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RESEARCH ARTICLE

Synthesis of some novel 2,5-disubstituted thiazolidinones from a long chain fatty acid as possible anti-inflammatory, analgesic and hydrogen peroxide scavenging agents

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Abstract

Some new decanoic acid [2,5-disubstituted-4-oxo-thiazolidin-3-yl]amides (**6a-j**) have been synthesised by the condensation of decanoic acid hydrazide with various aromatic aldehydes to yield the Schiff's bases. Cyclocondensation of the Schiff's bases with thioglycollic acid afforded 4-thiazolidinone derivatives. The structures of the newly synthesised compounds were confirmed by analytical and spectral methods. The anti-inflammatory, analgesic and antioxidant activity of the title compounds were evaluated. Compound **6j** exhibited 44.84 % inhibition of inflammation and was the most potent anti-inflammatory agent of the series whereas compound **6f** demonstrated the most potent analgesic activity (69.82% inhibition of writhing) followed by compounds **6e** and **6g**. All the synthesised compounds exhibited a potent antioxidant activity.

Keywords: 4-Thiazolidinone, capric acid, anti-inflammatory activity, analgesic activity, hydrogen peroxide scavenging activity

Introduction

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having a value as human therapeutic agents [1]. Small ring heterocycles containing nitrogen, sulphur and oxygen have been under investigation for a long time because of their important medicinal properties. The thiazolidine template is one of the privileged structural fragments in modern medicinal chemistry due to its broad pharmacological vistas [2]. The broad and potent activity profile of thiazolidinones has established them as one of the biologically most active scaffolds. A myriad spectrum of biological activities such as antimicrobial [3,4], anticonvulsant [5,6], antitubercular [7,8], anticancer [9,10], anti-inflammatory and analgesics [11,12], antipsychotic [13], anti-HIV [14,15], antidiarrheal [16], CNS and CVS [17], antioxidant [18,19], diuretic [20] and hypnotic [21] activities have been reported to be associated with thiazolidinone. Moreover, some derivatives of thiazolidin-4-ones have been used for the treatment of cardiac disease. Modification of the 2, 3 and 5 positions of thiazolidin-4-one affords antidiabetic drugs and potent aldose reductase inhibitors, which are used in the treatment of diabetic complications such as cataracts, neuropathy, nephropathy etc [22].

On the other hand, decanoic acid, also known as capric acid has been reported to exhibit several pharmacological activities such as antibacterial [23–25], antifungal [26,27], cytotoxic, cytolytic [28], and has found a place in topical antimicrobial compositions [29]. Hence, in the light of these findings, it was felt worthwhile to undertake the synthesis and biological evaluation of some novel thiazolidin-4-ones employing capric acid as a starting material.

Inflammation is part of the host response to either internal or external environmental stimuli. This response serves to counteract the insult incurred by these stimuli to the host. Chronic inflammation has been found to mediate a wide variety of diseases including cardiovascular diseases, cancer, diabetes, arthritis, Alzheimer's disease, pulmonary diseases and autoimmune diseases [30]. However, nevertheless NSAIDs are the most widely used drugs, their long term clinical employment is associated with significant side effects and their steady use determines the onset of gastrointestinal

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lesions, bleeding and nephrotoxicity. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area [31].

The 4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the fourth position. Substituents at the 2, 3 and 5 positions may be varied, but the greatest difference in structure and properties is exerted by the groups attached to the carbon atom at the second position. Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible [1].

Thus, as a part of our desire to search for biologically active heterocyclic compounds containing sulphur and nitrogen atoms, we have synthesised some novel 2,5-disubstituted thiazolidin-4-ones and evaluated them for their anti-inflammatory, analgesic and hydrogen peroxide scavenging potential.

Experimental

Chemistry

All the chemicals and solvents used in this study were procured from Merck AG (Mumbai, India), SD Fines (Mumbai, India) and Qualigens (Navi Mumbai, India). Melting points were determined on a Labindia MR-VIS visual melting range apparatus and are uncorrected. The IR spectra (Navi Mumbai, India) were obtained on a Perkin Elmer IR spectrophotometer (potassium bromide disk). ^{1}H NMR spectra (Massachusetts, USA) were recorded using a Bruker 400 spectrometer (Fallanden, Switzerland) and chemical shifts are expressed as δ (ppm) with tetramethylsilane as an internal standard. Mass spectra were recorded on Waters Q-TOF micro mass spectrometer (Manchester, UK), using electron spray ion isation method.

General procedure for the preparation of compounds

*Decanoic acid methyl ester (**2**).* A mixture of capric acid (0.25 M) (**1**) and an excess of methanol (250 mL) with 1mL of sulphuric acid was refluxed for 3–4 h. The solution was cooled and poured into crushed ice. Sodium bicarbonate was added to remove excess acid and then the product was extracted with ether. The ether layer was evaporated to obtain a thick concentrated ester (**2**).

*Decanoic acid hydrazide (**3**).* Decanoic acid methyl ester (0.2 M) (**2**) and excess of hydrazine hydrate (0.30 M) were suspended in ethanol (250 mL), refluxed for about 3 h and cooled. The solid was separated by filtration and recrystallised from ethanol to afford decanoic acid hydrazide (**3**).

*Schiff's base (**4a–i**).* A mixture of decanoic acid hydrazide (0.025 M) (**3**) and the respective aromatic aldehyde (0.025 M) was refluxed in methanol (50 mL) in the presence of small amount of glacial acetic acid for about 2 h. The mixture was cooled and poured in ice cold water. The solid thus obtained was separated by filtration and recrystallised from methanol to give the corresponding Schiff's bases (**4a**–**i**).

*2-Substituted thiazolidin-4-one (**5a–i**).* The synthesised Schiff's base (0.02M) (**4**) and the appropriate quantity of thioglycollic acid (0.02 M) in dimethyl formamide (DMF) (50 mL), containing a pinch of anhydrous $ZnCl_2$ were refluxed for about 6 h. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water and the product (**5a**–**i**) was recrystallised from ethanol.

*2, 5-Disubstituted thiazolidin-4-ones (**6a–j**).* A mixture of 2-substituted thiazolidin-4-one (0.01 M) (**5a**–**i**), the required aromatic aldehydes (0.01 M) and anhydrous sodium acetate was prepared in glacial acetic acid and refluxed for 5–7 h. After cooling, the solution was poured on to crushed ice to precipitate the product (**6a**–**j**). The product obtained was recrystallised from ethanol.

The synthetic pathway for the formation of the title compounds is depicted in Figure 1.

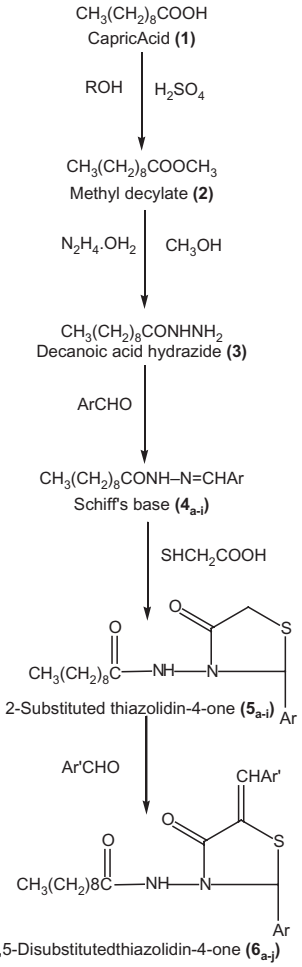
*Decanoic acid [2-(3-nitro phenyl)-5-(3-nitro benzylidene)-4-oxo-thiazolidin-3-yl]amide (**6a**).* Yield 81.32%; mp 170–173°C; IR (cm^{-1}, KBr): 3266 (N-H of CONH), 3044 (C-H *str* of aromatic), 2930–2870 (C-H *str* of alkane), 1750 (C=O of thiazolidinone), 1662 (C=O of CONH), 1610–1480 (C=C aromatic), 1544 (N-O of NO_2), 1149, 686 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.83–0.85 (3H, t, J = 6.5 Hz -CH_3), 1.26-1.47 (14 H, m, (-CH_2)$_7$), 2.01–2.08 (2 H, t, J = 7.5 Hz $COCH_2$), 5.81–5.92 (1H, s, SCHN), 6.61-6.95 (1H, s, -C=CH), 7.71–8.69 (m, 8H, Ar), 10.51–10.65 (1H, s, CONH). (M$^+$) 527. CHN Anal. Calcd. for $C_{26}H_{30}N_4O_6S$: C, 59.3; H, 5.74; N%, 10.64. Found C, 59.28; H, 5.71; N, 10.65%.

*Decanoic acid [5-(4-hydroxy-3,5-dimethoxy-benzylidene)-2-(3-nitro phenyl)- 4-oxo-thiazolidin-3-yl]amid (**6b**).* Yield 75.14%; mp 185–186°C; IR (cm^{-1}, KBr): 3295 (O-H *str* Hydroxy), 3266 (N-H of CONH), 3054 (C-H *str* of aromatic), 2930–2879 (C-H *str* of alkane), 1755 (C=O of thiazolidinone), 1660 (C=O of CONH), 1610–1485 (C=C aromatic), 1545 (N-O of NO_2), 1147, 680 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.81–0.99 (3H, t, *J* = 6.5 Hz -CH_3), 1.36–1.44 (14 H, m, (-CH_2)$_7$), 2.2–2.23 (2 H, t, *J* = 7.5 Hz $COCH_2$), 3.78 (6H, s, -OCH_3) 5.98–6.16 (1H, s, SCHN), 6.56–7.01 (1H, s, -C=CH), 7.76–8.35 (m, 6H, Ar), 8.1 (1H, s, -OH) 10.51–10.83 (1H, s, CONH). (M$^+$) 558. CHN Anal. Calcd. for $C_{28}H_{35}N_3O_7S$: C, 60.31; H, 6.33; N, 7.54%. Found C, 60.29; H, 6.31; N, 7.5%.

*Decanoic acid [2-(4-fluoro phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3-yl]amide (**6c**).* Yield 61.25%; mp 137–139°C; IR (cm^{-1}, KBr): 3264 (N-H of CONH), 3040 (C-H *str* of aromatic), 2936–2871 (C-H *str* of alkane), 1750 (C=O of thiazolidinone), 1662 (C=O of CONH), 1610–1478 (C=C aromatic), 1540 (N-O of NO_2), 1149, 685 (C-S of thiazolidinone).^{1}H NMR, δ ppm (DMSO-d_6): 0.81–0.85 (3H, t, *J* = 6.3 Hz -CH_3), 1.21–1.56 (14 H, m, (-CH_2)$_7$), 2.1–2.18 (2 H, t, *J* = 7.5 Hz $COCH_2$), 5.91–6.21 (1H, s, SCHN), 6.65–6.99 (1H, s, -C=CH), 7.78–8.71 (m, 8H, Ar), 10.55–10.61 (1H, s, CONH).). (M$^+$) 499. CHN Anal. Calcd. for $C_{26}H_{30}FN_3O_4S$: C, 62.51; H, 6.05; N, 8.41%. Found C, 62.49; H, 6.06; N, 8.4%.

Decanoic acid [2-(4-fluoro phenyl)-5-(4-hydroxy-3,5-dimethoxy-benzylidene]-4-oxo- thiazolidin-3-yl]amide

*(**6d**)*. Yield 81.34%; mp 131–134°C; IR (cm^{-1}, KBr): 3194 (O-H *str*.with C-H *str*), 3256 (N-H of CONH), 3042 (C-H *str* of aromatic), 2935–2870 (C-H *str* of alkane), 1759 (C=O of thiazolidinone), 1666 (C=O of CONH), 1615–1485(C=C aromatic), 1150, 696 (C-S of thiazolidinone).^{1}H NMR, δ ppm (DMSO-d_6): 0.85–0.93 (3H, t, J=6.5 Hz -CH_3), 1.31–1.46 (14 H, m, (-CH_2)$_7$), 2.25–2.3 (2 H, t, J=7.8 Hz $COCH_2$), 3.81 (6H, s, -OCH_3) 5.91–6.11 (1H, s, SCHN), 6.5–7.25 (1H, s, -C=CH), 7.76–8.45 (m, 6H, Ar), 8.12 (1H, s, -OH) 10.61–10.88 (1H, s, CONH). (M^+) 531. CHN Anal. Calcd. for $C_{28}H_{35}FN_2O_5S$: C, 63.37; H, 6.65; N, 5.28%. Found C, 63.34; H, 6.62; N, 5.21%.



No	-Ar	-Ar•	No	-Ar	-Ar•
6_a	O_2N	O_2N	6_f	Cl	H_3CO, HO, OCH_3
6_b	O_2N	H_3CO, HO, OCH_3	6_g	H_3CO	O_2N
6_c	F	O_2N	6_h	H_3CO	H_3CO, HO, OCH_3
6_d	F	H_3CO, HO, OCH_3	6_i	H_3CO, HO, OCH_3	O_2N
6_e	Cl	O_2N	6_j	H_3CO, HO, OCH_3	H_3CO, HO, OCH_3

Figure 1. Synthetic pathway for the formation of the title compounds.

*Decanoic acid [2-(4-chloro phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3-yl]amide (**6e**)*. Yield 81.5%; mp 175–178°C; IR (cm^{-1}, KBr): 3260 (N-H of CONH), 3046 (C-H *str* of aromatic), 2930–2871 (C-H *str* of alkane), 1757 (C=O of thiazolidinone), 1662 (C=O of CONH), 1610–1475 (C=C aromatic), 1540 (N-O of NO_2), 1149, 688 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.87–0.91 (3H, t, J=6.5 Hz -CH_3), 1.24–1.57 (14 H, m, (-CH_2)$_7$), 2.1–2.18 (2 H, t, J=7.3 Hz $COCH_2$), 5.76–5.85 (1H, s, SCHN), 6.63–6.98 (1H, s, -C=CH), 7.61–8.71 (m, 8H, Ar), 10.55–10.69 (1H, s, CONH). (M^+) 516. CHN Anal. Calcd. for $C_{26}H_{30}ClN_3O_4S$: C, 60.51; H, 5.86; N, 8.14%. Found C, 60.54; H, 5.83; N, 8.12%.

*Decanoic acid [2-(4-chloro phenyl)-5-(4-hydroxy-3,5-dimethoxy-benzylidene]-4-oxo- thiazolidin-3-yl]amide (**6f**)*. Yield 78.45%; mp 161–163°C; IR (cm^{-1}, KBr): 3190 (O-H *str*.with C-H *str*), 3245 (N-H of CONH), 3040 (C-H *str* of aromatic), 2925–2865 (C-H *str* of alkane), 1757 (C=O of thiazolidinone), 1668 (C=O of CONH), 1620–1480(C=C aromatic), 1150, 696 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.84–1.11 (3H, t, J=6.5 Hz -CH_3), 1.36–1.74 (14 H, m, (-CH_2)$_7$), 2.19–2.32 (2 H, t, J=7.5 Hz $COCH_2$), 3.81 (6H, s, -OCH_3) 5.82-–6.15 (1H, s, SCHN), 6.52–7.21 (1H, s, -C=CH), 7.26–8.55 (m, 6H, Ar), 8.14 (1H, s, -OH) 10.44–10.49 (1H, s, CONH). (M^+) 547. CHN Anal. Calcd. for $C_{28}H_{35}ClN_2O_5S$: C, 61.47; H, 6.45; N, 5.12%. Found C, 61.43; H, 6.43; N, 5.10%.

*Decanoic acid [2-(4-methoxy phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3-yl]amide (**6g**)*. Yield 60.3%; mp 124–127°C; IR (cm^{-1}, KBr): 3275 (N-H of CONH), 3042 (C-H *str* of aromatic), 2931–2874 (C-H *str* of alkane), 1760 (C=O of thiazolidinone), 1668 (C=O of CONH), 1615–1482 (C=C aromatic), 1545 (N-O of NO_2), 1140, 682 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.88–0.96 (3H, t, J=6.3 Hz -CH_3), 1.23–1.41 (14 H, m, (-CH_2)$_7$), 2.04–2.1 (2 H, t, J=7.5 Hz $COCH_2$), 3.61–3.73 (3H, s, -OCH_3) 5.85–5.96 (1H, s, SCHN), 6.69–7.05 (1H, s, -C=CH), 7.51–8.29 (m, 8H, Ar), 10.45–10.74 (1H, s, CONH). (M^+) 544. CHN Anal. Calcd. for $C_{27}H_{33}N_3O_5S$: C, 63.38; H, 6.5; N, 8.21%. Found C, 63.41; H, 6.48; N, 8.18%.

*Decanoic acid [5-(4-hydroxy-3,5-dimethoxy-benzylidene]-2-(4-methoxy phenyl)-4-oxo- thiazolidin-3-yl]amide (**6h**)*. Yield 62.75%; mp 202–203°C; IR (cm^{-1}, KBr): 3190 (O-H *str*.with C-H *str*), 3250 (N-H of CONH), 3048 (C-H *str* of aromatic), 2935–2870 (C-H *str* of alkane), 1759 (C=O of thiazolidinone), 1664 (C=O of CONH), 1615–1485(C=C aromatic), 1152, 688 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.89–1.1 (3H, t, J=6.3 Hz -CH_3), 1.26–1.43 (14 H, m, (-CH_2)$_7$), 2.25–2.29 (2 H, t, J=7.5 Hz $COCH_2$), 3.69 (9H, s, -OCH_3) 5.79–6.06 (1H, s, SCHN), 6.61–7.05 (1H, s, -C=CH), 7.70–8.38 (m, 6H, Ar), 8.08 (1H, s, -OH) 10.5–10.78 (1H, s, CONH). (M^+) 543. CHN Anal. Calcd. for $C_{29}H_{38}N_2O_6S$: C, 64.18; H, 7.06; N, 5.16%. Found C, 64.14; H, 7.09; N, 5.12%.

*Decanoic acid [2-(4-hydroxy-3,5-dimethoxy-phenyl)-5-(3-nitro-benzylidene)-4-oxo-thiazolidin-3-yl]amide (**6i**)*. Yield 70.34%; mp 221–224°C; IR (cm^{-1}, KBr): 3291 (O-H *str* Hydroxy), 3269 (N-H of CONH), 3049 (C-H *str* of aromatic),

2937–2870 (C-H *str* of alkane), 1750 (C=O of thiazolidinone), 1661 (C=O of CONH), 1618–1480 (C=C aromatic), 1540 (N-O of NO_2), 1140, 670 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.85–0.91 (3H, t, J=6.5 Hz -CH_3), 1.26–1.44 (14 H, m, (-CH_2)$_7$), 2.08–2.13 (2 H, t, J=7.8 Hz $COCH_2$), 3.74 (6H, s, -OCH_3) 5.68–5.76 (1H, s, SCHN), 6.65–7.01 (1H, s, -C=CH), 7.56–8.2 (m, 6H, Ar), 8.11 (1H, s, -OH) 10.41–10.79 (1H, s, CONH). (M^+) 558. CHN Anal. Calcd. for $C_{28}H_{35}N_3O_7S$: C, 60.31; H, 6.33; N, 7.54%. Found C, 60.19; H, 6.3; N, 7.56%.

*Decanoic acid [5-(4-hydroxy-3,5-dimethoxy-benzylidene]-2 -(4-hydroxy-3,5-dimethoxy-phenyl)-4-oxo- thiazolidin-3-yl] amide (**6j**).* Yield 67.7%; mp 236–238°C; IR (cm^{-1}, KBr): 3194 (O-H *str.*with C-H *str*), 3258 (N-H of CONH), 3040 (C-H *str* of aromatic), 2945–2868 (C-H *str* of alkane), 1754 (C=O of thiazolidinone), 1661 (C=O of CONH), 1621–1492(C=C aromatic), 1150, 695 (C-S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.82–0.91 (3H, t, J=6.3 Hz -CH_3), 1.30–1.44 (14 H, m, (-CH_2)$_7$), 2.21–2.25 (2 H, t, J=7.8 Hz $COCH_2$), 3.71–3.82 (12H, s, -OCH_3) 5.69–5.91 (1H, s, SCHN), 6.56–7.01 (1H, s, -C=CH), 7.72–8.3 (m, 6H, Ar), 8.05 (1H, s, -OH) 10.32–10.67 (1H, s, CONH). (M^+) 589. CHN Anal. Calcd. for $C_{30}H_{40}N_2O_8S$ C: 61.2; H, 6.85; N, 4.76%. Found C, 61.17; H, 6.82; N, 4.74%.

Pharmacological Screening

Methods

Wistar rats weighing 180–250 g and Swiss albino mice weighing 25–30 g were housed in a room maintained under controlled room temperature of 22 ± 2°C, with a relative humidity 60–70% and provided with food and water *ad libitum*. All the experimental procedures and protocols used in the study were reviewed by the Institutional Animal Ethics Committee (Registration No 563/02/a/CPCSEA) and were in accordance with the guidelines of the CPCSEA, Ministry of Forests and Environment, Government of India. The animals were deprived of food for 24 h before experimentation but allowed free access to water throughout.

Anti-inflammatory activity

The anti-inflammatory activity of the synthesised compounds using the carrageenan-induced paw oedema test was studied according to the method of Winter et al. [32]. The animals were divided into different groups each consisting of 6 rats. The control group received normal saline: tween 80 (95:5), the standard group received the standard drug diclofenac sodium 50 mg/Kg body weight and the test groups received the synthesised compounds at a dose of 50 mg/Kg body weight. Thirty minutes after the administration of the test and standard drugs, 0.1 mL of 1% w/v of carrageenan suspension in normal saline was injected into all the animals into the left hind paw (plantar region). The paw volume, up to the tibiotarsal articulation, was measured using a plethysmometer (Model 7140, Ugo Basile, Italy). Results of the anti-inflammatory screening are presented in Table 1.

The percentage protection of oedema (inhibition of inflammation) was calculated according to the formula, percentage anti-inflammatory activity = 100 × (1–Vt/Vc) where Vt and Vc are the volume of oedema for the test compounds and control groups, respectively. It is pertinent to mention here that maximum activity was obtained at 90 min and thus the percentage inhibition was calculated at 90 min.

Analgesic activity

The analgesic activity was measured against chemical stimuli. For analgesic activity, the animals were divided into groups consisting of six mice each. The control group received normal saline: tween 80 (95:5). The standard group received nimesulide 4 mg/Kg body weight and the test groups received the synthetic compounds at a dose of 50 mg/Kg body weight. Thirty minutes later, nociception was induced by an intraperitoneal (IP) injection of acetic acid (1%), 0.1 mL/10 g. The numbers of stretching or writhing movements were recorded from 5 min to 15 min. The results of this study have been summarised in Table 1. The percentage protection was calculated by

Table 1. Anti-inflammatory and analgesic activity of the synthesised compounds.

	Anti-inflammatory activity			Analgesic activity		
Compound	Dose mg/Kg	Oedema (ΔT) (mm) ± SEM	Activity (%) (at 90 min)	Dose mg/Kg	Mean number of writhing ± SEM	Inhibition (%)
6a	50	0.61 ± 0.05*	39.79	50	15.6 ± 1**	45.26
6b	50	0.72 ± 0.08	27.28	50	14.1 ± 1**	50.53
6c	50	0.8 ± 0.01	17.53	50	16.6 ± 0.6**	41.75
6d	50	0.65 ± 0.02	33.66	50	13.3 ± 1.7**	53.3
6e	50	0.57 ± 0.01**	41.84	50	11.5 ± 1.4**	59.65
6f	50	0.59 ± 0.05*	39.8	50	8.6 ± 1.3**	69.82
6g	50	0.75 ± 0.06	24.25	50	11.5 ± 1.4**	59.65
6h	50	0.73 ± 0.06	25.52	50	12.5 ± 2.**	56.14
6i	50	0.6 ± 0.04*	38.78	50	15.1 ± 0.9**	47.01
6j	50	0.57 ± 0.01**	44.84	50	13.1 ± 0.9**	54.03
Diclofenac sodium	50	0.49 ± 0.09**	51.51	-	-	-
Nimesulide	-	-	-	4	13.1 ± 0.9**	54.03

Values of paw thickness are mean ± SEM from 6 animals in each group, p<0.05, **p<0.01, compared with control

the following formula: Percentage Protection = 100 – (No. of writhes in test/No. of writhes in control) × 100.

Hydrogen peroxide scavenging activity

A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4). Different concentrations (100, 300 and 500 μg/mL) of all the synthesised compounds were added to a hydrogen peroxide solution (0.6 mL, 40 mM). The absorbance of the hydrogen peroxide at 230 nm was determined after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage scavenging of hydrogen peroxide of the synthesised compounds and the standard compounds were calculated using the following formula: Percentage scavenging $[H_2O_2] = [(A_0\text{-}A_1)/A_0] \times 100$, where A_0 was the absorbance of the blank, and A_1 was the absorbance in the presence of the sample and standards [33]. The percentage scavenging of hydrogen peroxide by the synthesised compounds at 100, 300 and 500 μg/mL concentrations were observed and the results are summarised in Table 2.

Results and discussion

In this study ten novel compounds incorporating the scaffold of thiazolidinone have been synthesised and their anti-inflammatory, analgesic and antioxidant activities were evaluated. At the first stage, Schiff's bases of decanoic acid hydrazide and aromatic aldehydes were prepared. Further, reaction of these Schiff's bases with mercapto acid i.e. thioglycollic acid in DMF and in presence of a small amount of $ZnCl_2$ yielded the corresponding 2-substituted thiazolidin-4-ones (**5a**–**i**). All the 2-substituted thiazolidin-4-ones were recrystallised and the purity of the compounds was ascertained by TLC using different solvent systems and iodine vapours as visualising agents. Finally, the compounds (**5a**–**i**) were refluxed with suitable aromatic aldehydes in the presence of sodium acetate and glacial acetic acid for 5–7 h to yield the title compounds i.e. 2,5-disubstituted thiazolidin-4-ones (**6a**–**j**). The structures of all the newly synthesised compounds were confirmed by suitable spectroscopic methods such as IR and NMR. In the IR spectra, bands in the 3275–3245 and 1760–1750 cm^{-1} regions attributed to N-H and C=O (of the thiazolidione ring) stretching of the compounds (**6a**–**j**) respectively. In the ^1H NMR spectra of the compound 2-substituted thiazolidinones (**5**), the lack of a CH=N signal at δ 10.01 provided confirmatory evidence for ring closure from the Schiff's bases. The presence of a peak at δ 7.87 confirmed the formation of the 1H singlet of –SCHN. Moreover, the disappearance of the peaks in the spectra of **6a**–**j** at δ 2.08–3.02 indicated an absence of the two singlet hydrogens of SCH_2 which were present in the 2-substituted thiazolidinones. The ^1H NMR spectrum showed a singlet at 0.8–0.9 integrating for the three protons of the CH_3 group and a multiplet at δ 7.78 integrating for the eight aromatic protons.

Table 2. Hydrogen peroxide scavenging activity of synthesised compounds.

	Scavenging of hydrogen peroxide at different concentrations (%)		
Compound	100 μg	300 μg	500 μg
$\mathbf{6}_a$	47.52	55.46	54.18
$\mathbf{6}_b$	41.03	43.06	44.14
$\mathbf{6}_c$	40	39.72	39.72
$\mathbf{6}_d$	40	39.57	39.5
$\mathbf{6}_e$	39.57	41.62	41.98
$\mathbf{6}_f$	45.82	39.72	39.57
$\mathbf{6}_g$	51.21	43.12	39.57
$\mathbf{6}_h$	43.03	43.96	44.5
$\mathbf{6}_i$	42.98	39.72	39.57
$\mathbf{6}_j$	53.62	54.18	53.76
BHA	64.6	66.4	67.2
Ascorbic Acid	49.3	53	56

The anti-inflammatory activity of the synthesised compounds was determined using the carrageenan-induced paw oedema method. All the compounds exhibited moderate to significant anti-inflammatory activity. Compound **6j** with its electron releasing group substituents (four methoxy and two hydroxyl groups) was the most active compound of the series with a percentage activity of 44.84 (p value <0.01). Compound **6c**, bearing two electron withdrawing groups i.e. with fluoro and nitro functionalities, was found to be the least potent anti-inflammatory agent. However, no direct correlation could be justified between the nature of functionality and the anti-inflammatory activity of the compounds.

Analgesic screening was performed using the acetic acid-induced abdominal writhing test using Swiss albino mice. For the abdominal writhing test, nociception was induced by an intraperitoneal (IP) injection of acetic acid. Nimesulide was used as the standard drug. All the compounds exhibited significant analgesic activities. Compound **6f** demonstrated the most potent activity with 69.82% (p value < 0.01) inhibition of writhing. It was followed by compounds **6e** and **6g** with an analgesic activity of 59.65% (p value < 0.01).The standard drug nimesulide exhibited 54.03% inhibition at a dose of 4 mg/kg.

The evaluation of antioxidant activities was carried out by the method of scavenging of hydrogen peroxide. For this purpose, a solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4) and different concentrations (100, 300 and 500 μg/mL) of all the synthesised compound were added to a hydrogen peroxide solution (0.6 mL, 40 mM). The absorbance of hydrogen peroxide at 230 nm was determined after 10 min. The percentage scavenging of hydrogen peroxide of synthesised compounds and standard compound were calculated. All the synthesised compounds exhibited potent hydrogen peroxide scavenging activities. Compound **6a** with two nitro groups was the most active with scavenging of hydrogen peroxide of 54.18 at 500 microgram per mL concentration, followed by compound **6j** having four methoxy and two hydroxyl substitutions. Hence it was concluded that the presence of similar functionalities at both the 2 and 5 positions of the thiazolidinone ring imparts an improved hydrogen peroxide scavenging activity when compared to the different

substitutions. The same correlation was found to be true in the case of the anti-inflammatory activity where the presence of similar substituents at both these positions (2 and 5) of the thiazolidinone ring led to anincreased activity compared to the different substituents. However, this correlation could not be observed in the analgesic screening results where compound **6f**, bearing chloro and 4-hydroxy-3,5-dimethoxy groups, was found to be the most active with 69.82 % inhibition of writhing. It was followed by compounds **6e** and **6g** with 59.65 % inhibition.

Conclusion

In conclusion, the present investigation has described the preparation of a series of novel thiazolidinones and the evaluation of their potential for biological activities such as anti-inflammatory, analgesic and hydrogen peroxide scavenging activity. The synthesised compounds exhibited moderate anti-inflammatory and analgesic activities *in vivo* and significant hydrogen peroxide scavenging activities *in vitro*.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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