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Design, synthesis and molecular docking of benzophenone conjugated with oxadiazole sulphur bridge pyrazole pharmacophores as anti inflammatory and analgesic agents

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ABSTRACT

The prostaglandins (PG) a group of physiologically active lipid compounds having diverse hormone like effects are important mediators of the body's response to pain and inflammation, and are formed from essential fatty acids found in cell membranes. This reaction is catalyzed by cyclooxygenase, a membrane associated enzyme occurring in two isoforms, COX-1 and COX-2. Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the activity of COX. In view of this, a series of novel benzophenones conjugated with oxadiazole sulphur bridge pyrazole moiety **8a-l** were designed, synthesized, characterized and subsequently evaluated for anti-inflammatory and analgesic property. The investigation of novel analogues **8a-l** for potential anti-inflammatory activity showed high levels of COX-1 and COX-2 inhibitory activity. Among the series, compound **8i** with electron withdrawing fluoro group at the para position of the benzoyl ring of benzophenone was characterized by highest IC_{50} values for both COX-1 and COX-2 inhibition, which is comparable to the standard drug. Further, molecular docking studies have been performed for the potent compound.

1. Introduction

From long time the human being has used several remedies for the administration of pain [1], in this regard heterocyclic compounds are frequently used due to their accessibility, affordability and less side effects [2,3]. For instance, the standard drugs valdecoxib, celecoxib, naproxen, ibuprofen, etc. are heterocyclic compounds and are used in the treatment of pain [4]. Today strategy and study of new compounds profoundly useful in the control of pain. As per the literature survey the mechanism of pain transmission is very composite and involves various neuro modulators of pain response [5]. Pain is a disagreeable sensory and emotional experience connected with potential damage of tissue. Nevertheless inflammation is a complex stereotypical reaction of the body expressing the response to damage of its cells and vascularized tissues [6]. Inflammatory responses are deliberated to be mediated in part by the prostaglandins (PGs) derived from arachidonic acid by the action of prostaglandin H synthase, which is also referred as cyclooxygenase (COX) [7]. COX inhibitors with only pyrazole moiety are lonazolac, antipyrine, SC 560, etc., and with sulphonyl moiety are rofecoxib, etoricoxib, parecoxib, valdecoxib, nimesulide, meloxicam, etc. [8–10]. Further, our group has also synthesized benzophenone analogues as COX inhibitor [11]. In view of this, we have designed the synthesis of compounds **8a-l** containing both pyrazole and benzophenone moiety. Nevertheless, nitrogen containing heterocylic compounds such as, 1,3,4-oxadiazole [12–15] and pyrazole [16,17] are very vast in nature and have been extensively studied for its many promising pharmaceutical properties. Further, benzophenones are of great importance fundamental compounds due to their diverse biological activities [18–21].

Moreover, chemical modification and combination of two or more bioactive compounds is one of the most efficient approach in drug development. Based on the information from literature survey and our search for new molecules, we have reported the design and synthesis of potential anti-inflammatory molecules containing three bioactive molecules namely, benzophenone, oxadiazole and pyrazole with amide linkage collectively as benzophenone conjugated with oxadiazole sulphur bridge pyrazole pharmacophores **8a-l** to attain pharmacologically efficacious single molecule as anti-inflammatory agents. Also, in the present study, we describe binding properties of target compounds to the COX-1 and COX-2, using molecular docking studies to approve the *in vitro* and *in vivo* studies [22]. The study also supported by molecular docking to understand the interaction of synthesized compounds and

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similarity with standard drugs.

2. Results and discussion

2.1. Structure based design

Initially the adequate literature survey was carried out to demonstrate the significance of the nitrogen containing heterocyclic compounds such as, 1,3,4-oxadiazole and pyrazole and also about benzophenone analogues. The study revealed that, researchers have reported the anti-inflammatory activity of 1,3,4-oxadiazole, pyrazole and benzophenone analogues [8–11].

In addition, drugs lonazolac, antipyrine and SC 560 comprises a pyrazole ring and they are renowned COX inhibitors [10]. Nevertheless the title compounds contain essential pharmacoporic elements that are essential for a molecule to exhibit anti-inflammatory activity. These requirements are the presence of the phenyl ring as lipophilic aryl ring, N—CO as hydrogen bonding domain, N as electron donor atom and the presence of a distal benzoyl ring. Benzoyl oxygen forms hydrogen bonding interaction with tyrosine amino acid. It has also been anticipated that the benzoyl oxygen plays a vital role in enhancing the affinity for COX. Based on these points we designed new analogues containing N—CO and other pharmacophores necessary to show anti-inflammatory performance (Fig. 1).

2.2. Chemistry

The synthesis of the title compounds 8a–l was accomplished by a synthetic procedure as illustrated in Scheme 1. All the synthesized compounds were established by IR, ^{1}H NMR and mass spectral data. Among 2a-l series, the spectrum of compound **2a** is taken as a representative example. The formation of this compound was confirmed by the disappearance of the OH stretching of compound 1a and appearance of the carbonyl stretching band for the ester group at 1760 cm^{-1} in the IR absorption spectrum. The proton NMR observations of compound **2a** revealed the disappearance of broad singlet for the OH proton of compound 1a and appearance of a triplet and quartet for CH_3 and CH_2 protons at δ 1.33 and 4.30 ppm respectively. Also,

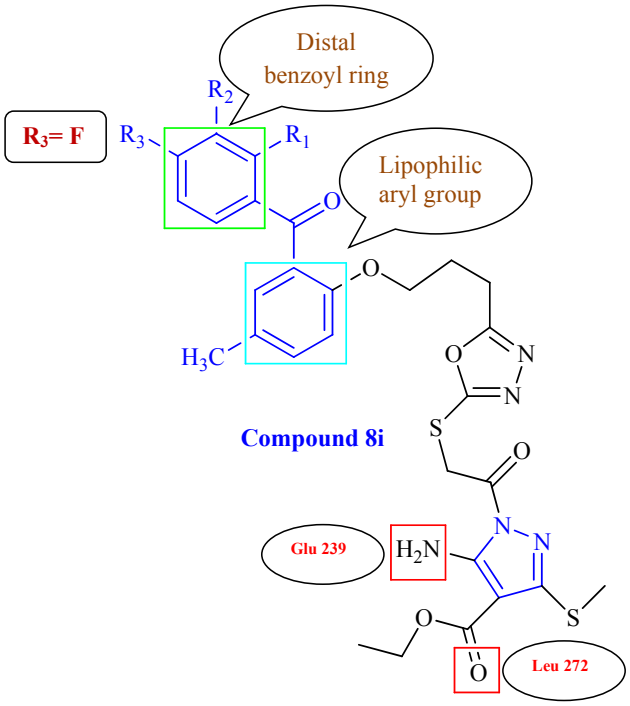
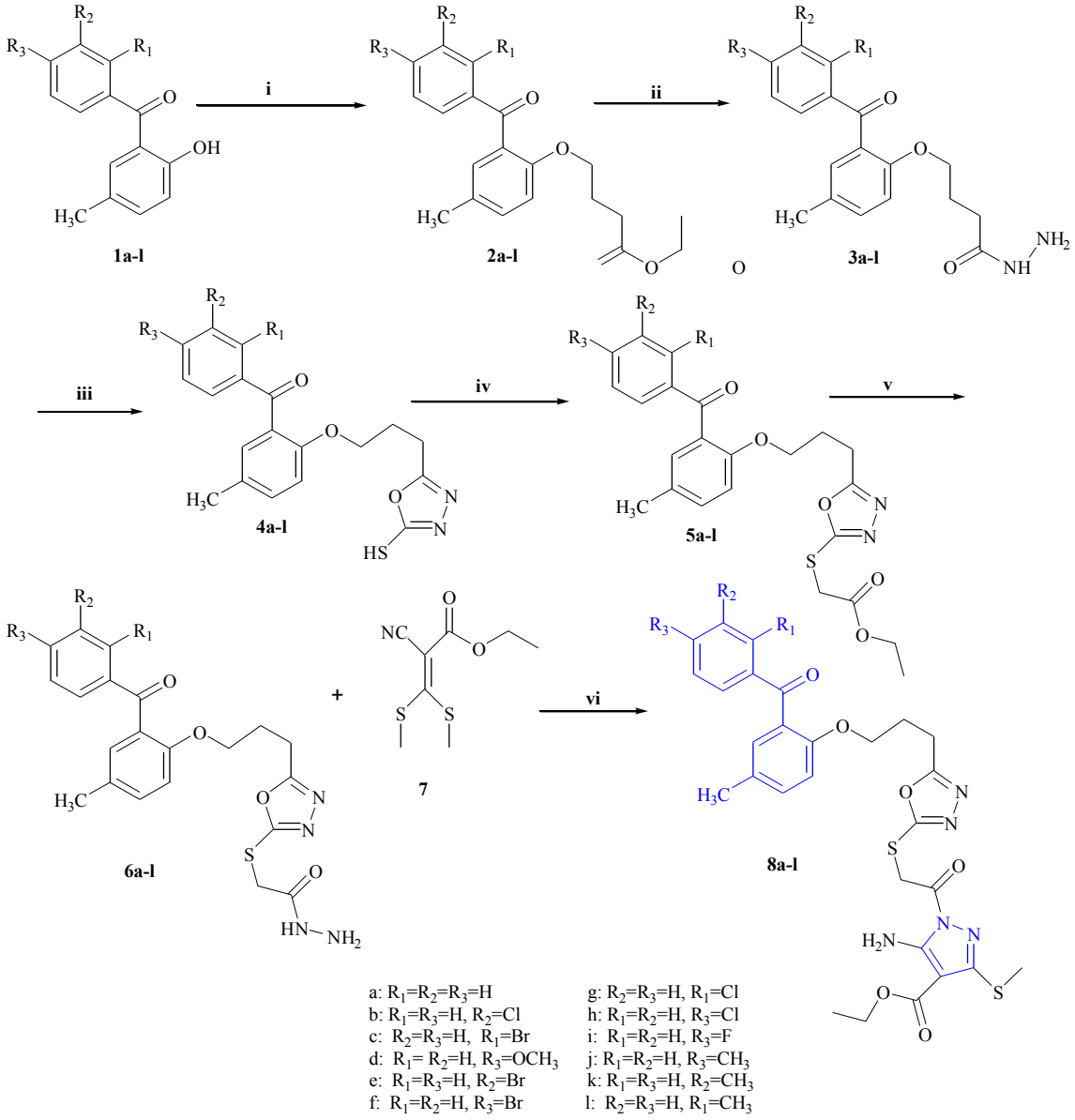


Fig. 1. Design strategy.

mass spectra gave significant stable M+1 peak at *m/z* 327 which clearly affirmed the formation of compound **2a**. In the similar manner, compound **3a** is taken as a representative for the **3a-l** series, in this compound the appearance of NH and NH_2 stretching bands in IR spectrum were observed in the range 3120–3220 and 3300–3410 cm^{-1} respectively. On the other hand, in proton NMR, the appearance of NH_2 and NH protons at δ 3.87 and 8.52 ppm respectively, and disappearance of triplet and quartet peaks of CH_2 and CH_3 protons of compound **2a** confirmed the formation of product. The mass spectra of compound **3a** gave a significant M+1 peak at *m/z* 313, which also confirmed the formation of the product **3a**. The IR spectrum of compound **4a** in the series **4a-l** was confirmed by the disappearance of NH and NH_2 stretching of compound **3a** and appearance of C=N and S—H stretching bands at 1685 and 2550 cm^{-1} respectively. Also by the disappearance of NH and NH_2 proton peaks of compound **3a** and appearance of singlet peak for SH proton at δ 10.72 ppm in NMR spectrum. The mass spectra of compound **4a** gave a significant stable M+1 peak at *m/z* 355 which also proves the formation of the compound **4a**. Besides, compound **5a** is taken as a representative example to explain the formation of compounds **5a-l**. The compound **5a** was confirmed by the disappearance of the SH stretching of compound **4a** in the IR spectrum and singlet peak of SH proton in NMR spectrum. Further by the appearance of carbonyl stretching band for the ester group at 1760 cm^{-1} and a triplet and quartet signal for CH_3 and CH_2 protons at δ 1.32 and 4.79 ppm in the IR and proton NMR spectrum respectively. A significant stable M+1 peak at *m/z* 441 was observed in the mass spectrum. Similarly the formation of compound **6a** was confirmed with the disappearance of carbonyl stretching of the compound **5a** and appearance of NH and NH_2 stretching bands at 3120–3220 and 3310–3430 cm^{-1} in the IR spectrum, whereas in the NMR spectrum disappearance of the proton signal of CH_2 and CH_3 and appearance of NH_2 and NH proton signal at δ 4.57 and δ 10.92 ppm. At the same time, the mass spectrum of compound **6a** shown significant stable M+1 peak at *m/z* 427. Finally, in the title series **8a-l**, compound **8a** is taken as a representative example to explain characterizations. This was supported by the disappearance of NH stretching of the compound 6a and appearance of the carbonyl stretching band at 1730 cm^{-1} in the IR spectrum of compound **8a**. Besides, in proton NMR spectrum the disappearance of NH proton signal of 6a and appearance of triplet, quartet and singlet peaks of CH_3, CH_2 and S-CH_3 at δ 1.31, 4.37 and 2.49 ppm respectively, revealed the formation of product. The mass spectrum of compound **8a** exhibited M+1 peak at *m/z* 596 which also affirmed the formation of the title compound **8a**.

2.3. Molecular docking studies of lead compound *8i*

In order to know the selectivity of the synthesized compounds for COX-1 and COX-2, docking studies were carried out with the help of autodock software to study the molecular interactions involved in between active binding sites of the protein target and potent compound **8i**. The COX inhibitory activity of the compound **8i** was ranked based on their lowest binding energy involved in the complex formation at the active sites. The compound **8i** interacts strongly with COX-1 and COX-2 proteins and 3D structure shows the interaction compound **8i** in the active site C-terminal trans activation in COX-1 and in the active site of COX-2. The possible binding conformation and orientations were analyzed by clustering methods, embedded in MOE 2015. The binding energy of the docked compounds on COX-1 and COX-2 was found in the range of −4.62 and −6.62 kcal/mol, respectively. It is evident that the interaction energy of compound **8i** is lower in COX-2 as compared to COX-1 suggesting it to be a selective COX-2 inhibitor. Several amino acid residues are involved in a particular binding mode, however, only two hydrogen bonds interactions could be observed between the compound and COX-1 and COX-2. Although, the carboxylic group of compound **8i** form hydrogen bonds with residues of COX-1 (GLU239 and LEU272) and COX-2 (ARG44). Hence, this compound was selected for



Scheme 1. Synthesis of benzophenone conjugated with oxadiazole sulphur bridge pyrazole pharmacophores **8a-l**. Reaction conditions and yield: (i) Cl$(CH_2)_3COOC_2H_5$/Dry Acetone, K_2CO_3, Reflux, 60 °C for 8–10 h, yield: 73–83%, (ii) NH_2-NH_2·H_2O, Ethanol, Stirring 5 h, yield: 73–88%, (iii) CS_2/KOH, Ethanol, Reflux, yield: 72–87%, (iv) $BrCH_2COOC_2H_5$/Dry Acetone, K_2CO_3, Reflux, 60 °C for 6–8 h, yield: 68–81%, (v) NH_2-NH_2·H_2O, Ethanol, Stirring 6 h, yield: 72–85%, (vi) CH_3OH, Reflux 5–6 h, yield: 75–85%.

docking studies to study the effect of the compound **8i** on binding affinity to COX-1 and COX-2 in order to get the better understanding of the effect of additional oxygen in linker chain on inhibition of the COX enzyme. Further, the interaction of compound **8i** at the pocket site and the residue amino acid of the complex COX-1-**8i** and complex COX-1-**8i** is predicted [Figs. 2 and 3]. The structure of complex **8i**-COX-1 and **8i**-COX-2 are composed mostly of beta sheets and the Phi Psi plot shows a broad range of values in the −90, +140 and −120, +180 region respectively as shown in Figs. 4 and 5 [23,24].

2.4. Pharmacology

2.4.1. COX-1 and COX-2 in vitro inhibitory activity

The efficacy of synthesized compounds **8a-l** to inhibit ovine COX-1 and COX-2 enzymes was determined through measuring their peroxidase activity using colorimetric enzyme immune assay. Then the inhibitory activity of synthesized compounds and standard compounds celecoxib, diclofenac and indomethacin were expressed as IC_{50} values. Also, COX-2 selectivity index (SI) values were calculated [IC_{50} (COX-1)/IC_{50} (COX-2)] as shown in Table 1. The colorimetric assays, data exhibited weak COX-1 inhibition for the title compounds **8a-l** (IC_{50} = 7.09–11.18 μM) compared to selective COX-1 inhibitor (indomethacin, IC_{50} = 0.04 μM) and the non selective COX inhibitor (diclofenac, IC_{50} = 4.9 μM). Besides, the title compounds **8a-l** exhibited adequate COX-2 inhibition (IC_{50} = 0.1–0.34 μM) compared to the selective COX-2 inhibitor (celecoxib, IC_{50} = 0.09 μM) and diclofenac (IC_{50} = 0.83 μM). Among the series **8a-l**, compounds **8b**, **8c**, **8e**, **8f**, **8g**, **8h** and **8i** displayed potent COX-2 inhibition (IC_{50} = 0.10–0.17 μ*M*) nearby to celecoxib, whereas the remaining compounds **8a**, **8d**, **8j**, **8k** and **8l** displayed less potency towards COX-2 inhibition (IC_{50} = 0.22–0.34 μM). In relation to a COX-2SI, compounds with electron withdrawing groups ie. **8h** with chloro group and **8i** with the fluoro group at the para position in the benzoyl ring of benzophenone, indicated the highest SI values (SI = 109.80 and 111.80 respectively).

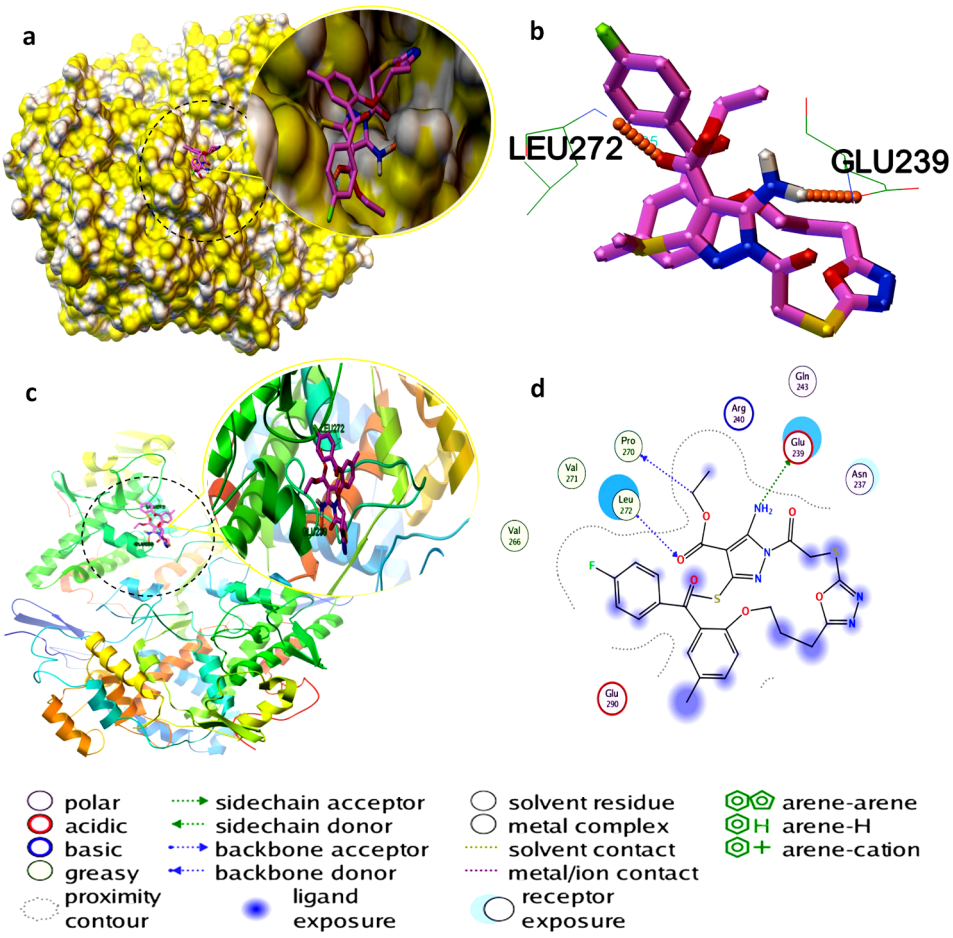


Fig. 2. *In silico* interaction of compound with COX-1. (a) Enfolding of molecule compound in the active site pocket of COX-1 complex. (b) Hydrogen bond interaction of the compound **8i** with COX-1. (c) Ribbon models of the COX-1 catalytic domain and the ligand molecule in compound **8i**. (d) 2D interactions analysi of s compound **8i** with COX-1.

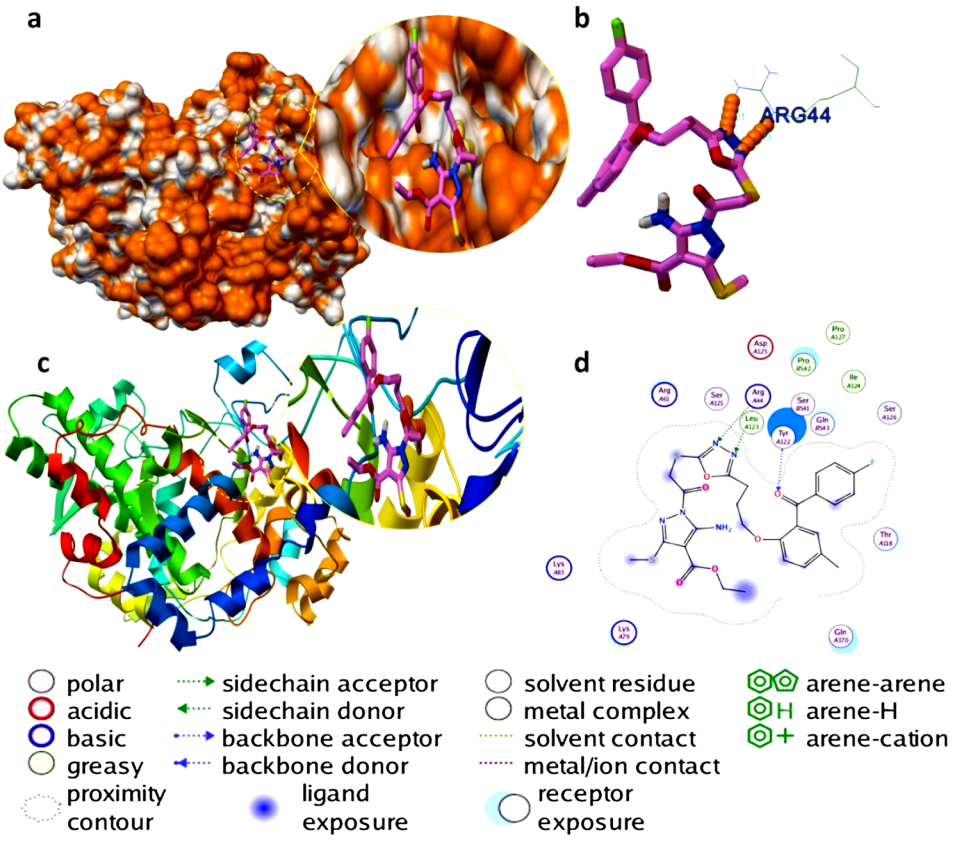


Fig. 3. *In silico* interaction of compound with COX-2. (a) Enfolding of molecule compound in the active site pocket of COX-2 complex. (b) Hydrogen bond interaction of the ligand **8i** with COX-2. (c) Ribbon models of the COX-2 catalytic domain and the ligand molecule in compound **8i**. (d) 2D interactions analysis of compound **8i** with COX-2.

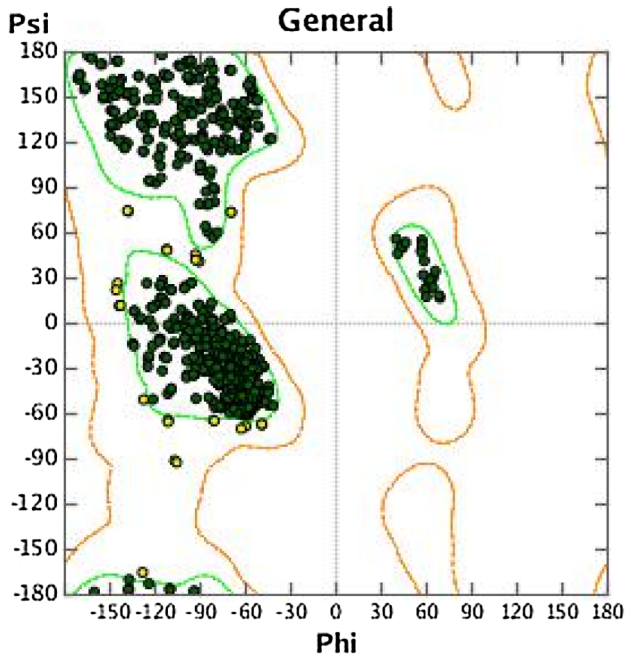


Fig. 4. Protein geometry of COX-1 amino acids in protein structure in various regions of Phi Psi plot.

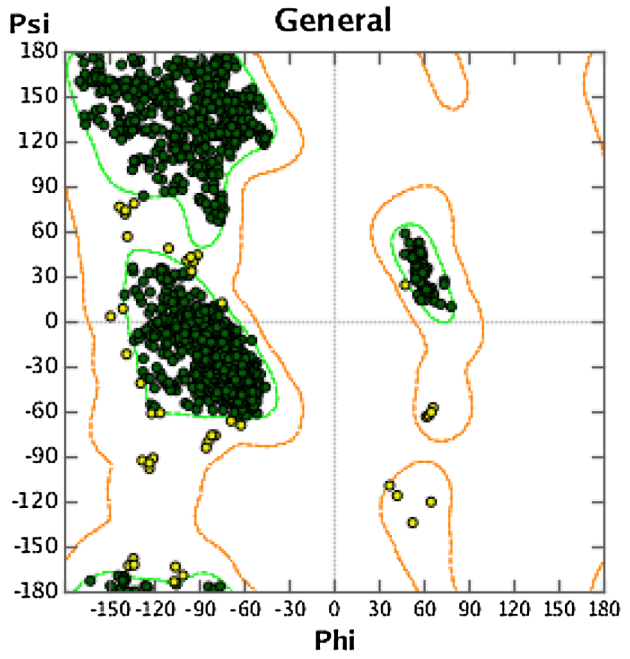


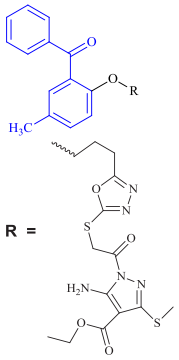
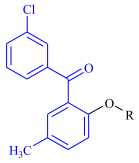
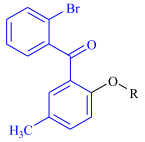
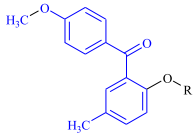
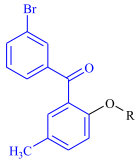
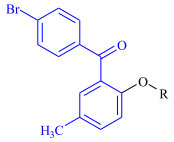
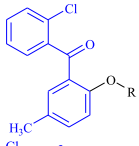
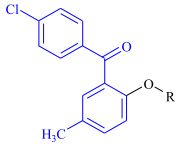
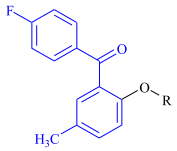
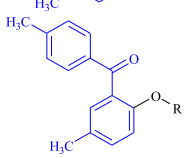
Fig. 5. Protein geometry of COX-2 amino acids in protein structure in various regions of Phi Psi plot.

Whereas compounds **8b**, **8c**, **8e**, **8f** and **8g** exhibited moderate COX-2SI values (SI = 66.75, 101.00, 53.05, 91.36, and 82.33 respectively). Conversely, compounds **8a** with no substituent and compounds **8d**, **8j**, **8k** and **8l** with electron donating groups, displayed lower SI values (SI = 37.18, 26.79, 21.96, 29.54 and 32.14 respectively) as shown in Table 1.

2.4.2. Structure activity relationship (SAR)

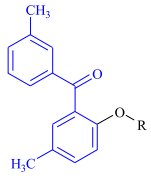
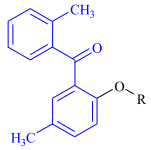
The benzophenones, oxadiazoles and pyrazoles are known to be pharmacologically active molecules against various pathological conditions including inflammation [11–21]. The current exploration involves the multistep synthesis and combination of these three bioactive

Table 1
COX-1 and COX-2 enzyme *in vitro* inhibition of compounds **8a-l.**

Compound		IC50 (μM)[a]		COX-2SI[b]
		COX-1	COX-2	
8a		8.18	0.22	37.18
8b		10.68	0.16	66.75
8c		10.10	0.14	101.00
8d		9.11	0.34	26.79
8e		9.02	0.17	53.05
8f		10.05	0.11	91.36
8g		9.88	0.12	82.33
8h		10.98	0.10	109.80
8i		11.18	0.10	111.80
8j		7.25	0.33	21.96

(*continued on next page*)

Table 1 (*continued*)

Compound	IC50 (μM)[a]		COX-2SI[b]
	COX-1	COX-2	
8k 	7.09	0.24	29.54
8l 	8.68	0.27	32.14
Celecoxib	14.9	0.09	165.55
Diclofenac	4.9	0.83	5.90
Indomethacin	0.04	0.50	0.08

[a] *In vitro* concentration of synthesized compound that produce 50% inhibition of COX-1 and COX-2 enzymes, the result (IC_{50}, μM) is the mean of two values obtained using an ovine COX-1/COX-2 assay. The deviation from the mean is < 10% of the mean value.

[b] The *in vitro* COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

molecules to attain pharmacologically efficacious in a single molecule as anti-inflammatory pharmacophores. Structurally, the title compounds **8a-l** are having a basic backbone of substituted benzophenone conjugated with oxadiazole sulphur bridge pyrazole pharmacophores. The IC50 values for compounds as depicted in Tables 1–4, which suggest that the compound **8i** with with electron withdrawing fluoro group at the para position of the benzoyl ring of benzophenone showed remarkable activity compared to the standard drug. The activity data revealed that the compounds **8c**, **8e**, **8f**, **8g**, **8h** and **8i** with electron withdrawing halo groups showed potent anti-inflammatory activity. While the other compounds with different substituent's have not shown significant activity. From the current investigation, SAR of these compounds suggests that the position and the type of substituent's on the benzoyl ring of benzophenone in **8a-l** are important for the activity. In this connection, the compound **8i** was selected as a lead compound based on its significant SAR compared with other analogues.

2.4.3. *In vivo anti-inflammatory activity of compound **8a-l***

The title compounds **8a-l** were evaluated for *in vivo* anti-inflammatory activity by adopting formalin-induced rat paw edema assay using diclofenac as a standard drug. The inflammation was induced in the rat paw through subcutaneous formalin injection and the paw-volume change (% edema inhibition) due to treatment of rats by the title compounds **8a-l** and the standard diclofenac (10 mg/kg) was observed after 1, 3 and 6 h from initiation of inflammation (Table 2). The result exhibited a wide range of anti-inflammatory activity (13.04–52.17%; 1 h), (15.38–65.38%; 3 h) and (10.00–46.66%; 6 h) compared to the standard compound diclofenac (30.43%; 1 h, 23.07%; 3 h, 23.33%; 6 h). Among the series **8a-l,** compounds **8b, 8c, 8e, 8f, 8g, 8h** and **8i** displayed more anti-inflammatory activity after 1 h, compared to diclofenac. Moreover, the compounds **8i** (52.17% edema inhibition) with electron withdrawing fluoro group at para position, **8e** (47.82% edema inhibition) with the bromo group at meta position, and **8g** (47.82% edema inhibition) with the chloro group at ortho position in the benzoyl ring of benzophenone, possessed potent activity.

Further, the compounds **8d**, **8k** and **8l** exhibited lower potency (13.04–26.08% edema inhibition), whereas compounds **8a**, **8b**, **8c, 8f**, **8h** and **8j** demonstrated moderate activity (34.78–43.47%). Interestingly, after 3 h, compounds **8b**, **8c**, **8f**, **8g**, **8h** and **8i** displayed more anti-inflammatory activity as compared to the standard diclofenac, compounds **8a**, **8d**, **8e**, **8j** and **8l** showed moderate activity and compound **8k** exhibited lower potency (15.38% edema inhibition) as compared to the standard (diclofenac 23.07% edema inhibition). However, compounds **8i** (65.38% edema inhibition) with the fluoro group at para position, **8c** and **8g** (61.53% edema inhibition) with bromo and the chloro group at ortho position respectively, and **8h** (57.69% edema inhibition) with the chloro group at the para position in the benzoyl ring of benzophenone, possessed more potent activity. After 6 h, compounds **8c**, **8f**, **8g**, **8h** and **8i** displayed more potent anti-inflammatory activity as compared to standard diclofenac (diclofenac 23.33% edema inhibition). Moreover, the compounds **8c** with bromo group at ortho position, **8f** with bromo at para position and **8i** with the fluoro group at the para position in the benzoyl ring of benzophenone, possessed a highest edema inhibition (46.66%) as shown in Fig. 6. Compounds **8b, 8d, 8e, 8j** and **8l** showed moderate activity and compounds **8a** and **8k** exhibited lower potency (10.00% edema inhibition) as compared to the standard diclofenac with 23.33% edema inhibition (Table 2).

Together, compounds **8c**, **8e**, **8f**, **8g**, **8h** and **8i** exhibited encouraging anti-inflammatory activity (46.66–61.53%, 30.00–47.82%, 39.13–46.66%, 40.00–61.53%, 40.00–57.69% and 46.66–65.38% edema inhibition respectively) at 1, 3 and 6 h time intervals and were more potent than diclofenac (23.07–30.43%).

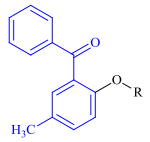
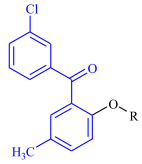
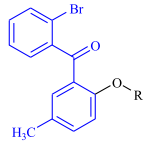
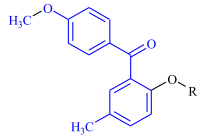
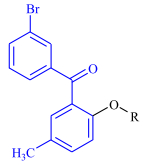
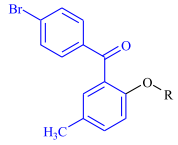
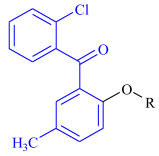
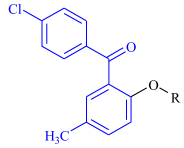
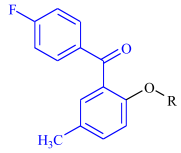
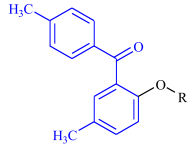
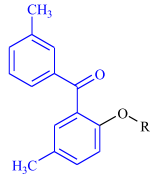
In brief, the anti-inflammatory activity of synthesized compounds **8a-l** demonstrated that the integration of benzophenone moiety with oxadiazole sulphur bridge pyrazole pharmacophores generated active anti-inflammatory activity. This perhaps may be due to the COX pathway of arachidonate metabolism produces prostaglandins, which have a variety of effects on blood vessels, on nerve endings and on cells involved in inflammation [4]. These compounds possibly create its anti-inflammatory effect by inhibiting the release synthesis of inflammatory mediators including polypeptide kinins and prostaglandins.

2.4.4. *Analgesic activity of the title series **8a-l***

Analgesic activity was evaluated for the synthesized title compounds **8a-l** by employing two different methods, namely acetic acid induced writhing test and the hot plate latency test.

2.4.4.1. Acetic acid-induced writhing test. The anti-nociception activity was evaluated by acetic acid-induced writhing response method. The intraperitoneal administration of acetic acid produced both central nociception and peripheral actions which acted by the release of endogenous mediators and blocked through nonsteroidal anti-inflammatory drugs [25]. This study revealed that, the title compounds **8a-l** exhibited the wide range of analgesic effect. The analgesic activity of the compound **8i** (64.04% inhibition) was significantly and very closed to the standard piroxicam (64.64% inhibition) against acetic acid induced writhing behavior relative to vehicle-treated mice, moreover compound **8b** (58.88% inhibition) and **8h** (63.23% inhibition) exhibited good activity (Table 3). On the other hand, acetic acid-induced writhing was significantly reduced in mice receiving the compounds **8a, 8d, 8j, 8k** and **8l**. The degree of inhibition of the writhing response by these compounds was 28.22, 17.57, 21.21, 25.15 and 24.04%, respectively. The remaining compounds **8c, 8e, 8f** and **8g** exhibited moderate analgesic activity in the range 39.79–54.74% inhibition. According to the structure activity relationship point of view, it is apparent that the activity of halo compounds **8b, 8h** and **8i** with the chloro group at meta position, chloro group at para position and fluoro group at the para position of benzoyl ring of benzophenone respectively, are more potent than compounds **8a** with no substituent**, 8d** with methoxy group at para position**, 8j** with methyl group at para position **8k** with methyl group at meta position and **8l** with methyl group at ortho position of the benzoyl ring of benzophenone.

Table 2
Anti-inflammatory activity of compounds **8a-l.**

Compounds		Paw volume change (ml)			% Edema inhibition			IC50 μM
		1 h	3 h	6 h	1 h	3 h	6 h	
8a		1.5 ± 0.02*	1.9 ± 0.34	2.7 ± 0.27	34.78	26.92	10.00	12.80 ± 0.38
8b		1.3 ± 0.09*	1.4 ± 0.15	2.3 ± 0.15	43.47	46.15	23.33	10.10 ± 0.57
8c		1.1 ± 0.07*	1.0 ± 0.12*	1.6 ± 0.19*	52.17	61.53	46.66	8.08 ± 0.13
8d		1.7 ± 0.05	1.8 ± 0.32	2.0 ± 0.25*	26.08	30.76	33.33	9.0 ± 0.27
8e		1.2 ± 0.19*	1.6 ± 0.26*	2.1 ± 0.06*	47.82	38.46	30.00	9.2 ± 0.30
8f		1.4 ± 0.11*	1.4 ± 0.07*	1.6 ± 0.37*	39.13	46.15	46.66	8.5 ± 0.50
8g		1.2 ± 0.09*	1.0 ± 0.14*	1.8 ± 0.23*	47.82	61.53	40.00	7.11 ± 0.0
8h		1.3 ± 0.05*	1.1 ± 0.12*	1.8 ± 0.22*	43.47	57.69	40.00	7.8 ± 0.33
8i		1.1 ± 0.08*	0.9 ± 0.12*	1.6 ± 0.34*	52.17	65.38	46.66	8.2 ± 0.42
8j		1.5 ± 0.10*	1.6 ± 0.15*	2.0 ± 0.16	34.78	38.46	33.33	9.5 ± 0.31
8k		1.7 ± 0.28	2.2 ± 0.19	2.7 ± 0.42	26.08	15.38	10.00	13.0 ± 0.45

(*continued on next page*)

Table 2 (*continued*)

Compounds	Paw volume change (ml)			% Edema inhibition			IC50 μ*M*
	1 h	3 h	6 h	1 h	3 h	6 h	
8l 	2.0 ± 0.14	1.8 ± 0.12	2.0 ± 0.17*	13.04	30.76	33.33	9.8 ± 0.22
Vehicle	2.3 ± 0.28	2.6 ± 0.08	3.0 ± 0.36	0	0	0	
Diclofenac	1.6 ± 0.19*	2.0 ± 0.33	2.3 ± 0.45	30.43	23.07	23.33	9.8 ± 0.43

Values are means ± SEM (n = 3–4).

* Significantly different from the normal control group at $p < 0.05$.

2.4.4.2. Hot plate latency test. Pain induced by thermal stimulus of the hot plate is precise for centrally mediated nociception [26]. The competence of the synthesized compounds **8a-l** to prolong the reaction latency to pain thermally induced in mice suggests that these compounds have some central analgesic activity, this is in accordance with Williamson *et al.* [27] and Koster *et al.,* [28]. The oral administration of the title compounds **8a-l** increased the latency time in comparison with basal values. In this study, compounds **8a**, **8b**, **8c**, **8e**, **8f**, **8g**, **8h**, **8i** and **8j** showed an increase in pain threshold after 1 h in the range (42.10–92.30%). Remarkably, the increase in pain threshold after 2 h was for the compounds **8b**, **8e**, **8f**, **8h** and **8i** in the range (46.66–57.14%) and this signifies might be due to decrease in nociception by these compounds (Table 4).

Furthermore, among the series **8a-l**, compounds **8h** (85.71%) with the chloro group at para position and **8i** (92.30%) with the fluoro group at the para position of the benzoyl ring of benzophenone exhibited potent central analgesic activity at 1 h more than the standard piroxicam (80.00%). Besides, compounds **8d**, **8k** and **8l** exhibited weak potency after 1 h (13.33–28.57%) and 2 h (06.66–22.22%). The attained results were in accordance with the *in vitro* COXs data as compounds **8h** and **8i** exhibited potent COX-2 inhibitory activity (IC_{50} = 0.10 μM). These results disclosed that there is an equivalent relationship between the analgesic and anti-inflammatory activities of synthesized compounds **8a-l**.

3. Conclusion

Summarizing the current investigation, we efficiently designed and synthesized a series of benzophenones conjugated with oxadiazole sulphur bridge pyrazole pharmacophores **8a-l** by incorporating, fluoro, cholro, bromo, methoxy and methyl groups at different position of the benzoyl ring of benzophenone and evaluated for anti-inflammatory and analgesic activities. The activity data revealed that the compounds **8c**, **8e**, **8f**, **8g**, **8h** and **8i** with electron withdrawing halo groups showed potent anti-inflammatory activity. Interestingly, compound **8i** with the electron withdrawing fluoro group at the para position of the benzoyl ring of benzophenone showed remarkable activity compared to the standard drug. Further, the analgesics activity data also revealed that the halo group compounds in the **8a-l** series showed a significant result and compound **8i** is found to be highest potent compound among the series for analgesic effect on acetic acid induced writhing response and thermal pain. These results disclosed that there is a relationship between the analgesic and anti-inflammatory activities of synthesized compounds **8a-l**. The *in silico* result are also concordant with *in vitro* and *in vivo* results more accurately.

4. Materials and methods

All solvents and reagents were purchased from Sigma Aldrich Chemicals Private Limited with purity 90–99%, analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel plates (Merck 60 F 254) by using different solvent system and visualized by UV-light. Melting point was determined on a Chemi Line Micro Controller based melting point apparatus with a digital thermometer. The IR spectrum was recorded by the potassium bromide pellet method on Cary 630 FTIR Agilent spectrophotometer, NMR spectrum was recorded on a VNMRS-400 MHz Agilent-NMR spectrophotometer in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO). Mass spectrum was obtained with a VG70-70H spectrometer. Elemental analysis results are within 0.4% of the theoretical calculated value.

4.1. Chemistry

The synthesis of the title compounds 2(2-benzoyl-4-methyl-phenoxy-propyl)-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazoles 8a-l were accomplished by a synthetic procedure as illustrated in Scheme 1. All the synthesized compounds were established by IR, ^{1}H NMR and mass spectral data. First, a mixture of substituted benzophenones 1a-l and ethyl chlorobutyrate was refluxed using dry acetone as a solvent, which gave substituted benzophenone butyric acid ethyl esters 2a-l. The compounds 2a-l on treatment with 99% hydrazine hydrate yield substituted benzophenone butyric acid hydrazides **3a-l**. Then, the mixture of compounds **3a-l**, carbon disulfide, potassium hydroxide was refluxed using ethanol as solvent to afford substituted 5(benzoyl-phenoxy)propyl-[1,3,4]oxadiazole-2-thiols **4a-l**. Further, compounds 4a-l on etherification with ethyl bromoacetate using dry acetone as a solvent furnished substituted benzoyl-phenoxy-propyl]-[1,3,4]oxadiazole-2-thio ethyl acetates 5a–l. To achieve substituted benzoyl-phenoxy-propyl]-[1,3,4] oxadiazole-2-thio acetyl hydrazides **6a-l**, compounds **5a-l** were treated with hydrazine hydrate in methanol. Finally, compounds 6a-l, on treatment with [bis(methylthio)methylene]malononitrile **7** under reflux condition using methanol as solvent afforded the expected title compounds 8a-l in a good yield (75–85%).

*4.1.1. General procedure for the synthesis of ethyl 4-(2-benzoyl-4-methylphenoxy)butanoate analogues **2a-l***

A typical procedure is described for the synthesis of ethyl 4-(2-benzoyl-4-methylphenoxy)butanoate **2a:**

A mixture of hydroxy benzophenone **1a** (0.05 mol) and ethyl chlorobutyrate (0.075 mol) in dry acetone (40 mL) with anhydrous potassium carbonate (0.075 mol) was refluxed for 8 h. The reaction mixture was cooled and solvent removed by distillation. The residual product was triturated with cold water to remove potassium carbonate, and then extracted with ether (3 × 25 mL). The ether layer was washed with 10% sodium hydroxide solution (3 × 25 mL) followed by water (3 × 30 mL) and then dried over anhydrous sodium sulfate and evaporated the solvent to afford compound **3a** as pasty mass.

Table 3
Analgesic effect of compounds **8a-l** on acetic acid induced writhing response.

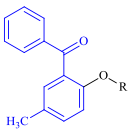
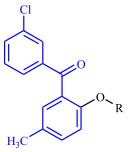
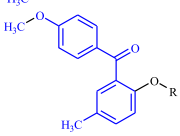
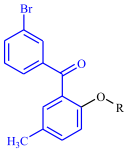
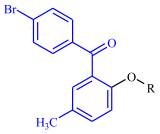
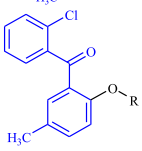
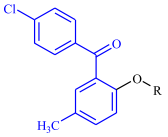
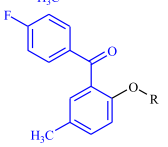
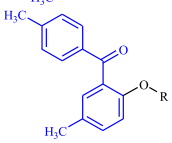
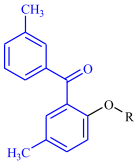
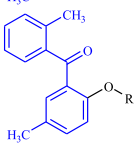
Compounds	Number of writhing	% inhibition	IC50 μM
8a 	35.53 ± 1.99	28.22	12 ± 0.38
8b 	20.35 ± 2.33	58.88	8.3 ± 0.57
8c 	25.55 ± 2.05	48.38	9 ± 0.13
8d 	40.80 ± 1.15	17.57	15.3 ± 0.27
8e 	22.40 ± 2.67	54.74	9.2 ± 0.30
8f 	29.80 ± 0.77*	39.79	11.5 ± 0.50
8g 	29.80 ± 0.77*	39.79	10.9 ± 0.0
8h 	18.20 ± 2.20	63.23	6.8 ± 0.33
8i 	17.80 ± 2.93*	64.04	6.1 ± 0.42
8j 	39.00 ± 1.04	21.21	13.5 ± 0.31
8k 	37.05 ± 2.10	25.15	12.8 ± 0.45
8l 	37.60 ± 2.07	24.04	11.2 ± 0.22
Vehicle	49.50 ± 5.11	0	

Table 3 (*continued*)

Compounds	Number of writhing	% inhibition	IC50 μM
Piroxicam	17.50 ± 2.54*	64.64	7.8 ± 0.43

Data represent the mean value ± SE of four mice per group. Drugs were, s.c., administered 30 min before testing. Statistical comparisons are made between control group and synthesized compounds treated group and denoted by $p < 0.05$.

* Significantly different from the normal control group at $p < 0.05$.

4.1.1.1. Ethyl 4-(2-benzoyl-4-methylphenoxy)butanoate ***2a***. Yield: 80%. M.P.: 134–136 °C; IR (KBr) ν_{max} (cm^{-1}): 1685 (C═O), 1760 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.25 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.71 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.12 (t, J = 7.50 Hz, 2H, OCH_2), 4.30 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.93–7.56 (m, 8H, Ar—H). LC-MS m/z 327 (M + 1). Anal. Cal. for $C_{20}H_{22}O_4$ (326): C, 73.60; H, 6.79. Found: C, 73.51; H, 6.73%.

4.1.1.2. Ethyl 4-[2-(3-chlorobenzoyl)-4-methylphenoxy]butanoate ***2b***. Yield: 78%. M.P.: 153–155 °C; IR (KBr) ν_{max} (cm^{-1}): 1660 (C═O), 1750 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.20 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.64 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.05 (t, J = 7.50 Hz, 2H, OCH_2), 4.18 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.84–7.44 (m, 7H, Ar—H). LC-MS m/z 360 (M+), 362 (M+2). Anal. Cal. for $C_{20}H_{21}ClO_4$ (360): C, 66.57; H, 5.87. Found: C, 66.49; H, 5.81%.

4.1.1.3. Ethyl 4-[2-(2-bromobenzoyl)-4-methylphenoxy]butanoate ***2c***. Yield: 75%. M.P.: 139–141 °C; IR (KBr) ν_{max} (cm^{-1}): 1680 (C═O), 1730 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.27 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.54 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.13 (t, J = 7.0 Hz, 2H, OCH_2), 4.34 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.81–7.49 (m, 7H, Ar—H). LC-MS m/z 404 (M+), 406 (M+2). Anal. Cal. for $C_{20}H_{21}BrO_4$ (404): C, 59.27; H, 5.22. Found: C, 59.23; H, 5.14%.

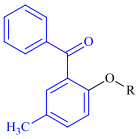
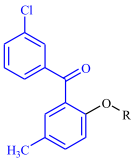
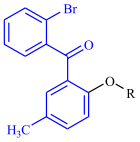
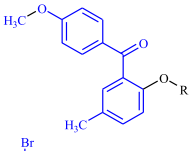
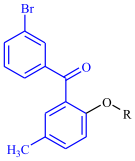
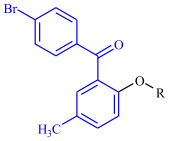
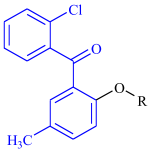
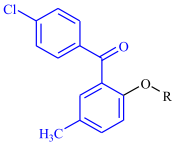
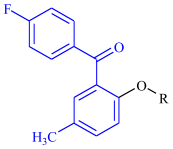
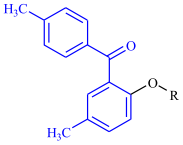
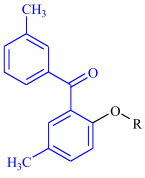
4.1.1.4. Ethyl 4-[2-(4-methoxybenzoyl)-4-methylphenoxy]butanoate ***2d***. Yield: 83%. M.P.: 143–145 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1750 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.38 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.64 (t, J = 7.50, 2H,$COCH_2$), 3.52 (s, 3H, OCH_3), 4.21 (t, J = 7.50 Hz, 2H, OCH_2), 4.54 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.82–7.41 (m, 7H, Ar—H). LC-MS m/z 357 (M + 1). Anal. Cal. for $C_{21}H_{24}O_5$ (356): C, 70.77; H, 6.79. Found: C, 70.69; H, 6.54%.

4.1.1.5. Ethyl 4-[2-(3-bromobenzoyl)-4-methylphenoxy]butanoate ***2e***. Yield: 82%. M.P.: 151–153 °C; IR (KBr) ν_{max} (cm^{-1}): 1670 (C═O), 1760 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.17 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.57 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.22 (t, J = 7.50 Hz, 2H, OCH_2), 4.37 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.74–7.52 (m, 7H, Ar—H). LC-MS m/z 404 (M+), 406 (M+2). Anal. Cal. for $C_{20}H_{21}BrO_4$ (404): C, 59.27; H, 5.22. Found: C, 59.19; H, 5.15%.

4.1.1.6. Ethyl 4-[2-(4-bromobenzoyl)-4-methylphenoxy]butanoate ***2f***. Yield: 78%. M.P.: 164–166 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1740 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.27 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.49 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.35 (t, J = 7.50 Hz, 2H, OCH_2), 4.54 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.69–7.67 (m, 7H, Ar—H). LC-MS m/z 404 (M+), 406 (M+2). Anal. Cal. for $C_{20}H_{21}BrO_4$ (404): C, 59.27; H, 5.22. Found: C, 59.15; H, 5.18%.

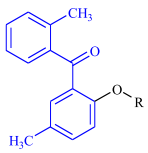
4.1.1.7. Ethyl 4-[2-(2-chlorobenzoyl)-4-methylphenoxy]butanoate ***2g***. Yield: 78%. M.P.: 155–157 °C; IR (KBr) ν_{max} (cm^{-1}): 1685 (C═O), 1775 (ester,

Table 4
Analgesic effect of compounds **8a-l** on thermal pain induced by hot plate method.

Compounds	Basal	1 h		2 h		IC50 μM
		Latency time (s)*	% Latency change	Latency time (s) *	% Latency Change	
8a 	19 ± 3.4	27 ± 4.5*	42.10	26 ± 4.8*	36.84	12 ± 0.38
8b 	15 ± 3.9	22 ± 3.80	46.66	22 ± 6.9	46.66	10 ± 0.36
8c 	19 ± 3.7	28 ± 2.4*	47. 36	26 ± 3.8*	36.84	8 ± 0.12
8d 	21 ± 6.8	27 ± 1.0*	28. 57	25 ± 3.1*	19.04	14 ± 0.27
8e 	19 ± 2.1	27 ± 1.1*	42.10	19 ± 2.1*	46.15	9.2 ± 0.50
8f 	18 ± 6.7	27 ± 1.3*	50.00	19 ± 2.1*	46.15	8.9 ± 0.40
8g 	18 ± 3.8	27 ± 2.3*	50.00	25 ± 3.7*	38.88	9.2 ± 0.0
8h 	14 ± 3.8	26 ± 1.6*	85.71	27 ± 2.9*	50.00	8.8 ± 0.33
8i 	13 ± 3.4	25 ± 1.1*	92.30	22 ± 6.3*	57.14	7.1 ± 0.32
8j 	13 ± 3.8	19 ± 2.2*	46.15	15 ± 2.2*	15.38	15.5 ± 0.31
8k 	18 ± 7.1	23 ± 3.30	27.77	22 ± 5.4	22.22	13 ± 0.45

(*continued on next page*)

Table 4 (*continued*)

Compounds	Basal	1 h		2 h		IC50 μM
		Latency time (s)*	% Latency change	Latency time (s) *	% Latency Change	
8l 	15 ± 4.4	17 ± 2.20	13.33	16 ± 1.5	06.66	20.8 ± 0.22
Saline	18 ± 5.1	17 ± 5.60	0	15 ± 1.2	0	
Piroxicam	15 ± 5.1	27 ± 2.2*	80.00	26 ± 2.4*	73.33	6.8 ± 0.43

Values are means ± SD of four mice per group. Statistical comparisons between basal and post-drug values were analyzed for statistical significance using one-way ANOVA test and denoted by $p < 0.05$.

* Significantly different from normal control group at $p < 0.05$.

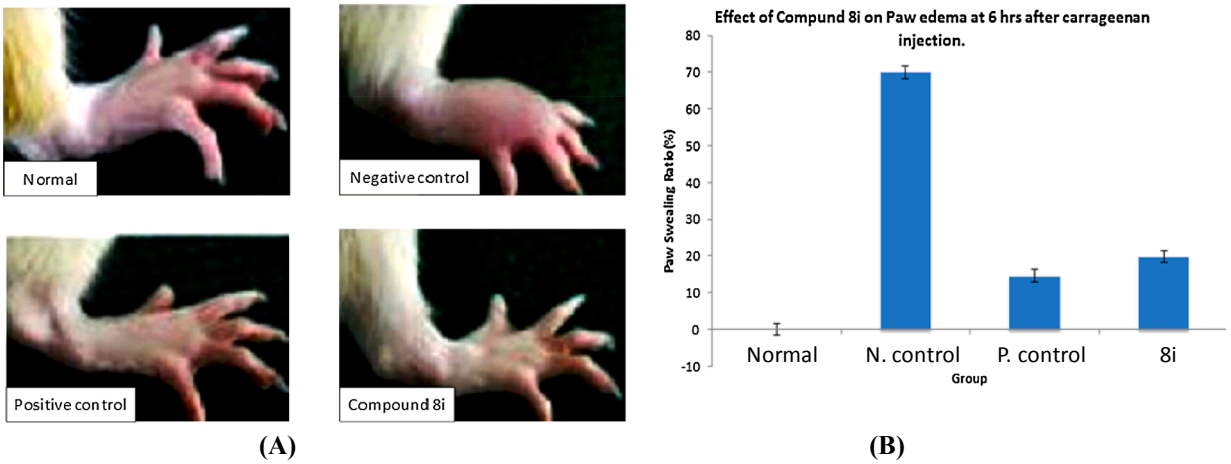


Fig. 6. Effect of compound **8i** on carrageenan-induced paw edema in mice. (A) Typical representative macroscopic photographs of paw from the Normal, carrageenan + Saline, carrageenan + Indomethacin, carrageenan + compound 8i. (B) Paw swelling percentage after 6 h carrageenan injection in different experimental animal.

C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.21 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.57 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.09 (t, J = 7.50 Hz, 2H, OCH_2), 4.21 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.80–7.44 (m, 7H, Ar−H). LC-MS *m/z* 360 (M+), 362 (M+2). Anal. Cal. for $C_{20}H_{21}ClO_4$ (360): C, 66.57; H, 5.87. Found: C, 66.47; H, 5.59%.

4.1.1.8. Ethyl 4-[2-(4-chlorobenzoyl)-4-methylphenoxy]butanoate ***2h***. Yield: 78%. M.P.: 140–142 °C; IR (KBr) ν_{max} (cm^{-1}): 1654 (C═O), 1730 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.36 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.23 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.58 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.15 (t, J = 7.50 Hz, 2H, OCH_2), 4.24 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.74–7.53 (m, 7H, Ar−H). LC-MS *m/z* 360 (M+), 362 (M+2). Anal. Cal. for $C_{20}H_{21}ClO_4$ (360): C, 66.57; H, 5.87. Found: C, 66.48; H, 5.77%.

4.1.1.9. Ethyl 4-[2-(4-fluorobenzoyl)-4-methylphenoxy]butanoate ***2i***. Yield: 80%. M.P.: 127–129 °C; IR (KBr) ν_{max} (cm^{-1}): 1680 (C═O), 1760 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.37 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.18 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.51 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.20 (t, J = 7.50 Hz, 2H, OCH_2), 4.34 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.64–7.59 (m, 7H, Ar−H). LC-MS *m/z* 345 (M+1). Anal. Cal. for $C_{20}H_{21}FO_4$ (344): C, 69.75; H, 6.15. Found: C, 69.69; H, 6.08%.

4.1.1.10. Ethyl 4-[4-methyl-2-(4-methylbenzoyl)phenoxy]butanoate ***2j***. Yield: 80%. M.P.: 113–115 °C; IR (KBr) ν_{max} (cm^{-1}): 1664 (C═O), 1750 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.18 (m, 2H, CH_2), 2.35 (s, 6H, $2CH_3$), 2.68 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.17 (t, J = 7.50 Hz, 2H, OCH_2), 4.41 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.74–7.57 (m, 7H, Ar−H). LC-MS *m/z* 341 (M+1). Anal. Cal. for $C_{21}H_{24}O_4$ (340): C, 74.09; H, 7.11. Found: C, 74.02; H, 7.07%.

4.1.1.11. Ethyl 4-[3-methyl-2-(4-methylbenzoyl)phenoxy]butanoate ***2k***. Yield: 73%. M.P.: 119–121 °C; IR (KBr) ν_{max} (cm^{-1}): 1675 (C═O), 1760 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.37 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.14 (m, 2H, CH_2), 2.27 (s, 6H, $2CH_3$), 2.63 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.19 (t, J = 7.50 Hz, 2H, OCH_2), 4.38 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.76–7.67 (m, 7H, Ar−H). LC-MS *m/z* 341 (M+1). Anal. Cal. for $C_{21}H_{24}O_4$ (340): C, 74.09; H, 7.11. Found: C, 74.01; H, 7.05%.

4.1.1.12. Ethyl 4-[2-methyl-2-(4-methylbenzoyl)phenoxy]butanoate ***2l***. Yield: 78%. M.P.: 125–127 °C; IR (KBr) ν_{max} (cm^{-1}): 1665 (C═O), 1760 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.21 (m, 2H, CH_2), 2.39 (s, 6H, $2CH_3$), 2.67 (t, J = 7.50 Hz, 2H, $COCH_2$), 4.19 (t, J = 7.50 Hz, 2H, OCH_2), 4.45 (q, J = 6.0 Hz, 2H, CH_2 of ester), 6.77–7.67 (m, 7H, Ar−H). LC-MS *m/z* 341 (M+1). Anal. Cal. for $C_{21}H_{24}O_4$ (340): C, 74.09; H, 7.11. Found: C, 74.03; H, 7.09%.

4.1.2. General procedure for the synthesis of benzophenone butyric acid hydrazide analogues ***3a-l***

A typical procedure is described for the synthesis of 4-(2-benzoyl-4-methylphenoxy)butane hydrazide **3a**:

Hydrazine hydrate (0.045 mol) was added to the solution of

compound **2a** (0.03 mol) in ethanol (20 mL) and stirred the reaction mixture at room temperature for 5 h. The completion of the reaction was monitored by TLC using hexane:ethyl acetate (2:1) as the mobile phase and allowed to stand overnight. The white crystals of compound **3a** formed were filtered, washed, dried and recrystallized from ethanol.

*4.1.2.1. 4-(2-Benzoyl-4-methylphenoxy)butane hydrazide **3a***. Yield: 88%. M.P.: 112–114 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1680 (amide, C═O), 3120–3220 (NH), 3300–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.22 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.75 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.87 (s, 2H, NH_2), 4.24 (t, J = 7.50 Hz, 2H, OCH_2), 6.75–7.44 (m, 8H, Ar−H), 8.52 (s, 1H, NH). LC-MS *m/z* 313 (M + 1). Anal. Cal. for $C_{18}H_{20}N_2O_3$ (312): C, 69.21; H, 6.45; N, 8.97. Found: C, 69.15; H, 6.32; N, 8.84%.

*4.1.2.2. 4-[2-(3-Chlorobenzoyl)-4-methylphenoxy]butane hydrazide **3b***. Yield: 83%. M.P.: 119–121 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1670 (amide, C═O), 3310–3410 (NH), 3315–3415 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.14 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.55 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.68 (s, 2H, NH_2), 4.14 (t, J = 7.50 Hz, 2H, OCH_2), 6.71–7.41 (m, 7H, Ar−H), 8.47 (s,1H, NH). LC-MS *m/z* 346 (M +), 348 (M + 2). Anal. Cal. for $C_{18}H_{19}ClN_2O_3$ (346): C, 62.34; H, 5.52; N, 8.08. Found: C, 62.27; H, 5.44; N, 8.04%.

*4.1.2.3. 4-[2-(2-Bromobenzoyl)-4-methylphenoxy]butane hydrazide **3c***. Yield: 75%. M.P.: 105–107 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1685 (amide, C═O), 3100–3205 (NH), 3315–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.04 (m, 2H, CH_2), 2.14 (s, 3H, CH_3), 2.65 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.49 (s, 2H, NH_2), 4.21 (t, J = 7.50 Hz, 2H, OCH_2), 6.72–7.61 (m, 7H, Ar−H), 8.58 (s, 1H, NH). LC-MS *m/z* 390 (M +), 392 (M + 2). Anal. Cal. for $C_{18}H_{19}BrN_2O_3$ (390): C, 55.26; H, 4.89; N, 7.16. Found: C, 55.14; H, 4.79; N, 7.07%.

*4.1.2.4. 4-[2-(4-Methoxybenzoyl)-4-methylphenoxy]butane hydrazide **3d***. Yield: 79%. M.P.: 129–131 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1675 (amide, C═O), 3135–3270 (NH), 3300–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.04 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.57 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.39 (s, 2H, NH_2), 3.68 (s, 3H, OCH_3), 4.22 (t, J = 7.50 Hz, 2H, OCH_2), 6.62–7.71 (m, 7H, Ar−H), 8.64 (s, 1H, NH). LC-MS *m/z* 341 (M + 1). Anal. Cal. for $C_{19}H_{22}N_2O_4$ (342): C, 66.65; H, 6.48; N, 8.18. Found: C, 66.57; H, 6.41; N, 8.13%.

*4.1.2.5. 4-[2-(3-Bromobenzoyl)-4-methylphenoxy]butane hydrazide **3e***. Yield: 79%. M.P.: 115–117 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1655 (amide, C═O), 3210–3310 (NH), 3320–3420 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.12 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.58 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.39 (s, 2H, NH_2), 4.17 (t, J = 7.50 Hz, 2H, OCH_2), 6.62–7.75 (m, 7H, Ar−H), 8.75 (s, 1H, NH). LC-MS *m/z* 390 (M +), 392 (M + 2). Anal. Cal. for $C_{18}H_{19}BrN_2O_3$ (390): C, 55.26; H, 4.89; N, 7.16. Found: C, 55.17; H, 4.77; N, 7.09%.

*4.1.2.6. 4-[2-(4-Bromobenzoyl)-4-methylphenoxy]butane hydrazide **3f***. Yield: 82%. M.P.: 117–119 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1660 (amide, C═O), 3155–3270 (NH), 3330–3420 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.17 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.54 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.47 (s, 2H, NH_2), 4.15 (t, J = 7.50 Hz, 2H, OCH_2), 6.62–7.81 (m, 7H, Ar−H), 8.81 (s, 1H, NH). LC-MS *m/z* 390 (M +), 392 (M + 2). Anal. Cal. for $C_{18}H_{19}BrN_2O_3$ (390): C, 55.26; H, 4.89; N, 7.16. Found: C, 55.14; H, 4.80; N, 6.99%.

*4.1.2.7. 4-[2-(2-Chlorobenzoyl)-4-methylphenoxy]butane hydrazide **3g***. Yield: 73%. M.P.: 121–123 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1665 (amide, C═O), 3110–3270 (NH), 3305–3415 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.04 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.56 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.67 (s, 2H, NH_2),4.29 (t, J = 7.50 Hz, 2H, OCH_2), 6.66–7.72 (m, 7H, Ar−H), 8.81 (s, 1H, NH). LC-MS *m/z* 346 (M +), 348 (M + 2). Anal. Cal. for $C_{18}H_{19}ClN_2O_3$ (346): C, 62.34; H, 5.52; N, 8.08. Found: C, 62.23; H, 5.45; N, 8.01%.

*4.1.2.8. 4-[2-(4-Chlorobenzoyl)-4-methylphenoxy]butane hydrazide **3h***. Yield: 80%. M.P.: 131–133 °C; IR (KBr) ν_{max} (cm^{-1}): 1645 (C═O), 1660 (amide, C═O), 3320–3420 (NH), 3310–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.21 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.60 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.69 (s, 2H, NH_2), 4.27 (t, J = 7.50 Hz, 2H, OCH_2), 6.69–7.75 (m, 7H, Ar−H), 8.47 (s,1H, NH). LC-MS *m/z* 346 (M +), 348 (M + 2). Anal. Cal. for $C_{18}H_{19}ClN_2O_3$ (346): C, 62.34; H, 5.52; N, 8.08. Found: C, 62.23; H, 5.41; N, 8.02%.

*4.1.2.9. 4-[2-(4-Fluorobenzoyl)-4-methylphenoxy]butane hydrazide **3i***. Yield: 81%. M.P.: 123–125 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1685 (amide, C═O), 3115–3200 (NH), 3330–3430 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.01 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.53 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.51 (s, 2H, NH_2),4.02 (t, J = 7.50 Hz, 2H, OCH_2), 6.75–7.45 (m, 7H, Ar−H), 9.03 (s, 1H, NH). LC-MS *m/z* 331 (M + 1). Anal. Cal. for $C_{18}H_{19}FN_2O_3$ (330): C, 65.44; H, 5.80; N, 8.48. Found: C, 65.37; H, 5.74; N, 8.41%.

*4.1.2.10. 4-[4-Methyl-2-(4-methylbenzoyl)phenoxy]butane hydrazide **3j***. Yield: 79%. M.P.: 129–131 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1675 (amide, C═O), 3160–3280 (NH), 3310–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.98 (m, 2H, CH_2), 2.29 (s, 6H, $2CH_3$), 2.59 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.27 (s, 2H, NH_2), 4.21 (t, J = 7.50 Hz, 2H, OCH_2), 6.67–7.79 (m, 7H, Ar−H), 8.94 (s, 1H, NH). LC-MS *m/z* 327 (M + 1). Anal. Cal. for $C_{19}H_{22}N_2O_3$ (326): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.88; H, 6.72; N, 8.51%.

*4.1.2.11. 4-[3-Methyl-2-(4-methylbenzoyl)phenoxy]butane hydrazide **3k***. Yield: 80%. M.P.: 120–122 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1685 (amide, C═O), 3150–3270 (NH), 3310–3430 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.95 (m, 2H, CH_2), 2.15 (s, 6H, $2CH_3$), 2.54 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.17 (s, 2H, NH_2), 4.25 (t, J = 7.50 Hz, 2H, OCH_2), 6.69–7.78 (m, 7H, Ar−H), 8.87 (s, 1H, NH). LC-MS *m/z* 327 (M + 1). Anal. Cal. for $C_{19}H_{22}N_2O_3$ (326): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.87; H, 6.75; N, 8.43%.

*4.1.2.12. 4-[2-Methyl-2-(4-methylbenzoyl)phenoxy]butane hydrazide **3l***. Yield: 85%. M.P.: 123–125 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1680 (amide, C═O), 3110–3210 (NH), 3315–3415 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.02 (m, 2H, CH_2), 2.17 (s, 6H, $2CH_3$), 2.43 (t, J = 7.50 Hz, 2H, $COCH_2$), 3.34 (s, 2H, NH_2), 4.22 (t, J = 7.50 Hz, 2H, OCH_2), 6.67–7.78 (m, 7H, Ar−H), 8.99 (s, 1H, NH). LC-MS *m/z* 327 (M + 1). Anal. Cal. for $C_{19}H_{22}N_2O_3$ (326): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.83; H, 6.69; N, 8.52%.

*4.1.3. General procedure for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5-mercapto[1,3,4]oxadiazole analogues **4a-l***

*A typical procedure is described for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5-mercapto[1,3,4]oxadiazole **4a*:**

A mixture of compound **3a** (3 mmol), carbon disulfide (3 mL), potassium hydroxide (6 mmol) and ethanol (60 mL) was heated under reflux till evolution of hydrogen sulfide was ceased. Afterwards the reaction mixture was cooled to room temperature. The solvent was evaporated at reduced pressure, cold water was poured and acidified with diluted hydrochloric acid solution to bring the pH between 3 and 4. The precipitate thus separated out was allowed to stand overnight, filtered, washed and after drying recrystallized from acetone to achieve compound **4a**.

*4.1.3.1. 2(2-Benzoyl-4-methyl-phenoxy-propyl)-5-mercapto[1,3,4] oxadiazole **4a***. Yield: 79%. M.P.: 137–139 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1685 (C═N), 2550 (S−H) . ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.12 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.81 (t, J = 7.50 Hz, 2H,

CH_2), 4.30 (t, J = 7.50 Hz, 2H, OCH_2), 6.83–7.45 (m, 8H, Ar—H), 10.72 (s, 1H, SH). LC-MS *m/z* 355 (M + 1). Anal. Cal. for $C_{19}H_{18}N_2O_3S$ (354): C, 64.39; H, 5.12; N, 7.90. Found: C, 64.32; H, 5.04; N, 7.81%.

4.1.3.2. 2-[2-(3-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4b***. Yield: 75%. M.P.: 125–127 °C; IR (KBr) ν_{max} (cm^{-1}): 1615 (C═O), 1680 (C═N), 2570 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.13 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.88 (t, J = 7.50 Hz, 2H, CH_2), 4.35 (t, J = 7.50 Hz, 2H, OCH_2), 6.86–7.47 (m, 7H, Ar—H), 10.75 (s, 1H, SH). LC-MS *m/z* 388 (M +), 390 (M + 2). Anal. Cal. for $C_{19}H_{17}ClN_2O_3S$ (3 8 8): C, 58.68; H, 4.41; N, 7.20. Found: C, 58.58; H, 4.35; N, 7.15%.

4.1.3.3. 2-[2-(2-Bromobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4c***. Yield: 82%. M.P.: 118–120 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1690 (C═N), 2610 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.19 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.81 (t, J = 7.50 Hz, 2H, CH_2), 4.40 (t, J = 7.50 Hz, 2H, OCH_2), 6.78–7.75 (m, 7H, Ar—H), 10.55 (s, 1H, SH). LC-MS *m/z* 432 (M +), 434 (M + 2). Anal. Cal. for $C_{19}H_{17}BrN_2O_3S$ (432): C, 52.66; H, 3.95; N, 6.46. Found: C, 52.63; H, 3.87; N, 6.41%.

4.1.3.4. 2-[2-(4-Methoxybenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4d***. Yield: 81%. M.P.: 139–141 °C; IR (KBr) ν_{max} (cm^{-1}): 1620 (C═O), 1675 (C═N), 2580 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.22 (m, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.86 (t, J = 7.50 Hz, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.37 (t, J = 7.50 Hz, 2H, OCH_2), 6.77–7.79 (m, 7H, Ar—H), 10.55 (s, 1H, SH). LC-MS *m/z* 385 (M + 1). Anal. Cal. for $C_{20}H_{20}N_2O_4S$ (384): C, 62.48; H, 5.24; N, 7.29. Found: C, 62.35; H, 5.19; N, 7.21%.

4.1.3.5. 2-[2-(3-Bromobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4e***. Yield: 78%. M.P.: 134–136 °C; IR (KBr) ν_{max} (cm^{-1}): 1625 (C═O), 1695 (C═N), 2620 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.05 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.74 (t, J = 7.50 Hz, 2H, CH_2), 4.33 (t, J = 7.50 Hz, 2H, OCH_2), 6.69–7.77 (m, 7H, Ar—H), 10.61 (s, 1H, SH). LC-MS *m/z* 432 (M +), 434 (M + 2). Anal. Cal. for $C_{19}H_{17}BrN_2O_3S$ (4 3 2): C, 52.66; H, 3.95; N, 6.46. Found: C, 52.61; H, 3.78; N, 6.34%.

4.1.3.6. 2-[2-(4-Bromobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4f***. Yield: 73%. M.P.: 130–132 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1685 (C═N), 2555 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.14 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 2.84 (t, J = 7.50 Hz, 2H, CH_2), 4.32 (t, J = 7.50 Hz, 2H, OCH_2), 6.78–7.77 (m, 7H, Ar—H), 10.71 (s, 1H, SH). LC-MS *m/z* 432 (M +), 434 (M + 2). Anal. Cal. for $C_{19}H_{17}BrN_2O_3S$ (432): C, 52.66; H, 3.95; N, 6.46. Found: C, 52.59; H, 3.81; N, 6.33%.

4.1.3.7. 2-[2-(2-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4g***. Yield: 72%. M.P.: 137–139 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1695 (C═N), 2605 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.29 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.81 (t, J = 7.50 Hz, 2H, CH_2), 4.22 (t, J = 7.50 Hz, 2H, OCH_2), 6.76–7.57 (m, 7H, Ar—H), 10.91 (s, 1H, SH). LC-MS *m/z* 388 (M +), 390 (M + 2). Anal. Cal. for $C_{19}H_{17}ClN_2O_3S$ (3 8 8): C, 58.68; H, 4.41; N, 7.20. Found: C, 58.47; H, 4.27; N, 7.12%.

4.1.3.8. 2-[2-(4-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4h***. Yield: 75%. M.P.: 149–151 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1670 (C═N), 2610 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.31 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.93 (t, J = 7.50 Hz, 2H, CH_2), 4.51 (t, J = 7.50 Hz, 2H, OCH_2), 6.86–7.59 (m, 7H, Ar—H), 10.57 (s, 1H, SH). LC-MS *m/z* 388 (M +), 390 (M + 2). Anal. Cal. for $C_{19}H_{17}ClN_2O_3S$ (388): C, 58.68; H, 4.41; N, 7.20. Found: C, 58.59; H, 4.37; N, 7.03%.

4.1.3.9. 2-[2-(4-Fluorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4i***. Yield: 87%. M.P.: 168–170 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1680 (C═N), 2550 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.35 (m, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.88 (t, J = 7.50 Hz, 2H, CH_2), 4.52 (t, J = 7.50 Hz, 2H, OCH_2), 6.76–7.52 (m, 7H, Ar—H), 10.59 (s, 1H, SH). LC-MS *m/z* 373 (M + 1). Anal. Cal. for $C_{19}H_{17}FN_2O_3S$ (372): C, 61.28; H, 4.60; N, 7.52. Found: C, 61.17; H, 4.43; N, 7.51%.

4.1.3.10. 2-[2-(4-Methylbenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4j***. Yield: 81%. M.P.: 151–153 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1695 (C═N), 2560 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.07 (m, 2H, CH_2), 2.35 (s, 6H, $2CH_3$), 2.77 (t, J = 7.50 Hz, 2H, CH_2), 4.40 (t, J = 7.50 Hz, 2H, OCH_2), 6.87–7.78 (m, 7H, Ar—H), 10.55 (s, 1H, SH). LC-MS *m/z* 369 (M + 1). Anal. Cal. for $C_{20}H_{20}N_2O_3S$ (368): C, 65.20; H, 5.47; N, 7.60. Found: C, 65.04; H, 5.37; N, 7.51%.

4.1.3.11. 2-[2-(3-Methylbenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4k***. Yield: 84%. M.P.: 169–171 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1670 (C═N), 2580 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.05 (m, 2H, CH_2), 2.39 (s, 6H, $2CH_3$), 2.74 (t, J = 7.50 Hz, 2H, CH_2), 4.33 (t, J = 7.50 Hz, 2H, OCH_2), 6.88–7.68 (m, 7H, Ar—H), 10.58 (s, 1H, SH). LC-MS *m/z* 369 (M + 1). Anal. Cal. for $C_{20}H_{20}N_2O_3S$ (3 6 8): C, 65.20; H, 5.47; N, 7.60. Found: C, 65.09; H, 5.34; N, 7.45%.

4.1.3.12. 2-[2-(2-Methylbenzoyl)-4-methylphenoxy-propyl]-5-mercapto [1,3,4]oxadiazole ***4l***. Yield: 79%. M.P.: 144–146 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1680 (C═N), 2620 (S—H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.09 (m, 2H, CH_2), 2.39 (s, 6H, $2CH_3$), 2.66 (t, J = 7.50 Hz, 2H, CH_2), 4.45 (t, J = 7.50 Hz, 2H, OCH_2), 6.78–7.7 (m, 7H, Ar—H), 10.87 (s, 1H, SH). LC-MS *m/z* 369 (M + 1). Anal. Cal. for $C_{20}H_{20}N_2O_3S$ (3 6 8): C, 65.20; H, 5.47; N, 7.60. Found: C, 65.09; H, 5.32; N, 7.45%.

4.1.4. General procedure for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5-ethyl mercaptoacetate-[1,3,4]oxadiazole analogues ***5a-l***

A typical procedure is described for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5-ethyl mercaptoacetate-[1,3,4]oxadiazole ***5a:***

Anhydrous potassium carbonate (55 mmol) was added to a solution of compound **4a (**100 mmol) in acetone (50 mL). To the reaction mixture, ethyl bromoacetate (100 mmol) was added slowly at room temperature with stirring. The progress of the reaction was monitored by TLC using a mixture of ethyl acetate and *n*-hexane (3:7) as eluent. The by-product potassium bromide was removed by filtration. The mother liquor containing the product was concentrated under vacuum to remove acetone and the residual acetone was removed using methanol to afford compound **5a**. The residue was used for the next step without purification.

4.1.4.1. 2(2-Benzoyl-4-methyl-phenoxy-propyl)-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5a***. Yield: 75%. M.P.: 275–277 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1675 (C═N), 1760 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.03 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.75 (t, J = 7.50 Hz, 2H, CH_2), 3.89 (s, 2H, SCH_2), 4.12 (t, J = 7.50 Hz, 2H, OCH_2), 4.79 (q, J = 6.0 Hz, 2H, CH_2), 6.71–7.30 (m, 8H, Ar—H). LC-MS *m/z* 441 (M + 1). Anal. Cal. for $C_{23}H_{24}N_2O_5S$ (440): C, 62.71; H, 5.49; N, 6.36. Found: C, 62.62; H, 5.36; N, 6.31%.

4.1.4.2. 2-[2-(3-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5b***. Yield: 81%. M.P.: 289–291 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1685 (C═N), 1750 (ester, C═O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.10 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.69 (t, J = 7.50 Hz, 2H, CH_2),

3.87 (s, 2H, SCH_2), 4.15 (t, J = 7.50 Hz, 2H, OCH_2), 4.66 (q, J = 6.0 Hz, 2H, CH_2), 6.79–7.54 (m, 7H, Ar—H). LC-MS m/z 474 (M +), 476 (M + 2). Anal. Cal. for $C_{23}H_{23}ClN_2O_5S$ (474): C, 58.16; H, 4.88; N, 5.90. Found: C, 58.09; H, 4.81; N, 5.79%.

4.1.4.3. 2-[2-(2-Bromobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5c***. Yield: 70%. M.P.: 215–217 °C; IR (KBr) ν_{max} (cm^{-1}): 1660 (C═O), 1695 (C═N), 1770 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.05 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.77 (t, J = 7.50 Hz, 2H, CH_2), 3.67 (s, 2H, SCH_2), 4.23 (t, J = 7.50 Hz, 2H, OCH_2), 4.61 (q, J = 6.0 Hz, 2H, CH_2), 6.69–7.44 (m, 7H, Ar—H). LC-MS m/z 518 (M +), 520 (M + 2). Anal. Cal. for $C_{23}H_{23}BrN_2O_5S$ (518): C, 53.18; H, 4.46; N, 5.39. Found: C, 53.07; H, 4.41; N, 5.35%.

4.1.4.4. 2-[2-(4-Methoxybenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5d***. Yield: 68%. M.P.: 198–200 °C; IR (KBr) ν_{max} (cm^{-1}): 1620 (C═O), 1675 (C═N), 1750 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.22 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.71 (t, J = 7.50 Hz, 2H, CH_2), 3.58 (s, 3H, OCH_3), 3.79 (s, 2H, SCH_2), 4.31 (t, J = 7.50 Hz, 2H, OCH_2), 4.72 (q, J = 6.0 Hz, 2H, CH_2), 6.66–7.74 (m, 7H, Ar—H). LC-MS m/z 471 (M + 1). Anal. Cal. for $C_{24}H_{26}N_2O_6S$ (470): C, 61.26; H, 5.57; N, 5.95. Found: C, 61.20; H, 5.56; N, 5.87%.

4.1.4.5. 2-[2-(3-Bromobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5e***. Yield: 79%. M.P.: 236–238 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1680 (C═N), 1760 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.15 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.75 (t, J = 7.50 Hz, 2H, CH_2), 3.74 (s, 2H, SCH_2), 4.32 (t, J = 7.50 Hz, 2H, OCH_2), 4.60 (q, J = 6.0 Hz, 2H, CH_2), 6.59–7.39 (m, 7H, Ar—H). LC-MS m/z 518 (M +), 520 (M + 2). Anal. Cal. for $C_{23}H_{23}BrN_2O_5S$ (518): C, 53.18; H, 4.46; N, 5.39. Found: C, 53.06; H, 4.39; N, 5.28%.

4.1.4.6. 2-[2-(4-Bromobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5f***. Yield: 77%. M.P.: 241–243 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1690 (C═N), 1750 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.41 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.03 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.64 (t, J = 7.50 Hz, 2H, CH_2), 3.77 (s, 2H, SCH_2), 4.24 (t, J = 7.50 Hz, 2H, OCH_2), 4.53 (q, J = 6.0 Hz, 2H, CH_2), 6.67–7.78 (m, 7H, Ar—H). LC-MS m/z 518 (M +), 520 (M + 2). Anal. Cal. for $C_{23}H_{23}BrN_2O_5S$ (518): C, 53.18; H, 4.46; N, 5.39. Found: C, 53.11; H, 4.33; N, 5.25%.

4.1.4.7. 2-[2-(2-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5g***. Yield: 81%. M.P.: 267–269 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1670 (C═N), 1750 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.38 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.15 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.62 (t, J = 7.50 Hz, 2H, CH_2), 3.82 (s, 2H, SCH_2), 4.24 (t, J = 7.50 Hz, 2H, OCH_2), 4.58 (q, J = 6.0 Hz, 2H, CH_2), 6.71–7.63 (m, 7H, Ar—H). LC-MS m/z 474 (M +), 476 (M + 2). Anal. Cal. for $C_{23}H_{23}ClN_2O_5S$ (474): C, 58.16; H, 4.88; N, 5.90. Found: C, 58.03; H, 4.82; N, 5.84%.

4.1.4.8. 2-[2-(4-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5h***. Yield: 81%. M.P.: 248–250 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1675 (C═N), 1780 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.11 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.64 (t, J = 7.50 Hz, 2H, CH_2), 3.64 (s, 2H, SCH_2), 4.23 (t, J = 7.50 Hz, 2H, OCH_2), 4.59 (q, J = 6.0 Hz, 2H, CH_2), 6.68–7.74 (m, 7H, Ar—H). LC-MS m/z 474 (M +), 476 (M + 2). Anal. Cal. for $C_{23}H_{23}ClN_2O_5S$ (474): C, 58.16; H, 4.88; N, 5.90. Found: C, 58.08; H, 4.77; N, 5.78%.

4.1.4.9. 2-[2-(4-Fluorobenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5i***. Yield: 76%. M.P.: 211–213 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1690 (C═N), 1770 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.36 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.12 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.68 (t, J = 7.50 Hz, 2H, CH_2), 3.77 (s, 2H, SCH_2), 4.25 (t, J = 7.50 Hz, 2H, OCH_2), 4.69 (q, J = 6.0 Hz, 2H, CH_2), 6.69–7.77 (m, 7H, Ar—H). LC-MS m/z 459 (M +1). Anal. Cal. for $C_{23}H_{23}FN_2O_5S$ (458): C, 60.25; H, 5.06; N, 6.11. Found: C, 60.19; H, 4.98; N, 6.07%.

4.1.4.10. 2-[2-(4-Methylbenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5j***. Yield: 76%. M.P.: 186–188 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1675 (C═N), 1760 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.29 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.23 (m, 2H, CH_2), 2.29 (s, 6H, $2CH_3$), 2.76 (t, J = 7.50 Hz, 2H, CH_2), 3.69 (s, 2H, SCH_2), 4.43 (t, J = 7.50 Hz, 2H, OCH_2), 4.71 (q, J = 6.0 Hz, 2H, CH_2), 6.62–7.73 (m, 7H, Ar—H). LC-MS m/z 455 (M +1). Anal. Cal. for $C_{24}H_{26}N_2O_5S$ (454): C, 63.42; H, 5.77; N, 6.16. Found: C, 63.33; H, 5.69; N, 6.11%.

4.1.4.11. 2-[2-(3-Methylbenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5k***. Yield: 79%. M.P.: 151–153 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1685 (C═N), 1750 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.29 (m, 2H, CH_2), 2.35 (s, 6H, $2CH_3$), 2.79 (t, J = 7.50 Hz, 2H, CH_2), 3.62 (s, 2H, SCH_2), 4.41 (t, J = 7.50 Hz, 2H, OCH_2), 4.65 (q, J = 6.0 Hz, 2H, CH_2), 6.67–7.78 (m, 7H, Ar—H). LC-MS m/z 455 (M +1). Anal. Cal. for $C_{24}H_{26}N_2O_5S$ (454): C, 63.42; H, 5.77; N, 6.16. Found: C, 63.31; H, 5.68; N, 6.07%.

4.1.4.12. 2-[2-(2-Methylbenzoyl)-4-methylphenoxy-propyl]-5-ethyl mercaptoacetate-[1,3,4] oxadiazole ***5l***. Yield: 80%. M.P.: 172–174 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1675 (C═N), 1760 (ester, C═O). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.25 (m, 2H, CH_2), 2.39 (s, 6H, $2CH_3$), 2.79 (t, J = 7.50 Hz, 2H, CH_2), 3.75 (s, 2H, SCH_2), 4.46 (t, J = 7.50 Hz, 2H, OCH_2), 4.73 (q, J = 6.0 Hz, 2H, CH_2), 6.66–7.67 (m, 7H, Ar—H). LC-MS m/z 455 (M +1). Anal. Cal. for $C_{24}H_{26}N_2O_5S$ (454): C, 63.42; H, 5.77; N, 6.16. Found: C, 63.35; H, 5.67; N, 6.12%.

4.1.5. General procedure for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5- mercapto acetohydrazide-[1,3,4]oxadiazole analogues ***6a-l***

A typical procedure is described for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5- mercapto acetohydrazide-[1,3,4]oxadiazole ***6a:***

Hydrazine hydrate (0.045 mol) was added to the solution of compound **5a** (0.03 mol) in ethanol (20 mL) and stirred the reaction mixture at room temperature for 6 h. The completion of the reaction was monitored by TLC using hexane:ethyl acetate (2:1) as the mobile phase and allowed to stand overnight. The white crystals of compound **6a** formed were filtered, washed, dried and recrystallized from ethanol.

4.1.5.1. 2(2-Benzoyl-4-methyl-phenoxy-propyl)-5-mercapto acetohydrazide-[1,3,4] oxadiazole ***6a***. Yield: 85%. M.P.: 285–287 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1650 (amide, C═O), 1680 (C═N), 3120–3220 (NH), 3310–3430 (NH_2). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.11 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.80 (t, J = 7.50 Hz, 2H, CH_2), 3.93 (s, 2H, SCH_2), 4.31 (t, J = 7.50 Hz, 2H, OCH_2), 4.57 (s, 2H, NH_2), 6.93–7.57 (m, 8H, Ar—H), 10.92 (s, 1H, NH). LC-MS m/z 427 (M +1). Anal. Cal. for $C_{21}H_{22}N_4O_4S$ (426): C, 59.14; H, 5.20; N, 13.14. Found: C, 59.09; H, 5.13; N, 13.07%.

4.1.5.2. 2-[2-(3-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6b***. Yield: 82%. M.P.: 263–265 °C; IR (KBr) ν_{max} (cm^{-1}): 1620 (C═O), 1660 (amide, C═O), 1685 (C═N),

3160–3270 (NH), 3320–3420 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.03 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.71 (t, J = 7.50 Hz, 2H, CH_2), 3.83 (s, 2H, SCH_2), 4.29 (t, J = 7.50 Hz, 2H, OCH_2), 4.60 (s, 2H, NH_2), 6.71–7.65 (m, 7H, Ar−H), 10.03 (s, 1H, NH). LC-MS *m/z* 460 (M +), 462 (M + 2). Anal. Cal. for $C_{21}H_{21}ClN_4O_4S$ (460): C, 54.72; H, 4.59; N, 12.16. Found: C, 54.61; H, 4.49; N, 12.02%.

4.1.5.3. 2-[2-(2-Bromobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6c***. Yield: 72%. M.P.: 274–276 °C; IR (KBr) ν_{max} (cm^{-1}): 1630 (C═O), 1665 (amide, C═O), 1680 (C═N), 3125–3225 (NH), 3325–3425 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.23 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.68 (t, J = 7.50 Hz, 2H, CH_2), 3.91 (s, 2H, SCH_2), 4.25 (t, J = 7.50 Hz, 2H, OCH_2), 4.57 (s, 2H, NH_2), 6.66–7.79 (m, 7H, Ar−H), 10.03 (s, 1H, NH). LC-MS *m/z* 504 (M +), 506 (M + 2). Anal. Cal. for $C_{21}H_{21}BrN_4O_4S$ (504): C, 49.91; H, 4.19; N, 11.09. Found: C, 49.87; H, 4.02; N, 10.99%.

4.1.5.4. 2-[2-(4-Methoxybenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6d***. Yield: 80%. M.P.: 237–238 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1670 (amide, C═O), 1690 (C═N), 3110–3230 (NH), 3225–3425 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.23 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.65 (t, J = 7.50 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.98 (s, 2H, SCH_2), 4.31 (t, J = 7.50 Hz, 2H, OCH_2), 4.49 (s, 2H, NH_2), 6.72–7.75 (m, 7H, Ar−H), 10.03 (s, 1H, NH). LC-MS *m/z* 457 (M + 1). Anal. Cal. for $C_{22}H_{24}N_4O_5S$ (456): C, 57.88; H, 5.30; N, 12.27. Found: C, 57.81; H, 5.24; N, 12.21%.

4.1.5.5. 2-[2-(3-Bromobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6e***. Yield: 75%. M.P.: 268–270 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═O), 1655 (amide, C═O), 1680 (C═N), 3120–3220 (NH), 3320–3420 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.24 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.74 (t, J = 7.50 Hz, 2H, CH_2), 3.84 (s, 2H, SCH_2), 4.23 (t, J = 7.50 Hz, 2H, OCH_2), 4.59 (s, 2H, NH_2), 6.59–7.67 (m, 7H, Ar−H), 9.84 (s, 1H, NH). LC-MS *m/z* 504 (M +), 506 (M + 2). Anal. Cal. for $C_{21}H_{21}BrN_4O_4S$ (504): C, 49.91; H, 4.19; N, 11.09. Found: C, 49.82; H, 4.11; N, 11.02%.

4.1.5.6. 2-[2-(4-Bromobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6f***. *Yield:* 79%. M.P.: 251–253 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═O), 1650 (amide, C═O), 1685 (C═N), 3140–3250 (NH), 3335–3425 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.29 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.75 (t, J = 7.50 Hz, 2H, CH_2), 3.79 (s, 2H, SCH_2), 4.21 (t, J = 7.50 Hz, 2H, OCH_2), 4.65 (s, 2H, NH_2), 6.51–7.77 (m, 7H, Ar−H), 9.92 (s, 1H, NH). LC-MS *m/z* 504 (M +), 506 (M + 2). Anal. Cal. for $C_{21}H_{21}BrN_4O_4S$ (504): C, 49.91; H, 4.19; N, 11.09. Found: C, 49.81; H, 4.03; N, 10.95%.

4.1.5.7. 2-[2-(2-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6g***. Yield: 82%. M.P.: 239–241 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1660 (amide, C═O), 1685 (C═N), 3140–3250 (NH), 3325–3425 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.05 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.78 (t, J = 7.50 Hz, 2H, CH_2), 3.86 (s, 2H, SCH_2), 4.39 (t, J = 7.50 Hz, 2H, OCH_2), 4.75 (s, 2H, NH_2), 6.76–7.69 (m, 7H, Ar−H), 9.95 (s, 1H, NH). LC-MS *m/z* 460 (M +), 462 (M + 2). Anal. Cal. for $C_{21}H_{21}ClN_4O_4S$ (460): C, 54.72; H, 4.59; N, 12.16. Found: C, 54.62; H, 4.51; N, 12.08%.

4.1.5.8. 2-[2-(4-Chlorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6h***. Yield: 82%. M.P.: 277–279 °C; IR (KBr) ν_{max} (cm^{-1}): 1615 (C═O), 1650 (amide, C═O), 1685 (C═N), 3120–3220 (NH), 3330–3450 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.12 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.71 (t, J = 7.50 Hz, 2H, CH_2), 3.84 (s, 2H, SCH_2), 4.19 (t, J = 7.50 Hz, 2H, OCH_2), 4.58 (s, 2H, NH_2), 6.73–7.70 (m, 7H, Ar−H), 10.05 (s, 1H, NH). LC-MS *m/z* 460 (M +), 462 (M + 2). Anal. Cal. for $C_{21}H_{21}ClN_4O_4S$ (460): C, 54.72; H, 4.59; N, 12.16. Found: C, 54.58; H, 4.45; N, 12.09%.

4.1.5.9. 2-[2-(4-Fluorobenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6i***. Yield: 78%. M.P.: 203–205 °C; IR (KBr) ν_{max} (cm^{-1}): 1620 (C═O), 1645 (amide, C═O), 1675 (C═N), 3125–3225 (NH), 3320–3450 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.08 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.73 (t, J = 7.50 Hz, 2H, CH_2), 3.87 (s, 2H, SCH_2), 4.23 (t, J = 7.50 Hz, 2H, OCH_2), 4.64 (s, 2H, NH_2), 6.72–7.74 (m, 7H, Ar−H), 9.92 (s, 1H, NH). LC-MS *m/z* 445 (M +1). Anal. Cal. for $C_{21}H_{21}FN_4O_4S$ (444): C, 56.75; H, 4.76; N, 12.61. Found: C, 56.69; H, 4.66; N, 12.54%.

4.1.5.10. 2-[2-(4-Methylbenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6j***. Yield: 76%. M.P.: 185–187 °C; IR (KBr) ν_{max} (cm^{-1}): 1620 (C═O), 1640 (amide, C═O), 1680 (C═N), 3130–3250 (NH), 3425–3325 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.25 (m, 2H, CH_2), 2.43 (s, 6H, CH_3), 2.64 (t, J = 7.50 Hz 5, 2H, CH_2), 3.87 (s, 2H, SCH_2), 4.30 (t, J = 7.50 Hz, 2H, OCH_2), 4.42 (s, 2H, NH_2), 6.62–7.79 (m, 7H, Ar−H), 10.21 (s, 1H, NH). LC-MS *m/z* 441 (M +1). Anal. Cal. for $C_{22}H_{24}N_4O_4S$ (440): C, 59.98; H, 5.49; N, 12.72. Found: C, 59.88; H, 5.41; N, 12.66%.

4.1.5.11. 2-[2-(3-Methylbenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6k***. Yield: 79%. M.P.: 177–179 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1630 (amide, C═O), 1690 (C═N), 3150–3270 (NH), 3335–3455 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.23 (m, 2H, CH_2), 2.45 (s, 6H, CH_3), 2.65 (t, J = 7.50 Hz, 2H, CH_2), 3.79 (s, 2H, SCH_2), 4.29 (t, J = 7.50 Hz, 2H, OCH_2), 4.52 (s, 2H, NH_2), 6.66–7.78 (m, 7H, Ar−H), 10.19 (s, 1H, NH). LC-MS *m/z* 441 (M +1). Anal. Cal. for $C_{22}H_{24}N_4O_4S$ (440): C, 59.98; H, 5.49; N, 12.72. Found: C, 59.91; H, 5.42; N, 12.65%.

4.1.5.12. 2-[2-(2-Methylbenzoyl)-4-methylphenoxy-propyl]-5-mercapto acetohydrazide-[1,3,4]oxadiazole ***6l***. Yield: 76%. M.P.: 185–187 °C; IR (KBr) ν_{max} (cm^{-1}): 1610 (C═O), 1635 (amide, C═O), 1675 (C═N), 3125–3225 (NH), 3330–3450 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.29 (m, 2H, CH_2), 2.45 (s, 6H, CH_3), 2.67 (t, J = 7.50 Hz, 2H, CH_2), 3.83 (s, 2H, SCH_2), 4.35 (t, J = 7.50 Hz, 2H, OCH_2), 4.41 (s, 2H, NH_2), 6.66–7.78 (m, 7H, Ar−H), 10.09 (s, 1H, NH). LC-MS *m/z* 441 (M +1). Anal. Cal. for $C_{22}H_{24}N_4O_4S$ (440): C, 59.98; H, 5.49; N, 12.72. Found: C, 59.87; H, 5.43; N, 12.65%.

4.1.6. General procedure for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5(5-amino-3-methylmercapto-4-proponate pyrazole) mercapto aceto-[1,3,4]-oxadiazoles ***8a-l***

A typical procedure is described for the synthesis of 2(2-benzoyl-4-methyl-phenoxy-propyl)-5(5-amino-3-methylmercapto-4-proponate pyrazole) mercapto aceto-[1,3,4]-oxadiazole ***8a:***

A mixture of compound **6a** (100 mmol) and [bis(methylthio) methylene]malononitrile **7** (500 mmol) in methanol (70 mL) was heated under reflux till completion of the reaction. The reaction was monitored by TLC using a mixture of chloroform and methanol (4:1) as eluent. The reaction mass was allowed to stand at room temperature and then cooled to 0-5 °C to crystallize the product. On filtration and washing with chilled methanol it afforded compound **8a**.

4.1.6.1. 2(2-Benzoyl-4-methyl-phenoxy-propyl)-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8a***. Yield: 85%. M.P.: 205–207 °C; IR (KBr) ν_{max} (cm^{-1}): 1665 (C═N), 1675 (C═O), 1690 (pyrazole, C═O), 1730 (ester, C═O), 3310–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.12 (t, J = 7.0 Hz, 3H, CH_3), 2.13 (m, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 2.82 (t, J = 7.50 Hz, 2H, CH_2), 3.39 (t, J = 7.50 Hz, 2H, OCH_2), 4.24 (s, 2H, $COCH_2$), 4.24 (q, J = 6.0 Hz, 2H, OCH_2), 4.69 (s, 2H, NH_2), 6.73–7.26 (m, 8H, Ar−H). ^{13}C NMR (DMSO-d_6) δ: 14.14, 17.03, 21.63, 39.42, 40.47, 40.67, 57.44, 66.69, 66.76, 70.85, 107.36, 116.85, 117.03, 117.51, 117.72, 125.45, 127.30, 129.64, 129.75, 130.29, 133.90, 144.14, 157.06, 166.08, 166.71, 166.90, 192.64. LC-

MS *m/z* 596 (M + 1). Anal. Cal. for $C_{28}H_{29}N_5O_6S_2$ (595): C, 56.46; H, 4.91; N, 11.76. Found: C, 56.39; H, 4.87; N, 11.71%.

4.1.6.2. 2-[2-(3-Chlorobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8b***. Yield: 80%. M.P.: 182–184 °C; IR (KBr) ν_{max} (cm^{-1}): 1650 (C═N), 1680 (C═O), 1695 (pyrazole, C═O), 1750 (ester, C═O), 3320–3420 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.25 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.99 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.44 (s, 3H, SCH_3), 2.60 (t, J = 7.50 Hz, 2H, CH_2), 3.88 (t, J = 7.50 Hz, 2H, OCH_2), 4.22 (s, 2H, $COCH_2$), 4.37 (q, J = 6.0 Hz, 2H, OCH_2), 4.57 (s, 2H, NH_2), 6.67–7.59 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 14.62, 17.45, 20.96, 26.95, 32.47, 37.28, 59.13, 75.92, 95.56, 113.85, 123.42, 128.23, 129.07, 129.67, 130.52, 131.41, 132.01, 132.64, 133.56, 135.51, 141.27, 144.27, 151.84, 156.58, 160.47, 169.28, 184.45, 199.64. LC-MS *m/z* 629 (M+), 631 (M+2). Anal. Cal. for $C_{28}H_{28}ClN_5O_6S_2$ (629): C, 53.37; H, 4.48; N, 11.11. Found: C, 53.32; H, 4.44; N, 11.03%.

4.1.6.3. 2-[2-(2-Bromobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8c***. Yield: 83%. M.P.: 196–198 °C; IR (KBr) ν_{max} (cm^{-1}): 1650 (C═N), 1665 (C═O), 1690 (pyrazole, C═O), 1760 (ester, C═O), 3210–3310 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.23 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.89 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.35 (s, 3H, SCH_3), 2.59 (t, J = 7.50 Hz, 2H, CH_2), 3.71 (t, J = 7.50 Hz, 2H, OCH_2), 4.23 (s, 2H, $COCH_2$), 4.35 (q, J = 6.0 Hz, 2H, OCH_2), 4.54 (s, 2H, NH_2), 6.69–7.60 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 13.52, 18.42, 19.67, 25.93, 30.74, 35.33, 58.12, 75.92, 95.56, 113.85, 125.42, 127.73, 128.57, 129.67, 130.52, 131.46, 132.01, 133.64, 135.56, 136.29, 141.27, 144.27, 153.25, 157.58, 164.47, 168.21, 185.28, 194.22. LC-MS *m/z* 673 (M+), 675 (M+2). Anal. Cal. for $C_{28}H_{28}BrN_5O_6S_2$ (673): C, 49.85; H, 4.18; N, 10.38. Found: C, 49.73; H, 4.15; N, 10.33%.

4.1.6.4. 2-[2-(4-Methoxy)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8d***. Yield: 78%. M.P.: 209–211 °C; IR (KBr) ν_{max} (cm^{-1}): 1655 (C═N), 1680 (C═O), 1695 (pyrazole, C═O), 1755 (ester, C═O), 3215–3315 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.10 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.48 (s, 3H, SCH_3), 2.61 (t, J = 7.50 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.94 (t, J = 7.50 Hz, 2H, OCH_2),4.21 (s, 2H, $COCH_2$), 4.34 (q, J = 6.0 Hz, 2H, OCH_2), 4.48 (s, 2H, NH_2), 6.82–7.73 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 15.62, 17.57, 20.92, 25.79, 31.42, 34.24, 56.25, 59.15, 71.97, 92.20, 112.83, 123.44, 128.13, 129.47, 130.42, 131.01, 133.66, 134.23, 136.51, 138.84, 150.26, 152.14, 158.02, 160.17, 164.86, 187.57, 192.41. LC-MS *m/z* 626 (M+1). Anal. Cal. for $C_{29}H_{31}N_5O_7S_2$ (625): C, 55.67; H, 4.99; N, 11.19. Found: C, 55.61; H, 4.92; N, 11.15%.

4.1.6.5. 2-[2-(3-Bromobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8e***. Yield: 75%. M.P.: 183–185 °C; IR (KBr) ν_{max} (cm^{-1}): 1635 (C═N), 1660 (C═O), 1700 (pyrazole, C═O), 1740 (ester, C═O), 3225–3325 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.87 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.36 (s, 3H, SCH_3), 2.55 (t, J = 7.50 Hz, 2H, CH_2), 3.72 (t, J = 7.50 Hz, 2H, OCH_2), 4.19 (s, 2H, $COCH_2$), 4.32 (q, J = 6.0 Hz, 2H, OCH_2), 4.49 (s, 2H, NH_2), 6.65–7.69 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 16.52, 18.45, 21.96, 25.95, 36.47, 38.28, 57.12, 78.46, 93.56, 113.81, 123.41, 125.90, 127.08, 128.15, 130.52, 131.41, 132.51, 133.64, 134.26, 135.51, 142.77, 143.25, 151.84, 159.28, 160.09, 167.28, 184.41, 189.30. LC-MS *m/z* 673 (M+), 675 (M+2). Anal. Cal. for $C_{28}H_{28}BrN_5O_6S_2$ (673): C, 49.85; H, 4.18; N, 10.38. Found: C, 49.71; H, 4.09; N, 10.29%.

4.1.6.6. 2-[2-(4-Bromobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8f***. Yield: 84%. M.P.: 185–188 °C; IR (KBr) ν_{max} (cm^{-1}): 1650 (C═N), 1670 (C═O), 1695 (pyrazole, C═O), 1750 (ester, C═O), 3220–3320 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.32 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.84 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.35 (s, 3H, SCH_3), 2.49 (t, J = 7.50 Hz, 2H, CH_2), 3.71 (t, J = 7.50 Hz, 2H, OCH_2), 4.20 (s, 2H, $COCH_2$), 4.37 (q, J = 6.0 Hz, 2H, OCH_2), 4.52 (s, 2H, NH_2), 6.66–7.79 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 13.62, 18.57, 19.97, 25.79, 32.42, 35.24, 56.15, 71.97, 97.29, 113.83, 123.45, 125.27, 128.57, 129.12, 130.42, 132.45, 133.73, 135.27, 137.84, 150.26, 155.18, 157.25, 159.27, 167.06, 187.02, 198.74. LC-MS *m/z* 673 (M+), 675 (M+2). Anal. Cal. for $C_{28}H_{28}BrN_5O_6S_2$ (673): C, 49.85; H, 4.18; N, 10.38. Found: C, 49.76; H, 4.07; N, 10.23%.

4.1.6.7. 2-[2-(3-Chlorobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8g***. Yield: 79%. M.P.: 195–197 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═N), 1660 (C═O), 1685 (pyrazole, C═O), 1760 (ester, C═O), 3310–3410 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.29 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.86 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.34 (s, 3H, SCH_3), 2.53 (t, J = 7.50 Hz, 2H, CH_2), 3.81 (t, J = 7.50 Hz, 2H, OCH_2), 4.18 (s, 2H, $COCH_2$), 4.35 (q, J = 6.0 Hz, 2H, OCH_2), 4.55 (s, 2H, NH_2), 6.61–7.67 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 15.57, 17.27, 21.96, 25.95, 36.47, 40.28, 57.12, 79.92, 90.56, 113.81, 123.41, 125.90, 127.08, 128.67, 129.12, 130.21, 131.53, 132.64, 133.26, 135.51, 140.27, 145.25, 153.84, 157.28, 162.47, 165.27, 184.23, 188.79. LC-MS *m/z* 629 (M+), 631 (M+2). Anal. Cal. for $C_{28}H_{28}ClN_5O_6S_2$ (629): C, 53.37; H, 4.48; N, 11.11. Found: C, 53.28; H, 4.35; N, 10.97%.

4.1.6.8. 2-[2-(4-Chlorobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8h***. Yield: 79%. M.P.: 199–201 °C; IR (KBr) ν_{max} (cm^{-1}): 1650 (C═N), 1675 (C═O), 1715 (pyrazole, C═O), 1770 (ester, C═O), 3215–3315 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.27 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.89 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.38 (s, 3H, SCH_3), 2.47 (t, J = 7.50 Hz, 2H, CH_2), 3.86 (t, J = 7.50 Hz, 2H, OCH_2), 4.24 (s, 2H, $COCH_2$), 4.36 (q, J = 6.0 Hz, 2H, OCH_2), 4.54 (s, 2H, NH_2), 6.66–7.79 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 13.14, 15.87, 20.46, 26.95, 37.42, 39.28, 55.20, 77.11, 89.56, 114.81, 123.41, 125.90, 126.08, 127.67, 130.89, 133.38, 134.26, 137.51, 140.27, 142.25, 154.84, 158.28, 162.47, 168.28, 184.25, 190.20.LC-MS *m/z* 629 (M+), 631 (M+2). Anal. Cal. for $C_{28}H_{28}ClN_5O_6S_2$ (629): C, 53.37; H, 4.48; N, 11.11. Found: C, 53.31; H, 4.37; N, 11.05%.

4.1.6.9. 2-[2-(4-Fluorobenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8i***. Yield: 85%. M.P.: 208–210 °C; IR (KBr) ν_{max} (cm^{-1}): 1655 (C═N), 1675 (C═O), 1690 (pyrazole, C═O), 1750 (ester, C═O), 3320–3420 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.25 (t, J = 7.0 Hz, 3H, CH_3 of ester), 1.65 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.35 (s, 3H, SCH_3), 2.49 (t, J = 7.50 Hz, 2H, CH_2), 3.87 (t, J = 7.50 Hz, 2H, OCH_2), 4.18 (s, 2H, $COCH_2$), 4.36 (q, J = 6.0 Hz, 2H, OCH_2), 4.55 (s, 2H, NH_2), 6.78–7.69 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 15.62, 17.08, 20.27, 24.49, 31.42, 33.29, 58.25, 72.37, 88.30, 113.43, 127.45, 128.27, 129.52, 130.62, 131.91, 133.56, 136.72, 137.67, 139.34, 151.46, 154.58, 156.55, 158.17, 167.66, 186.52, 198.94. LC-MS *m/z* 614 (M+1). Anal. Cal. for $C_{28}H_{28}FN_5O_6S_2$ (613): C, 54.80; H, 4.60; N, 11.41. Found: C, 54.73; H, 4.55; N, 11.39%.

4.1.6.10. 2-[2-(4-Methylbenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8j***. Yield: 80%. M.P.: 210–212 °C; IR (KBr) ν_{max} (cm^{-1}): 1640 (C═N), 1670 (C═O), 1700 (pyrazole, C═O), 1760 (ester, C═O), 3210–3310 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.30 (t,

J = 7.0 Hz, 3H, CH_3 of ester), 2.16 (m, 2H, CH_2), 2.41 (s, 6H, $2CH_3$), 2.45 (s, 3H, SCH_3), 2.57 (t, J = 7.50 Hz, 2H, CH_2), 3.82 (t, J = 7.50 Hz, 2H, OCH_2),4.23 (s, 2H, $COCH_2$), 4.37 (q, J = 6.0 Hz, 2H, OCH_2), 4.51 (s, 2H, NH_2), 6.72–7.63 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 13.67, 16.79, 18.12, 20.04, 24.79, 32.41, 35.24, 60.15, 75.97, 97.29, 113.83, 123.45, 127.27, 129.02, 130.12, 132.41, 135.95, 136.25, 137.22, 140.84, 151.26, 154.08, 157.25, 159.27, 168.06, 185.74, 197.95. LC-MS m/z 610 (M + 1). Anal. Cal. for $C_{29}H_{31}N_5O_6S_2$ (609): C, 57.13; H, 5.12; N, 11.49. Found: C, 57.01; H, 5.03; N, 11.44%.

4.1.6.11. 2-[2-(3-Methylbenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8k***. Yield: 80%. M.P.: 190–192 °C; IR (KBr) ν_{max} (cm^{-1}): 1650 (C═N), 1670 (C═O), 1690 (pyrazole, C═O), 1755 (ester, C═O), 3210–3310 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.27 (m, 2H, CH_2), 2.34 (s, 6H, $2CH_3$), 2.45 (s, 3H, SCH_3), 2.59 (t, J = 7.50 Hz, 2H, CH_2), 3.94 (t, J = 7.50 Hz, 2H, OCH_2),4.30 (s, 2H, $COCH_2$), 4.39 (q, J = 6.0 Hz, 2H, OCH_2), 4.58 (s, 2H, NH_2), 6.61–7.77 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 14.29, 17.22, 19.57, 20.57, 24.79, 31.77, 35.82, 59.28, 72.79, 92.29, 113.83, 125.45, 126.25, 127.27, 128.02, 129.12, 130.41, 133.58, 134.57, 135.29, 138.57, 139.84, 150.26, 153.25, 156.25, 158.27, 166.28, 185.02, 196.17. LC-MS m/z 610 (M + 1). Anal. Cal. for $C_{29}H_{31}N_5O_6S_2$ (609): C, 57.13; H, 5.12; N, 11.49. Found: C, 57.09; H, 5.05; N, 11.38%.

4.1.6.12. 2-[2-(2-Methylbenzoyl)-4-methylphenoxy-propyl]-5(5-amino-3-methylmercapto-4-proponate pyrazole)mercapto aceto-[1,3,4]-oxadiazole ***8l***. Yield: 80%. M.P.: 201–203 °C; IR (KBr) ν_{max} (cm^{-1}): 1650 (C═N), 1675 (C═O), 1695 (pyrazole, C═O), 1740 (ester, C═O), 3210–3310 (NH_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.35 (t, J = 7.0 Hz, 3H, CH_3 of ester), 2.29 (m, 2H, CH_2), 2.35 (s, 6H, $2CH_3$), 2.41 (s, 3H, SCH_3), 2.60 (t, J = 7.50 Hz, 2H, CH_2), 3.85 (t, J = 7.50 Hz, 2H, OCH_2),4.25 (s, 2H, $COCH_2$), 4.40 (q, J = 6.0 Hz, 2H, OCH_2), 4.59 (s, 2H, NH_2), 6.65–7.75 (m, 7H, Ar—H). ^{13}C NMR (DMSO-d_6) δ: 15.23, 16.47, 18.47, 21.58, 26.54, 32.45, 35.88, 55.85, 72.52, 91.29, 113.15, 124.45, 125.28, 126.53, 127.25, 129.57, 130.42, 131.85, 133.03, 134.85, 135.27, 138.54, 151.26, 154.18, 157.25, 158.27, 164.46, 183.78, 194.29. LC-MS m/z 610 (M + 1). Anal. Cal. for $C_{29}H_{31}N_5O_6S_2$ (609): C, 57.13; H, 5.12; N, 11.49. Found: C, 57.01; H, 5.04; N, 11.40%.

4.2. Pharmacology

4.2.1. Biological evaluation, animal models and ethics

For the entire biological assay adult male Swiss albino mice (20–25 g) and Wistar rats (150–175 g) were used and were housed in controlled conditions at a temperature of 26 ± 1 °C and relative humidity of 50–90% with free access to standard pellet diet and tap water. Before the experiment all the animals were housed for a week to allow them to adapt to the experimental environment. All the experimental procedures and animal handling were performed according to guidelines of the Research Ethical Committee of the Farooquia Pharmacy, College, Mysuru.

4.2.2. COX-1 and COX-2 in vitro inhibitory activity

The efficacy of the title compounds **8a-l** to inhibit COX-1 and COX-2 enzymes was determined by adopting the colorimetric enzyme immune assay [29]. The inhibitory efficacy of synthesized compounds against COX-1 and COX-2 was determined using COX inhibitor screening assay kit [30]. The inhibitory activity of the compounds was measured by monitoring the production of oxidized *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine (TMPD) at 590 nm followed by incubation of either COX-1 or COX-2 with arachidonic acid. The enzyme was preincubated independently for 5 min at 25 °C with the test compound prior to the addition of arachidonic acid (final concentration 1.1 mM) and TMPD. The reaction mixture was incubated for 5 min at 25 °C and the percent inhibition was calculated according to the following equation.

$$\text{COX inhibiting activity}\,(\%) = [(1 - (A_1 - A_2)/A_0] \times 100$$

where A_0 is the absorbance of the control (without the test compound), A_1 is the absorbance in the presence of the test compound and A_2 is the absorbance sample blank (without TMPD). The IC_{50} values were calculated using a calibration curve with different concentrations of samples.

4.2.3. Anti-inflammatory in vivo activity

The efficacy of anti-inflammatory activity of the synthesized compounds **8a-l** was evaluated adopting the *in vivo* formalin-induced rat foot paw edema model [31]. The synthesized compounds **8a-l** (10 mg/kg) and the standard compound diclofenac (10 mg/kg) were administered through oral route just previous to induction of inflammation, which was achieved using 6% formal in solution as a subcutaneous injection on the plantar surface of the left hind-paw. Then the anti-inflammatory activity was calculated based on the change in paw-volume using plethysmometer at 1, 3 and 6 h after injecting formalin. Besides, the right hind-paw of the animals was served as a reference for comparison with the opposite limb. The percentage edema inhibition was expressed as percentage paw-volume change in mL.

The percentage inhibition of the inflammatory effect of the title compounds, compared to control, was calculated using the following expression:

$$\%\,\text{Inhibition} = \frac{[\text{Degree of inflammation by the (control group - test group)}]}{\text{Degree of inflammation by the control group}} \times 100$$

4.2.4. Analgesic activity

4.2.4.1. Acetic acid induced writhing test. This test was performed according to the earlier described method [28,32]. In brief, the synthesized compounds **8a-l** (10 mg/kg) and vehicle, standard compound piroxicam (10 mg/kg) were administered orally 30 min before intra-peritoneal injection of 0.7% acetic acid solution (10 mL/kg). Then the mice were kept separately in glass cages for observation, and the number of writhing movements (abdominal constriction followed by dorsiflexion and extension) was counted for the next 30 min and starting 5 min after acetic acid injection. The results are expressed as the number of writhes per 30 min period. Percentage inhibition of writhing was calculated using the formula.

$$\text{Inhibition}\,\% = \frac{\text{Mean No. of writhes (Control) - Mean No. of writhes (Test)}}{\text{Mean number of writhes (control)}} \times 100$$

4.2.4.2. Hot plate latency test. This test was carried out as described previously [33]. Hot plate latency (seconds) was assessed in animals receiving normal saline or test agents (10 mg/kg) at 0, 1 and 2 h after administration. Piroxicam (10 mg/kg) was used as a standard compound. The synthesized compounds were administered using an oral gavage 1 h earlier to the experimental procedure. Response latency was determined as the difference in time between the placement of the mouse on the hot plate and occurrence of the licking of hind-paws at 50 °C. A cutoff latency of 30 *sec* was used to prevent heat-induced tissue damage.

The increase in baseline (in percentage) was calculated by the formula

$$\frac{[\text{Reaction time} \times 100]}{\text{Baseline}} - 100$$

4.2.5. Statistical analysis

Statistical comparisons between different groups were analyzed for statistical significance using one-way ANOVA test with a value of $p < 0.05$ considered significant. Data were articulated as the mean value ± standard deviation (SD).

4.3. Modeling studies

The ligand preparation done by using Chem Bio Draw Ultra 14.0, geometries was optimized using Chem Bio 3D Ultra 14.0 and for protein preparation autodock tools 1.5.6 is used. Molecular docking calculation has done by autodock tools 1.5.6 and MGL tools 1.5.6 packages. Three-dimensional coordinates COX-2 (pdb code 4 m11) and COX-1 (pdb code 1eqg.C) were retrieved from protein data bank (pdb). The pdb files were submitted to "Build/check/repair model" and "Prepare pdb file for docking programs" modules where missing side chains were modeled in, a small regularization was performed, water positions and symmetry were corrected, and hydrogens were added. Water molecules and non-standard residues were removed, only polar hydrogen was maintained, and Gasteiger charges were computed for protein atoms by autodock tools. The potent molecule was constructed with Chem Bio Draw Ultra 14.0 programm and these geometries were optimized using the Chem Bio 3D Ultra 14.0 to the corresponding pdb file that was submitted to autodock tools for pdbqt file preparation and docking with autodock. The geometry of built compound was optimized, partial charges were also calculated, and saved as pdb files that was passed, as usual, to autodock tools for pdbqt file preparation.

Autodock 4.2.6 was employed for docking simulations. A Lamarckian genetic algorithm with local search (GALS) was used as a search engine, with a total of 100n runs. The region of interest, used by autodock 4.2.6 for docking runs, and by autogrid for affinity grid map preparation, was defined in such a way to comprise the whole catalytic binding site using a grid of 60 × 60 × 60 points with a grid space of 0.375 Å, centers of grid box: x = 25.089; y = 28.886; z = 42.114. Cluster analysis was performed on the docked results using an RMS tolerance of 2.0 Å. Finally, the more energetically favourable cluster poses were evaluated by using a Python molecule viewer and PyMOL [22–24].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103220.

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