SYNTHESIS AND ANTI-INFLAMMATORY EVALUATION OF 2-(3-(2-(1,3-DIOXOISOINDOLIN-2-YL) ACETAMIDO)-4-OXO-2-SUBSTITUTED THIAZOLIDIN-5-YL) ACETIC ACID DERIVATIVES

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ABSTRACT

Herein, we had reported microwave assisted synthesis of 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-phenylthiazolidin-5-yl) acetic acid derivatives **7(a-l)** by cyclo-condensation of *(E)-N'*-substituted benzylidene/methylene-2-(1,3-dioxo isoindolin-2-yl) acetohydrazide **6(a-l)** with mercaptosuccinic acid. The newly synthesized compounds were evaluated for anti-inflammatory activity using *in-vitro* and *in-vivo* models. The tested compounds had shown promising anti-inflammatory activity in both the models. The aliphatic groups (-CH_3, C_2H_5) on thiazolidinone ring showed better anti-inflammatory activity than substitution of bulkier group (substituted phenyl and heteryl) on thiazolidinone when compared to diclofenac. The electron donating polar groups (4-methoxy phenyl and furyl group) on thiazolidinone ring have also shown good activity when compared to diclofenac. The selected compounds, which have shown better activity, were studied for ulcerogenic toxicity and have shown good gastrointestinal safety profile.

KEYWORDS: Thiazolidinone, Microwave assisted synthesis, *in-vivo* and *in-vitro* anti-inflammatory activity.

INTRODUCTION

Most of the nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the enzyme Cyclooxygenase, an important step in biosynthesis of prostaglandin.[1,2] The usefulness of these agents is limited due to its undesirable effects like gastrointestinal ulceration and renal dysfunction.[3]

The search for new and more effective anti-inflammatory agents has led medicinal chemist to explore a wide variety of chemical structures. Previously thalidomide, phthalimide containing drug, used as antihistaminics, but later on due to its teratogenic effects it was withdrawn from the market.[4] In 1965, Sheskin found new use of thalidomide in painful neuritis.[5] This activity was due to selective blockage of tumor necrosis factor-α (TNF-α), suggests new drug as an anti-inflammatory and immunomodulator agents.[6,7] Phthalimide, the potent basic pharmacodynamic nucleus has been also reported to possess a wide variety of pharmacological properties including anti-inflammatory activity.[8-11] Besides these, thiazolidinone have also been reported to have anti-inflammatory activity. [12-17] From the discovery of aspirin, much attention has given in development of acidic NSAID's and some of them are having acetic acid groups possesses significant anti-inflammatory activity. [18-20] Furthermore it was also known that reactive oxygen species (ROS) have a significant role in inflammatory conditions. It is noted that some antioxidants can exhibit as anti-inflammatory compounds. This is supported from the finding that indomethacin administration results in increased ROS production in gastric mucosa, followed by gastric ulceration.[21]

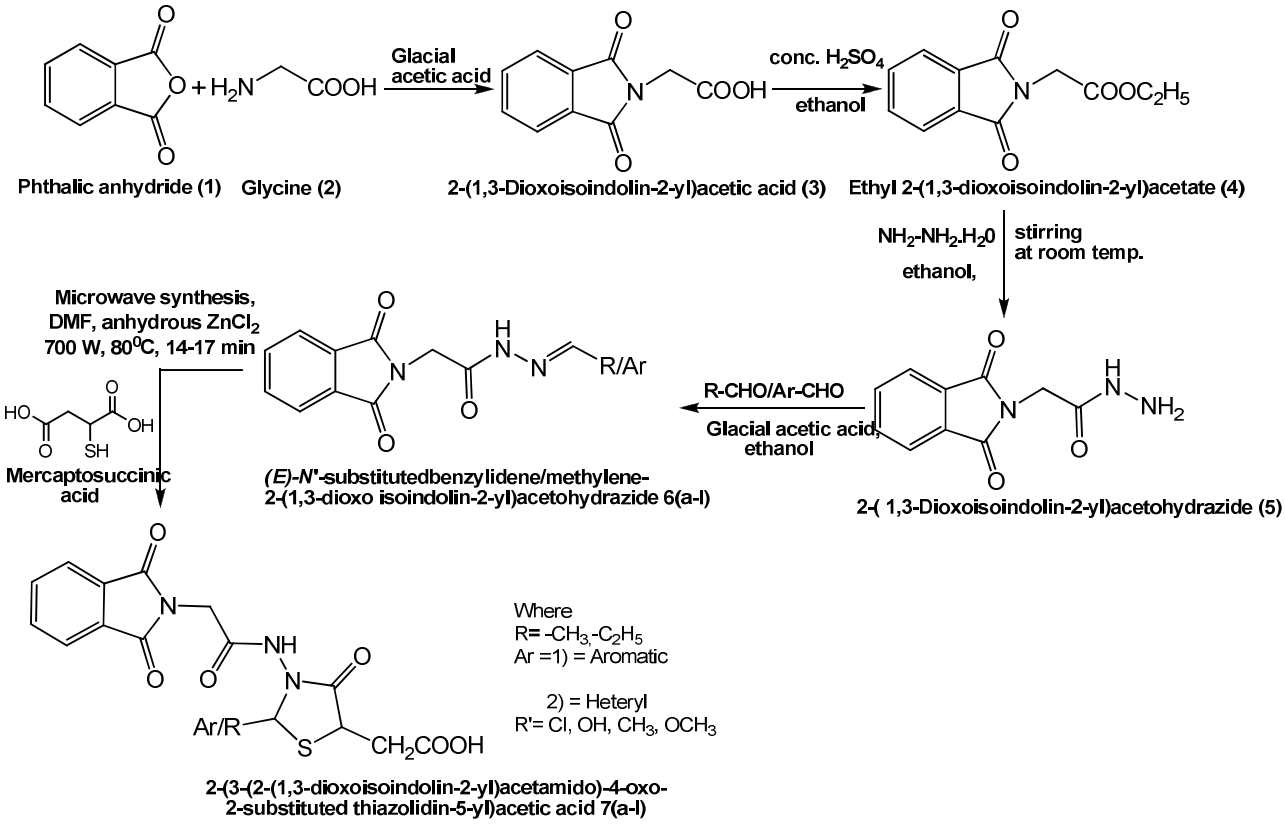
Based on the above mentioned facts, we aim to prepare a pharmacophore hybrid molecule of phthalimide and thiazolidinone ring with acetic acid group with an enhanced bioactivity. The pharmacophore hybrid approach for exploration of highly active compounds is effective and commonly used in medicinal chemistry. Hybridization of two different bioactive molecules with complementary pharmacophoric functions or with different mechanisms of action often showed synergistic effects.

In this report, we reported microwave assisted synthesis, anti-inflammatory activity and ulcerogenic toxicity study of thiazolidinon-5-yl acetic acid analogues. *In-vivo* anti-inflammatory activity was performed by Carrageenan induced rat paw edema model and *in-vitro* activity was performed by protein denaturation inhibition assay model. The ulcerogenic toxicity study was also assessed for selected compounds.

EXPERIMENTAL

Chemistry

The synthetic scheme for synthesis of titled compounds 2-(3-(2-(1, 3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives **7(a-l)** is presented in **Scheme 1**.



Scheme 1 Scheme of synthesis for titled compounds **7(a-l)**

In first step, 2-(1,3-Dioxoisoindolin-2-yl) acetic acid **3** was obtained by the refluxing phthalic anhydride **1** (0.05 mol) with glycine **2** (0.05 mol) in glacial acetic acid.[22] Then compound **3** was esterified using catalytic amount of conc. H_2SO_4 in absolute ethanol to give ethyl 2-(1, 3-dioxoisoindolin-2-yl) acetate **4**.[23] 2-(1,3-Dioxoisoindolin-2-yl) acetohydrazide **5** was prepared by conventional route, reacting hydrazine hydrate (0.05 mol) in ethanol with compound **4** (0.05 mol).[24] Then equimolar quantities of 2-(1,3-Dioxoisoindolin-2-yl) acetohydrazide **5** (0.05 mol) refluxed with different aliphatic, aromatic and heterocyclic aldehydes (0.05 mol) in presence of catalytic amount of glacial acetic acid (0.1 mol) in ethanol (20 ml) to prepare corresponding Schiff's bases **6(a-l)**. The Schiff' bases were recrystallized in ethanol. The titled compounds **7(a-l)** was obtained by irradiating above Schiff's bases **6(a-l)** (0.1 mol) with thioglycollic acid (0.1 mol) and anhydrous zinc chloride (0.004 mol) in DMF (15 ml) as solvent in microwave for about 14-17 min (700 W) at 80°C.

Representative spectral data for some compounds

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-ethyl-4-oxothiazolidin-5-yl)acetic acid ***(7b)***

M.P. (^{0}C)= 298-300, Yield (%)= 93; IR (KBr, *v*-max in cm^{-1}); 3498 (OH), 3341 (NH), 3021 (C-H aromatic), 2901 (C-H of aliphatic), 1788 (C=O of thiazolidinone), 1728 (C=O of carboxyl) 1724, 1720 (C=O of phthalimide), 1656 (C=O of amide), 749 (C-S); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 10.1 (s, 1H, OH), 7.2-7.6 (m, 4H, Ar-H), 7.68 (s, 1H,-NH), 5.2 (t, 1H,), 4.7 (t, 1H), 4.3(s, 2H), 2.6 (d, 2H), 2.45 (d, 2H), 0.95 (t, 3H); ^{13}C-NMR δ ppm; 174, 170, 167, 163 (carbonyl carbons), 133, 130, 123 (aromatic carbons), 65 (-CH of thiazolidinone), 45 (-CH of thiazolidinone), 43 (-CH_2), 39 (-CH_2 attached to carboxyl), 22 (-CH_2 of aliphatic), 21 (-CH_3); MS m/z: M+1: 392, Anal. Calcd. for $C_{17}H_{17}N_3O_6S$: C, 52.17; H, 4.38; N, 10.74; Found: C, 52.13;H,4.34; N,10.71.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-4-oxo-2-phenyl thiazolidin-5-yl)acetic acid ***(7c)***

M.P. (^{0}C)= 308-312, Yield (%)= 92; IR (KBr, *v*-max in cm^{-1}); 3528 (OH of carboxyl), 3128 (NH of amide), 3011 (C-H aromatic) 2985 (C-H of aliphatic), 1760 (C=O of thiazolidinone), 1733-1721 (C=O of phthalimide), 1723 (C=O of carboxyl), 1685 (C=O of Amide), 737 (C-S). ^{1}-H NMR ($CDCl_3$, 300 MHz) δ ppm; 10.12 (s, 1H, OH), 8.17 (s, 1H -NH), 7.81-7.71 (m, 4H, Ar-H), 7.56 (m, 4H, Ar-H), 6.26 (d, 1H, -CH), 4.64 (s, 2H, -CH_2), 4.31 (t,1H, -CH), 2.27 (d, 1H, -CH). ^{13}C-NMR δ ppm: 174, 167, 167, 163, 141 (carbonyl carbons), 131, 130, 129, 123, 121, 119 (aromatic carbons), 66 (-CH_2), 43 (-CH of thiazolidinone), 41 (-CH of thiazolidinone), 38 (-CH_2 attached to carboxyl). MS m/z: M+1: 439, Anal. Calcd. for $C_{21}H_{17}N_3O_6$ S: C, 57.40; H, 3.90; N, 9.56; Found: C, 57.45; H, 3.93;N, 9.59.

2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(3-hydroxy phenyl)-4-oxothiazolidin-5-yl)acetic acid ***(7e)***

M.P. (^{0}C)= 224-226, Yield (%)= 85; IR (KBr, *v*-max in cm^{-1}): 3457 (OH of carboxyl), 3346 (NH of amide), 3151 (C-H aromatic), 2976 (C-H of aliphatic), 1768 (C=O of thiazolidinone), 1730 (C=O of carboxyl), 1728, 1713 (C=O of phthalimide), 1640 (C=O of amide), 716 (C-S); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ ppm: 10.2 (s, 1H, -OH), 8.80-8.89 (m, 4H, Ar-H), 7.33 (s, 1H, -NH), 6.52 (s, 1H, -CH), 4.65 (s, 2H, -CH_2), 4.31 (t, 1H, -CH), 2.63 (d, 2H,CH_2), ^{13}C-NMR δ ppm: 174, 165, 161, 158, (carbonyl carbons), 155 (aromatic carbon attached to -OH), 139, 131, 130, 123, 118 (aromatic carbons), 67 (-CH of thiazolidinone), 45(-CH of thiazolidinone), 40 (-CH_2), 38 (-CH_2 attached to carboxyl); MS m/z: M+1:456, Anal. Calcd. for $C_{21}H_{17}N_3O_7$ S: C, 55.38; H, 3.76; N, 9.23; Found:C,55.34 H, 3.81;N,9.28.

*2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-2-(4-fluorophenyl)-4-oxothiazolidin-5-yl)acetic acid **(7h)***

M.P. (^{0}C)= 273-276, Yield (%)= 85; IR (KBr, *v*-max in cm^{-1}): 3459 (OH of carboxyl), 3314 (NH of amide), 3042 (C-H aromatic), 2890 (C-H of aliphatic),1758 (C=O of thiazolidinone) 1735 (C=O of carboxyl), 1712, 1710 (C=O of phthalimide), 1680 (C=O of amide), 1329 (Ar-F), 736 (C-S); ^{1}H-NMR ($CDCl_3$, 300 MHz); 10.18 (s, 1H, -OH), 8.40 (s, 1H, -NH), 7.18-7.81 (m, 4H, Ar-H), 6.32 (s, 1H, -CH), 4.61 (s, 2H, -CH_2) 4.25 (t, 1H, -CH), 2.41 (d, 2H, CH_2), ^{13}C-NMR δ ppm; 174,167, 164, 163, 162 (carbonyl carbons), 138, 138, 133,130,127, 127, 123 (aromatic carbons), 68 (CH_2), 45 (-CH of thiazolidinone), 42 (-CH of thiazolidinone), 38 (-CH_2 attached to carboxyl); MS m/z: M+1:457, Anal. Calcd. for $C_{21}H_{16}FN_3O_6$ S: C, 55.14; H, 3.53; N, 9.19; Found: C, 55.11;H, 3.58; N, 9.16.

*2-(3-(2-(1,3-Dioxoisoindolin-2-yl)acetamido)-4-oxo-2-(thiophen-2-yl)thiazolidin-5-yl)acetic acid **(7k)***

M.P. (^{0}C)= 284-288, Yield (%)= 88; IR (KBr, *v*-max in cm^{-1}): 3563(OH of carboxyl), 3325 (NH of amide), 3108 (CH aromatic), 2852 (CH of aliphatic), 1780 (C=O of thiazolidinone), 1735 (C=O of carboxyl), 1733,1721 (C=O of phthalimide), 1688 (C=O of amide), 785, 737 (C-S) ^{1}H-NMR ($CDCl_3$, 300 MHz): 11.1(s, 1H, -OH), 7.81-7.89 (m, 4H, Ar-H), 7.36 (s, 1H, NH), 6.07-7.09 (m, 4H, heterocyclic), 6.32 (s, 1H, -CH), 4.58 (s, 2H, -CH_2), 4.25 (t, 1H, -CH), 2.81 (d, 2H, CH_2), ^{13}C-NMR δ ppm: 174, 170, 167, 163 (carbonyl carbons), 142, 133, 130, 125, 125, 123 (aromatic carbons), 68 (CH_2), 45 (-CH of thiazolidinone), 42 (-CH of thiazolidinone), 38 (-CH_2 attached to carboxyl); MS m/z: M+1:445, Anal. Calcd. for $C_{19}H_{15}N_3O_6S$: C, 51.23; H, 3.39; N, 9.43;Found:C, 51.20;H,3.36;N,9.39.

Pharmacological activity

The synthesized compounds were evaluated for *in-vivo* and *in-vitro* anti-inflammatory activity. The Carrageenan induced paw edema method was used for *in-vivo* evaluation and protein denaturation method was used for *in-vitro* anti-inflammatory evaluation. Diclofenac is used as standard for both *in-vivo* and *in-vitro* evaluation.

PHARMACOLOGICAL ACTIVITY

Anti-inflammatory evaluation

The *in-vivo* anti-inflammatory evaluation was performed according to Winter et al.[25] It has been observed that the new series of 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives exhibited the significant anti-inflammatory activity except **7b, 7k** and **7l** when compared with control. Some of the synthesized

derivatives have shown enhanced anti-inflammatory activity than diclofenac as shown in **Table 1**. The most significant (**P < 0.01) anti-inflammatory activity is found at 3 hr and gradually reduces at subsequent hours. The compound with highest percent inhibition is **7a** and is found to be most significant at 1 hr. From the overall percent inhibition the compound **7c**, **7f** and **7j** have exhibited the enhanced activity.

The synthesized compounds were also evaluated for *in-vitro* anti-inflammatory activity through inhibition of albumin denaturation technique described by Muzushima *et al.* [26] and Bhalgat *et al.*[27] Amongst all the synthesized compounds **7a, 7b** and **7e** have shown more inhibition as compared to diclofenac. The activity data is presented in **Table 2**.

Ulcerogenic activity

The ulcerogenic toxicity was performed[28, 29] for selected compounds which have shown better anti-inflammatory activity in compounds **7a, 7b, 7c, 7f** and **7j**. As shown in **Table 3**, it was observed that all the compounds exhibited lesser ulcerogenic index than diclofenac. Thus the synthesized derivatives have shown minimum toxicity effects.

STRUCTURE ACTIVITY RELATIONSHIP (SAR)

The structure activity relationship (SAR) reveals some important facts about the structure specific variation in anti-inflammatory activity (**Fig. 1**) The acetic acid group is a structural prerequisite indispensable for anti-inflammatory activity. It was observed for *in-vivo* anti-inflammatory activity that compounds **7a** and **7b** having lower aliphatic groups attached to C2 of thiazolidinone ring, such as $–CH_3$, $-C_2H_5$, respectively, exhibited better activity when compared to diclofenac. All the compounds have resulted in decrease in paw edema and hence showed excellent anti-inflammatory activity. Compound **7c** having phenyl ring without any substitution attached on C2 of thiazolidinone ring, exhibited significant and enhanced anti-inflammatory activity. Other derivatives possessing 4-nitro phenyl, 4-fluro phenyl, 4-chloro phenyl, 3- hydroxy phenyl, 4-hydroxy phenyl, on C2 of thiazolidinone ring i.e. **7i, 7h, 7g, 7e** and **7d** respectively, are less active than diclofenac but are significant when compared to control. The bulky derivatives such as indole and thiophene rings at C2 of thiazolidinone ring as in compound **7k** and **7l** have exhibited lesser activity as compared to diclofenac.

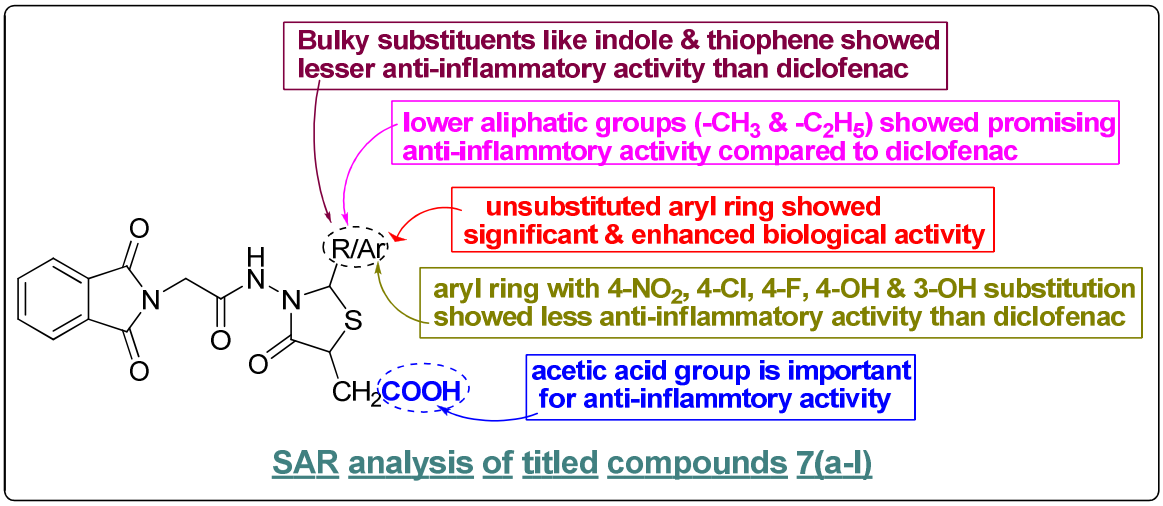


Fig. 1 SAR of synthesized compounds

CONCLUSION

A series of 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid **7(a-l)** were synthesized by microwave irradiation and structure were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MASS spectra and elemental analysis. These compounds were screened for *in-vivo* anti-inflammatory activity by carrageenan-induced paw edema method and *in-vitro* evaluation through inhibition of albumin denaturation technique. The compound **7a** found to be most significant as shows highest inhibition in *in-vivo* anti-inflammatory evaluation. Other compounds **7c**, **7f** and **7j** also showed enhanced biological activity. The compounds **7a, 7b** and **7e** had shown more inhibition as compared to diclofenac in *in-vivo* anti-inflammatory evaluation. The ulcerogenic toxicity study had shown minimum toxicity effects of selected synthesized compounds.

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Table 1 Mean paw volume (ml) and % inhibition of compounds **7(a-l)**

Entry	Mean paw volume in ml ± SEM					% inhibition				
	1 hr	2 hr	3 hr	4 hr	6 hr	1 hr	2 hr	3 hr	4 hr	6 hr
Control	1.34±0.15	1.53±0.017	1.926±0.15	1.776±0.061	1.856±0.053	-	-	-	-	-
7a	0.7±0.30**	0.91±0.069*	0.846±0.037	1.243±0.098	1.433±0.19	47.76	87.58	**50.07**	30.01	22.79
7b	1.023±0.038	0.88±0.017	0.97±0.011	1.153±0.075	1.33±0.050	23.65	42.48	**49.63**	35.07	28.34
7c	1.29±0.084	0.96±0.04	1.09±0.005**	1.243±0.035	1.19±0.078	3.7	37.25	**43.40**	30.01	35.88
7d	1.26±0.072	1.216±0.029	1.42±0.14**	1.43±0.12*	1.286±0.10	5.9	20.52	26.27	19.48	30.71
7e	0.91±0.07	1.06±0.060	1.296±0.046	1.13±0.047	1.346±0.069	32.08	30.71	32.71	36.37	27.47
7f	1.29±0.04	1.253±0.089	1.12±0.10**	1.61±0.065	1.4±0.061	3.7	18.10	**41.84**	9.34	24.56
7g	0.96±0.037	1.22±0.058	1.34±0.14*	1.003±0.093**	1.06±0.06	28.35	20.26	30.42	43.52	42.88
7h	1.223±0.017	1.013±0.080*	1.43±0.052*	1.123±0.035**	1.583±03031	8.73	33.79	25.75	36.76	14.70
7i	1.143±0.086	1.11±0.055	1.333±0.071**	1.38±0.127	1.113±0.014	14.70	64.26	30.94	22.29	40.03
7j	0.896±0.031	1.366±0.023	1.1±0.10**	1.206±0.053	1.22±0.11	33.13	10.71	**42.88**	32.09	32.26
7k	1.22±0.035	1.29±0.036	1.496±0.139	1.256±0.089	1.486±0.069	8.95	15.66	22.32	29.27	19.93
7l	1.25±0.075	1.33±0.75	1.556±0.15	1.273±0.72	1.643±0.68	6.7	13.07	19.21	28.32	11.47
Diclofenac	1.123±0.16	1.056±0.99	1.156±0.098**	1.133±0.021**	1.36±0.033	16.19	30.98	39.97	36.20	26.72

The observations are mean ± SEM, n= 5, $**P < 0.01$, $*P < 0.05$, Test compounds = 10 mg/kg. Reference standard, Diclofenac = 10 mg/kg, Statistical analysis were done by one way ANOVA followed by Dunnett's test

Table 2 Mean absorbance± SEM and % inhibition of compounds (**7a-l**).

Entry	Mean Absorbance	SEM	% Inhibition
Control	0.1023	0.060	-
7a	0.1890	0.026	**84.75**
7b	0.1784	0.014	**74.38**
7c	0.1501	0.03	46.72
7d	0.1212	0.02	18.96
7e	0.1697	0.020	**65.88**
7f	0.1091	0.015	6.64
7g	0.1276	0.015	24.73
7h	0.1289	0.014	26.00
7i	0.1346	0.30	31.57
7j	0.1566	0.15	53.07
7k	0.1493	0.2	45.94
7l	0.1176	0.026	14.95
Std (Diclofenac)	0.1673	0.019	63.53

Table 3 Ulcerogenic potential in rat stomach

Groups	Dose mg/kg	Ulcer index
Control	0.5% sodium CMC	0
Diclofenac	100	11.4 ± 0.2082
7a	100	3.348 ± 0.0833
7b	100	7.21±0.02887
7c	100	4.13± 0.04410
7f	100	4.66 ± 0.0333
7j	100	6.15± 0.05774

The observations are mean ± SEM, n= 6, $^{**}P < 0.01$, $^{*}P < 0.05$,

Test compounds = 100 mg/kg.

Reference standard, Diclofenac = 100 mg/kg.

Statistical analysis were done by one way ANOVA followed by Dunnett's test