.29 (s, 1H, NH), 12.88 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 36.35 (S-CH_2), 101.87, 102.12, 103.27, 107.12, 109.19, 110.64, 112.19, 112.51, 114.65, 117.71, 126.43, 128.95, 129.66, 137.87, 138.01, 147.09, 147.98, 149.51, 151.13, 151.89, 156.89 (Ar-C), 169.87 (CO); MS (ESI) *m/z*: 428.0 (M−1). Anal. calcd. for $C_{21}H_{14}ClFN_2O_3S$: C, 58.82; H, 3.29; N, 6.52. Found: C, 58.68; H, 3.20; N, 6.49.

4-((5-Fluoro-6-(4-fluorophenoxy)-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acid (4g)

White solid; yield 58%; mp 150–152°C; IR (KBr cm^{-1}): 3422 (NH str), 3210 (OH str), 3070 (Ar CH str), 2910 (CH_2 str), 1692 (Ar CO str), 1610 (C═N str), 1545, 1500, 1475 (CC ring str), 1350 (Ar C-N str), 1200 (Ar-O-Ar, C-O-C str), 1152 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.59 (s, 2H, CH_2), 6.92–6.95 (d, 2H, *J* = 12.0 Hz, ArH), 7.06–7.08 (d, 2H, *J* = 8.0 Hz, ArH), 7.10–7.11 (m, 2H, ArH), 7.51–7.53 (d, 2H, *J* = 8.0 Hz, ArH), 7.87–7.89 (d, 2H, *J* = 8.0 Hz, ArH), 8.17 (s, 1H, NH), 12.64 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 34.80 (S-CH_2), 99.46, 99.89, 108.30, 115.89, 116.26, 123.25, 128.73, 129.39, 133.35, 138.55, 149.15, 150.25, 158.33, 163.25 (Ar-C), 168.73 (CO); MS (ESI) *m/z*: 412.3 (M−1). Anal. calcd. for $C_{21}H_{14}F_2N_2O_3S$: C, 61.17; H, 3.42; N, 6.79. Found: C, 61.02; H, 3.29; N, 6.69.

4-((5-Fluoro-6-(pyrrolidin-1-yl)-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acid (4h)

Off-white solid; yield 68%; mp 122–124°C; IR (KBr cm^{-1}): 3420 (NH str), 3223 (OH str), 3000 (Ar CH str), 2925 (CH_2 str), 2880 (pyrrolidine CH_2 str), 1692 (Ar CO str), 1625 (C═N str), 1550, 1525, 1510 (C═C ring str), 1226 (R C-N str), 1173 (C-F str); ^{1}H NMR ($CDCl_3$): δ 1.55–1.62 (m, 4H, pyrrolidine), 2.52–2.71 (m, 4H, pyrrolidine), 4.47 (s, 2H, CH_2), 5.87–5.90 (d, 2H, *J* = 12.0 Hz, ArH), 6.80–6.82 (d, 1H, *J* = 8.0 Hz, ArH), 6.89–6.91 (d, 1H, *J* = 8.0 Hz, ArH), 7.01 (s, 1H, NH), 7.06 (d, 2H, ArH), 12.81 (s, 1H, COOH); MS (ESI) *m/z*: 371.1 (M+1). Anal. calcd. for $C_{19}H_{18}FN_3O_2S$: C, 61.45; H, 4.88; N, 11.30. Found: C, 61.29; H, 4.74; N, 11.19.

4-((5-Fluoro-6-(piperidin-1-yl)-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acid (4i)

Off-white solid; yield 59%; mp 135–137°C; IR (KBr cm^{-1}): 3420 (NH str), 3211 (OH str), 3080 (Ar CH str), 2920 (CH_2 str), 2860 (piperidine CH_2 str), 1699 (Ar CO str), 1609 (C═N str), 1547, 1507, 1476 (C═C ring str), 1228 (R C-N str), 1175 (C-F str); ^{1}H NMR ($CDCl_3$): δ 1.52 (m, 6H, piperidine), 2.92–2.96 (m, 4H, piperidine), 4.61 (s, 2H, CH_2), 7.40–7.42 (d, 1H, *J* = 8.0 Hz, ArH), 7.53–7.58 (m, 3H, ArH), 7.86–7.88 (d, 2H, *J* = 8.0 Hz, ArH), 8.22 (s, 1H, NH), 12.57 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$): δ 25.99 (CH_2), 29.40 (CH_2), 34.99 (S-CH_2), 49.19 (CH_2), 115.78, 116.40, 131.30, 131.89, 132.99, 133.65, 134.55, 135.59, 136.55, 152.55, 161.75 (Ar-C), 169.99 (CO); MS (ESI) *m/z*: 385.1 (M+1). Anal. calcd. for $C_{20}H_{20}FN_3O_2S$: C, 62.33; H, 5.23; N, 10.89. Found: C, 62.17; H, 5.17; N, 10.77.

4-((5-Fluoro-6-(1*H*-imidazol-1-yl)-1*H*-benzo[*d*]imidazol-2-ylthio)-methyl)benzoic acid (4j)

Brown solid; yield 65%; mp 212–214°C; IR (KBr cm^{-1}): 3410 (NH str), 3222 (OH str), 3050 (Ar CH str), 2910 (CH_2 str), 1689 (Ar CO str), 1606 (C═N str), 1500, 1550 (CC ring str), 1340 (Ar C-N str), 1150 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.63 (s, 2H, CH_2), 7.30–7.55 (m, 3H, ArH), 7.75 (br.s, 1H, ArH), 7.89–7.91 (d, 2H, *J* = 8.0 Hz, ArH), 8.09–8.13 (d, 2H, imidazole), 8.77 (s, 1H, imidazole), 12.83 (br.s, 2H, NH and COOH); MS (ESI) *m/z*: 368.0 (M−1). Anal. calcd. for $C_{18}H_{13}FN_4O_2S$: C, 58.70; H, 3.55; N, 15.20. Found: C, 58.52; H, 3.41; N, 15.15.

4-((5-Fluoro-6-(1*H*-1,2,4-triazol-1-yl)-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)benzoic acid (4k)

Brown solid; yield 67%; mp 227–229°C; IR (KBr cm^{-1}): 3413 (NH str), 3210 (OH str), 3092 (Ar CH str), 2915 (CH_2 str), 1690 (Ar CO str), 1615 (C═N str), 1511, 1450 (C═C ring str), 1350 (Ar C-N str), 1145 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.65 (s, 2H, CH_2), 7.54–7.61 (m, 3H, ArH), 7.75–7.76 (d, 1H, ArH), 7.85–7.87 (d, 2H, *J* = 8.0 Hz, ArH), 8.24 (s, 1H, triazole), 8.93 (s, 1H, triazole), 12.98 (br.s, 2H, NH and COOH); ^{13}C NMR (DMSO-d_6): δ 34.88 (S-CH_2), 116.20, 126.31, 126.86, 127.99, 128.61, 128.71, 129.39, 134.65, 139.56, 148.40, 151.15, 152.25, 157.78 (Ar-C), 167.70 (CO); MS (ESI) *m/z*: 369.2 (M+1). Anal. calcd. for $C_{17}H_{12}FN_5O_2S$: C, 55.29; H, 3.27; N, 18.95. Found: C, 55.20; H, 3.18; N, 18.86.

4-((5-Fluoro-6-(4-phenoxyphenoxy)-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)benzoic acid (4l)

White solid; yield 62%; mp 149–151°C; IR (KBr) cm^{-1}: 3425 (NH str), 3222 (OH str), 3082, 3066, 3039 (Ar CH str), 2929, 2854 (CH_2 str), 1710 (Ar CO str), 1639 (C═N str), 1593, 1487, 1467 (C═C ring str), 1354 (Ar C-N str), 1222 (Ar-O-Ar, C-O-C str), 1165 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.60 (s, 2H, CH_2), 6.98–7.00 (d, 2H, *J* = 8.0 Hz, ArH), 7.28–7.32 (d, 2H, ArH), 7.39–7.43 (m, 3H, ArH), 7.50–7.53 (d, 2H, *J* = 12.0 Hz, ArH), 7.57–7.60 (m, 4H, ArH), 7.87–7.89 (d, 2H, *J* = 8.0 Hz, ArH), 8.23 (s, 1H, NH), 12.77 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 33.91 (S-CH_2), 98.30, 98.54, 103.18, 116.76, 126.40, 127.10, 128.09, 128.20, 128.68, 128.77, 128.88, 135.05, 138.09, 138.23, 139.39, 149.36, 151.75, 157.27 (Ar-C), 169.55 (CO); MS (ESI) *m/z*: 486.1 (M−1). Anal. calcd. for $C_{27}H_{19}FN_2O_4S$: C, 66.65; H, 3.93; N, 5.75. Found: C, 66.46; H, 3.81; N, 5.69.

4-((6-(Benzo[*d*][1,3]dioxol-5-yloxy)-5-fluoro-1*H*-benzo[*d*]-imidazol-2-ylthio)methyl)benzoic acid (4m)

White solid; yield 70%; mp 140–142°C; IR (KBr) cm^{-1}: 3387 (NH str), 3215 (OH str), 3072, 3039 (Ar CH str), 2939 (CH_2 str), 2847 (—OCH_2O— str), 1705 (Ar CO str), 1625 (C═N str), 1580, 1550, 1470 (C═C ring str), 1320 (Ar C-N str), 1222 (Ar-O-Ar, C-O-C str), 1170 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.95 (s, 2H, CH_2), 5.87 (s, 2H, —OCH_2O—), 7.09–7.13 (d, 2H, ArH), 7.16–7.21 (d, 2H, ArH), 7.28–7.30 (d, 1H, *J* = 8.0 Hz, ArH), 7.98–8.08 (m, 4H, ArH), 8.29 (s, 1H, NH), 12.59 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 35.60 (S-CH_2), 99.89, 100.35 (OCH_2O), 101.98, 103.61, 108.72, 109.32, 114.66, 114.73, 114.90, 122.81, 128.42, 129.12, 131.53, 132.04, 136.35, 143.50, 148.64, 153.42 (Ar-C), 169.22 (CO); MS (ESI) *m/z*: 438.3 (M−1). Anal. calcd. for $C_{22}H_{15}FN_2O_5S$: C, 60.27; H, 3.44; N, 6.38. Found: C, 60.04; H, 3.30; N, 6.29.

4-((6-(4-(1*H*-Imidazol-1-yl)phenoxy)-5-fluoro-1*H*-benzo[*d*]-imidazol-2-ylthio)methyl)benzoic acid (4n)

Pale brown solid; yield 73%; mp 203–205°C; IR (KBr) cm^{-1}: 3462 (NH str), 3208 (OH str), 3091, 3072 (Ar CH str), 2940 (CH_2 str), 1719 (Ar CO

str), 1647 (C═N str), 1600, 1485 (C═C ring str), 1323 (Ar C-N str), 1230 (Ar-O-Ar, C-O-C str), 1161 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.60 (s, 2H, CH_2), 7.14–7.17 (dd, 4H, *J* = 12.0 Hz, ArH), 7.40–7.46 (m, 3H, ArH), 7.80–7.83 (d, 2H, *J* = 12.0 Hz, ArH), 8.07–8.09 (dd, 4H, *J* = 8.0 Hz, ArH), 8.31 (s, 1H, NH), 12.22 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 32.00 (SCH_2), 104.87, 110.20, 112.39, 117.22, 117.60, 118.86, 119.83, 122.79, 122.87, 130.17, 132.35, 136.14, 149.44, 151.00, 153.76, 153.91, 156.94, 157.27, 157.54, 159.86 (Ar-C), 170.00 (CO); MS (ESI) *m/z*: 460.3 (M−1). Anal. calcd. for $C_{24}H_{17}FN_4O_3S$: C, 62.60; H, 3.72; N, 12.16. Found: C, 62.39; H, 3.64; N, 12.05.

4-((5-Fluoro-6-phenoxy-1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-benzoic acid (4o)

White solid; yield 66%; mp 145–147°C; IR (KBr) cm^{-1}: 3408 (NH str), 3300 (OH str), 3050 (Ar CH str), 2925, 2855 (CH_2 str), 1705 (Ar CO str), 1637 (CN str), 1629, 1512 (C═C ring str), 1350 (Ar C-N str), 1220 (Ar-O-Ar, C-O-C str), 1178 (C-F str); ^{1}H NMR (DMSO-d_6): δ 4.60 (s, 2H, CH_2), 6.87–6.89 (d, 1H, *J* = 7.2 Hz, ArH), 6.93–6.95 (m, 3H, ArH), 7.09–7.17 (m, 4H, ArH), 7.32–7.36 (m, 2H, ArH), 12.57 (br.s, 2H, NH and COOH); ^{13}C NMR (DMSO-d_6): δ 32.07 (SCH_2), 102.85, 109.61, 114.28, 115.63, 125.79, 128.09, 128.20, 128.97, 129.91, 132.84, 140.90, 142.98, 143.61, 146.11, 151.95, 153.71 (Ar-C), 166.30 (CO); MS (ESI) *m/z*: 394.3 (M−1). Anal. calcd. for $C_{21}H_{15}FN_2O_3S$: C, 63.95; H, 3.83; N, 7.09. Found: C, 63.71; H, 3.69; N, 7.01.

4.1.3 | General procedure for the synthesis of 2-(5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acids (8a–e)

The following propanoic acids **8a–e** were synthesized from appropriate 5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazole-2-thiols **5a–e** and ethyl-2-bromo-2-methylpropionate **6** according to the procedure described for benzoic acids **4a–e**.

A mixture of 5-fluoro-6-(substituted)-1*H*-benzo[*d*]imidazole-2-thiol **5a–e** (2 mmol), ethyl-2-bromo-2-methylpropionate **6** (2 mmol), and K_2CO_3 (4 mmol) in dry DMF (10 mL) was stirred at room temperature for 5 h in a nitrogen-flushed flask (completion of the reaction was monitored by TLC). Further steps of work-up and purification were done in a similar manner as described for benzoic acids **4a–o**.

2-(6-(4-Phenylphenoxy)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acid (8a)

Off-white solid; yield 62%; mp 166–169°C; IR (KBr) cm^{-1}: 3421 (NH str), 3250 (OH str), 3050 (Ar CH str), 2920 (CH_3 str), 1717 (R CO str), 1604 (C═N str), 1514, 1485 (CC ring str), 1355 (Ar C-N str), 1222 (Ar-O-Ar, C-O-C str), 1172 (C-F str); ^{1}H NMR (DMSO-d_6): δ 1.53 (s, 6H, $(CH_3)_2$), 6.99–7.02 (d, 2H, *J* = 12.0 Hz, ArH), 7.29–7.35 (m, 2H, ArH), 7.41–7.44 (d, 2H, *J* = 12.0 Hz, ArH), 7.59–7.63 (m, 5H, ArH), 7.52 (s, 1H, NH), 13.55 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 30.63 ($\underline{C}H_3)_2$, 50.13 ($\underline{C}(CH_3)_2$), 98.30, 98.54, 103.18, 116.76, 126.40, 127.10, 128.09, 128.20, 128.68, 128.77, 128.88, 135.05, 138.09, 138.23, 139.39, 149.36, 151.75, 157.27 (Ar-C), 169.55 (CO); MS (ESI) *m/z*: 423.3 (M+1). Anal. calcd. for $C_{23}H_{19}FN_2O_3S$: C, 65.39; H, 4.53; N, 6.62. Found: C, 65.15; H, 4.47; N, 6.51.

2-(5-Fluoro-6-(naphthalen-2-yloxy)-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acid (8b)

Off-white solid; yield 65%; mp 145–147°C; IR (KBr) cm^{-1}: 3421 (NH str), 3221 (OH str), 3064 (Ar CH str), 2926, 2966 (CH_3 str), 1700 (R CO str), 1629 (C═N str), 1597, 1577, 1473 (C═C ring str), 1356 (Ar C-N str), 1230 (Ar-O-Ar, C-O-C str), 1159 (C-F str); ^{1}H NMR (DMSO-d_6): δ 1.54 (s, 6H, $(CH_3)_2$), 6.72–6.74 (d, 1H, *J* = 8.0 Hz, ArH), 7.29–7.31 (d, 1H, *J* = 8.0 Hz, ArH), 7.35–7.39 (t, 1H, *J* = 8.0 Hz, ArH), 7.53–7.65 (m, 5H, ArH), 7.98 (s, 1H, NH), 8.25–8.27 (d, 1H, *J* = 8.0 Hz, ArH), 13.59 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 26.75 ($\underline{C}H_3)_2$, 52.93 ($\underline{C}(CH_3)_2$), 109.67, 113.36, 121.24, 122.44, 124.78, 125.98, 126.10, 126.80, 127.71, 134.34, 138.88, 146.08, 147.11, 149.00, 151.65, 153.61 (Ar-C), 174.38 (CO); MS (ESI) *m/z*: 397.0 (M+1). Anal. calcd. for $C_{21}H_{17}FN_2O_3S$: C, 63.62; H, 4.32; N, 7.06. Found: C, 63.41; H, 4.22; N, 6.97.

2-(6-(4-*tert*-Butylphenoxy)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acid (8c)

Off-white solid; yield 59%; mp 132–135°C; IR (KBr) cm^{-1}: 3406 (Ar NH str), 3240 (OH str), 3060 (Ar CH str), 2929, 2964 (CH_3 str in 2-methyl propanoic acid), 2885 (CH_3 str in tertiary butyl group), 1706 (R CO str), 1597 (C═N str), 1508, 1473 (C═C ring str), 1354 (Ar C-N str), 1224 (Ar-O-Ar, C-O-C str), 1178 (C-F str); ^{1}H NMR (DMSO-d_6): δ 1.25 (s, 9H, $(CH_3)_3$), 1.54 (s, 6H, $(CH_3)_2$), 6.84–6.86 (d, 2H, *J* = 8.0 Hz, ArH), 7.21–7.23 (d, 1H, *J* = 8.0 Hz, ArH), 7.33–7.35 (d, 2H, *J* = 8.0 Hz, ArH), 7.47–7.49 (d, 1H, *J* = 8.0 Hz, ArH), 8.70 (s, 1H, NH), 13.00 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 26.74 ($\underline{C}H_3)_2$, 31.22 ($\underline{C}H_3)_3$, 33.91 $\underline{C}(CH_3)_3$, 53.08 ($\underline{C}(CH_3)_2$), 102.37, 115.86, 126.49, 128.83, 129.83, 138.84, 138.99, 145.05, 148.63, 149.53, 151.91, 155.58 (Ar-C), 174.57 (CO); MS (ESI) *m/z*: 403.3 (M+1). Anal. calcd. for $C_{21}H_{23}FN_2O_3S$: C, 62.66; H, 5.76; N, 6.95. Found: C, 62.43; H, 5.63; N, 6.87.

2-(6-(4-Chlorophenoxy)-5-fluoro-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acid (8d)

Off-white solid; yield 68%; mp 115–117°C; IR (KBr) cm^{-1}: 3425 (NH str), 3210 (OH str), 3050 (Ar CH str), 2920 (CH_3 str), 1715 (R CO str), 1603 (C═N str), 1510, 1475 (C═C ring str), 1355 (Ar C-N str), 1220 (Ar-O-Ar, C-O-C str), 1170 (C-F str), 1110 (C-Cl str); ^{1}H NMR (DMSO-d_6): δ 1.60 (s, 6H, $(CH_3)_2$), 6.95–6.97 (d, 2H, *J* = 8.0 Hz, ArH), 7.19 (s, 1H, ArH), 7.35–7.38 (d, 2H, *J* = 12.0 Hz, ArH), 7.52 (br.s, 1H, ArH), 8.27 (br.s, 1H, NH), 12.88 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 26.39 ($\underline{C}H_3)_2$, 52.71 ($\underline{C}(CH_3)_2$), 87.40, 95.69, 98.96, 104.98, 112.77, 117.77, 126.58, 128.34, 129.65, 147.93, 156.87, 163.25, 168.03 (Ar-C), 173.99 (CO); MS (ESI) *m/z*: 381.5 (M+1). Anal. calcd. for $C_{17}H_{14}ClFN_2O_3S$: C, 53.61; H, 3.70; N, 7.35. Found: C, 53.42; H, 3.61; N, 7.24.

2-(5-Fluoro-6-(4-fluorophenoxy)-1*H*-benzo[*d*]imidazol-2-ylthio)-2-methylpropanoic acid (8e)

Off-white solid; yield 60%; mp 124–126°C; IR (KBr) cm^{-1}: 3410 (NH str), 3240 (OH str), 3066, 3101 (Ar CH str), 2969, 2914 (CH_3 str), 1735 (R CO str), 1609 (CN str), 1505, 1475 (C═C ring str), 1350 (Ar C-N str),

1200 (Ar-O-Ar, C-O-C str), 1151 (C-F str); ^{1}H NMR (DMSO-d_6): δ 1.54 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 6.96–6.99 (d, 2H, J = 12.0 Hz, ArH), 7.13–7.19 (m, 2H, ArH), 7.24–7.26 (d, 1H, J = 8.0 Hz, ArH), 7.47–7.50 (d, 1H, J = 12.0 Hz, ArH), 8.25 (br.s, 1H, NH), 12.92 (br.s, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 26.30 ($\underline{C}H_3)_2$), 52.36 ($\underline{C}(CH_3)_2$), 111.82, 117.84, 118.61, 126.13, 127.56, 129.00, 131.68, 135.61, 136.45, 149.35, 151.71, 154.18, 157.18 (Ar-C), 173.05 (CO); MS (ESI) m/z: 365.3 (M+1). Anal. calcd. for $C_{17}H_{14}F_2N_2O_3S$: C, 56.04; H, 3.87; N, 7.68. Found: C, 55.85; H, 3.78; N, 7.61.

4.2 | Biological evaluation

4.2.1 | Determination of *in vitro* IC_{50} for soybean lipoxygenase inhibitory activity[41]

UV absorbance-based enzyme assay was adopted for the evaluation of synthesized compounds for soybean lipoxygenase inhibitory activity. The use of soybean lipoxygenase enzyme as a model for the discovery of novel 5-LOX inhibitors is widely accepted because of its structural and functional similarities with the mammalian LOXs. The principle involves the measurement of absorbance at 234 nm to monitor the conversion of sodium linoleate to 13-hydroperoxylinoleic acid, and commercially purchased sample of nordihydroguaiaretic acid (NDGA) was used as the standard inhibitor. Sodium linoleate (linoleic acid sodium salt), soybean lipoxygenase, and NDGA were obtained from Sigma Chemical Co. (Sigma–Aldrich, India). The enzymatic reaction was initiated by adding the substrate (sodium linoleate) to the preincubated mixture of the test compounds and NDGA with soybean lipoxygenase. The *in vitro* IC_{50} values of the target compounds dissolved in DMSO was determined by incubating with fixed concentration of soybean lipoxygenase (0.2 mL of enzyme solution at $1/3 \times 10^{-4}$ w/v in saline) at 28°C for 5 min and later followed by addition of sodium linoleate (0.1 mM).

4.2.2 | Determination of *in vitro* IC_{50} for soluble epoxide hydrolase inhibitory activity[42]

The *in vitro* IC_{50} values of the target compounds on human recombinant sEH were carried out using the screening assay kit (Cayman Chemicals-Item No. 10011671), according to the instructions provided with it. The *in vitro* study utilized (3-phenyl-oxiranyl)-acetic acid cyano-(6-methoxy-naphthalen-2-yl)-methyl ester (PHOME) as the specific substrate and a potent sEH inhibitor, *trans*-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (t-AUCB) as the reference standard. Solutions of the test compounds were freshly prepared in DMSO and the IC_{50} values of inhibitors were determined after carrying out assays at 10 different concentrations of each compound. Recombinant human sEH was incubated with the test compounds and t-AUCB before addition of the substrate (PHOME). Incubated for 15 min at 25°C in 25 mM Bis-Tris/HCl buffer at pH 7.0 (total assay volume = 200 µL), and the activity was determined by monitoring the appearance of 6-methoxy-2-naphthaldehyde (emits fluorescence at 465 nm) by fluorescence detection with an excitation wavelength of 330 nm and an emission wavelength of 465 nm.

4.2.3 | Determination of *in vivo* anti-inflammatory acitivity[43]

The experimental protocol was reviewed and accepted by the Institutional Animal Ethics Committee (IAEC) prior to the initiation of the experiment (Proposal No. IAEC/NCP/50/10). Carrageenan-induced rat paw edema was utilized as the model for acute inflammation as previously described to carry out the evaluation of test compounds for anti-inflammatory activity and is presented as the percentage inhibition of induction of edema at the right hind paw. Wister albino rats of either sex, in the weight range of 150–200 g were used for the study. They were housed in groups of six animals in plastic cages at 20–25°C and maintained on a standard pellet diet with free access of water. Animals were fasted for 24 h before the experiment and were marked with picric acid for individual animal identification. Edema was induced in the right hind paw of male rats (150–200 g) by the subplantar injection of 0.1 mL of a 1% carrageenan suspension in saline. Six rats were used in each test group. Each group of animals were orally dosed with the test compounds or drug free vehicle (1% CMC) 1 h prior to carrageenan injection. Group I served as the control group and received vehicle (1% CMC in water in a volume of 10 mL/kg); group II received the reference standard ibuprofen at a dose of 100 mg/kg body weight. All the remaining groups received the test compounds and were administered orally as suspensions in vehicle (10 mL/kg) at the same dose orally. Paw volume was determined by calculating the amount of mercury displaced after immersing the paw to the level of the lateral malleolus. Foot volumes were measured using the plethysmometer (model 7140, Ugo-Basile, Italy) at 0, 1, 2, 3, and again 4 h after carrageenan injection, and the difference was designated as edema volume. The percent inhibition of edema for the treated groups was calculated by following formula:

$$\% \text{ Inhibition} = 100\ [1 - V_t/V_c]$$

where V_t and V_c are the volumes of edema for the drug treated and control groups, respectively. Compounds **4a–o**, **8a**, and **8e** were screened for anti-inflammatory activity and the results are expressed as the mean ± SEM of six animals per group. Statistical evaluation was performed using analysis of variance followed by t-test for sub-group comparison and $p < 0.001$ was considered significant. Statistical analysis was performed using STATISTICA 6.1 for Windows.

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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REFERENCES

[1] L. J. Roberts, *Cell. Mol. Life. Sci*. **2002**, *59*, 727.
[2] J. H. Capdevila, J. R. Falck, R. W. Estabrook, *FASEB J*. **1992**, *6*, 731.
[3] R. M. McMillan, E. R. Walker, *Trends. Pharmacol. Sci*. **1992**, *13*, 323.
[4] A. W. Ford-Hutchinson, M. Gresser, R. N. Young, *Annu. Rev. Biochem*. **1994**, *63*, 383.
[5] J. Y. Fu, J. L. Masferrer, K. Seibert, A. Raz, P. Needleman, *J. Biol. Chem*. **1990**, *265*, 16737.
[6] W. L. Smith, R. M. Garavito, D. L. Dewitt, *J. Biol. Chem*. **1996**, *271*, 33157.
[7] G. F. Fabiola, V. Pattabhi, K. Nagarajan, *Bioorg. Med. Chem*. **1998**, *6*, 2337.
[8] J. D. Imiq, B. D. Hammock, *Nat. Rev. Drug. Discov*. **2009**, *8*, 794.
[9] K. R. Schmelzer, L. Kubala, J. W. Newman, I. H. Kim, J. P. Eiserich, B. D. Hammock, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 9772.
[10] B. Inceoglu, K. R. Schmelzer, C. Morisseau, S. L. Jinks, B. D. Hammock, *Prostaglandins Other Lipid Mediat*. **2007**, *82*, 42.
[11] J. Y. Liu, J. Yang, B. Inceoglu, H. Qiu, A. Ulu, S. H. Hwang, N. Chiamvimonvat, B. D. Hammock, *Biochem. Pharmcol*. **2010**, *79*, 880.
[12] K. Wagner, B. Inceoglu, H. Dong, J. Yang, S. H. Hwang, P. Jones, C. Morisseau, B. D. Hammock, *Eur. J. Pharmacol*. **2013**, *700*, 93.
[13] L. Tang, W. H. Ma, Y. L. Ma, S. R. Ban, X. E. Feng, Q. S. Li, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 2380.
[14] F. Celotti, S. Laufer, *Pharmacol. Res*. **2001**, *43*, 429.
[15] C. L. Nickerson-Nutter, E. D. Medvedeff, *Arthritis Rheum*. **1996**, *39*, 515.
[16] S. H. Hwang, K. M. Wagner, C. Morisseau, J. Y. Liu, H. Dong, A. T. Wecksler, B. D. Hammock, *J. Med. Chem*. **2011**, *54*, 3037.
[17] K. Meirer, C. B. Rodl, J. M. Wisniewska, S. George, A. Hafner, E. Buscato, F. M. Klinger, S. Hahn, D. Berressem, S. K. Wittmann, D. Steinhilber, B. Hofmann, E. Proschak, *J. Med. Chem*. **2013**, *56*, 1777.
[18] N. R. McElroy, P. C. Jurs, C. Morisseau, B. D. Hammock, *J. Med. Chem*. **2003**, *46*, 1066.
[19] S. H. Hwang, H. J. Tsai, J. Y. Liu, C. Morisseau, B. D. Hammock, *J. Med. Chem*. **2007**, *50*, 3825.
[20] J. Y. Liu, S. Park, C. Morisseau, B. D. Hammock, R. H. Weiss, *Mol. Cancer Ther*. **2009**, *8*, 2193.
[21] T. Kirchner, D. C. Argentieri, A. G. Barbone, M. Singer, M. Steber, J. Ansell, S. A. Beers, M. P. Wachter, W. Wu, E. Malloy, A. Stewart, D. M. Ritchie, *J. Pharmacol. Exp. Ther*. **1997**, *282*, 1094.
[22] E. Buscato, D. Buttner, A. Bruggerhoff, F. M. Klingler, J. Weber, B. Scholz, A. Zivkovic, R. Marschalek, H. Stark, D. Steinhilber, H. B. Bode, E. Proschak, *Chem. Med. Chem*. **2013**, *8*, 919.
[23] D. Moser, J. M. Wisniewska, S. Hahn, J. Achenbach, E. Buscato, F. M. Klingler, B. Hofmann, D. Steinhilber, E. Proschak, *ACS Med. Chem. Lett*. **2012**, *3*, 155.
[24] R. De Simone, M. G. Chini, I. Bruno, R. Riccio, D. Mueller, O. Werz, G. Bifulco, *J. Med. Chem*. **2011**, *54*, 1565.
[25] M. G. Chini, R. De Simone, I. Bruno, R. Riccio, F. Dehm, C. Weinigel, D. Barz, O. Werz, G. Bifulco, *Eur. J. Med. Chem*. **2012**, *54*, 311.
[26] R. Paramashivappa, P. Phani kumar, P. V. Subba Rao, A. Srinivasa Rao, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 657.
[27] H. Nakano, T. Inoue, N. Kawasaki, H. Miyataka, H. Matsumoto, T. Taguchi, N. Inagaki, H. Nagai, T. Satoh, *Chem. Pharm. Bull*. **1999**, *47*, 1573.
[28] D. R. Buckle, K. A. Foster, J. F. Taylor, J. M. Tedder, V. E. Thody, R. A. Webster, J. Bermudez, R. E. Markwell, S. A. Smith, *J. Med. Chem*. **1987**, *30*, 2216.
[29] M. Gaba, D. Singh, S. Singh, V. Sharma, P. Gaba, *Eur. J. Med. Chem*. **2010**, *45*, 2245.
[30] S. Kankala, R. K. Kankala, P. Gundepaka, N. Thota, S. Nerella, M. R. Gangula, H. Guguloth, M. Kagga, R. Vadde, C. S. Vasam, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 1306.
[31] I. N. Shaikh, K. M. Hosamani, H. R. Seetharamareddy, M. H. Hugar, *Arch. Pharm. Chem. Life. Sci*. **2012**, *345*, 65.
[32] G. Mariappan, N. R. Bhuyan, P. Kumar, D. Kumar, K. Murali, *Indian J. Chem*. **2011**, *50B*, 1216.
[33] S. J. Taylor, F. Soleymanzadeh, A. B. Eldrup, N. A. Farrow, I. Muegge, A. Kukulka, A. K. Kabcenell, S. D. Lombaert, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5864.
[34] S. Pecic, S. Deng, C. Morisseau, B. D. Hammock, D. W. Landry, *Bioorg. Med. Chem. Lett*. **2012**, *22*, 601.
[35] H. C. Shen, F. X. Ding, Q. Deng, S. Xu, X. Tong, X. Zhang, Y. Chen, G. Zhou, L. Y. Pai, M. Alonso-Galicia, S. Roy, B. Zhang, J. R. Tata, J. P. Berger, S. L. Colletti, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5716.
[36] E. R. Zavareh, M. Hedayati, L. H. Rad, S. Shahhosseini, M. Faizi, S. A. Tabatabai, *Iran. J. Pharm. Res*. **2014**, *13*, 51.
[37] R. Morphy, C. Kay, Z. Rankovic, *Drug Discov. Today* **2004**, *9*, 641.
[38] J. R. Morphy, Z. Rankovic, *J. Med. Chem*. **2005**, *48*, 6523.
[39] R. Morphy, Z. Rankovic, *J. Med. Chem*. **2006**, *49*, 4961.
[40] B. Nandha, L. V. G. Nargund, S. L. Nargund, K. G. Bhat, *Iran. J. Pharm. Res*. **2017**, *16*(3), 929.
[41] A. Detsi, M. Majdalani, C. A. Kontogiorgis, D. Hadjipavlou-Litina, P. Kefalas, *Bioorg. Med. Chem*. **2009**, *17*, 8073.
[42] N. M. Wolf, C. Morisseau, P. D. Jones, B. Hock, B. D. Hammock, *Anal. Biochem*. **2006**, *355*, 71.
[43] C. A. Winter, E. A. Risley, C. W. Nuss, *Proc. Soc. Exp. Biol. Med*. **1962**, *111*, 544.
[44] J. Y. Liu, H. J. Tsai, S. H. Hwang, P. D. Jones, C. Morisseau, B. D. Hammock, *Br. J. Pharmacol*. **2009**, *156*, 284.

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