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SYNTHESIS OF THIAZOLIDINE-4-ONE DERIVATIVES FOR THEIR ANTI INFLAMMATORY ACTIVITY

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ABSTRACT

A new series of thiazolidine-4-one derivatives were synthesized in order to determine their anti-inflammatory activity. The compounds were combined in acceptable yield and the structures of all recently blended compounds were set up based on their IR, ^{1}HNMR, and elemental analysis. The synthesized compounds were tested for anti-inflammatory activity, and the compound 4(a) and 4(b) shows significant anti-inflammatory activity and compound 4(c), 4(d), 4(e) also shows appreciable anti-inflammatory activity.

KEYWORDS

Thiazolidine derivatives, Anti-inflammatory activity and Elemental analysis.

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INTRODUCTON

Heterocyclic bearing nitrogen, sulphur, and thiazole moieties constitute the core structure of a number of biologically interesting compounds. Writing overview shows that thiazole subordinates assume a significant part in biological fields. The study is of great interest both from the theoretical as well as practical importance. Different compounds, for example, alkaloids, basic amino acids, nutrients, hemoglobin, hormones, enormous number of synthetic drugs and dyes contain heterocyclic ring frameworks. There are huge number of synthetic heterocyclic compounds like pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine and thiazole. Among this thiazole having important application

and important intermediates in synthesis. Thiazolidine-4-ones are usually solids, often melting with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. Thiazolidine-4-ones are subsidiaries of thiazolidine with carbonyl gathering at the fourth position. The carbonyl group of thiazolidine-4-ones is highly un-reactive. Literature review shows that thiazole subordinates assume a significant function in biological fields, for example, antimicrobial[1-4], antidiabetic[5], antiviral[6], anti-inflammatory[7], antituberculosis[8], and anticancer[9] activities. Thiazolidin-4-one[10] derivatives are known to exhibit diverse bioactivities such as antidiarrheal[11], anticonvulsant[12], antimicrobial[13-16], antidiabetic[17,18], antihistaminic[19], anticancer[20,21], anti-HIV[22], cyclooxygenase inhibitory[23], antiplatelet activating factor[24-26].

EXPERIMENTAL SECTION

Anti-inflammatory activity

The anti-inflammatory activity of NSAIDs is based on the **inhibition of the cyclo-oxygenase (COX) enzyme**, resulting in prostaglandin synthesis inhibition. Anti-inflammatory is the property of a substance or treatment that reduces inflammation or swelling and these drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system to block pain signaling to the brain.

MATERIAL AND METHODS

Inflammation is a tissue reaction to infection, irritation or foreign substances. It is a part of host defense mechanism but when it became great it is a hopeless condition. The inflammatory reaction is readily produced in rats in the form of paw odema with the help of irritants or inflammogens substances such as carrageen in, formalin, bradykinin, histamine, 5-hydroxy tryptamine, mustard and egg white when injected in the dorsal of the foot in rats produce acute paw odema with in few minutes of the injection. Formalin induced paw odemais the most commonly used method in experimental pharmacology, formalin by causing the release of histamine, 5-HT bradykinin and prostaglandins produces the inflammation.

Plethysmometer

It is a simple apparatus containing mercury. The mercury displacement due to dipping of the paw can be directly read from the scale attached to the mercury column or adjusted the mercury level in the arm B to the original level by moving arm B up/down and noting the volume required to bring the level in both the arms equal.

Toxicity studies

The acute toxicity study was done as per the OECD guidelines (407). The compounds were administered orally in different doses, where 24 h toxicity was recorded to identify the toxic doses. The doses of the test compounds were then fixed on the basis of their acute toxicity as 40mg/kg for evaluation. The anti-inflammatory activity was studied using acute and chronic models.

Chemicals and Drugs

Formalin prepared 1% w/v solution and injected 0.1ml dose underneath the plantar region. Diclofenac sodium-dose 50mg/kg. Prepare a stock solution containing 4mg/ml of the drug and inject 0.5ml/100g of the body weight.

ANIMAL GROUPING AND DRUG ADMINISTRATION

Animals healthy wister albino rats (150-200gms) was selected for the activity. They were fed with standard laboratory chow (Hindustan lever foods, Bangalore, India) and provided with water adlibitum, experimental protocols were approved by the institutional ethical committee for animal experiment.

Animals were divided into 7 groups and the drugs were administered orally.

1st group of animals served as control.

2nd group of animals were treated with the standard diclofenac sodium-50mg/kg administered orally.

The animals of the other groups (3-7) were treated with calculated dose.

The synthesized compounds 6(a-e) were administered at single dose levels (40/200mg/kg) as an oral suspension in 1% carboxy methyl cellulose,30 minutes prior to formalin(0.1ml of 1%

w/v) administration in to the tibotarrsal joint of right hind paw. The volume of the left and right hind paw at 0, 30, 60, 90 and 120 minutes after the formalin administration by plethysmograph. Diclofenac sodium (oral 50mg/kg) served as standard and 1% carboxy methyl cellulose (oral 2ml) served as control. The result were tabulated. The percentage inhibition of odema was calculated by using the formula

Relative Paw Edema = [v2−v1/v1] × 100

Where v_1 = The animal paw volume before formalin injection and v_2 = The paw volume after drugs and formalin injection at different time points.

RESULTS AND DISCUSSION

In this present work, a series of new compounds was synthesized. Thus, starting from,

Synthesis of benzoxyzene-4-one compound

Scheme -1[27]

The solution of benzoyl chloride (0.03mole) (4.2ml) (1) and anthranilic acid (0.02mole) (2.74) (2)gms in dry pyridine (30 ml) is refluxed on water bath for 3Hrs at 35°C. The reaction mixture was cooled and poured into cold dilute hydrochloric acid. The solid benzoxyzene-4-one (3) thus obtained is filtered and recryatallized from benzene.

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one

Scheme-2

An intermediate mixture of benzoxyzene4-one (3) compound (0.036mole) (8gms) and hydrazine hydrate (6ml) is refluxed in water bath using ethanol (30 ml) as solvent for 6 Hrs at 45°C, then the reaction mixture3-amino-2-phenylquinazolin-4(3H)-one (4) is poured into cold water, filtered, dried and recrystallized from ethanol.

Synthesis of some intermediates 5 (a-e)

Scheme -3

An equimolar mixture of the 3-amino-2-phenylquinazolin-4(3H)-one (0.01mole) (4) and the appropriate aromatic aldehyde (0.015mole) in absolute n-butanol (50ml) is heated under reflux on water bath for 2 Hrs in 45°C in the presence of 2 drops of dry piperidine to get various aldehyde derivatives of 3(substituted)- amino-2-phenylquinazolin-4(3H)-one 5(a-e).

Synthesis of thiazolidin-4-one derivatives 6(a-e)

Scheme -4

A mixture of Schiff's base of 3(substituted)-amino-2-phenylquinazolin4 (3H)-one (6 a-e) (0.005moles) which was obtained from Scheme 3 was refluxed with thioglycollic acid and dimethyl formamide (15ml) containing a pinch of anhydrous zinc chloride for 6 Hrs at 450°C. The reaction mixture was then cooled and poured in to crushed ice. The solid (6a-e) thus obtained was filtered and recrystallized from ethanol. The structures of the various synthesized compounds were assigned on the basis of elemental analysis, IR, and ^{1}HNMR spectral data. Spectral and analytical data of the title compounds (6a-e) are shown in Tables No.1. The compounds are evaluated for their anti-inflammatory activity, and results are summaries in Table No.2. From the, anti-inflammatory activity it was observed that all the compounds exhibited activity against all the organisms employed. Whereas compound (6a-e) showed moderate to good activity.

Statistical Analysis

Data were shown as mean ± SD of different groups. The Data of this study were statistically analyzed using one-way ANOVA and Tukey tests. The $P < 0.05$ was considered statistically significant.

Table No.1: Compound 6(a-e)

S.No	Compound Code	R	Molecular Formula	Mol. Wt	R_f	Found % (Calc %)		
						C	H	N
1	6a	Benzaldehyde	$C_{24}H_{17}N_3O_3S$	399.46	0.6	69.15 (72.09)	4.29 (4.26)	12.55 (10.52)
2	6b	2-chloro benzaldehyde	$C_{24}H_{17}ClN_3O_3S$	433.07	0.8	63.66 (66.51)	3.72 (3.92)	9.68 (9.69)
3	6c	2-nitro benzaldehyde	$C_{24}H_{16}N_4O_3S$	472.47	0.7	61.87 (61.01)	4.06 (3.38)	12.55 (11.86)
4	6d	Anisaldehyde	$C_{24}H_{17}N_3O_4S$	443.47	0.8	65.00 (65.01)	3.86 (3.83)	9.48 (9.48)
5	6e	salicylaldehyde	$C_{24}H_{18}N_3O_4S$	444.47	0.9	65.12 (64.86)	3.86 (4.05)	9.48 (9.45)

Table No.2: Anti-inflammatory activity of compound 6(a-e)

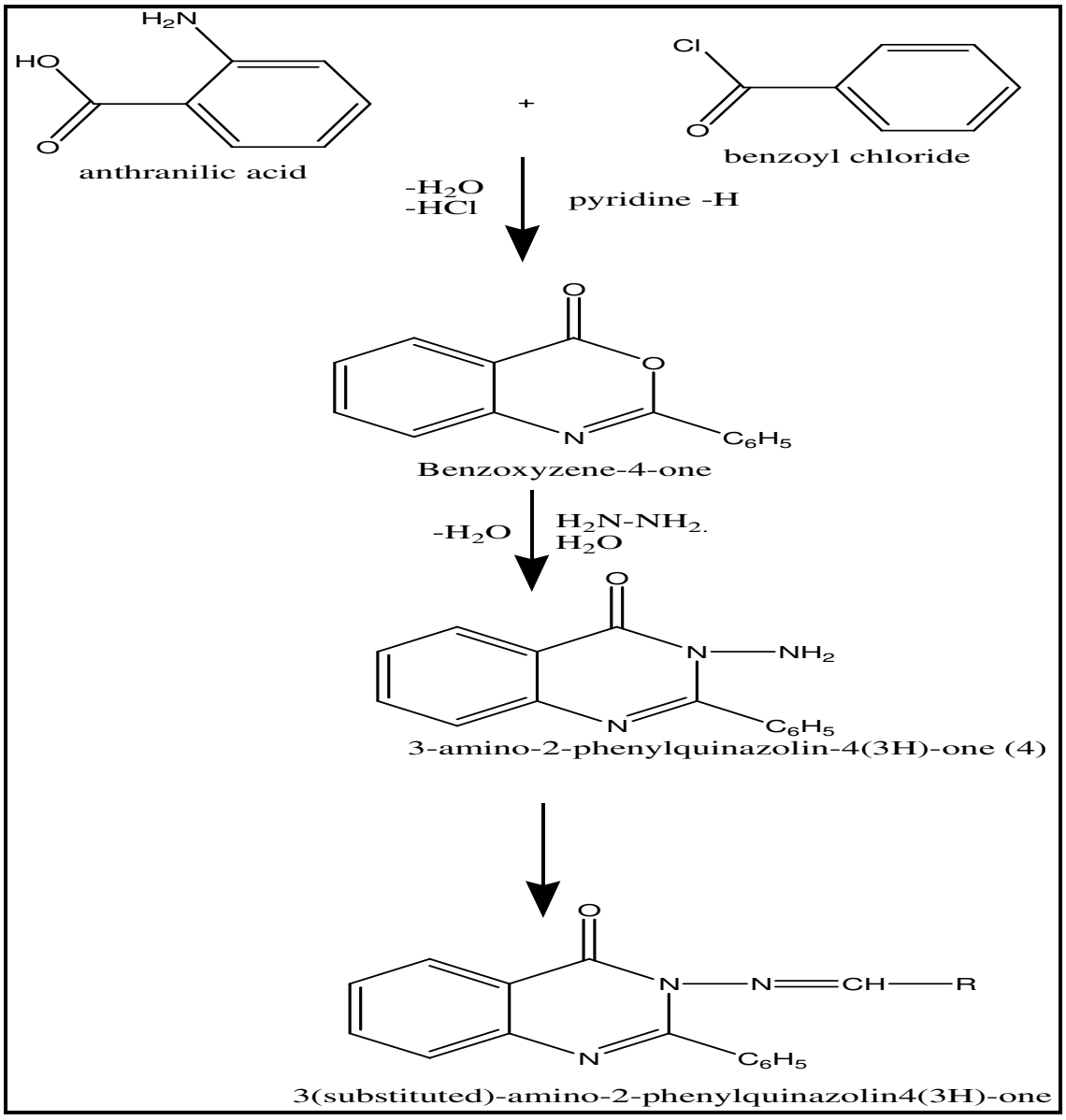
S.No	Group and treatment	Dose mg/kg	Time (min)				
			0	30	60	90	120
1	Control(cmc)	2ml	0.33±0.04	0.6± 0.01	0.82± 0.01	1.00 ±0.04	1.05 ±0.05
2	Diclofenac sodium (standard)	50	0.56± 0.01(43.1) *	0.18± 0.03(51.0) *	0.42± 0.01(60.1) *	0.2± 0.05(65.0) *	0.05± 0.08(97.0)*
3	Compound 6(a)	40	0.13± 0.4	0.15± 0.07	0.42 ±0.01	0.12± 0.037	0.16 ±0.07
4	Compound 6(b)	40	0.23± 0.04	0.25± 0.05	0.12± 0.03	0.18± 0.06	0.21± 0.05
5	Compound 6(c)	40	0.2± 0.08	0.61 ±0.02	0.24± 0.07	0.13± 0.04	0.12± 0.03
6	Compound 6(d)	40	0.62± 0.02	0.13± 0.04	0.27± 0.04	0.17± 0.04	0.27± 0.06
7	Compound 6(e)	40	0.64± 0.02	0.12± 0.03	0.15 ±0.05	0.15± 0.05	0.17± 0.04

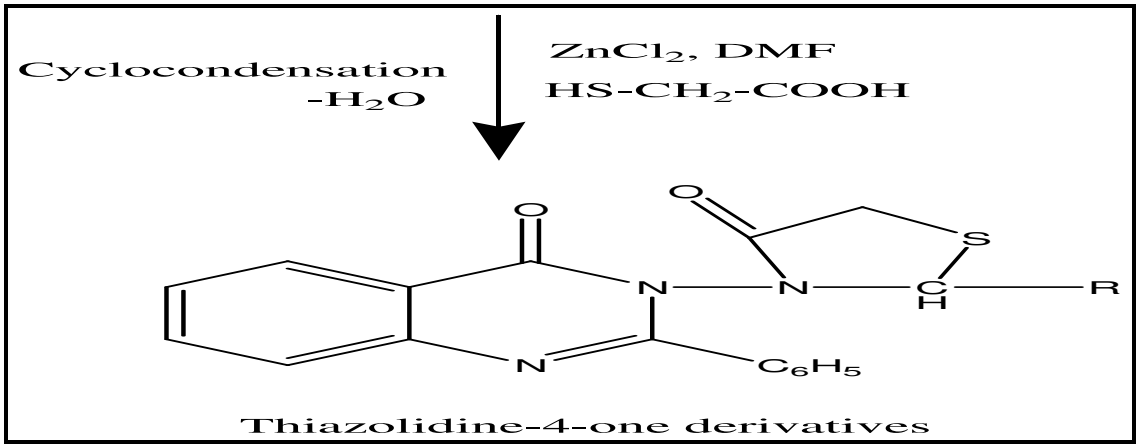
Increase in paw volume (ml) at differential intervals (min)
Sample size n=6. Values are in mean + standard *p Values

Table No.3: Percentage inhibition of increase in Paw volume

S.No	Compounds	Dose mg/kg	parameter	Time (min)				
				0	30	60	90	120
1	Compound 6(a)	40	% reduction of inflammation	(48.0)	(54.5)	(60.0) *	(74.0) *	(80.0) *
2	Compound 6(b)	40	% reduction of inflammation	(51.0)	(56.0)	(66.0) *	(68.0) *	(79.5*)
3	Compound 6(c)	40	% reduction of inflammation	(20.0)	(39.4)	(47.2) *	(54.2) *	(67.2) *
4	Compound 6(d)	40	% reduction of inflammation	(38.1)	(48.2)	(54.2) *	(69.2) *	(73.1) *
5	Compound 6(e)	40	% reduction of inflammation	(36.0)	(48.0)	(59.0) *	(68.8) *	(70.0) *

Indicates significant anti-inflammatory activity at $p \leq 0.001$ compared to control. Values in parenthesis are percent inhibition of increase in paw volume.


anthranilic acid
benzoyl chloride
-H2O
-HCl
pyridine -H
Benzoxyzene-4-one
-H2O
H2N-NH2.
H2O
3-amino-2-phenylquinazolin-4(3H)-one (4)
3(substituted)-amino-2-phenylquinazolin4(3H)-one


Cyclocondensation
-H2O
ZnCl2, DMF
HS-CH2-COOH
Thiazolidine-4-one derivatives

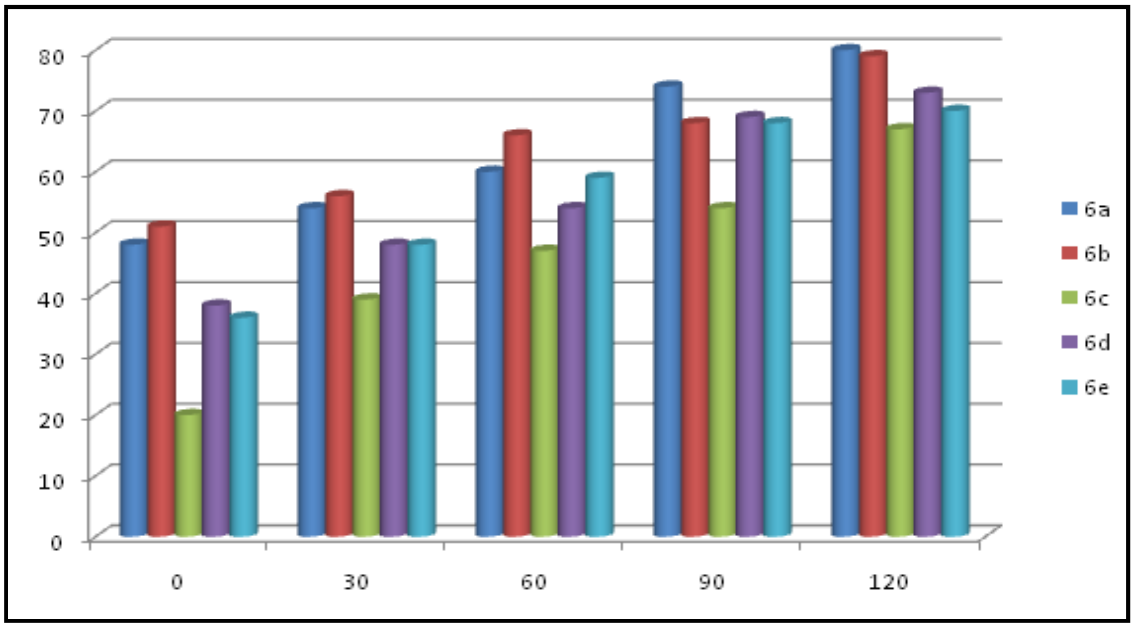


Figure No.1: Anti-inflammatory activity of synthesized compound (percentage inhibition)

CONCLUSION

The anti-inflammatory activity of all the incorporated compounds were screened by formalin induced paw oedema strategy by utilizing plethesmograph apparatus. The results tabulated in Table No.2 and Table No.3 showed that the compound 6(a) and 6(b) shows significant anti-inflammatory activity and compound 6(c), 6(d) and 6(e) also shows appreciable anti-inflammatory activity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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