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SYNTHESIS, MOLECULAR DOCKING AND BIOLOGICAL EVALUATION OF 1,2,4-OXADIAZOLE AMIDES OF CHROMONE-2-ACID AND CHROMONE-3-ACID

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ABSTRACT: In the present study, we prepared a series of 1,2,4-oxadiazole amides of 6-Fluoro-chromone-2-acid and chromone-3-acids are synthesized from an efficient and straightforward procedure from the reaction of 6-Fluoro-chromone-2-acid and chromone-3-acid with 1,2,4-oxadiazole amines. Molecular interactions of the synthesized compounds are studied by Discovery Studio v3.5, molecular docking with COX-2 enzyme. The compounds with high LibDock scores are screened for their *invivo* analgesic and anti-inflammatory activities. These compounds were screened for analgesic and anti-inflammatory activities.
Keywords: 1,2,4-oxadiazole sulfonamide, molecular docking, analgesic, anti-inflammatory activity

INTRODUCTION

The chromone scaffold [(4H)-1-benzopyran-4-one] is well known as a pharmacophore of a large number of natural and synthetic bioactive molecules. This heterocycle constitutes the basic nucleus of flavones, an important and widespread class of compounds from plants with a large number of biological activities[i]. Natural and synthetic chromones have shown a large spectrum of biological activities such as anti tubercular[ii-iii], anti-inflammatory[iv], antiviral[v], and anticancer activity[vi-xi] associated with low toxicity.

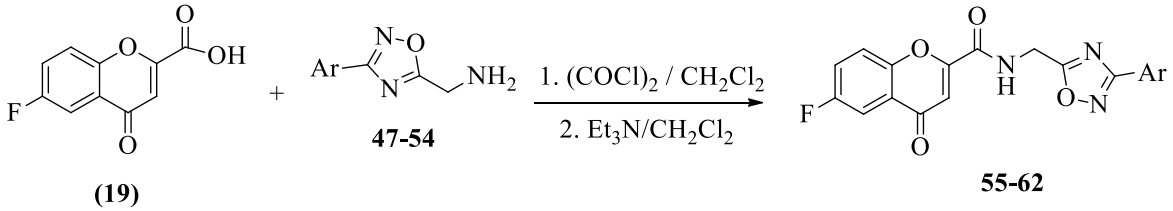
EXPERIMENTAL

All materials and solvents were industrially available and used as purchased. Melting points were recorded on a Polmon instrument, India (model MP96). IR spectra (KBr discs) were recorded on a Perkin-Elmer 337 Spectrophotometer. 1H and 13C NMR spectra were measured on a Bruker 400 MHz spectrometer in CDCl3 using TMS as an internal standard. Mass spectra were measured on an Agilent 6310 ion trap mass spectrometer, USA. All synthesized compounds were purified by recrystallization or column chromatography on silica gel (60– 120 mesh, Spectrochem, Mumbai, India).

Synthesis of 1,2,4-oxadiazole amides of 6-fluoro-chromone-2-acid (55-62)

1,2,4-oxadiazole amides of 6-fluoro-chromone-2-acid **(55-62)** were synthesized from the amide coupling reaction of 6-fluoro-chromone-2-acid **(19)** with (3-aryl-1,2,4-oxadiazol-5-yl)-methanamines **(47-54)** via acid chloride method and characterized from their spectral data[x-xviii].

*Scheme 7: Synthesis of 1,2,4-oxadiazole amides of 6-fluoro-chrmone-2-acid (**55-62**):*



47, 55) Ar = Benzyl

48, 56) Ar = Phenyl

49, 57) Ar = 2-Methoxy phenyl

50, 58) Ar = 2-Chloro phenyl

51, 59) Ar = 4-Methyl phenyl

52, 60) Ar = 4- Methoxy phenyl

53, 61) Ar = 4-Fluoro phenyl

54, 62) Ar = 4-Cyano pyridyl

6-fluoro-chromone-2-acid **(19)** (0.3g, 1.44 mmol) was taken in DCM and oxalyl chloride (1mL) was added. To this a catalytic amount of DMF was added and stirring was continued at RT for 2h. After completion of the reaction by TLC reference, solvents were removed under vacuum. Acid chloride was dissolved in DCM (20 mL), Et_3N (1mL) was added. To this (3-Benzyl-1,2,4-oxadiazole-5-yl)-methanamine **(47)** (0.32g, 1.73 mmol) was added dropwise and stirring was continued for 2h at RT. After completion of the reaction by TLC reference, reaction mixture was quenched with 30 mL of H_2O. It was extracted into DCM (2× 30mL) dried over Na_2SO_4 concentrated under vacuum. Crude was purified by column chromatography using 60-120 silicagel by eluting with petether : ethylacetate (4:6) to give pure compound as white solid. Yield = 210 mg, m.p. 273-275 ºC.

Benzyl 1,2,4 oxadiazole amide of 6-fluoro chromone-2-acid **(55)** is characterized from its spectral data. In its ^{1}H NMR ($CDCl_3$, 400 MHz) **(Fig-2.4)** newly formed -CONH proton appearing at 7.75 (t); 1"-CH_2 & 5'-CH_2 protons appeared at 4.08 (s), 4.78 (d), aromatic protons appeared at 7.05 (s, H-3), 7.21-7.33 (m, H-2" to H-6"), 7.39-7.48 (m, H-5 & H-7), 7.8 (m, H-8).

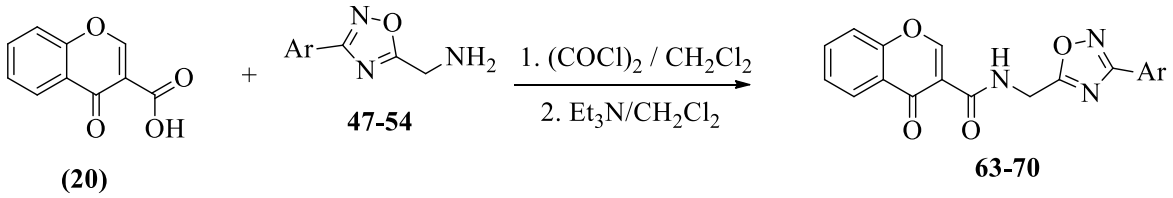
In the ^{13}C NMR ($CDCl_3$, 100.6 MHz) (**Fig-2.5)** the newly formed amide and oxadiazole carbons appeared at δ 169.8 (-CONH), 176.8 (C-3'), 159.9 (C-5'), 1"-CH_2, 5'-CH_2 carbons appeared at 31.7, 36.0. Aromatic carbons appeared at 110.2 (C-5), 110.6 (C-3), 122.0 (C-8), 123.8 (C-7), 125.4 (C-4a), 127.3 (C-6), 129.4 (C-3" & C-5"), 136.0 (C-2" & C-6"), 151.9 (C-1"), 152.2 (C-8a), 158.4 (C-6), 160.9 (C-2), 177.0 (4-C=O).

The DIPMS of **55** showed the quasi-molecular ion peak at m/z 378 $[M-H]^+$ (**Fig-2.6).**

6) Synthesis of 1,2,4-oxadiazole amides of chromone-3-acid (63-70)

1,2,4-oxadiazole amides of chromone-3-acid **(63-70)** were synthesized from the amide coupling reaction of chromone-3-acid **(20)** with (3-aryl-1,2,4-oxadiazol-5-yl)-methanamines **(47-54)** via acid chloride method and characterized from their spectral data.

*Scheme 8: Synthesis of 1,2,4-oxadiazole amides of chromone-3-acid **(63-70):***



47, 63) Ar = Benzyl
48, 64) Ar = Phenyl
49, 65) Ar = 2-Methoxy phenyl
50, 66) Ar = 2-Chloro phenyl
51, 67) Ar = 4-Methyl phenyl
52, 68) Ar = 4- Methoxy phenyl
53, 69) Ar = 4-Fluoro phenyl
54, 70) Ar = 4-Cyano pyridyl

To a mixture of chromone-3-acid **(20)** (0.3g, 1.57 mmol) in DCM, oxalyl chloride was added (1 mL) and catalytic amount of DMF was added and stirring continued at RT for 2 h. After completion of the reaction by TLC reference, solvents were removed under vacuum. Acid chloride was dissolved in DCM (20 mL), Et_3N (1 mL) was added followed by drop wise addition of (3-Benzyl-1,2,4-oxadiazole-5-yl)-methanamine **(47) (**0.35g, 1.85 mmol) and stirring continued for 2 h at RT. After completion of the reaction by TLC reference, reaction mixture was quenched with 30 mL of H_2O, extracted into DCM (2× 30mL) dried over Na_2SO_4 concentrated under vacuum. Crude was purified by column chromatography using 60-120 silica gel by eluting with pet ether: ethyl acetate (4:6) to give pure compound as white solid. Yield = 240 mg.

Benzyl 1,2,4 oxadiazole amide of chromone-3-acid **(63)** is characterized from its spectral data. In its ^{1}H NMR ($CDCl_3$, 400 MHz) **(Fig-2.7)** newly formed -CONH proton appearing at 9.95 (t); 1"-CH_2 & 5'-CH_2 protons appeared at 4.08 (s), 4.86 (d), aromatic protons appeared at 7.22-7.34 (m, H-2" to H-6"), 7.54-7.58 (m, H-6), 7.73-7.8 (m, H-7), 8.29-8.31 (dd, J=1.6Hz, J=1.6Hz, H-5), 8.98 (s, H-2).

In the ^{13}C NMR ($CDCl_3$, 100.6 MHz) (**Fig-2.8)** the newly formed amide and oxadiazole carbons appeared at δ 163.1 (-CONH), 176.6 (C-3'), 169.7 (C-5'), 1"-CH_2, 5'-CH_2 carbons appeared at 31.7, 35.9. Aromatic carbons appeared at 115.2 (C-3), 119.1 (C-8), 124.0 (C-6), 125.9 (C-4a), 127.1 (C-5), 127.3 (C-4"), 129.0 (C-3" & C-5"), 129.3 (C-2" & C-6"), 135.7 (C-7), 136.1 (C-1"), 156.0 (C-8a), 163.8 (C-2), 177.4 (4-C=O).

The DIPMS of **63** showed the quasi-molecular ion peak at m/z 362 $[M+H]^+$ (**Fig-2.9)**

Molecular docking. Molecular docking method was used for studying the binding modes and affinities of the synthesized compounds with Musmusculus COX 2 (PDB ID: 3LN1). All the ligands were targeted to celecoxib bound at the COX-2 site. The three-dimensional structure of celecoxib bound at the COX2 active site (PDB ID: 3LN1) was retrieved from the Brookhaven Protein Data Bank (PDB), USA (http:// www.rcsb.org/pdb). Protein and ligand preparation wizard were used, respectively. Initially, ions, water molecules, and all the internal ligands were removed and missing atoms were inserted before minimization of the target protein. Alternative conformations (disorder) were removed. The best ligand conformation was chosen on the base of Lib Dock score and highly interacting amino acid residues. Of ten conformations generated for each compound, the compound with the highest Lib Dock score was chosen for interaction analysis of the hydrogen bonding.

INVIVO ANALGESIC ACTIVITY

a. Hot plate method: The hot-plate test was performed to measure response latencies according to the method described by Eddy and Leimbach (1953) [20]. Swiss albino male wistar rats (170–210 g body weight) were divided into groups of six animals each. Group I served as control; group II served as standard, received aspirin (10 mg/kg); Groups III and IV served as test samples, received 20 and 40 mg/kg of 3d, 3f, 3l, 3n test samples respectively. The animals were placed on the hot plate, maintained at 55±2°C. The pain threshold was

considered to be reached when the animals lifted and licked their paws or attempted to jump out of the hot plate. Time needed for the rats to react in this fashion was considered as basal reaction time. A latency period of 30 s (cut-off) was defined as complete analgesia, and the measurement was terminated if it exceeded the latency period in order to avoid injury. The reaction time was reinvestigated at 30, 60, 120, and 180 min after the treatment and changes in the reaction time were noted.

b. Tail immersion method: Young Male Albino Wistar rats (170–210 g body weight) are used. The lower 5 cm portion of the tail was marked. This part of the tail was immersed in a cup of freshly filled water at 55°C. Within a few seconds the rat reacted by withdrawing the tail. After each determination the tail was dried. The reaction time was determined before and periodically after oral administration of the test substance (30, 60, 90, 120, 180 min). The cut off time of the immersion was 15 s.

In vivo anti-inflammatory activity by Carrageenan induced rat paw edema method[xix-xxi] . Anti-inflammatory activity of synthesized compounds was assessed by the carrageenan-induced rat paw edema method [21]. The animals were housed under standard environmental conditions, one week before the start and also during the experiment as per the rules and regulations of the institutional ethics committee (registered no. RBVRR1328/ 01/2017/CPCSEA).

RESULTS AND DISCUSSION:

In the present study, we have synthesized 1,2,4- oxadiazole sulfonamides via coupling reaction of 1,2,4- oxadiazole amines with aryl sulfonyl chlorides at room temperature. Initial (3-aryl-1,2,4-oxadiazol-5-yl)-methanamines were synthesized by alkylation of potassium phthalimide with 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles in DMF followed by the reaction with NH2· NH2· H2O in ethanol. Structures of the title compounds 3a– 3o were elucidated from IR, 1H NMR and MS data.

MOLECULAR DOCKING STUDIES:

All synthesized compounds have been docked with Structure of celecoxib bound at the COX-2 active site (PDB ID: 3LN1) for determining binding affinities and molecular interactions. The Lib dock scores of the compounds were measured. All 1,2,4-oxadiazole sulfonamide analogues displayed better Lib dock scores than aspirin and indomethacin but lower than celecoxib.

INVIVO ANALGESIC AND ANTIINFLAMMATORY ACTIVITIES:

Analgesic activity of the newly synthesized oxadiazole fused sulfonamides 3d, 3f, 3l, 3n were evaluated by the hot plate and tail immersion methods using male albino wistar rats **(Tables 2, 3)**. Aspirin was used as a standard. Anti-inflammatory activity of the compounds was tested by the carrageenan induced rat paw edema method using indomethacin as a standard **(Tables 4, 5).** All target compounds were tested at the doses of 20 and 40 mg/kg p.o., and demonstrated high analgesic and anti-inflammatory activity at the higher dose **(Table 4)**. Various potencies of the compounds suggested their structure dependent activity. The compound **3l** exhibited the highest analgesic and anti- inflammatory activity. Compound 3f demonstrated the lowest activity.

N-((3-benzyl-1,2,4-oxadiazol-5-yl) methyl)-6-fluoro-chromone-2-carboxamide:

White solid, yield = 78%, m.p. 273-275 ºC. IR (KBr): 1215 (-C-N), 1534 (-C=N), 1739 (-C=O), 3257 (-NH) cm $^{-1}$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.08 (s, 1"-CH_2), 4.78 (d, 5'-CH_2), 7.05 (s, H-3), 7.21-7.33 (m, H-2" to H-6"), 7.39-7.48 (m, H-5 & H-7), 7.75 (t, -NH), 7.8 (m, H-8).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 31.7 (1"-CH_2), 36.0 (5'-CH_2), 110.2 (C-5), 110.6 (C-3), 122.0 (C-8), 123.8 (C-7), 125.4 (C-4a), 127.3 (C-6), 129.4 (C-3" & C-5"), 136.0 (C-2" & C-6"), 151.9 (C-1"), 152.2 (C-8a), 158.4 (C-6), 159.9 (C-5), 160.9 (C-2), 169.8 (-CONH), 176.8 (C-3'), 177.0 (4-C=O).
DIPMS: m/z at 378 $[M-H]^+$

6-Fluoro-N-((3-phenyl-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (56):
Off-white solid, yield = 81%, m.p. 211-213 ºC
IR (KBr): 1273 (-C-N), 1521 (-C=N), 1740 (-C=O), 3273 (-NH) cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.92 (d, 5'-CH_2), 6.85 (s, H-3), 7.42-7.58 (m, H-5, H-7 & H-4"), 7.65-7.81 (m, H-8 & H-3", H-5"), 8.01-8.11 (m, H-1' & H-6"), 10.2 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.2 (1"-CH_2), 110.6 (C-5), 121.9 (C-3), 122.0 (C-8), 123.8 (C-7), 125.4 (C-4a), 126.3 (C-4"), 127.4 (C-2" & C-6"), 129.7 (C-3" & C-5"), 132.1 (C-1"), 151.9 (C-8a), 155.3 (C-6), 158.5 (C-5'), 160.9 (C-2), 168.1 (-CONH), 177.0 (C-3'), 177.3 (4-C=O).
DIPMS: m/z at 366 $[M+H]^+$

6-Fluoro-N-((3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (57):
Off-white solid, yield = 75%, m.p. 195-197 ºC. IR (KBr): 1261 (-C-N), 1543 (-C=N), 1739 (-C=O), 3275 (-NH) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.95 (s, -OCH_3), 5.02 (d, 5'-CH_2), 7.21-7.29 (m, H-3" & H-5"), 7.18 (s, H-3), 7.46-7.59 (m, H-5, H-8 & H-4"), 7.64 (t, -NH), 7.84-7.88 (m, H-7), 7.9-7.94 (m, H-6").
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (1"-CH_2), 56.2 (2"-OCH_3), 110.2 (C-5), 110.6 (C-3"), 112.8 (C-1"), 115.3 (C-3), 121.9 (C-5"), 122.0 (C-8), 123.8 (C-7), 125.4 (C-4a), 131.1 (C-4"), 133.2 (C-6"), 151.9 (C-8a), 155.3 (C-2"), 158.5 (C-6), 160.0 (C-5'), 166.6 (C-2), 175.8 (O=C-NH), 177.0 (C-3'), 177.1 (4-C=O).
DIPMS: m/z at 396 $[M+H]^+$

6-Fluoro-N-((3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (58):
Light yellow solid, yield = 77%, m.p. 201-203 ºC. IR (KBr): 1274 (-C-N), 1525 (-C=N), 1694 (-C=O), 3267 (-NH) cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.03 (d, 5'-CH_2), 7.20 (s, H-3), 7.37-7.50 (m, H-5, H-7, H-4"), 7.54-7.58 (m, H-8 & H-5"), 7.66 (t, -NH), 7.84-7.90 (m, H-3" & H-6").
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (1"-CH_2), 110.2 (C-5), 110.7 (C-3), 121.9 (C-8), 122.0 (C-7), 123.8 (C-4a), 125.6 (C-5"), 128.1 (C-6"), 131.3 (C-3"), 132.1 (C-4"), 132.5 (C-2"), 133.1 (C-1"), 151.9 (C-8a), 151.9 (C-6), 155.3 (C-5'), 166.0 (C-2), 166.9 (O=C-NH), 176.8 (C-3'), 177.0 (4-C=O).
DIPMS: m/z at 400 $[M+H]^+$, 402 $[MH+2]^+$

v) 6-Fluoro-N-((3-p-tolyl-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (59):
Off-white solid, yield = 82%, m.p. 227-229 ºC. IR (KBr): 1275 (-C-N), 1532 (-C=N), 1740 (-C=O), 3265 (-NH) cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 4-CH_3), 4.97 (d, 5'-CH_2), 7.18 (s, H-3), 7.26-7.29 (m, H-3" & H-5"), 7.45-7.58 (m, H-5 & H-7), 7.69 (t, -NH), 7.84-7.95 (m, H-8, H-2" & H-6").

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.5 (4-CH_3), 36.1 (1"-CH_2), 110.0 (C-5), 110.2 (C-3), 110.6 (C-8), 121.9 (C-7), 122.0 (C-1"), 123.6 (C-4a), 123.8 (C-2" & C-6"), 125.4 (C-3" & C-5"), 127.4 (C-4"), 130.2 (C-8a), 142.1 (C-6), 151.9 (C-5'), 155.3 (C-2), 160.0 (-CONH), 168.1 (C-3'), 177.1 (4-C=O).
DIPMS: m/z at 380 $[M+H]^+$

vi) 6-Fluoro-N-((3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (60):
White solid, yield = 84%, m.p. 244-246 ºC. IR (KBr): 1259 (-C-N), 1529 (-C=N), 1740 (-C=O), 3257 (-NH) cm $^{-1}$.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 4-OCH_3), 4.92 (d, 5'-CH_2), 6.97 (m, H-3" & H-5"), 7.14 (m, H-3), 7.48-7.64 (m, H-5 & H-7), 7.82-8.00 (m, H-8, H-2" & H-6"), 8.95 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (1"-CH_2), 55.8 (4-OCH_3), 110.2 (C-5), 110.6 (C-3" & C-5"), 115.1 (C-1"), 118.6 (C-3), 121.9 (C-8), 122.0 (C-7), 123.8 (C-4a), 125.4 (C-2" & C-6"), 129.1 (C-8a), 151.9 (C-4"), 155.3 (C-6), 160.0 (C-5'), 162.2 (C-2), 167.8 (-CONH), 176.9 (C-3'), 177.0 (4-C=O).
DIPMS: m/z at 396 $[M+H]^+$

vii) 6-Fluoro-N-((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (61):
Light yellow solid, yield = 83%, m.p. 176-178 ºC. IR (KBr): 1223 (-C-N), 1522 (-C=N), 1739 (-C=O), 3266 (-NH) cm $^{-1}$.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.91 (d, 5'-CH_2), 6.90 (s, H-3), 7.37-7.43 (m, H-3" & H-5"), 7.73-7.83 (m, H-5 & H-7, H-8), 8.03-8.08 (m, H-2" & H-6"), 10.0 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.2 (1"-CH_2), 110.2 (C-5), 110.6 (C-3" & C-5"), 116.7 (C-1"), 117.0 (C-3), 121.9 (C-8), 122.9 (C-7), 123.8 (C-4a), 125.4 (C-2" & C-6"), 130.0 (C-8a), 155.2 (C-4"), 158.5 (C-6), 160.9 (C-5'), 163.2 (C-2), 165.7 (-CONH), 167.4 (C-3'), 177.4 (4-C=O).
DIPMS: m/z at 384 $[M+H]^+$

viii) 6-Fluoro-N-((3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-2-carboxamide (62):
Off-white solid, yield = 86%, m.p. 188-190 ºC. IR (KBr): 1286 (-C-N), 1522 (-C=N), 1740 (-C=O), 3256 (-NH) cm $^{-1}$.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.94 (d, 5'-CH_2), 6.90 (s, H-3), 7.74-7.83 (m, H-5 & H-7, H-8), 7.93-7.94 (m, H-2" & H-6"), 8.80-8.81 (m, H-3" & H-5"), 10.0 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.2 (1"-CH_2), 110.7 (C-5), 121.9 (C-2" & C-6"), 122.0 (C-8), 122.4 (C-3), 123.9 (C-7), 125.4 (C-4a), 133.6 (C-1"), 151.4 (C-5" & C-3"), 151.9 (C-8a), 155.2 (C-6), 158.5 (C-5'), 160.1 (C-2), 166.9 (-CONH), 177.0 (C-3'), 178.2 (4-C=O).
DIPMS: m/z at 367 $[M+H]^+$

6) Synthesis of 1,2,4-oxadiazole amides of chromone-3-acid (63-70)

i) N-((3-benzyl-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (63):
White solid, yield = 76%, m.p. 163-165 ºC. IR (KBr): 1235 (-C-N), 1525 (-C=N), 1673 (-C=O), 3295 (-NH) cm $^{-1}$.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.08 (s, 1"-CH_2), 4.86 (d, J=5.6Hz, 5'-CH_2), 7.22-7.34 (m, H-2" to H-6"), 7.54-7.58 (m, H-6), 7.73-7.8 (m, H-7), 8.29-8.31 (dd, J=1.6Hz, J=1.6Hz, H-5), 8.98 (s, H-2), 9.95 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 31.7 (1"-CH_2), 35.9 (5'-CH_2), 115.2 (C-3), 119.1 (C-8), 124.0 (C-6), 125.9 (C-4a), 127.1 (C-5), 127.3 (C-4"), 129.0 (C-3" & C-5"), 129.3 (C-2" & C-

6"), 135.7 (C-7), 136.1 (C-1"), 156.0 (C-8a), 163.1 (O=C-NH), 163.8 (C-2), 169.7 (C-5'), 176.6 (C-3'), 177.4 (4-C=O).
DIPMS: m/z at 362 $[M+H]^+$

ii) N-((3-phenyl-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (64):
Off-white solid, yield = 80%, m.p. 155-157 ºC. IR (KBr): 1279 (-C-N), 1531 (-C=N), 1727 (-C=O), 3282 (-NH) cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ 4.96 (d, 5'-CH_2), 7.42-7.58 (m, H-2" to H-6"), 7.75-7.85 (m, H-7), 8.11-8.19 (m, H-6 & H-8), 8.32-8.38 (m, H-5), 8.99 (s, H-2), 10.2 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (5'-CH_2), 115.3 (C-3), 119.1 (C-8), 124.0 (C-6), 125.9 (C-4a), 126.5 (C-5), 127.1 (C-1"), 127.4 (C-2" & C-6"), 129.7 (C-3" & C-5"), 132.0 (C-4"), 135.7 (C-7), 156.0 (C-8a), 163.2 (O=C-NH), 163.8 (C-2), 168.1 (C-5'), 176.6 (C-3'), 177.9 (4-C=O).
DIPMS: m/z at 348 $[M+H]^+$

iii) N-((3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (65):
Off-white solid, yield = 73%, m.p. 182-184 ºC. IR (KBr): 1251 (-C-N), 1542 (-C=N), 1715 (-C=O), 3260 (-NH) cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ 3.96 (s, -OCH_3), 5.03 (d, 5'-CH_2), 7.11-7.17 (m, H-3" & H-5"), 7.42-7.59 (m, H-8, H-4" & H-6"), 7.71-7.73 (m, H-6), 8.01-8.04 (dd, J=1.2 Hz, J=1.2 Hz, H-7), 8.26-8.3 (dd, J=1.2 Hz, J=1.2Hz, H-5) 9.01 (s, H-2), 10.2 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.0 (5'-CH_2), 56.2 (2"-OCH_3), 112.7 (C-3), 115.3 (C-8), 115.5 (C-3"), 119.1 (C-1"), 120.9 (C-5"), 124.0 (C-6), 125.9 (C-4a), 127.1 (C-5), 131.2 (C-4"), 133.1 (C-6"), 135.7 (C-7), 156.0 (C-2"), 158.1 (C-8a), 163.2 (O=C-NH), 163.8 (C-2), 166.5 (C-1'), 176.4 (C-3'), 176.6 (4-C=O).
DIPMS: m/z at 378 $[M+H]^+$

iv) N-((3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (66):
Light yellow solid, yield = 79%, m.p. 171-173 ºC. IR (KBr): 1263 (-C-N), 1529 (-C=N), 1681 (-C=O), 3247 (-NH) cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ 5.04 (d, 5'-CH_2), 7.38-7.46 (m, H-2", H-4" & H-5", H-6"), 7.52-7.56 (m, H-6), 7.75-7.8 (m, H-8), 7.92-7.94 (dd, J=1.2Hz, J=1.2Hz, H-7), 8.30-8.32 (dd, J=1.2Hz, J=1.2Hz, H-5), 9.01 (s, H-2), 10.07 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (5'-CH_2), 115.2 (C-5), 119.1 (C-3), 124.0 (C-8), 125.8 (C-7), 125.9 (C-4a), 127.1 (C-5"), 128.1 (C-6"), 131.2 (C-3"), 132.1 (C-4"), 132.5 (C-2"), 133.0 (C-1"), 135.7 (C-8a), 156.0 (C-6), 163.2 (C-5'), 163.8 (C-2), 166.9 (O=C-NH), 176.6 (C-3'), 177.4 (4-C=O).
DIPMS: m/z at 382 $[M+H]^+$, 384 $[MH+2]^+$

v) N-((3-p-tolyl-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (67):
Off-white solid, yield = 81%, m.p. 205-207 ºC. IR (KBr): 1299 (-C-N), 1533 (-C=N), 1737 (-C=O), 3249 (-NH) cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 4-CH_3), 4.96 (d, 5'-CH_2), 7.25-7.27 (m, H-3" & H-5"), 7.5-7.52 (m, H-6 & H-8), 7.75-7.8 (m, H-7), 7.96 (dd, J=1.6Hz, J=1.6Hz , H-2" & H-6"), 8.31 (dd, J=1.2Hz, J=1.2Hz, H-5), 9.0 (s, H-2), 10.04 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.5 (4"-CH_3), 36.1 (5'-CH_2), 115.3 (C-3), 119.2 (C-8), 123.7 (C-6), 124.0 (C-1"), 125.9 (C-4a), 127.1 (C-5), 127.4 (C-2" & C-6"), 130.2 (C-3" & C-5"), 135.7 (C-4"), 142.0 (C-7), 156.1 (C-8a), 163.2 (O=C-NH), 163.8 (C-2), 168.0 (C-1'), 176.6 (C-3'), 177.8 (4-C=O).

DIPMS: m/z at 362 $[M+H]^+$

vi) N-((3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (68):
White solid, yield = 82%, m.p. 216-218 ºC. IR (KBr): 1247 (-C-N), 1524 (-C=N), 1737 (-C=O), 3253 (-NH) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 3.86 (s, 4-OCH_3), 4.94 (d, 5'-CH_2), 6.96-6.98 (m, H-3" & H-5"), 7.53-7.59 (m, H-6 & H-8), 7.78-7.82 (m, H-7), 8.01-8.03 (m, H-2" & H-6"), 8.31 (dd, J=1.6Hz, J=1.6Hz, H-5), 9.01 (s, H-2), 10.02 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (5'-CH_2), 55.8 (4"-OCH_3), 115.1 (C-5), 115.3 (C-3" & C-5"), 118.7 (C-1"), 119.2 (C-3), 124.0 (C-8), 125.9 (C-7), 127.1 (C-4a), 129.1 (C-2" & C-6"), 135.7 (C-8a), 156.1 (C-4"), 162.1 (C-6), 163.2 (C-5'), 163.8 (C-2), 167.8 (-CONH), 176.6 (C-3'), 177.6 (4-C=O).
DIPMS: m/z at 378 $[M+H]^+$

vii) N-((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (69):
Light yellow solid, yield = 80%, m.p. 192-194 ºC. IR (KBr): 1222 (-C-N), 1521 (-C=N), 1735 (-C=O), 3276 (-NH) cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ 4.95 (d, 5'-CH_2), 7.13-7.17 (m, H-3" & H-5"), 7.52-7.60 (m, H-6 & H-8), 7.74-7.8 (m, H-7), 8.07-8.11 (m, H-2" & H-6"), 8.32-8.34 (dd, J=1.2Hz, J=1.2Hz, H-5), 9.01 (s, H-2), 10.02 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.1 (1"-CH_2), 115.2 (C-5), 116.7 (C-3" & C-5"), 117.0 (C-1"), 119.1 (C-3), 123.0 (C-8), 124.0 (C-7), 127.1 (C-4a), 130.0 (C-2" & C-6"), 135.7 (C-8a), 156.0 (C-4"), 163.1 (C-6), 163.2 (C-5'), 165.6 (C-2), 167.3 (-CONH), 176.6 (C-3'), 178.1 (4-C=O).
DIPMS: m/z at 366 $[M+H]^+$
viii) N-((3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl) methyl)-chromone-3-carboxamide (70):
Off-white solid, yield = 84%, m.p. 171-172 ºC. IR (KBr): 1237 (-C-N), 1534 (-C=N), 1739 (-C=O), 3263 (-NH) cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ 4.92 (d, 5'-CH_2), 7.47-7.56 (m, H-6, H-7 & H-8), 8.01-8.09 (m, H-2" & H-6"), 8.75-8.79 (m, H-3" & H-5"), 8.31 (dd, J=1.6Hz, J=1.6Hz, H-5), 9.01 (s, H-2), 10.02 (t, -NH).
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.9 (5'-CH_2), 114.2 (C-5), 118.9 (C-1"), 119.1 (C-3), 121.3 (C-2" & C-6"), 124.1 (C-8), 125.7 (C-7), 127.8 (C-4a), 134.7 (C-8a), 149.3 (C-3" & C-5"), 156.2 (C-4"), 162.8 (C-6), 164.2 (C-5'), 164.8 (C-2), 168.8 (-CONH), 175.6 (C-3'), 176.6 (4-C=O).
DIPMS: m/z at 348 $[M+H]^+$

Table 2.3.2.1: Interaction of Ligand and Amino acids

Name	Interacting amino acids	Interacting atoms	H-Distance (A°)
Compd 55	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR371:HN2 - Comp55:O16 A:TYR371:HN2 - Comp55:N19 A:TRP373:HE1 - Comp55:O16 A:TRP373:HE1 - Comp55:N17	2.050000 2.441000 2.401000 2.385000
Compd 56	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR341:HH - Comp56:O9 A:ARG499:HH12 - Comp56:O20 A:ARG499:HH22 - Comp56:O11 Comp56:H32 - A:TYR341:OH	1.953000 2.307000 2.400000 2.440000

		A:SER339:CA - Comp 56:H34 A:ARG499:HH12 - Comp56:H31	2.207000 1.686000
Compd 57	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR341:HH - Comp57:O9 A:ARG499:HH12 - Comp57:O20 A:ARG499:HH22 - Comp57:O11 Comp57:H34 - A:TYR341:OH A:SER339:CA - Comp57:H36 A:ARG499:HH12 - Comp57:H33	1.978000 2.314000 2.359000 2.491000 2.215000 1.658000
Compd 58	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:ARG499:HN1 - Comp58:O11 Comp58:H33 - A:LEU338:O Comp58:H29 - A:LEU338:CD1	1.976000 1.793000 2.143000
Compd 59	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	Comp59:H33 - A:LEU338:O A:LEU338:CD1 - Comp59:H33 A:PHE504:HN1 - Comp59:H32 A:PHE504:HN1 - Comp59:C8	2.008000 2.093000 1.355000 2.133000
Compd 60	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TRP373:HE1 - Comp60:N17 A:VAL509:HN2 - Comp60:O16 A:VAL509:HN2 - Comp60:N19	2.104000 1.826000 2.318000
Compd 61	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TRP373:HE1 - Comp61:N17 A:VAL509:HN2 - Comp61:O16 A:VAL509:HN2 - Comp61:N19	2.106000 1.814000 2.306000
Compd 62	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TRP373:HE1 - Comp62:N17 A:VAL509:HN2 - Comp62:O16 A:VAL509:HN2 - Comp62:N19	2.014000 1.848000 2.407000
Compd 63	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:ARG106:HH22 - Comp63:N18 A:ARG499:HH11 - Comp63:O11 A:ARG499:HH12 - Comp63:O17 A:ARG499:HH22 - Comp63:N20 A:TYR341:HH - Comp63:H35 Comp63:C15 - A:TYR341:HH A:LEU338:CD1 - Comp63:H28 A:ARG499:NH2 - Comp63:H38 A:ARG499:HH22 - Comp63:H38	1.639000 1.855000 2.448000 1.655000 1.321000 2.188000 2.140000 1.974000 1.225000
Compd 64	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:ARG499:NH2 - Comp64:O11 A:ARG499:NH12 - Comp64:O11 A:ARG499:NH12 - Comp64:O13 Comp64:O9 - A:TYR341:OH Comp64:H31 - A:TYR341:CE1 Comp64:H31 - A:TYR341:CZ Comp64:H31 - A:TYR341:HH	2.069000 1.860000 2.364000 2.467000 1.920000 2.217000 1.432000
Compd 65	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR341:HH - Comp65:N18 A:TYR341:HH - Comp65:O27 A:ARG499:HH12 - Comp65:O17 A:ARG499:HH12 - Comp65:N20	2.133000 2.238000 1.671000 2.266000
Compd 66	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR341:HH - Comp66:N18 A:TYR341:HH - Comp66:Cl27 A:ARG499:HH12 - Comp66:O17 A:ARG499:HH12 - Comp66:N20 A:SER339:O - Comp66:H35	2.037000 2.144000 1.998000 1.804000 2.032000

Compd 67	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR341:HH - Comp67:O9 A:ARG499:HH12 - Comp67:O11 A:ARG499:HH12 - Comp67:O13 A:ARG499:HH22 - Comp67:O11 A:TYR341:CE1 - Comp67:H33 A:TYR341:CE1 - Comp67:H32	2.340000 2.332000 1.714000 2.188000 2.204000 1.807000
Compd 68	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:TYR341:HH - Comp68:O9 A:ARG499:HH12 - Comp68:O11 A:ARG499:HH12 - Comp68:O13 A:TYR341:CE1 - Comp68:H33	2.357000 2.332000 1.741000 1.793000
Compd 69	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:ARG499:HH12 - Comp69:O11 A:ARG499:HH12 - Comp69:O13 A:ARG499:HH22 - Comp69:O11 Comp69:H33 - A:TYR341:OH Comp69:H35 - A:SER339:O Comp69:H33 - A:TYR341:CE1 A:TYR341:HH - Comp69:C7	2.315000 1.982000 2.197000 2.305000 2.004000 2.197000 2.096000
Compd 70	Tyr371,Trp373,Phe504,Gly512 Gln178,Arg499,Arg106,Leu517 Leu338,Phe504His75,Val509 Val335,Ala513,Leu345,Leu517	A:ARG499:NH11 - Comp70:O11 A:ARG499:NH12 - Comp70:O13 A:ARG499:NH12 - Comp70:O17 A:ARG499:NH12 - Comp70:N20 A:TYR341:OH - Comp70:N18 A:TYR341:HH - Comp70:C127	2.304000 2.274000 1.943000 2.178000 2.079000 2.233000
Celecoxib	Leu345,Leu157,Arg106,Val335, Tyr341,Leu338,Ser339,Gln178, Ala513,Gly512,Tyr371,Val509 His75,Trp373,Phe504,Gln178	Celecoxib:H28 - A:HIS75:NE2 Celecoxib:H28 - A:SER339:O A:ARG499:HH11 - Celecoxib:O6 Celecoxib:H28 - A:HIS75:NE2 A:PHE504:HN - Celecoxib:N9 Celecoxib:H28 - A:PHE504:HN	2.387000 2.413000 2.308000 2.387000 2.081000 1.396000

Table 2.3.2.2: LibDock scores of the compounds

Name	Electrostatic Energy (kJ/mol)	Van der Waals Energy (kJ/mol)	LibDockScore (kcal/mol)
Compd 55	-42.261	-0.208	140.408
Compd 56	-39.803	2.251	138.269
Compd 57	-42.754	2.348	142.696
Compd 58	-38.315	4.204	136.121
Compd 59	-41.717	2.154	121.486
Compd 60	-45.402	3.153	142.251
Compd 61	-43.915	2.536	122.894
Compd 62	-35.751	2.625	149.344
Compd 63	3.992	-0.418	132.504
Compd 64	11.483	2.923	133.726
Compd 65	12.965	5.404	127.192
Compd 66	12.287	4.709	120.372
Compd 67	8.503	2.525	124.983
Compd 68	6.761	3.73	133.628
Compd 69	7.873	3.128	121.532
Compd 70	7.873	3.128	135.122
Celecoxib	4.465	4.762	145.691

2.3.3. Biological activity

2.3.3.1. Anti-inflammatory activity

Carrageenan induced rat paw edema method:

Table 2.3.3.1.1: Anti-inflammatory activity of treatments by carrageenan induced rat paw edema method

Group	Treatment	Dose (mg/kg)	Paw edema volume (mL)			
			1hr	3hr	5hr	7hr
Group – I	Control	1% CMC	0.45 ± 0.024	0.65 ± 0.029	0.68 ± 0.027	0.59 ± 0.029
Group – II	Standard	10	0.26 ± 0.032**	0.19 ± 0.031***	0.32 ± 0.038***	0.36 ± 0.03***
Group –III	57	20	0.37 ± 0.013**	0.38 ± 0.039**	0.47 ± 0.026***	0.49 ± 0.013***
Group –IV	57	40	0.30 ± 0.026**	0.25 ± 0.057**	0.36 ± 0.036***	0.40 ± 0.044*
Group –V	60	20	0.35 ± 0.011**	0.37 ± 0.023***	0.46 ± 0.03**	0.48 ± 0.02**
Group –VI	60	40	0.29 ± 0.025**	0.24 ± 0.036***	0.37 ± 0.031***	0.39 ± 0.043*
Group –VII	62	20	0.34 ± 0.0095***	0.32 ± 0.026***	0.43 ± 0.021***	0.47 ± 0.019**
Group –VIII	62	40	0.27 ± 0.021***	0.22 ± 0.034***	0.34 ± 0.049**	0.38 ± 0.041**
Group –IX	64	20	0.4 ± 0.0088***	0.41 ± 0.022***	0.51 ± 0.028**	0.51 ± 0.023*
Group –X	64	40	0.36 ± 0.027*	0.31 ± 0.054**	0.43 ± 0.033**	0.44 ± 0.047*
Group –XI	68	20	0.39 ± 0.013**	0.40 ± 0.026***	0.50 ± 0.027**	0.50 ± 0.020*
Group –XII	68	40	0.35 ± 0.025*	0.29 ± 0.035***	0.41 ± 0.039**	0.43 ± 0.038*
Group –XIII	70	20	0.38 ± 0.012**	0.39 ± 0.020***	0.49 ± 0.025**	0.5 ± 0.020**
Group –XIV	70	40	0.34 ± 0.019**	0.27 ± 0.056**	0.40 ± 0.044**	0.42 ± 0.043*

CMC: Carboxy Methyl Cellulose, values are expressed as mean ± SEM (n=6) and analyzed by ANOVA using Graph pad prism 7. *** P<0.001,

$^{**}p$<0.01, $^{*}p$<0.05 when compared to control group.

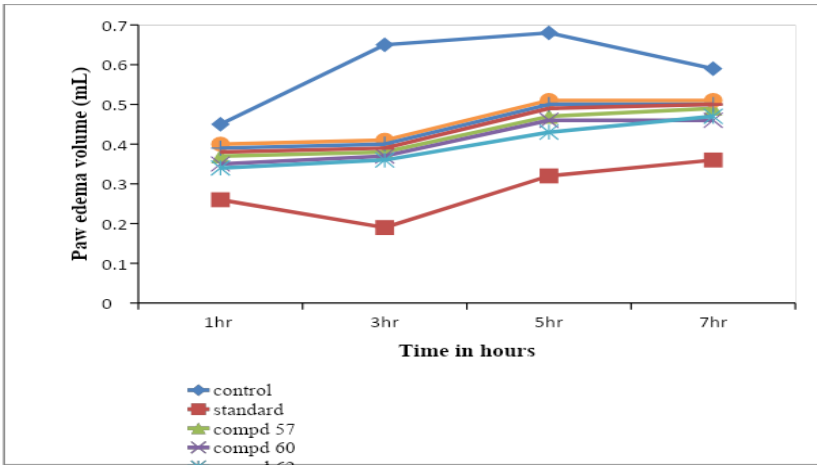


Fig 2.3.3.1.1: Effect of standard and test compounds (20 mg/kg) on paw edema volume

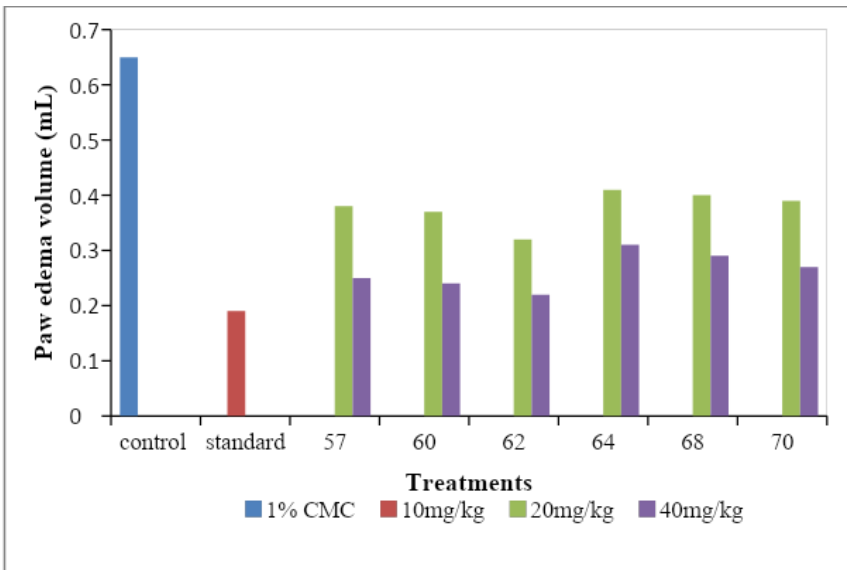


Fig 2.3.3.1.3: Paw edema volume at 3h time interval for all compounds

CONCLUSIONS

Herein, we report a simple and efficient method of synthesis of fused 1,2,4-oxadiazolo-sulfonamides via the coupling reaction. Molecular docking studies indicated high binding affinity of the compounds with 3LN1. In vivo analgesic and anti-inflammatory tests demonstrated that 4-methoxy-N-{[(4-methoxyphenyl)- 1,2,4-oxadiazol-5-yl] methyl} benzenesulfonamide had the highest activity. If the phenyl ring contained the electron releasing substituents, like methoxy and methyl groups, the compounds demonstrated high Lib Dock scores, as well as significant analgesic and anti-inflammatory activities.

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