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ORIGINAL ARTICLE

Thiazolidin-4-one and hydrazone derivatives of capric acid as possible anti-inflammatory, analgesic and hydrogen peroxide-scavenging agents

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Abstract

Starting from capric acid, hydrazone and thiazolidin-4-one derivatives have been synthesized in the present investigation. Decanoic acid hydrazide was reacted appropriately to yield hydrazones, which were then cyclized to yield the corresponding thiazolidin-4-ones. The structures of the newly synthesized compounds were confirmed by analytical and spectral methods. Anti-inflammatory, analgesic, and hydrogen peroxide-scavenging activity of the title compounds were evaluated. Among synthesized compounds, 2-hydroxyphenyl thiazolidinone with 44.90% inhibition of inflammation was the most potent anti-inflammatory agent. Similarly, 4-methoxybenzylidine hydrazide with 64.90% inhibition of writhing was observed to be the most potent analgesic agent of the synthesized compounds. All the synthesized compounds exhibited potent hydrogen peroxide-scavenging activity.

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

Introduction

In the recent past, there has been a considerable interest and enthusiasm in developing novel and small heterocyclic moieties possessing significant biological activities. The presence of thiazole moiety in the structure of several naturally occurring molecules with important antibiotic, immunosuppressive, and antitumour activities has been well known for long.[1] Thiazolidinone derivatives have been reported to depict excellent anticancer,[2,3] anti-HIV,[4] antitubercular,[5] anti-inflammatory and analgesic,[6–8] antioxidant,[9] antimicrobial,[10–12] FSH agonists,[13] CFTR inhibitory[14] activities. Moreover, hydrazones have been found to possess many biological actions such as antibacterial, anticonvulsant, anti-inflammatory, antiprotozoal, and antitubercular. Therefore, synthesis, structure, and biological activities of novel hydrazones prepared from fatty acid hydrazides has been the focus of many researchers.[15,16]

Inflammation is a multifactorial process. It reflects the response of organisms to various stimuli and is related to many disorders such as arthritis, asthma, and psoriasis, which require repeated or prolonged treatment.[17,18] Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain, fever, and inflammation.[19,20] Generally, undesired gastrointestinal (GI) irritation[21] and other side effects limit clinical utility of most of the conventional NSAIDs. Therefore, discovery of new and safe anti-inflammatory agents represents a challenging goal to medicinal chemists. Recently, we have reported synthesis of novel 2,5-disubstituted thiazolidinone derivatives from capric acid with promising anti-inflammatory, analgesic, and hydrogen peroxide-scavenging activities.[22] In the lights of these facts, we anticipated that the 2-substituted thiazolidinones and hydrazones derived from capric acid may also possess commendable biological potential. Thus, it was felt worthwhile to undertake biological evaluation of these compounds and determine their possible pharmacological significance. Hence, in the present work, we report the synthesis with chemical

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characterization and biological activities of these hydrazones and 2-substituted thiazolidin-4-ones.

Materials and methods

Chemistry

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

General procedure for the preparation of compounds

Synthesis of methyl ester of capric acid (**2**). A mixture of decanoic acid (0.25 M) (**1**) and excess of methanol (250 mL) with 1 mL 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 product was extracted with ether. The ether layer was evaporated to get a thick concentrated ester (**2**).

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

Hydrazones ($\mathbf{4_{a-i}}$). A mixture of decanoic acid hydrazide (0.025 M) (**3**) and 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 recrystallized from methanol to give the corresponding hydrazone ($\mathbf{4_{a-i}}$).

2-Substituted thiazolidin-4-one ($\mathbf{5_{a-i}}$). Synthesized hydrazone (0.02 M) (**4**) and appropriate quantity of thioglycolic 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 ($\mathbf{5_{a-i}}$) was recrystallized from ethanol.

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

Decanoic acid benzylidene-hydrazide ($\mathbf{4_a}$). Yield 85.33%; m.p. 75–77°C; IR (cm^{-1}, KBr): 3256 (N–H of –CONH), 3020 (C–H *str* of aromatic), 2910-2870 (C–H *str* of alkane), 1660 (C=O of –CONH), 1610-1490 (C=C aromatic) 1449 (C=N); ^{1}H NMR, δ ppm ($CDCl_3$): 0.83 (3H, t, $-CH_3$), 1.24–1.58 (14H, m, $(CH_2)_7$), 2.18–2.59 (2H, t, $COCH_2$), 7.38–7.63 (5H, m, aromatic proton), 9.97 (1H, s, NCH), 11.02–11.14 (H, s, NH).

Decanoic acid (2-nitro benzylidene)hydrazide ($\mathbf{4_b}$). Yield 67.33%; m.p. 101–102°C; IR (cm^{-1}, KBr): 3257 (N–H of –CONH), 3045 (C–H *str* of aromatic), 2982-2845 (C–H *str* of alkane), 1650 (C=O of –CONH), 1610-1490 (C=C aromatic), 1552 (N–O of $-NO_2$) 1455 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.81 (3H, t, $-CH_3$), 1.22–1.57 (14H, m, $(-CH_2)_7$), 2.21–2.48 (2H, t, $COCH_2$), 7.68–8.65 (4H, m, aromatic proton), 10.12 (1H, s, NCH), 10.54–10.98 (H, s, NH).

Decanoic acid (4-chloro benzylidene)hydrazide ($\mathbf{4_c}$). Yield 79.73%; m.p. 107–108°C; IR (cm^{-1}, KBr): 3255 (N–H of –CONH), 3020 (C–H *str* of aromatic), 2910-2865 (C–H *str* of alkane), 1656 (C=O of –CONH), 1610-1490 (C=C aromatic) 1458 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.83 (3H, t, $-CH_3$), 1.23–1.59 (14H, m, $(-CH_2)_7$), 2.2–2.49 (2H, t, $COCH_2$), 7.60–8.56 (4H, m, aromatic proton), 10.02 (1H, s, NCH), 11.01–11.21 (H, s, NH).

Decanoic acid (4-fluoro benzylidene)hydrazide ($\mathbf{4_d}$). Yield 87.06%; m.p. 94–96°C; IR (cm^{-1}, KBr): 3258 (N–H of –CONH), 3050 (C–H *str* of aromatic), 2920-2880 (C–H *str* of alkane), 1650 (C=O of –CONH), 1610-1490 (C=C aromatic) 1459 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.87 (3H, t, $-CH_3$), 1.37–1.86 (14H, m, $(-CH_2)_7$), 2.84–2.87 (2H, t, $COCH_2$), 7.37–7.80 (4H, m, aromatic proton), 8.13–9.85 (1H, s, NCH), 10.78–11.03 (H, s, NH).

Decanoic acid (4-methoxy benzylidene)hydrazide ($\mathbf{4_e}$). Yield 89.55%; m.p. 75–78°C; IR (cm^{-1}, KBr): 3262 (N–H of –CONH), 3040 (C–H *str* of aromatic), 2925-2880 (C–H *str* of alkane), 1660 (C=O of –CONH), 1615-1492 (C=C aromatic) 1458 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.83 (3H, t, $-CH_3$), 1.24–1.57 (14H, m, $(-CH_2)_7$), 2.15–2.59 (2H, t, $COCH_2$), 3.22–3.77 (3H, t, OCH_3), 6.94–7.56 (4H, m, aromatic proton), 9.73 (1H, s, NCH), 10.99–11.18 (H, s, NH).

Decanoic acid (3-nitro benzylidene)hydrazide ($\mathbf{4_f}$). Yield 76.43%; m.p. 123–125°C; IR (cm^{-1}, KBr): 3255 (N–H of –CONH), 3046 (C–H *str* of aromatic), 2980-2840 (C–H *str* of alkane), 1655 (C=O of –CONH), 1610-1492 (C=C aromatic), 1550 (N–O of $-NO_2$) 1465 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.85 (3H, t, $-CH_3$), 1.38–1.85 (14H, m, $(-CH_2)_7$), 2.84–2.88 (2H, t, $COCH_2$), 7.18–7.37 (4H, m, aromatic proton), 8.55 (1H, s, NCH), 10.87–11.05 (H, s, NH).

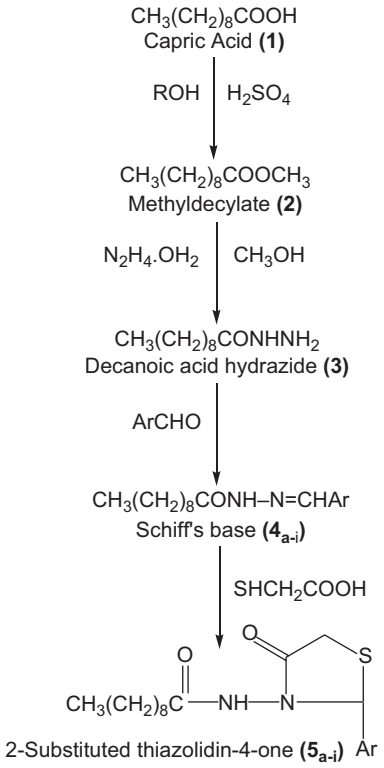
Decanoic acid (2-hydroxy benzylidene)hydrazide ($\mathbf{4_g}$). Yield 76.55%; m.p. 106–110°C; IR (cm^{-1}, KBr): 3250 (N–H of –CONH), 3195 (O–H *str*), 3059 (C–H *str* of aromatic), 2910-2876 (C–H *str* of alkane), 1656 (C=O of –CONH), 1610-1490 (C=C aromatic) 1457 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.83 (3H, t, $-CH_3$), 1.23–1.59 (14H, m, $(-CH_2)_7$), 2.2-2.49 (2H, t, $COCH_2$), 7.60–8.56 (4H, m, aromatic proton), 8.04 (1H. s, –OH), 10.02 (1H, s, NCH), 11.03–11.26 (H, s, NH).

Decanoic acid (4-dimethylamino benzylidene) hydrazide ($\mathbf{4_h}$). Yield 81.20%; m.p. 115–118°C; IR (cm^{-1}, KBr): 3255 (N–H of –CONH), 3025 (C–H *str* of aromatic), 2910-2875 (C–H *str* of alkane), 1660 (C=O of –CONH), 1610-1490 (C=C aromatic) 1447 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.84 (3H, t, $-CH_3$), 1.24–1.56 (14H, m, $(-CH_2)_7$),

2.13–2.15 (2H, t, $COCH_2$), 3.12 (6H, s, N–$(CH_3)_2$), 6.69–7.46 (4H, m, aromatic proton), 8.19 (1H, s, NCH), 10.76–10.88 (H, s, NH).

Decanoic acid (4-hydroxy-3,5-dimethoxy benzylidene) hydrazide (**4**$_i$). Yield 75.51%; m.p. 134–136°C; IR (cm^{-1}, KBr): 3250 (N–H of –CONH), 3192 (O–H *str*), 3051 (C–H *str* of aromatic), 2910-2876 (C–H *str* of alkane), 1656 (C=O of –CONH), 1610-1497 (C=C aromatic) 1450 (C=N). ^{1}H NMR, δ ppm ($CDCl_3$): 0.81 (3H, t, $-CH_3$), 1.23–1.55 (14H, m, $(-CH_2)_7$), 2.20–2.41 (2H, t, $COCH_2$), 3.75 (6H, s, $-OCH_3$), 7.76–8.26 (2H, m, aromatic proton), 8.05 (1H, s, –OH), 10.01 (1H, s, NCH), 11.03–11.26 (H, s, NH).

Decanoic acid (4-oxo-2-phenyl-thiazolidin-3yl)amide (**5**$_a$). Yield 84.01%; m.p. 160–165°C; IR (cm^{-1}, KBr): 3251 (N–H of –CONH), 3025 (C–H *str* of aromatic), 2910-2870 (C–H *str* of alkane), 1755 (C=O of thiazolidinone), 1650 (C=O of CONH), 1614-1485 (C=C aromatic), 1144, 690 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.85–0.88 (3H, t, $-CH_3$), 1.25–1.43 (14H, m, $(-CH_2)_7$), 1.70–1.77 (2H, t, $COCH_2$), 2.08–2.11 (2H, s, SCH_2),



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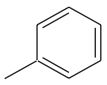
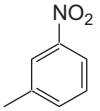
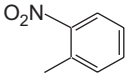
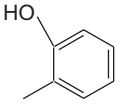
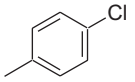
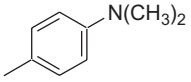
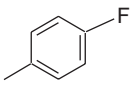
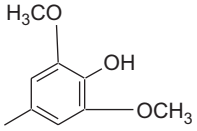
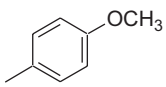
4/5$_a$		4/5$_f$	
4/5$_b$		4/5$_g$	
4/5$_c$		4/5$_h$	
4/5$_d$		4/5$_i$	
4/5$_e$			

Figure 1. Synthetic protocol for the preparation of hydrazones and thiazolidinones.

7.26–7.41 (5H, m, aromatic proton), 7.87 (1H, s, SCHN), 10.41 (1H, s, NH).

Decanoic acid [4-oxo-2-(2-nitro phenyl)-thiazolidin-3yl]amide (**5**$_b$). Yield 70.34%; m.p. 145–150°C; IR (cm^{-1}, KBr): 3260 (N–H of CONH), 3040 (C–H *str* of aromatic), 2930-2870 (C–H *str* of alkane), 1757 (C=O of thiazolidinone), 1665 (C=O of CONH), 1610-1485(C=C aromatic), 1544 (N–O of NO_2), 1149, 696 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.84–0.86 (3H, t, –CH_3), 1.26–1.45 (14H, m, (–CH_2)$_7$), 1.70–1.76 (2H, t, $COCH_2$), 2.08–2.11 (2H, s, SCH_2), 8.84–7.45 (m, 4H, aromatic proton), 7.87 (1H, s, SCHN), 10.41 (1H, s, NH).

Decanoic acid [4-oxo-2-(4-chloro phenyl)-thiazolidin-3yl]amide (**5**$_c$). Yield 78.46%; m.p. 170–172°C; IR (cm^{-1}, KBr): 3252 (N–H of CONH), 3058 (C–H *str* of aromatic), 2919-2848 (C–H *str* of alkane), 1756 (C=O of thiazolidinone), 1653 (C=O of CONH), 1610-1485 (C=C aromatic), 1147, 695 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.87–0.89 (3H, t, CH_3), 1.25–1.41 [14H, m, (–CH_2)$_7$], 1.69–1.76 (2H, t, –$COCH_2$), 2.73–2.77 (2H, s, –SCH_2), 7.34–7.61 (4H, m, aromatic proton), 7.86 (1H, s, –SCHN), 10.77 (1H, s, –NH).

Decanoic acid [4-oxo-2-(4-fluoro phenyl)-thiazolidin-3yl]amide (**5**$_d$). Yield 78.42%; m.p. 175–176°C; IR (cm^{-1}, KBr): 3255 (N–H of CONHN), 3050 (C–H *str* of aromatic), 2910-2868 (C–H *str* of alkane), 1752 (C=O of thiazolidinone), 1660 (C=O of –CONH), 1615-1490 (C=C aromatic), 1145, 692 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.85–0.87 (3H, t, CH_3), 1.25–1.39 [14H, m, –CH_2)$_7$], 1.69–1.76 (2H, t, –$COCH_2$), 2.75–2.79 (2H, s, –SCH_2), 7.64–7.85 (4H, m, aromatic proton), 7.80 (1H, s, –SCHN), 10.71 (1H, s, –NH).

Decanoic acid [4-oxo-2-(4-methoxy phenyl)-thiazolidin-3yl]amide (**5**$_e$). Yield 78.18%; m.p. 226–228°C; IR (cm^{-1}, KBr): 3250 (N–H of –CONH), 3050 (C–H *str* of aromatic), 2918-2852 (C–H *str* of alkane), 1760 (C=O of thiazolidinone), 1659 (C=O of CONH), 1485-1610 (C=C aromatic), 1150, 695 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.87–0.89 (3H, t, –CH_3), 1.16–1.29 [14H, m, (CH_2)$_7$], 1.60–1.92 (2H, t, –$COCH_2$), 2.30–3.02 (2H, s, –SCH_2), 3.63 (3H, s, –OCH_3), 7.10–7.41 (4H, m, aromatic proton), 7.73 (1H, s, –SCHN), 9.57 (1H, s, –NH).

Decanoic acid [4-oxo-2-(3-nitro phenyl)-thiazolidin-3yl]amide (**5**$_f$). Yield 74.41%; m.p. 203–208°C; IR (cm^{-1}, KBr): 3260 (N–H of –CONH), 3042 (C–H *str* of aromatic), 2930-2860 (C–H *str* of alkane), 1757 (C=O of thiazolidinone), 1665 (C=O of CONH), 1610-1485 (C=C aromatic), 1544 (N–O of NO_2), 1150, 696 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.84–0.86 (3H, t, –CH_3), 1.26–1.45 (14H, m, (–CH_2)$_7$), 1.70–1.76 (2H, t, $COCH_2$), 2.08–2.11 (2H, s, SCH_2), 8.84–7.45 (m, 4H, aromatic proton), 7.87 (1H, s, SCHN), 10.41 (1H, s, NH).

Decanoicacid[4-oxo-2-(2-hydroxyphenyl)-thiazolidin-3yl]amide (**5**$_g$). Yield 63.21%; m.p. 199–201°C; IR (cm^{-1}, KBr): 3265 (N–H of CONH), 3196 (O–H *str*), 3050 (C–H *str* of aromatic), 2925-2860 (C–H *str* of alkane), 1760 (C=O of thiazolidinone), 1665 (C=O of CONH), 1610-1485(C=C aromatic), 1149, 696 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.87–0.89 (3H, t, –CH_3), 1.16–1.29 [14H, m, (CH_2)$_7$], 1.60–1.92 (2H, t, –$COCH_2$), 2.30–3.02 (2H, s, –SCH_2), 6.89–7.26 (4H, m, aromatic proton), 7.73 (1H, s, –SCHN), 8.04–8.73 (1H, s, –OH), 9.57 (1H, s, –NH).

Decanoic acid [4-oxo-2-(4-N dimethyl amino phenyl)-thiazolidin-3yl]amide (**5**$_h$). Yield 65.16%; m.p. 150–153°C; IR (cm^{-1}, KBr): 3261 (N–H of CONH), 3020 (C–H *str* of aromatic), 2914-2872 (C–H *str* of alkane), 1760 (C=O of thiazolidinone), 1655 (C=O of CONH), 1614-1485 (C=C aromatic), 1144, 690 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.85–0.88 (3H, t, –CH_3), 1.25–1.43 (14H, m, (–CH_2)$_7$), 1.70–1.77 (2H, t, $COCH_2$), 2.08–2.11 (2H, s, SCH_2), 3.10 (6H, s, N–(CH_3)$_2$), 7.26–7.41 (H, m, aromatic proton), 7.87 (1H, s, SCHN), 10.41 (1H, s, NH).

Decanoic acid [4-oxo-2-(4-hydroxy-3,5-dimethoxy phenyl)-thiazolidin-3yl]amide (**5**$_i$). Yield 66.11%; m.p. 248–251°C; IR (cm^{-1}, KBr): IR (cm^{-1}, KBr): 3265 (N–H of CONH), 3190 (O–H *str*), 3040 (C–H *str* of aromatic), 2930-2865 (C–H *str* of alkane), 1760 (C=O of thiazolidinone), 1668 (C=O of CONH), 1615–1480 (C=C aromatic), 1149, 696 (C–S of thiazolidinone). ^{1}H NMR, δ ppm (DMSO-d_6): 0.87–0.89 (3H, t, –CH_3), 1.16–1.30 [14H, m, (CH_2)$_7$], 1.62–1.95 (2H, t, –$COCH_2$), 2.30–3.02 (2H, s, –SCH_2), 3.71 (6H, s, –OCH_3), 7.10–7.41 (H, m, aromatic proton), 8.01 (1H, s, –OH), 7.73 (1H, s, –SCHN), 9.57 (1H, s, –NH).

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 22 ± 2°C, 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 (Regn. 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 synthesized compounds using carrageenan-induced paw oedema was studied according to method of Winter et al.[23] The animals were divided into different groups each consisting of six rats. Control group received normal saline:Tween 80 (95:5), the standard group received standard drug diclofenac sodium 50 mg/kg body weight, and the test groups received the synthesized compounds at the dose of 50 mg/kg body weight. Thirty minutes after administration of test and standard drugs, 0.1 mL of 1% w/v of carrageenan suspension in normal saline was injected to all animals in 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 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 = $100 \times (1 - V_t/V_c)$ where V_t and V_c are the volume of oedema in test compounds and control groups, respectively. It is pertinent to mention here that maximum activity was obtained at 90 min and thus percentage inhibition was calculated at 90 min.

Analgesic activity

The analgesic activity was measured against chemical stimulus. 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 diclofenac sodium 50 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%), 0.1 mL/10 g. The number of stretching or writhing was recorded from 5 to 15 min. The percentage protection was calculated by following formula:

$$\text{Percentage protection} = 100 - (\text{No. of writhes in test}/\text{No. of writhes in control}) \times 100.$$

Results of this study have been summarized in Table 2.

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 synthesized compounds 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 against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage scavenging of hydrogen peroxide of synthesized compounds and standard compounds were calculated using the following formula:

$$\text{Percentage scavenging}[H_2O_2] = [(A_0 - A_1)/A_0] \times 100$$

where A_0 was the absorbance of the blank, and A_1 was the absorbance in the presence of the sample and standards.[24] Percentage scavenging of hydrogen peroxide by synthesized compounds at 100, 300, and 500 µg/mL concentration was observed. Results are summarized in Table 3.

Results and discussion

Synthetic chemistry

In the present investigation, synthesis of hydrazones and thiazolidinones has been carried out starting from a long chain fatty acid that is capric acid. Hydrazide (**3**) was obtained by reaction of the methyl ester of capric acid (**2**) with hydrazine hydrate and was further reacted with different aromatic aldehydes to yield corresponding hydrazones ($\mathbf{4}_{a-i}$). The hydrazones thus obtained were then reacted with mercapto acid in DMF and in presence of small amount of $ZnCl_2$ to yield 2-substituted thiazolidin-4-ones ($\mathbf{5}_{a-i}$). Synthesis of hydrazones and thiazolidinones was confirmed by spectral analysis. IR

Table 1. Anti-inflammatory activity of the synthesized compounds.

	Anti-inflammatory activity		
Compound	Dose (mg/kg)	Oedema (ΔT) (mm) ± SEM	Activity (% at 90 min)
$\mathbf{4}_a$	50	0.71 ± 0.03	28.29
$\mathbf{4}_b$	50	0.72 ± 0.07**	27.28
$\mathbf{4}_c$	50	0.75 ± 0.09**	24.25
$\mathbf{4}_d$	50	0.75 ± 0.06**	24.25
$\mathbf{4}_e$	50	0.68 ± 0.01**	31.32
$\mathbf{4}_f$	50	0.70 ± 0.01**	30.30
$\mathbf{4}_g$	50	0.55 ± 0.06**	44.70
$\mathbf{4}_h$	50	0.61 ± 0.05	37.76
$\mathbf{4}_i$	50	0.77 ± 0.09**	21.43
$\mathbf{5}_a$	50	0.60 ± 0.03	38.78
$\mathbf{5}_b$	50	0.65 ± 0.01**	33.68
$\mathbf{5}_c$	50	0.73 ± 0.04**	26.52
$\mathbf{5}_d$	50	0.68 ± 0.05**	31.32
$\mathbf{5}_e$	50	0.57 ± 0.02**	41.84
$\mathbf{5}_f$	50	0.70 ± 0.05**	30.30
$\mathbf{5}_g$	50	0.54 ± 0.04**	44.90
$\mathbf{5}_h$	50	0.55 ± 0.06**	44.70
$\mathbf{5}_i$	50	0.69 ± 0.08**	30.28
Diclofenac sodium	50	0.49 ± 0.09**	51.51

Values of paw thickness are mean ± SEM from six animals in each group, $P < 0.05$, $^{**}P < 0.01$, compared with control.

Table 2. Analgesic activity of synthesized compounds.

	Abdominal writhing method		
Compound	Dose (mg/kg)	Mean number of writhing ± SEM	Inhibition (%)
$\mathbf{4}_a$	50	14.0 ± 0.6**	50.87
$\mathbf{4}_b$	50	16.20 ± 1.18**	43.15
$\mathbf{4}_c$	50	10.60 ± 0.75**	62.80
$\mathbf{4}_d$	50	10.60 ± 0.92**	62.80
$\mathbf{4}_e$	50	10.00 ± 0.63**	64.90
$\mathbf{4}_f$	50	17.8 ± 0.4	37.54
$\mathbf{4}_g$	50	16.8 ± 0.4**	41.05
$\mathbf{4}_h$	50	13.1 ± 0.7	54.03
$\mathbf{4}_i$	50	17.50 ± 0.76**	38.60
$\mathbf{5}_a$	50	14.40 ± 0.90**	49.50
$\mathbf{5}_b$	50	17.10 ± 0.21**	40.22
$\mathbf{5}_c$	50	11.03 ± 0.97**	61.40
$\mathbf{5}_d$	50	15.70 ± 0.69**	47.36
$\mathbf{5}_e$	50	13.50 ± 0.56**	52.63
$\mathbf{5}_f$	50	14.10 ± 0.92**	50.87
$\mathbf{5}_g$	50	10.8 ± 1.0**	62.10
$\mathbf{5}_h$	50	13.6 ± 1.3**	52.28
$\mathbf{5}_i$	50	12.06 ± 0.75**	57.89
Diclofenac sodium	50	8.90 ± 0.28**	69.80

Values are mean ± SEM from six animals in each group, $P < 0.05$, $^{**}P < 0.01$, compared with control.

spectra of hydrazones ($\mathbf{4}_{a-i}$) depicted bands in the region 3262-3250, 1660-1650, and 1465-1447 attributed to N–H of CONH, C=O of CONH, and C=N stretching of compounds respectively. In the IR spectra of 2-substituted thiazolidinones bands of 3265-3250, 1760-1752, 1665-1650 cm^{-1} regions were attributed to N–H of CONH, C=O of thiazolidinone and C=O of CONH stretching of compounds ($\mathbf{5}_{a-i}$). The peaks of 1760-1752 (C=O of thiazolidinone) confirms the formation of thiazolidinone ring from the hydrazones. In the NMR spectra of hydrazones ($\mathbf{4}_{a-i}$), signal at δ 8.19–10.12 shows presence of CH=N in the compounds. Lack of this signal in the spectra of title compounds ($\mathbf{5}_{a-i}$), that is, thiazolidinones provides the confirmatory evidence for ring closure from the corresponding Schiff's bases. Presence of a peak at δ 7.87 confirmed formation of 1H singlet of –SCHN. Presence of a singlet peak at δ 10.54–11.26 in the ^{1}H NMR spectra of hydrazones signifies the presence of 1H of –NH(–CONH). However, in thiazolidin-4-ones, the same signal was seen at δ 9.57–10.77. Moreover, a singlet of 2H of $-SCH_2$ was also seen in the δ values ranging from 2.08 to 3.02 in NMR spectra of thiazolidinones.

Pharmacology

Keeping in view the biological potential of thiazolidin-4-ones, it was decided to perform biological evaluation of all the newly synthesized thiazolidinones, that is, compounds $\mathbf{5}_{a-j}$. Since hydrazones have also been exhibiting potent pharmacological activities, it was considered useful to screen all the hydrazones ($\mathbf{4}_{a-i}$) also for their pharmacological potential. Hence, all the synthesized compounds were subjected to anti-inflammatory, analgesic, hydrogen peroxide-scavenging activity evaluation.

Table 3. Hydrogen peroxide-scavenging activity of synthesized compounds.

	Scavenging of hydrogen peroxide at different concentrations (%)		
S. No.	100 µg	300 µg	500 µg
$\mathbf{4}_a$	51.63	54.04	39.72
$\mathbf{4}_b$	51.35	49.50	49.36
$\mathbf{4}_c$	68.51	71.35	75.32
$\mathbf{4}_d$	50.78	52.91	53.12
$\mathbf{4}_e$	54.04	49.79	49.79
$\mathbf{4}_f$	49.21	50.64	50.50
$\mathbf{4}_g$	43.97	39.86	45.82
$\mathbf{4}_h$	40.00	50.35	39.72
$\mathbf{4}_i$	49.21	50.21	49.50
$\mathbf{5}_a$	49.79	54.47	53.90
$\mathbf{5}_b$	39.86	40.43	40.00
$\mathbf{5}_c$	53.33	49.79	49.50
$\mathbf{5}_d$	61.28	64.40	60.85
$\mathbf{5}_e$	45.39	39.72	39.29
$\mathbf{5}_f$	53.90	56.74	54.89
$\mathbf{5}_g$	41.70	39.57	39.57
$\mathbf{5}_h$	41.70	39.57	39.57
$\mathbf{5}_i$	50.01	50.21	50.07
BHA	64.60	66.40	67.20
Ascorbic acid	49.30	53.00	56.00

Anti-inflammatory screening

The anti-inflammatory activity of synthesized compounds was determined using carrageenan-induced paw oedema method. The paw volume, up to the tibiotarsal articulation, was measured using a plethysmometer (Model 7140). The measures were determined at five time intervals, that is, 0 h and 30, 60, 90, and 120 min after drug/test compound treatment. Compounds have exhibited significant anti-inflammatory activity. Compound $\mathbf{5}_g$ with a hydroxyl group present depicted the most potent activity of 44.90% (*P*-value <0.01). Compounds $\mathbf{4}_g$ and $\mathbf{5}_h$ depicted the equivalent activity of 44.70%. Interestingly, compound $\mathbf{4}_g$ was also having a hydroxyl group at *ortho* position and was most active among the synthesized hydrazones. Standard drug diclofenac sodium exhibited 51.51% inhibition (*P*-value <0.01) of inflammation.

Analgesic screening

Determination of analgesic activity was done by adopting acetic acid-induced abdominal writhing test. Swiss albino mice weighing 25–30 g were used for carrying the evaluation. For abdominal writhing test, nociception was induced by an intraperitoneal (IP) injection of acetic acid and diclofenac sodium was used as a standard drug. The number of stretching or writhing was recorded from 5 to 15 min.[25–27] All the compounds exhibited significant analgesic activities. Most of the hydrazones (**4**) have shown significant activities in this test with compound $\mathbf{4}_e$ being the most potent compound of series (percentage inhibition 64.90, *P*-value <0.01) followed by compounds $\mathbf{4}_c$ and $\mathbf{4}_d$ (percentage inhibition 62.80, *P*-value <0.01). Among thiazolidin-4-ones compound $\mathbf{5}_g$ and $\mathbf{5}_c$ were observed to be most active and depicted 62.10% and 61.40% inhibition of writhing (*P*-value <0.01), respectively. The standard drug diclofenac sodium exhibited 69.80% inhibition at a dose of 50 mg/kg.

Antioxidant screening

Evaluation of antioxidant activities was done by 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 synthesized compound were added to a hydrogen peroxide solution (0.6 mL, 40 mM). Absorbance of 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 synthesized compounds and standard compound were calculated. Among synthesized compounds, $\mathbf{4}_c$, $\mathbf{5}_d$, and $\mathbf{5}_i$ were observed to be most active. However, all the compounds have exhibited potent antioxidant activities in general.

In conclusion, the present investigation describes preparation of a series of hydrazones and thiazolidin-4-ones from capric acid and evaluation of their potential

for biological activities such as anti-inflammatory, analgesic, and hydrogen peroxide-scavenging activity. The synthesized compounds exhibited significant anti-inflammatory and moderate 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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