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Synthesis, characterization and pharmacological activity of new 2- imino –thiazolidine-4-one derivatives

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ABSTRACT

A new 2-iminothiazolidin-4-ones compound and its derivatives were synthesized and characterized by FT-IR, CHN, and ^{1}HNMR techniques. The target compounds were assessed for their anti-inflammatory and analgesic activities, and the study was performed using Swiss albino mice (25-30 g) for investigation. A hind edema model caused by carrageenan, while the analgesic activity was assessed using an acetic acid-induced writhing and a hot plate test evaluated the anti-inflammatory activity.

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INTRODUCTION

The inflammation is a protective reaction that drives the body to various internal and external stimuli (Warren *et al.*, 2009). Chronic inflammation is often associated with the disease mechanism and the progress of many diseases such as cancer, arthritis, autoimmune, cardiovascular and neurological disorders. One of the major steps of inflammation is the activation of Cyclooxygenases enzymes (COX), which is responsible for the production of many inflammatory mediators of Arachidonic acid (Dennis and Norris, 2015). There are two isozymes of cyclooxygenase: COX-1 and COX-2 (Zarghi and Arfaei, 2011). COX-1 is involved in the synthesis of prostaglandins responsible for maintaining normal body functions in the kidneys, gastrointestinal tract and other organs, while COX-2 is stimulated during inflammation (Modi *et al.*, 2012).

Non-steroidal anti-inflammatory drugs (NSAIDs) are most frequently used as medications, which represent the choice of treatment in many inflammatory diseases like arthritis, rheumatisms (Daily *et al.*, 2016)such as aspirin, naproxen, diclofenac and indomethacin; they inhibit all of the COX isoforms leading to an effective anti-inflammatory response (Brune and Patrignani, 2015). These compounds share many of their therapeutic actions and adverse effects (Lichtenberger *et al.*, 2012) such as the ulcerogenic side effect, gastrointestinal upset and renal damage, which are inseparable from their pharmacological activities (Cooney *et al.*, 2015). As a result, the production and development of selective COX-2 inhibitors have been of much interest in recent years with the same anti-inflammatory efficacy as traditional non-steroidal anti-inflammatory agents, but with the minimal risk of gastrointestinal and renal toxicity by COX-1 inhibiting (Abdellatif

et al., 2016).

As the participation of ongoing studies in finding new effective anti-inflammatory agents, we report the synthesis of a new class of new structural derivatives 2-Imino Thiazolidine-4. The structural modifications were selected by introducing at the 5 positions of thiazolidinone moiety different arylidene substituents; we have recently been exploited as biologically active arms on heterocyclic scaffolds. Thiazolidinone, a saturated form of thiazoles have been represented as a magic moiety (wonder nucleus), and it is an important pharmacophore with diversity of biological activities according to the substituent and substitution (Haroon *et al.*, 2017) (Saravanan *et al.*, 2012). Thiazolidine-4-one is a five-member ring containing sulfur atom at position1, Nitrogen atom at position 3, and carbonyl at position 4, substitutions can occur on 2, 3 and 5 positions but substitution on second position carbon atom ring exert a valuable effect on structure and property of thiazolidinones (Joshi *et al.*, 2011). The thiazolidinone scaffold is very important in the design and synthesis of novel biologically active compounds (Manjal *et al.*, 2017).It present in large diversity of drug candidates like antifungal, antibacterial, anticancer (Appalanaidu *et al.*, 2016; Filho and Santiago, 2014), antiviral (Kaminskyy *et al.*, 2017), anticonvulsant (Patil *et al.*, 2011), antiglucoma (Silva *et al.*, 2016),antidiabetic anti-inflammatory (Omar *et al.*, 2018; Ma *et al.*, 2015; Ottanà *et al.*, 2011), antioxidant, and an analgesic (Liu *et al.*, 2000).

EXPERIMENTAL

Chemicals

4-Methyl sulfonyl aniline and Chloroacetyl chloride were purchased from Sigma Aldrich Germany. Methanol, ethanol, chloroform and dioxane are obtained from Riedel-De-Hane Germany. Ammonium thiocyanate and Sodium acetate (anhydrous) from ALPHA India, Benzaldehyde. 4-Trifluruo methyl benzaldehyde ,4-Hydroxy benzaldehyde, 4-Methoxy benzaldehyde ,4-Bromo benzaldehyde and Di methyl formanlide (DMF) obtained from Scharlab Spain, Glacial acetic acid from BDH, UK

Instruments

Melting point (SMP30), FT-IR spectrophotometer , CHNS flash EA 112 series, thermos Finnegan Autoclave for sterilizing tools and U.V lamp Tran's illuminator, were used in our study.

Animals

Swiss albino mice (25-30 g) in weight were used in this study. They were fed standard chow, and water *ad libitum* .and kept in the room of animals under controlled conditions at temperature pf 25±2°C, and the humidity is 30±15 % with the 12-h dark/12-h light cycle for a week before use to acclimatize.

Anti-inflammatory models

Carrageenan-induced paw edema in mice.

The paw edema induced by carrageenan assay in mice was employed with some modification (Arrigoni-Blank *et al.*, 2004), Test compounds and reference medication (Celecoxib) were administered orally at a dose 3 mg/kg body mass as a suspension in 0.5 ml of 0.5% sodium carboxymethyl cellulose (vehicle). Animals (mice) were divided into nine groups (n=6). All dealings were orally treated by oral gavage an hour before carrageenan injection. The induction of acute inflammation was achieved by intradermal injection of 25 µL of freshly prepared of 2% w/v carrageenan solution in normal saline(0.9%) into the right hind paws of mice. All animal groups (2–9) were injected with carrageenan, excepting for normal control group (Group 1), which were injected with 25 µL of 0.9% sterile saline solution. Animals of Group 1 and Group 2 were treated with the vehicle and functioned as normal control group and carrageenan-induced inflammation (negative) control group, respectively. Mice of Group 3 were treated with a standard nonsteroidal anti-inflammatory agent, Celecoxib to represent a positive control. Animals of groups (4–9) were treated with the test compounds (T, BT, BT1, BT2, BT3, BT4), respectively. The thickness of mice hind paws were measured using electronic Vernier caliper (Numit, China) at 0, 2, 4, 6 and 24 hours after carrageenan injection and the inflammatory edema were stated as a percentage of thickness variation (Δ).

Analgesic Activity

Writhing test

This test performed according to the acetic acid-induced writhing assay with modifications (Spindola *et al.*, 2012). Test compounds and indomethacin (standard drug) were administered orally by gastric gavage at a dose 10 mg/kg as a suspension in 0.5 ml of 0.5% sodium carboxymethyl cellulose (CMC) solution (vehicle). The inhibition percentage (I %) of number of writhings (abdominal restrictions) was achieved to determine the potency of analgesia and was determined as the following formula:

Inhibition % (I %) = $(N_c - N_t / N_c) \times 100$

Where N_c = is the average of writhing numbers in

the group of negative control

N_t = is the average of writhing numbers in the tested groups.

Hot plate test

One of the important methods of assessment of analgesic activity is the hot plate test in mice (Ponnaluri *et al.*, 2017; Upasani *et al.*, 2009). Test compounds and aspirin (standard drug) were orally administered at a dose of 10 mg/kg as a suspension in 0.5 ml of 0.5% sodium carboxymethyl cellulose (vehicle) solution. After one hour of all oral treatments, animals were placed inside a glass cylinder placed on the well-regulated hot plate. maintained 55±1°C. The time difference between the setting of animals on the hot plate surface and the incidence of licking or jumping of fore-hind paws was verified as reaction time. It has been taken into account that the cut-off period should not exceed 20 seconds maximum to avoid injury to the paws of mice.

Statistical analysis

Data of all trials in this study stated as mean± standard deviation (S.D.). Statistical analysis carried out by (ANOVA) pursued by the Dennett's t-test. The values of probability (P <0.05) are considered as statistically significant.

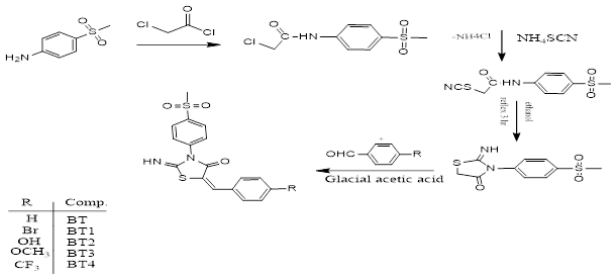
Synthesis

Synthesis of 2-chloro-N-(4-(methyl sulfonyl) acetamide

Chloroacetyl chloride (12gm, 0.12 mol.) was added dropwise to 4-methyl sulfonyl aniline (14gm, 0.07 mol.) which is dissolved in 50 ml of DMF (dimethyl formanlide) in a 250 mL round bottom flask as shown in theScheme 1 till the addition was complete (during 30 minutes) followed by stirring at room temperature for an overnight. The reaction content was added into cold water and stir for 30 min., then add 50 ml of methanol, 10 ml of concentrated HCl and water respectively then stir for one hour. The contents were filtered off and washed with cold water three times and let it dry at room temperature, and the crude product was recrystallized by methanol. The reaction was monitored by TLC (Geronikaki and Theophilidis, 1992; Papadopoulou *et al.*, 2005).

Synthesis of 2-imino -3-(4-(methyl sulfonyl) phenyl) thiazolidin-4-one

A solution of (18.3gm, 0.06 mol.)2-chloro-N-(4-(methylsulfonyl) phenyl) acetamide and (11gm, 0.12 mol.)of ammonium thiocyanate was refluxed in 50 ml of ethanol for 3 h in a 250 mL round bottom flask, the reaction was monitored by TLC till complete disappearance of starting material by using



R	Comp.
H	BT
Br	BT1
OH	BT2
OCH_3	BT3
CF_3	BT4

Scheme 1: Synthesis of 2-imino–thiazolidine-4-one and derivatives

eluent chloroform. The reaction content was added in to crush ice water and stirring for (15 min), the precipitate was filtered, washed with water, and recrystallized by dioxan (Sarkis *et al.*, 2014).

Synthesis of derivatives (BT-BT4)

A solution of (1.08gm ,0.004) mole of 2-amino -3-(4-(methylsulfonyl) phenyl) thiazolidine-4-one was added to (0.006mole) (0.636gm, 0.82gm, 1.04gm, 1.11gm, 0.73gm) of benzaldehyde,methoxy-benzaldehyde,trifluoro-methylbenzyldehyde,Bromo-benzaldehyde and hydroxyl-benzaldehyde receptively in a 250 mL round bottom flask in the presence of (0.565gm, 0.008 mole) of anhydrous sodium acetate in 40 ml of glacial acetic acid and reflex for 12 hr. (Vicini *et al.*, 2006). The reaction mixture was cooled to room temperature, and the precipitated solid was filtered, washed thoroughly with water, and recrystallized by dioxan and DMF in the ratio of (1:1), the reaction was monitored by TLC till complete disappearance of starting material by using eluent chloroform.

RESULTS AND DISCUSSION

2-imino -3-(4-(methyl sulfonyl) phenyl) thiazolidin-4-one

Shiny red crystals yield of 63% with M.wt of 270 and melting point (119-120). The FT-IR spectra(KBr) 1647 cm^{-1} (C=N), 1730 cm^{-1} (C=O), 1583 cm^{-1} (Aromatic C=C), 3159 cm^{-1}(-NH).analysis for CHNS ($C_{10}H_{10}N_2O_3S_2$) calculated is C,44.43 ; N,10.36; S,23.72; H,3.738 and found C,43.96 ; N,9.944 ; S,23.45; H, 3.73. ^{1}H NMR (DMSO-*d*6, 500 MHz) δ ppm: 3.21s (3H of CH_3) of sulfone, 4.05s (1H, CH Thiazolidinone ring, 7.165d,7.915d (2H, sulphone-phenyl ring), 11.91s (1H, -NH)

5-benzylidene-2-imino-3-(4-(methyl sulfonyl) phenyl) thiazolidin-4-one (BT)

Yellow powder yield 43% with M.wt of 358 and melting point (293-295). The FT-IR spectra (KBr) 1595 cm^{-1} (conjugated C=C), 1676cm^{-1}(C=O) Thiazolidinone, 3275cm^{-1} (-NH).analysis

for CHNS calculated ($C_{17}H_{14}N_2O_3S_2$) is C,56.97 ; N, 7.82 ; S,17.89 ;H,3.94 and found C,56.39 ; N, 7.305 ; S,17.89 ;H,3.90.^{1}H NMR (DMSO-*d*6, 500 MHz) δ ppm: 3.25s (3H of CH_3) of sulfone, 12.42s(1H, -NH), 7.28d,7.945d (2H, , sulphone-phenyl ring), 7.42-7.56 m of benzylidene ring

5-(4-bromobenzylidene)-2-imino-3-(4-(methyl sulfonyl) phenyl) thiazolidin-4-one (BT1)

Yellow powder yield 66% with M.wt of 437 and melting point (318-319). The FT-IR spectra (KBr) 1593 cm^{-1} (conjugated C=C), 1676cm^{-1}(C=O) Thiazolidinone, 642 cm^{-1} (C-Br), 1593cm^{-1}(conjugated C=C), 3277cm^{-1} (-NH). analysis for CHNS calculated ($C_{17}H_{13}BrN_2O_3S_2$) is C,46.69 ; N,6.41 ; S,14.66 ;H,3.00 and found C,46.25 ; N, 5.987 ; S,14.58 ;H,2.531. ^{1}H NMR (DMSO-*d*6, 500

MHz) δ ppm: 3.25s (3H of CH_3) of sulfone,12.56s(1H, -NH), 7.27d,7.95d (2H, sulphone-phenyl ring),7.455d, 7.665d (2H of bromo benzylidene ring),7.66s (C=CH-PH).

5-(4-hydroxybenzylidene)-2-imino-3-(4(methyl sulfonyl) phenyl) thiazolidin-4-one (BT2)

Pale orange crystals yield 66% with M.wt 374 and melting point(321-324), the FT-IR (KBr)1585 cm^{-1}(conjugated C=C) , 1674cm^{-1}(C=O) of Thiazolidinone ,3448cm^{-1} (OH) ,3199 cm^{-1} (-NH),analysis for CHNS calculated ($C_{17}H_{14}N_2O_4S_2$) is C,54.53 ; N,7.43 ; S,17.12 ;H,3.77and found C,54.01 ; N, 6.973 ; S,16.76 ;H,3.841. ^{1}H NMR (DMSO-*d*6, 500 MHz) δ ppm: 3.24s (3H of CH_3) of sulfone ,12.41s(1H, -NH), 6.865d,7.94d (2H, , sulphone-phenyl ring),7.265d, 7.375d (2H, hydroxyl benzylidene ring) ,7.59 s (C=CH-PH).

2-imino-5-(4-methoxybenzylidene)-3-(4(methylsulfonyl)phenyl)thiazyliden-4one(BT3)

Pale yellow powder yield 62% with M.wt 388 and melting point (316-317). The FT-IR (KBr) 1591 cm^{-1} (conjugated C=C),1668cm^{-1}(C=O) of Thiazolidinone and 1091cm^{-1} (C-O),3259 cm^{-1} (-NH),analysis for CHNS calculated ($C_{18}H_{16}N_2O_4S_2$) is C,55.66 ; N,7.21 ; S,16.51 ;H,4.15and found C,55.16 ; N, 6.632 ; S,16.48 ;H,4.14. ^{1}H NMR (DMSO-*d*6, 500 MHz) δ ppm: 3.25s (3H of CH_3) of sulfone,3.79s (3H,O-CH3),12.47s(1H, -NH), 7.055d,7.94d (2H, sulphone-phenyl ring),7.27d, 7.485d (2H, methoxy benzylidine ring),7.64 s (C=CH-PH).

2-imino-3-(4-(methyl sulfonyl) phenyl)-5-(4-(trifluoromethyl) benzylidene) thiazolidin-4-one (BT4)

Yellow powder yield 67% with M.wt 426 and melting point (311-313). The FT-IR spectra (KBr) 1597 cm^{-1} (conjugated C=C),1678cm^{-1}(C=O) Thiazolidinone , 1014cm^{-1} (C-F),3259 cm^{-1} (-NH),analysis for CHNS calculated ($C_{18}H_{13}F_3N_2O_3S_2$) is C,50.70 ; N,6.57 ; S,15.04 ;H,3.07and found C,50.27 ; N, 6.022 ; S,15.11 ;H,2.793. ^{1}H NMR (DMSO-*d*6, 500 MHz) δ ppm: 3.25s (3H of CH_3) of sulfone,12.65s(1H, -NH), 7.28d,7.95d (2H, sulphone-phenyl ring),7.73d, 7.79d (2H , trifluoromethyl benzylidene ring),7.83s (C=CH-PH).

Biologic activity

Anti-inflammatory effects

Analgesic effects

Table 2: Antinociceptive effect of Indomethacin and test compounds (10 mg/kg) on the acetic acid-induced writhing in mice.

Group	Number of writhings	Inhibition (%)
Negative control (vehicle)	40.31±5.26	-
Positive control (Indomethacin)	12.15±1.74***	69.85
T	20.48±2.54***	49.19
BT	18.36±3.52***	54.45
BT1	19.67±2.95***	51.20
BT2	15.61±3.21***	61.27
BT3	15.68±1.98***	61.10
BT4	17.95±1.19***	55.47

Each value is themean± S.D. for six mice, *p<0.05, **p<0.01, ***p<0.001 compared withnormal control. Data analyzed by using one -way ANOVA followed by Dennett'stest

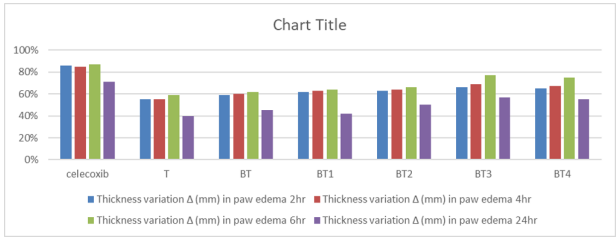


Figure 1: Effect of Celecoxib andtest compounds (10 mg/kg) on carrageenan-induced inflammation hind paw in mice.

Carrageenan-induced rat paw edema has been a well-known inflammatory model to evaluate the anti-inflammatory effect of compounds. In our study, we revealed that the parent compound and derivatives significantly reduced edema induced by carrageenan in all times (2, 4, 6,24) hr. As shown in-Figure 1. So they primarily inhibit cyclooxygenase enzyme responsible for prostaglandin synthesis, and the compounds show higher inhibition are BT3,

Table 1: Effect of Celecoxib and test compounds (10 mg/kg) on carrageenan-induced inflammation hind paw in mice

Group	Thickness variation Δ (mm) in paw edema (% Inhibition)			
	2h	4h	6h	24h
Normal control	0.41±0.58	0.29±0.46	0.21±0.28	0.18±0.15
Negative control	2.51±0.65	2.84±0.47	3.12±0.53	1.42±0.24
Positive control (Celecoxib)	0.35±0.52*** 86%	0.42±0.56*** 85%	0.38±0.29*** 87%	0.40±0.21*** 71%
T	1.12±0.19*** 55%	1.25±0.52*** 55%	1.28±0.34*** 59%	0.85±0.18** 40%
BT	1.01±0.47*** 59%	1.14±0.87*** 60%	1.16±0.51*** 62%	0.77±0.26*** 45%
BT1	0.94±0.79*** 62%	1.05±0.22*** 63%	1.1±0.93*** 64%	0.82±0.34** 42%
BT2	0.91±0.54*** 63%	1.0±0.62*** 64%	1.06±0.44*** 66%	0.71±0.41*** 50%
BT3	0.85±0.38*** 66%	0.87±0.17*** 69%	0.72±0.34*** 77%	0.61±0.23*** 57%
BT4	0.88±0.54*** 65%	0.91±0.96*** 67%	0.78±0.17*** 75%	0.64±0.23*** 55%

Each value is the mean S.D. for six mice, *p<0.05, **p<0.01,***p<0.001 compared with normal control. Data analyzed by using one -way ANOVA followed by Dennett'

Table 3: Antinociceptive effect of Aspirin and test compounds(10 mg/kg) by hot plate method in mice.

Group	Reaction time (seconds)	Inhibition (%)
Negative control (vehicle)	3.56±1.25	-
Positive control (Aspirin)	12.61±2.18***	71.76
T	6.32±1.26***	43.67
BT	7.38±0.85***	51.76
BT1	6.65±0.74***	46.47
BT2	9.86±1.37***	63.89
BT3	9.24±0.53***	61.47
BT4	8.26±0.67***	56.90

Each value is themean± S.D. for six mice, *p<0.05, **p<0.01, ***p<0.001 compared withnormal control. Data analyzed by using one -way ANOVA followed by Dennett's test

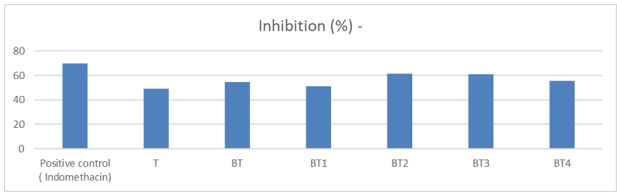


Figure 2: Antinociceptive effect of Indomethacin and test compounds (10 mg/kg) on the acetic acid-induced writhings in mice

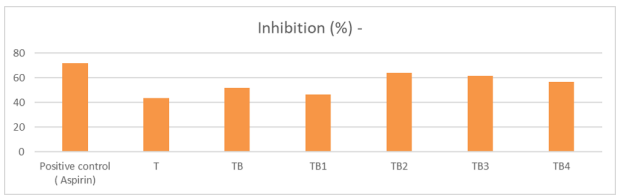


Figure 3: Antinociceptive effect of Aspirin and test compounds (10 mg/kg) by hot plate method in mice

BT4 (77%.75%) respectively after 6 hrs. (Table 1). The antinociception activity of new compounds can be verified by assessing their effects peripherally or centrally, the hot plate test used to evaluate the centrally acting analgesic effect while the acetic acid-induced writhing test used to evaluate the peripheral acting analgesic effect (Kodithuwakku *et al.*, 2013). The results presented in (Table 2) revealed that standard drug, indomethacin (10 mg/kg) significantly reduced the number of acetic acid-induced writhing in mice (69.75%) compared to the negative control group (p<0.001). All tested compounds significantly reduced the number of acetic acid-induced writhing in mice starting from parent drug (T) that give 49.19% and in derivatives give higher analgesic activity than the parent compound, but the

highest derivatives are BT2, BT3 (61.27%,61.1%) respectively. The percentage of inhibition is illustrated in Figure 2.and in the reaction time of pain responses to the thermal stimulation in hot plate test is shown in (Table 3), the dose significantly increased ($p<0.001$) the reaction times to the heat-induced pain in mice compared to the negative control group (vehicle). The positive drug, aspirin (10 mg/kg) had been markedly increased ($p<0.001$) the reaction times from 3.56 s at negative control group to 12.61 s. The percentage of inhibition is illustrated in Figure 3, writhing tests show that BT2, BT3 has a higher antinoceptive effect (61.27%,61.1%) and in hot plate method also BT2, BT3 have a higher antinoceptive effect (63.89%,61.47%).

CONCLUSION

The new thiazolidine-4-ones, BT3 and BT4 containing methoxy and trifloro-methyl group, respectively have promising anti-inflammatory activity, while BT2 and BT3 containing hydroxyl and methoxy group, respectively have promising anti-noceptive. The type of substituent in phenyl moiety had a great effect on its activity.

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Conflict of interest

There is no conflict between authors

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