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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HIGHLIGHTS

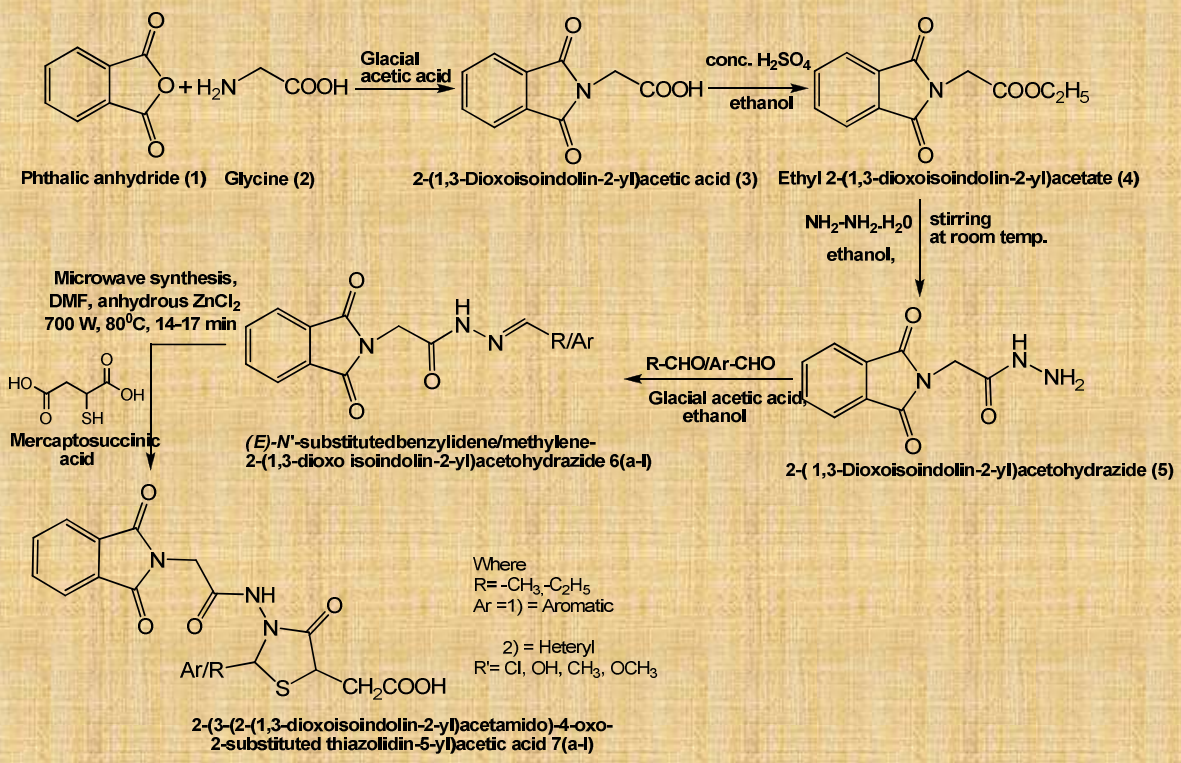
- Microwave assisted synthesis of 2-(3-(2-(1,3-dioxoisoindolin-2-yl) acetamido)-4-oxo-2-phenylthiazolidin-5-yl) acetic acid derivatives
- Anti-inflammatory activity of synthesized compounds using *in-vitro* and *in-vivo* models including ulcerogenic evaluation
- Structure activity relationship (SAR) analysis of compounds

INTRODUCTION

- Most of the nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the enzyme Cyclooxygenase, an important step in biosynthesis of prostaglandin
- The search for new and more effective anti-inflammatory agents has led medicinal chemist to explore a wide variety of chemical structures
- 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

EXPERIMENTAL

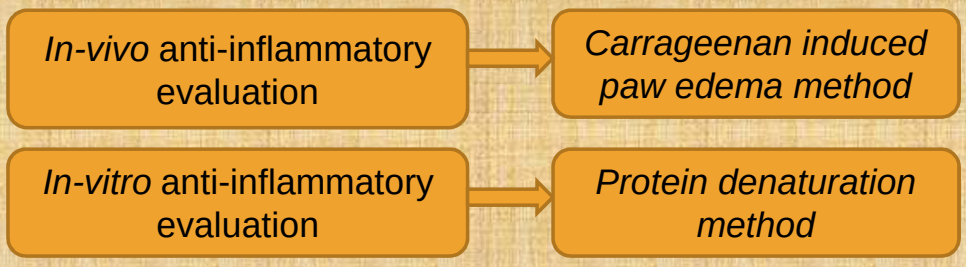
1. Chemistry



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

2. Pharmacological activity

- The synthesized compounds were evaluated for *in-vivo* and *in-vitro* anti-inflammatory activity.



- The ulcerogenic toxicity study were also performed

RESULT AND DISCUSSION

Anti-inflammatory evaluation

1. in-vivo anti-inflammatory evaluation

The *in-vivo* anti-inflammatory evaluation was performed according to Winter et al. 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.

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

2. in-vitro anti-inflammatory evaluation

The synthesized compounds were also evaluated for *in-vitro* anti-inflammatory activity through inhibition of albumin denaturation technique described by Muzushima *et al.* and Bhalgat *et al.* 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**.

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

3. Ulcerogenic activity

The ulcerogenic toxicity was performed 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.

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

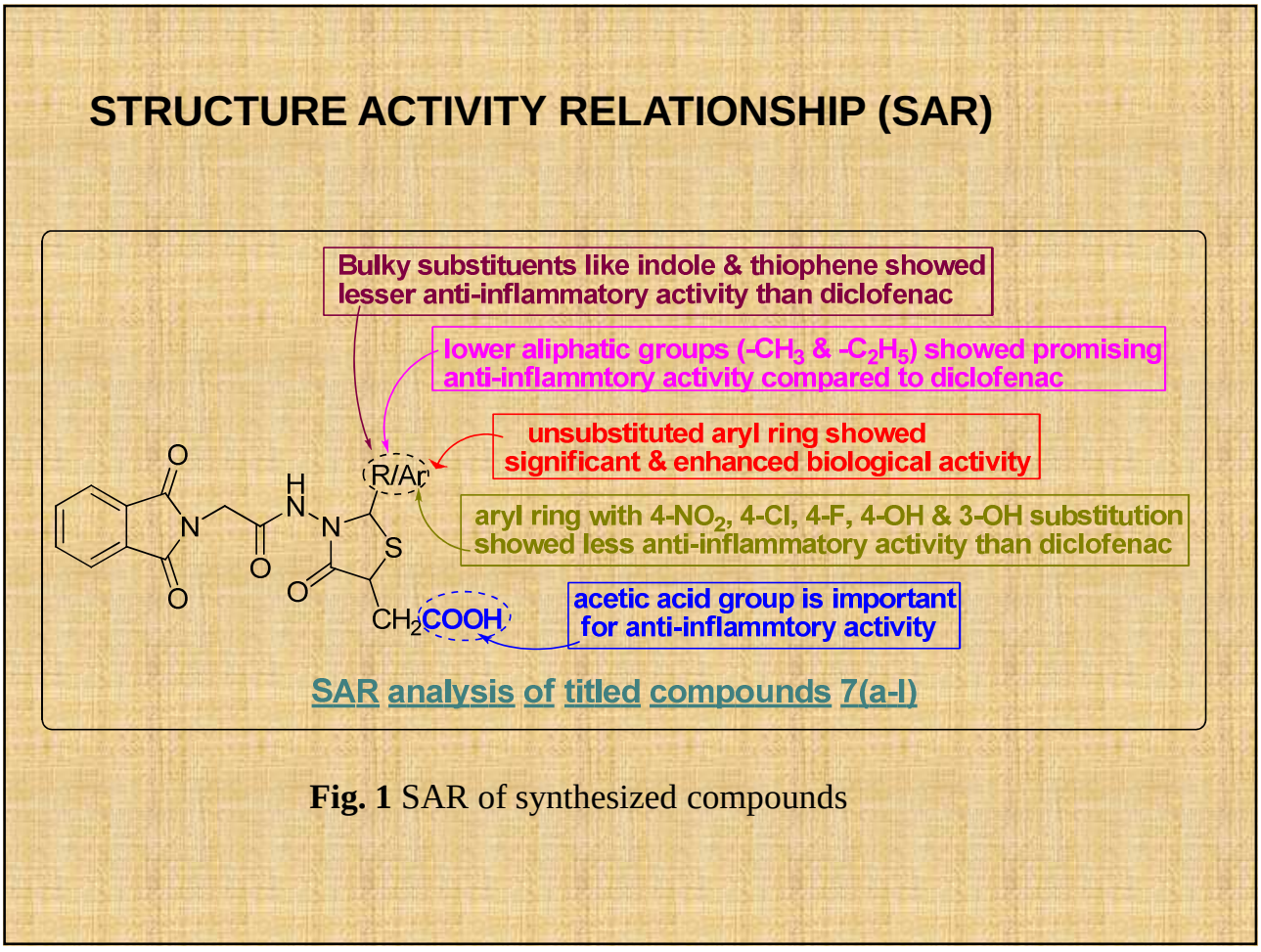


Fig. 1 SAR of synthesized compounds

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.
- 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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THANK YOU !