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Research Article

SYNTHESIS OF NOVEL 4-THIAZOLIDINONE DERIVATIVES WITH ANTIINFLAMMATORY ACTIVITY

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ABSTRACT

4-Thiazolidinone is an important biological scaffold. A series of 4-thiazolidinone derivatives were synthesized. The structures of the synthesized compounds were confirmed on the basis of IR and ^{1}H NMR. The synthesized compounds were screened for anti-inflammatory activity. Among the entire test compounds, III have shown promising anti-inflammatory activity as compared to the rest. All the experimental results were statistically significant.

Keywords: 4-Thiazolidinone, Anti-inflammatory, COX-2 inhibition, Sulfomethyl, Azide

INTRODUCTION

Thiazolidinones are derivatives of thiazolidine belonging to important group of heterocyclic compounds. Numerous reports have appeared in the literature highlighting their chemistry and use. Thiazolidinones scaffolds are reviewed extensively in literature for its vibrant activities such as anticonvulsant, hypnotic, anti-tubercular, anthelmintic, cardiovascular, antihypertensive, anticancer and antiviral activities[1-9]. We became interested in syntheses of thiazolidinones and evaluation of their anti-inflammatory activities. 4-Thiazolidinones have been reported to have anti-inflammatory activity as well as COX-2 inhibitory activity[10]. The greatest research in anti-inflammatory area has been performed to identify a true molecular target for the development of novel therapies for various arthritic disorders. Recent progress made in selective COX-2 inhibitors suggests a common structural feature such as a central heterocycle or carbocyle containing one or more double bonds[11, 12]. In present work a saturated 4-thiazolidinone is chosen as a central cyclic tensor with adjacently substituted with azide (N_3) or sulfomethyl group (SO_2CH_3)

MATERIALS AND METHODS

Starting materials were obtained from commercial suppliers and used without further purification. The melting points are uncorrected and recorded by open capillary method on Oswal Precision Melting Point apparatus. The reactions were monitored by TLC performed by ascending development. IR spectra were recorded on Buck Scientific Infrared Spectrometer, Model 500. ^{1}H NMR was recorded on Joel MYFT 60 MHz using tetramethylsilane as internal standard. The physical and spectral data of synthesized compounds are reported in table No. 1 and 2 respectively.

General scheme for the synthesis of 2, 3-diaryl-4-thiazolidinone

Equimolar quantities of suitably substituted aromatic aldehyde and aniline were taken in dry benzene and refluxed using a Dean- Stark separator about 6-8 h. 1.2 equivalents of thioglycolic acid were added and refluxing was continued till water ceased to separate and progress of the reaction was monitored by TLC. Residue after removal of benzene was treated with sodium bicarbonate solution and 10% sodium bisulphite. Finally residue washed with water.

Synthesis of 2 (4-azidophenyl) N-(4-fluro-3-chlorophenyl)-4-thiazolidinone (I)

Ten mmol (3.52 gm) of 2(4-Nitrophenyl)N-(4-fluro-3-chlorophenyl)-4-thiazolidinone (Ia) was dissolved in aqueous methanol(10%v/v, 75 ml). 50 Mmol (2.9 gm) of iron fillings and 0.4 ml of glacial acetic acid were added to above stirred solution. After 2 h reaction mixture was made alkaline with sodium bicarbonate. Mixture was then filtered. Solid obtained was 2(4-aminophenyl) N-(4-fluro-3-chlorophenyl)-4-thiazolidinone (48%) . 3 mMol (1 gm) of 2(4-aminophenyl)N-(4-fluro-3-chlorophenyl)-4-thiazolidinone was dissolved in 5 ml of concentrated HCl and temperature was maintained 0-5˚C. Cold solution of $NaNO_2$ in water (0.19 gm in 10 ml) was added maintaining the temperature followed by 1.9 gm of NaN_3 in 10ml of water. The reaction mixture was stirred for 2 hours at 5-10˚C and then brought to room temperature, extracted twice with 10 ml portion of dichloromethane and residue obtained after evaporation of solvent. (Yield: 81%), yellowish brown solid m.p.116-118˚C

Synthesis of 2(4-azidophenyl) N-(4-bromophenyl)-4-thiazolidinone (II)

Same as I starting from IIa Yield for amino derivative: 58%, Yield for II is 76%, Pale yellow solid m.p.127-129˚C

2(4-Methylsulfonylphenyl) N-(4-methoxyphenyl)-4-thiazolidinone (III)

2.6 Mmol (1 gm) of 2(4-thiomethylphenyl) N-(4-methoxyhenyl)-4-thiazolidinone was dissolved in 10 ml of dichloromethane and placed in ice-salt bath. 10 Mmol (1.7 gm) of m-chloroperbenzoic acid was added to above solution in portions. To the mixture further 30 ml of dichloromethane was added and washed with aqueous sodium bicarbonate. The combined organic fractions were concentrated to get solid. Final product III was obtained by column chromatography .Pale yellow solid, m.p. 148-149˚C (Yield: 70%)

2(4-Methylsulfonylphenyl)N-(4-trifluromethylphenyl)-4-thiazolidinone(IV)

Same as III starting from IVa Yield: 74%, pale solid, m.p.205-207˚C

2(4-Methoxyphenyl)N-(3-trifluromethylphenyl)-4-thiazolidinone,1,1-dioxide (V)

7.6Mmol (2.4 gm) of 2(4-Methoxyphenyl) N-(3-trifluromethylphenyl)-4-thiazolidinone (Va) was dissolved in 20 ml of glacial acetic acid. 15 Mmol (2.5 gm) of $KMnO_4$ was dissolved in 10 ml of water. This solution was added dropwise to above solution and temperature maintained below 30˚C. After addition reaction mixture appeared dark coloured. Solid sodium bisulphite was added till decolourisation. The mixture was diluted with water and tan coloured solid filtered off and recrystallised from methanol. Yield: 87%, Pale brown solid, m.p. 172-174˚C

Anti-inflammatory activity

Invivo assay method followed for testing anti-inflammatory activity was Carrageenan- induced rat paw edema model[13,14]

Animal study protocol was approved by institutional and animal ethical committee and CPCSEA. Wistar rats (150-175 gm) were acclimatized to laboratory condition for 7 days before

commencement of the experiment. The animals were received pelleted feed, water *ad libitum* during study. Wistar rats were divided into three group of six for rat paw edema method. Group I (Nimesulide 30mg/ kg), Group II (Test compound in vehicle containing suspending agent), Group III (vehicle+ suspending agent)

Compounds were given as oral suspension and vehicle made from PEG-PG in the ratio 3:4. After 1 hour animals are injected with 0.1 ml of 1% carrageenan. A line was drawn with permanent marker at the level above the ankle in one hind paw to define the area of the paw to be measured. The initial paw volume was measured using plethysmometer. The final paw volume was measured after injecting carrageenan. After administration of carrageenan solution the paw volume of control, standard and test groups were measured with Plethysmograph by water displacement method at 1 h, 2 h and 3 h time interval. The % Inhibition of edema after 3 h was measured by formula:

$$\% \text{ Inhibition} = 100 \times (1 - Vt/Vc)$$

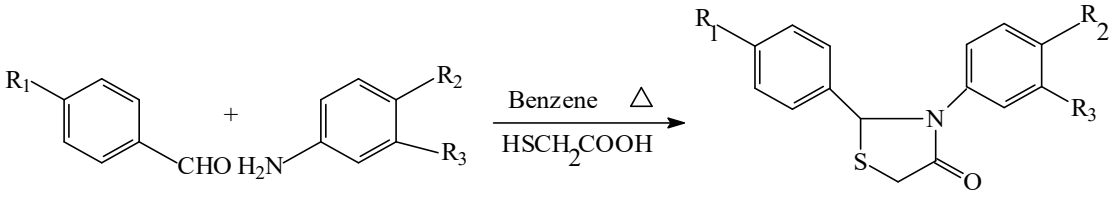
Where Vt: Edema volume for test And Vc: Edema volume for control

The values are expressed as mean±SEM and data was analysed by one way ANOVA Results were analysed for statistical significance at $p<0.05$. The results of anti-inflammatory testing are given in table 3.

RESULTS AND DISCUSSION

The novel 4-thiazolidinones were synthesised and synthetic scheme is presented in scheme. All the synthesized compounds are in conformity with the structures envisaged. Compounds tested for anti-inflammatory activity. Compound II, III and IV exhibited moderate anti-inflammatory activity. Amongst them compound III (% inhibition of paw edema 26.03 at 3 h) exhibit more activity than standard drug nimesulide (% inhibition of paw edema 21.86 at 3 h). No animal died during study. Compound III showed highest activity in series is containing SO_2CH_3 group on the aromatic ring. Compound II with N_3 functional group on aromatic ring is also showing anti-inflammatory activity. The biological activity of azide containing I and II was ascribed to the bioisosteric replacement of sulfomethyl group. Hence it again underlines the fact that SO_2CH_3 or N_3 is essential for showing anti-inflammatory activity. Also substitution at meta position on one of the aromatic rings compound I and V is detrimental to biological activity.

SCHEME



Ia -Va

Ia: R_1:4-NO_2, R_2: 4-F, R_3:3-Cl

IIa: R_1:4-NO_2, R_2: 4-Br, R_3:H

IIIa: R_1:4-SCH_3, R_2: 4- OCH_3, R_3:H

IVa: R_1:4-SCH_3, R_2: 4- CF_3, R_3:H

Va: R_1:4-OCH_3, R_2: H, R_3:3-CF_3

Scheme for functional group conversions on 4-thiazolidinones

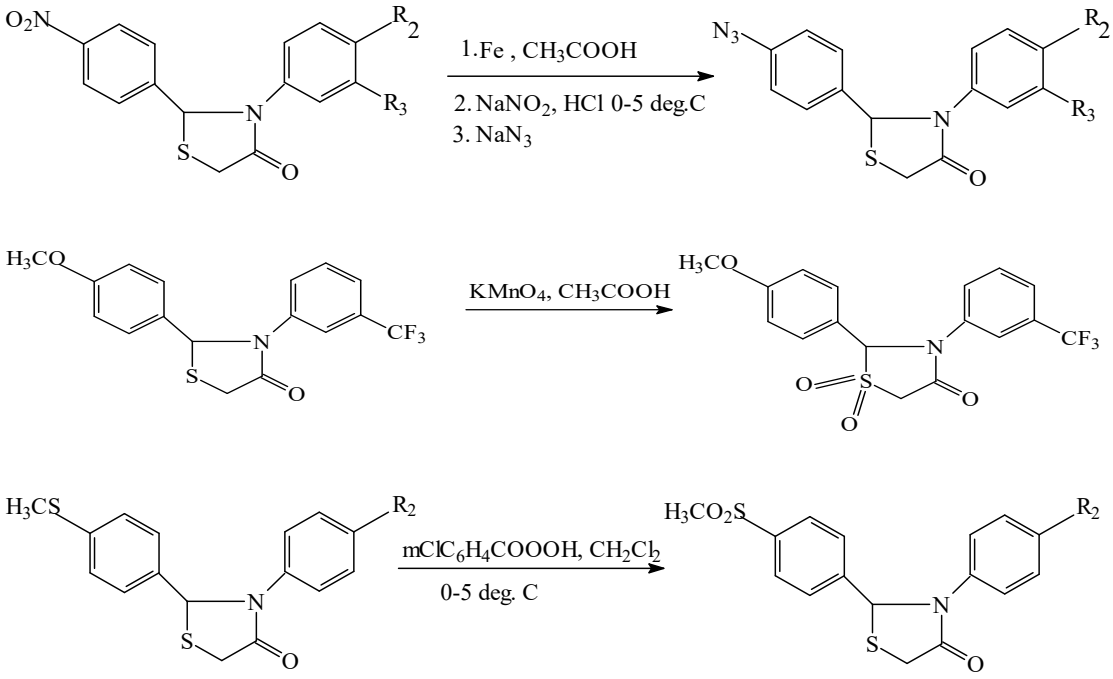


Table 1: Physical data of synthesized compounds

Compound Code.	IUPAC Nomenclature	Molecular formula	Molecular weight	M.P. (º C)	Yield (%)
I	2(4-Azidophenyl)N-(4-fluro-3-chlorophenyl)-4-thiazolidinone	$C_{15}H_{10}ClFN_4OS$	348.5	116-118	81
II	2(4-Azidophenyl)N-(4-bromophenyl)-4-thiazolidinone	$C_{15}H_{11}BrN_4OS$	375	127-129	76.5
III	2(4-Methylsulfonylphenyl)N-(4-methoxyphenyl)-4-thiazolidinone	$C_{17}H_{17}NO_4S_2$	363	148-149	70
IV	2(4-Methylsulfonylphenyl)N-(4-trifluromethylphenyl)-4-thiazolidinone	$C_{17}H_{14}F_3NO_3S_2$	401	205-207	74
V	2(4-Methoxyphenyl)N-(3-trifluromethylphenyl)-4-thiazolidinone,1,1-dioxide	$C_{17}H_{14}F_3NO_4S$	385	172-174	87

Table 2: Spectral data of compounds synthesized

Compound No.	IR spectrum (KBr, cm^{-1})	^{1}HNMR ($CDCl_3$, ppm)
I	3026(Aromatic –CH *str.*), 2127(Azide *str.*), 1688(C=O *str.*, lactam), 750(Ar-CH *bend*)	7.3-7.82 (m, 7H arom.) , 6.58 (s,1H, methine) , 4.32 (s,2H, methylene)
II	3020(Aromatic –CH *str.*), 2128(Azide str), 1691(C=O *str*, lactam)	6.81-7.42(m, 8H arom.) , 5.96 (s,1H, methine) , 3.73 (s, 2H, methylene)
III	1715(C=O *str.*, lactam), 1321, 1135 (S-O *str* in SO_2 group)	6.81-7.42 (m, 8H arom.) , 5.96 (s,1H, methine), 4.32 (s,2H, methylene) 3.73 (s,3H, methoxy) ,3.05 (s,3H, methylsulphonyl)
IV	3032(Aromatic –CH *str*), 2939(Aliph. –CH *str*), 1712(C=O *str*, lactam), 1324, 1147 (S-O *str* in SO_2 group)	7.25-8.0(m, 8H arom.), 6.09 (s,1H, methine) , 4.08 (s,2H, methylene) 3.05 (s,3H, methylsulphonyl)
V	3016(Aromatic –CH *str*), 2961(Aliph. –CH *str*), 1718(C=O *str*, lactam), 1331, 1174 (S-O *str* in SO_2 group)	7.25-7.86 (m, 8H arom.) , 6.09 (s,1H, methine) , 4.08 (s,2H, methylene) , 3.8 (s,3H, methoxy)

Str: stretching, *bend:* bending, s: singlet, m: multiplet

Table 3: Anti-inflammatory activity of synthesized compounds

Treatment 30 mg/kg	Paw volume in ml, Mean±SEM (% Inhibition of paw edema)		
	1h	2h	3 h
Control	1.059±0.037	1.117±0.021	1.120±0.013
I	0.778±0.005 (5.85)	0.785±0.025 (6.02)	0.886±0.018 (6.08)
II	0.925±0.010 (18.99)	1.067±0.025 (19.89)	0.901±0.021 (20.12)
III	0.768±0.116 (15.34)	0.922±0.145 (18.78)	0.900±0.142 (26.03)
IV	0.960±0.022 (8.57)	1.083±0.003 (11.11)	0.960±0.023 (12.08)
V	0.813±0.015 (3.65)	0.863±0.023 (4.27)	0.903±0.041 (4.79)
Standard (Nimesulide)	0.673±0.112 (15.22)	0.803±0.135 (19.99)	0.793±0.132 (21.86)

N=6 animals in each group, p*< 0.05 when compared with control.

Round brackets indicate percent inhibition; SEM: standard Error of Mean

CONCLUSION

In conclusion, we have synthesized some of 4-thiazolidinone derivatives and compound III has shown highest activity as compared to control. The new chemical entities designed for anti-inflammatory effect share structural similarity with selective cyclooxygenase-2 inhibitors and hence it would be interesting to look for the same. Investigation of this 4-thiazolidinone scaffold would open more encouraging results.

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REFERENCES

1. Parmar S., Dwivedi, Chaudhari A., Gupta T. Substituted thiazolidinones and their selective inhibition of nicotinamide adenine dinucleotide dependant oxidation. J. Med. Chem. 1972; 15: 99-101
2. M. Chaudhary, S. Parmar, S.K. Chaudhary, A.K. Chaturvedi, B.V. Ramasastry, CNS depressant activity of pyrimidylthiazolidin ones. J. Pharm. Sci.1976; 64: 443
3. Babaoglu K., Novel inhibitors of an emerging target in Mycobacterium tuberculosis: substituted thiazolidinones as inhibitors of dTDP rhamnose synthesis. Bioorg. Med. Chem. Lett. 2003; 13: 3227-3230.
4. Nagar S., Singh H. Anticonvulsant and cardiovascular effects of substituted thiazolidones J. Med. Chem.1973; 16:178-180
5. Suzuki Y., Akima M., Tamura K. Effects of CP-060S, a novel cardioprotective drug on cardiac functiona nd myocardial oxygen consumption. Gen. Pharmacol. 1999; 32: 57-63.
6. C. Kavitha, N. Basappa Synthesis of new bioactive venlafaxine analogs: novel thiazolidin-4-ones as antibacterials Bioorg. Med. Chem. 2006; 14: 2290-2299.
7. Bondock S., Khalifa W., Fadda A., Eur. J. Med. Chem. Synthesis and antimicrobial evaluation of some thiazole, thiazolidinone, thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde. 2007; 42: 948-954
8. V. Gududuru. Synthesis and antiproliferative activity 2-aryl-4-oxo-thiazolidin-3-yl- amides for prostate cancer Bioorg. Med. Chem. Lett. 2004; 14: 5289-5293
9. Rawal R. , 2-(Aryl) -3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT inhibitors Bioorg. Med. Chem. 2005; 13: 6771-6776.
10. Verma A., Saraf S. 4-Thiazolidinone- A biologically active scaffold. Eur. J. Med. Chem. 2008; 43: 897-905

11. Gerd D.,Werner K. Cyclooxygenase inhibitors – current status and future prospectus. Eur. J. Med.Chem.2000; 36:109-126
12. Habeeb A., P.N.P. Rao , Kanuss E . Design and synthesis of celecoxib and rofecoxib analogues as cyclooxygenase-2 inhibitors: Replacement of sulphonamide and methylsulfonyl pharmacophores by an azido bioisostere. J. Med. Chem. 2001, 44: 3039-42
13. Winter C.A. Carrageenan- induced edema in hind paw of the rat as an assay for anti-inflammatory drugs Proc. Soc. Exp Biol. Med. 1962, 544
14. Mittal G., Singh H. Indian J. Pharmacol. Inhibitory effect of certain nonsteoidal anti-inflammatory drugs against prostaglandin induced inflammation in rats 1977; 9(2):171-173.