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ORIGINAL ARTICLE

Synthesis and antibacterial studies of 2-aryl-3-alkanamido-4*H*-thiazolidin-4-one derivatives

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Abstract A series of 2-aryl-3-alkanamido-4*H*-thiazolidin-4-ones were synthesized from long chain fatty acid hydrazides and studied for their *in vitro* antibacterial activity. Long chain fatty acid hydrazides **1** on reaction with different aromatic aldehydes in the presence of catalytic amount of glacial acetic acid yielded the corresponding aryl hydrazones **2** which on further reaction with thioglycolic acid in the presence of anhydrous zinc chloride furnished the title compounds **3**. These compounds were characterized by CHN analyses, IR, mass and ^{1}H NMR spectral data. All the compounds were evaluated for their *in vitro* antibacterial activity against two Gram positive strains (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*) and their minimum inhibitory concentration (MIC) were determined.

1. Introduction

Infectious diseases are one of the major health problems of the world population. Certainly, the rapid development of resistance to the existing antimicrobial drugs is the root cause of this global issue. This opens the gate for the medicinal chemists for the development of novel antimicrobial drugs having a different mechanism of action to combat the problem of multidrug resistance (Wise, 2008; Coleman, 2004; Cassell and Mekalanos, 2001). In a wide variety of heterocyclic structures, the thiazolidin-4-one nucleus constitutes an important class displaying a broad spectrum of biological activities (Verma and Saraf, 2008). Thiazolidin-4-one ring also found in naturally occurring actithiazic acid [(−) 2-(5-carboxypentyl) (thiazolidin-4-one)] which has been isolated from Streptomyces strains and exhibited highly specific *in vitro* activity against *Mycobacterium tuberculosis* (Sobin, 1952). Thiazolidin-4-one

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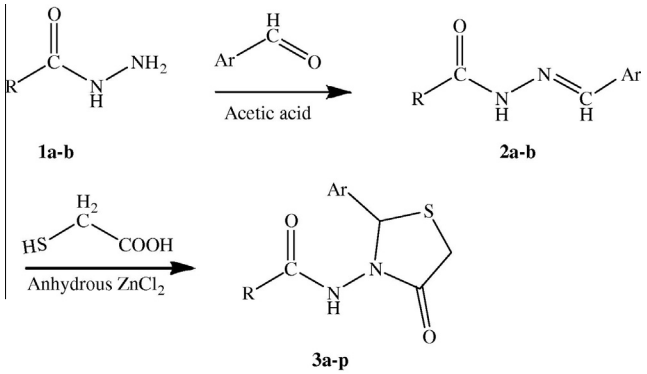
derivatives have been reported to possess diverse biological activities, such as antimicrobial (Ozkirimli et al., 2009; Mulwad et al., 2009; Saeed et al., 2007; Vicini et al., 2006; Kavitha et al., 2006; Mishra et al., 1999), anti-inflammatory (Sharma et al., in press; Deep et al., 2010), anti-HIV (Rao et al., 2004), anticancer (Guzel et al., 2006), anticonvulsant (Ragab et al., 1997), etc. It has been found that thiazolidin-4-one nucleus inhibits the bacterial enzyme MurB, a key enzyme responsible for the biosynthesis of peptidoglycan (Andres et al., 2000). Further, derivatives of long chain fatty acid hydrazides have been reported to possess the biological activity (Rauf et al., 2008; Awasthi et al., 2007). These reports including our ongoing research program in the field of synthesis and antimicrobial activity of medicinally important compounds (Deep et al., 2014; Kumar et al., 2011) inspired us to undertake the synthesis of some thiazolidin-4-ones as the novel derivatives of long chain fatty acid hydrazides. The synthesized compounds were characterized on the basis of elemental analysis, IR, ^{1}H NMR and Mass spectral data. All the compounds were screened for their *in vitro* antibacterial activity.

2. Results and discussion

2.1. Chemistry

The syntheses of 2-aryl-3-alkanamido-4*H*-thiazolidin-4-ones were achieved following the steps outlined in Scheme 1. Alkanoic acid hydrazides **1** were prepared by the reaction of hydrazine hydrate with the corresponding methyl esters of the acids. The hydrazides **1** then on refluxing with aromatic aldehydes and 2–3 drops of glacial acid in methanol furnished alkanoic acid hydrazones **2**. Thioglycolic acid reacted with **2** in the presence of anhydrous zinc chloride to give **3**. All the compounds were obtained in good yield. These compounds were characterized on the basis of elemental and spectral analyses. IR spectra of each compound showed a band for N–H *stretching* vibrations near 3340 cm^{-1}. The C=O *stretching* vibrations of amide I band were observed in the range of 1636–1650 cm^{-1} while the amide II, i.e., N–H bending vibrations displayed a band at about 1550–1557 cm^{-1}. The C–H stretching vibrations for alkyl chain were observed in the range of 2916–2919 cm^{-1} whereas *bending* vibrations for methylene *scissoring* were observed constantly at 1465 cm^{-1}. The characteristic methylene *rocking* vibrations of the long alkyl chain was observed at 720 cm^{-1}.The absorption for aromatic C–H *bending* vibrations was observed below 900 cm^{-1}. In case of ^{1}H NMR, the chemical shift value for the N–H group was observed in the range of 8.18–8.15 δ (ppm) and appeared as singlet (s). Aromatic protons appeared as multiplet (m) in the assigned value of 7.99–6.75 δ (ppm). The methine proton (S–CH–N) and the methylene protons (S–CH_2–C) of the thiazolidinone nucleus absorbed at 5.98–5.92 δ (ppm) and 2.76–2.71 δ (ppm), respectively, and appeared as singlets. The methylene protons *alpha* to the C=O group [CO–CH_2–CH_2–$(CH_2)_n$–CH_3] appeared as triplet in the range of 2.28–2.22 δ (ppm) whereas the methylene protons *beta* to the C=O group [CO–CH_2–CH_2–$(CH_2)_n$–CH_3] were observed at 1.73–1.67 δ (ppm) and appeared as multiplet. The multiplet was also observed at 1.39–1.22 δ (ppm) for the several methylene groups of the long fatty acyl chain [CO–CH_2–CH_2–$(CH_2)_n$–CH_3]. The methyl group of the long fatty acyl chain appeared as triplet at 0.89–0.85 δ (ppm). All the title compounds showed $[M+H]^+$ of 100% intensity as the molecular ion peak along with isotopic peak at $[M+2+H]^+$ of about 4% intensity of the parent ion peak due to the presence of sulfur atom. Compounds containing chlorine showed isotopic peak of about 35% intensity whereas the bromo compounds exhibited isotopic peak of about equal intensity. The results of elemental analyses were found in good agreement with the calculated values.



R	Ar
$CH_3(CH_2)_{12}$	C_6H_5
$CH_3(CH_2)_{14}$	*p*-$CH_3C_6H_4$
	p-$CH_3OC_6H_4$
	p-OHC_6H_4
	p-ClC_6H_4
	p-BrC_6H_4
	p-FC_6H_4
	p-$NO_2C_6H_4$

Scheme 1 Synthesis of 2-aryl-3-alkanamido-4*H*-thiazolidin-4-ones.

2.2. Antibacterial activity

All the synthesized title compounds were screened for their *in vitro* antibacterial activity against two Gram positive bacterial strains, i.e., *Bacillus subtilis* (MTCC 121) and *Staphylococcus aureus* (MTCC 96) and two Gram negative, i.e., *Escherichia coli* (MTCC 40) and *Pseudomonas aeruginosa* (MTCC 2453), respectively, and their minimum inhibitory concentration (MIC) were determined. All the title compounds were found to be active against all the bacterial strains used in this study. However, they showed more activity against the Gram negative than the Gram positive bacterial strains. Out of the two Gram negative bacterial strains, *E. coli* (MTCC 40) was found to be more susceptible than *P. aeruginosa* (MTCC 2453) against all the title compounds. The minimum inhibitory concentration (MIC) of the title compounds **3a**–**p** were found to be 0.65–0.35, 0.70–0.40, 0.85–0.60 and 0.80–0.60 μg/ml against *E. coli* (MTCC 40), *P. aeruginosa* (MTCC 2453), *B. subtilis* (MTCC 121) and *S. aureus* (MTCC 96), respectively. The MICs of the title compounds containing electron withdrawing groups like fluoro, chloro, bromo or nitro were found somewhat less than the compounds containing electron releasing groups like methyl, methoxyl or hydroxyl. The reference standard ciprofloxacin inhibited Gram negative bacteria viz., *E. coli* and *P. aeruginosa* at a MIC of 0.01 and 0.25 μg/ml, respectively, whereas against Gram positive bacteria viz., *S. aureus* and *B. subtilis* MIC was found to be 0.15 and 0.12 μg/ml, respectively. The results of the MIC for the stan-

dard drug, ciprofloxacin, against the bacterial strains used were found to be within the range as reported in the literature (Bauernfeind, 1997; Hoogkamp-Korstanje, 1997; Weber et al., 1988).

3. Experimental

3.1. Chemistry

The purity of all the synthesized compounds were checked by thin layer chromatography on silica gel G as a stationary phase and different solvent systems as a mobile phase using iodine vapors as a detecting agent. Melting points were determined by the Tempo melting point determination apparatus in open capillary tubes and are uncorrected. Elemental analyses were carried out on Carlo Erba1106 CHN Analyzer. Infrared spectra were recorded on Shimadzu 8000 FTIR Spectrophotometer in KBr phase. Proton NMR spectra were done on Bruker Avance II 400 NMR Spectrometer using tetramethyl silane as internal standard. Mass spectra of the compounds were carried out on API-4000 Quadrupole Mass Spectrometer using electro spray ionization (ESI) technique in positive ion mode. Long chain fatty acid hydrazides **1a**–**b** and their aryl hydrazones **2a**–**b** were prepared according to the procedure described in the literature (Yale et al., 1953).

3.2. General procedure for the synthesis of 2-aryl-3-alkanamido-4H-thiazolidin-4-ones (*3a*–*p*)

Alkanoic acid aryl hydrazone (**2a**–**b**, 0.01 M) and thioglycolic acid (0.01 M) were dissolved in dimethyl formamide (50–60 mL) containing a little quantity of anhydrous zinc chloride and refluxed for about 6 h. The reaction mixture after cooling was poured on to crushed ice with vigorous stirring. The precipitate thus obtained was filtered, washed thoroughly with cold distilled water, dried and then re-crystallized from ethanol. The physical and analytical data of the synthesized title compounds (**3a**–**p**) are given as follows.

3.2.1. 2-Phenyl-3-tetradecanamido-4H-thiazolidin-4-one (*3a*)

Yield: 87%; m.p.: 90–92 °C; IR (KBr, cm^{-1}): 3344 (N–H), 2916 (C–H), 1640 (C═O), 1550 (N–H), 1465 (CH_2), 720 (CH_2), 730 & 690 (mono substituted benzene); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.17 (s, 1H, NH), 5.98 (s, 1H, S–CH–N), 7.65–7.35 (m, 5H, ArH), 2.74 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.68–1.70 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.22–1.34 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 405 $[M+H]^+$ (100%), 407 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{23}H_{36}N_2O_2S$: C, 68.27; H, 8.97; N, 6.92. Found: C, 68.15; H, 8.90; N, 6.84.

3.2.2. 2-(4-Methylphenyl)-3-tetradecanamido-4H-thiazolidin-4-one (*3b*)

Yield: 82%; m.p.: 88–89 °C; IR (KBr, cm^{-1}): 3346 (N–H), 2916 (C–H), 1636 (C═O), 1555 (N–H), 1465 (CH_2), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.16 (s, 1H, NH), 5.94 (s, 1H, S–CH–N), 6.97–6.89 (m, 4H, ArH), 2.35 (s, 3H, Ar-CH_3), 2.75 (s, 2H, S–CH_2–C), 2.27 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.67–1.69 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.23–1.35 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 419 $[M+H]^+$ (100%), 421 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{24}H_{38}N_2O_2S$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.71; H, 9.23; N, 6.62.

3.2.3. 2-(4-Methoxyphenyl)-3-tetradecanamido-4H-thiazolidin-4-one (*3c*)

Yield: 85%; m.p.: 80–82 °C; IR (KBr, cm^{-1}): 3346 (N–H), 2916 (C–H), 1636 (C═O), 1555 (N–H), 1465 (CH_2), 1250 & 1040 (Ar–OCH_3), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.16 (s, 1H, NH), 5.94 (s, 1H, S–CH–N), 6.97–6.89 (m, 4H, ArH), 3.82 (s, 3H, OCH_3), 2.75 (s, 2H, S–CH_2–C), 2.27 [t, 2H, CO–CH_2–CH_2 $(CH_2)_{10}$–CH_3], 1.67–1.69 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.23–1.35 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 435 $[M+H]^+$ (100%), 437 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{24}H_{38}N_2O_3S$: C, 66.32; H, 8.81; N, 6.45. Found: C, 66.41; H, 8.75; N, 6.52.

3.2.4. 2-(4-Hydroxyphenyl)-3-tetradecanamido-4H-thiazolidin-4-one (*3d*)

Yield: 84%; m.p.: 96–98 °C; IR (KBr, cm^{-1}): 3420 (O–H), 3345 (N–H), 2916 (C–H), 1638 (C═O), 1555 (N–H), 1465 (CH_2), 1218 (C–O), 832 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 10.11 (s, 1H, OH), 8.16 (s, 1H, NH), 5.96 (s, 1H, S–CH–N), 6.85–6.75 (m, 4H, ArH), 2.72 (s, 2H, S–CH_2–C), 2.23 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.70–1.72 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.24–1.38 [m, 20H, CO– CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 421 $[M+H]^+$ (100%), 423 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{23}H_{36}N_2O_3S$: C, 65.68; H, 8.63; N, 6.66. Found: C, 65.76; H, 8.56; N, 6.59.

3.2.5. 2-(4-Chlorophenyl)-3-tetradecanamido-4H-thiazolidin-4-one (*3e*)

Yield: 83%; m.p.: 90–92 °C; IR (KBr, cm^{-1}): 3344 (N–H), 2918 (C–H), 1640 (C═O), 1550 (N–H), 1465 (CH_2), 1090 (Ar–Cl), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.15 (s, 1H, NH), 5.97 (s, 1H, S–CH–N), 7.60–7.33 (m, 4H, ArH), 2.71 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.68–1.70 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.25–1.38 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.86 (t, 3H, CH3); MS, *m*/*z* (%): 439 $[M+H]^+$ (100%), 441 $[M+2+H]^+$ (35%). Anal. Calcd for $C_{23}H_{35}ClN_2O_2S$: C, 62.92; H, 8.03; N, 6.38. Found: C, 62.81; H, 8.10; N, 6.29.

3.2.6. 2-(4-Bromophenyl)-3-tetradecanamido-4H-thiazolidin-4-one (*3f*)

Yield: 80%; m.p.: 95–97 °C; IR(KBr, cm^{-1}): 3340 (N–H), 2917 (C–H), 1642 (C═O), 1553 (N–H), 1465 (CH_2), 1220 (C–O), 830 (*p*-disubstituted benzene), 720 (CH_2);^{1}H NMR (DMSO-d_6): δ (ppm) 8.15 (s, 1H, NH), 5.97 (s, 1H, S–CH–N), 7.60–7.33 (m, 4H, ArH), 2.71 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.68–1.70 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.25–1.38 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 483 $[M+H]^+$ (100%), 485 $[M+2+H]^+$ (98%). Anal. Calcd for $C_{23}H_{35}BrN_2O_2S$: C, 57.13; H, 7.30; N, 5.79. Found: C, 57.28; H, 7.39; N, 5.71.

*3.2.7. 2-(4-Fluorophenyl)-3-tetradecanamido-4H-thiazolidin-4-one (**3g**)*

Yield: 81%; m.p.: 77–79 °C; IR (KBr, cm^{-1}): 3340 (N–H), 2919 (C–H), 1646 (C═O), 1553 (N–H), 1465 (CH_2), 1233 (Ar–Fl), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.16 (s, 1H, NH), 5.98 (s, 1H, S–CH–N), 7.65–7.05 (m, 4H, ArH), 2.73 (s, 2H, S–CH_2–C), 2.25 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.67–1.69 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.25–1.39 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 423 $[M+H]^+$ (100%), 425 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{23}H_{35}FN_2O_2S$: C, 65.37; H, 8.35; N, 6.63. Found: C, 65.28, H, 8.43; N, 6.69.

*3.2.8. 2-(4-Nitrophenyl)-3-tetradecanamido-4H-thiazolidin-4-one (**3h**)*

Yield: 82%; m.p.: 112–114 °C; IR (KBr, cm^{-1}): 3342 (N–H), 2916 (C–H), 1650 (C═O), 1557 (N–H), 1465 (CH_2), 1520 & 1340 (NO_2), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.18 (s, 1H, NH), 5.95 (s, 1H, S–CH–N), 7.99–7.57 (m, 4H, ArH), 2.76 (s, 2H, S–CH_2–C), 2.27 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.68–1.70 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 1.24–1.34 [m, 20H, CO–CH_2–CH_2–$(CH_2)_{10}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 450 $[M+H]^+$ (100%), 452 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{23}H_{35}N_3O_4S$: C, 61.44; H, 7.85; N, 9.35. Found: C, 61.52; H, 7.91, N, 9.28.

*3.2.9. 2-Phenyl-3-hexadecanamido-4H-thiazolidin-4-one (**3i**)*

Yield: 88%; m.p.:90–92 °C; IR (KBr, cm^{-1}): 3348 (N–H), 2917 (C–H), 1644 (C═O), 1555 (N–H), 1465 (CH2), 720 (CH_2), 735 & 690 (mono substituted benzene);^{1}H NMR (DMSO-d_6): δ (ppm) 8.16 (s, 1H, NH), 5.97 (s, 1H, S–CH–N) 7.64–7.34 (m, 5H, ArH), 2.73 (s, 2H, S–CH_2–C), 2.23 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.69–1.71 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.23–1.33 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 433 $[M+H]^+$ (100%), 435 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{25}H_{40}N_2O_2S$: C, 69.40; H, 9.32; N, 6.47. Found: C, 69.49; H, 9.24; N, 6.53.

*3.2.10. 2-(4-Methylphenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3j**)*

Yield: 84%; m.p.: 81–83 °C; IR (KBr, cm^{-1}): 3344 (N–H), 2918 (C–H), 1640 (C═O), 1553 (N–H), 1465 (CH_2), 832 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.17 (s, 1H, NH), 5.95 (s, 1H, S–CH–N), 6.97–6.89 (m, 4H, ArH), 2.35 (s, 3H, Ar-CH_3), 2.75 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.71–1.73 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.24–1.36 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 447 $[M+H]^+$ (100%), 449 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{26}H_{42}N_2O_2S$: C, 69.91; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.42; N, 6.19.

*3.2.11. 2-(4-Methoxyphenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3k**)*

Yield: 86%; m.p.: 80–82 °C; IR (KBr, cm^{-1}): 3344 (N–H), 2918 (C–H), 1640 (C═O), 1553 (N–H), 1465 (CH_2), 1250 & 1040 (Ar–OCH_3), 832 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.17 (s, 1H, NH), 5.95 (s, 1H, S–CH–N), 6.97–6.89 (m, 4H, ArH), 3.82 (s, 3H, °CH_3), 2.75 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.71–1.73 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.24–1.36 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 463 $[M+H]^+$ (100%), 465 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{26}H_{42}N_2O_3S$: C, 67.49; H, 9.15; N, 6.05. Found: C, 67.57; H, 9.22; N, 6.14.

*3.2.12. 2-(4-Hydroxyphenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3l**)*

Yield: 85%; m.p.: 96–98 °C; IR (KBr, cm^{-1}): 3415 (O–H), 3340 (N–H), 2918 (C–H), 1640 (C═O), 1550 (N–H), 1465 (CH_2), 1218 (C–O), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 10.11 (s, 1H, OH), 8.18 (s, 1H, NH), 5.96 (s, 1H, S–CH–N), 6.85–6.75 (m, 4H, ArH), 2.73 (s, 2H, S–CH_2–C), 2.23 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.69–1.71 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.25–1.39 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 449 $[M+H]^+$ (100%), 451 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{25}H_{40}N_2O_3S$: C, 66.92; H, 8.99; N, 6.24. Found: C, 66.85; H, 8.89; N, 6.17.

*3.2.13. 2-(4-Chlorophenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3m**)*

Yield: 84%; m.p.: 90–92 °C; IR (KBr, cm^{-1}): 3340 (N–H), 2916 (C–H), 1642 (C═O), 1555 (N–H), 1465 (CH_2), 1090 (Ar–Cl), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.16 (s, 1H, NH), 5.98 (s, 1H, S–CH–N), 7.60–7.35 (m, 4H, ArH), 2.71 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.70–1.72 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.24–1.38 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 467 $[M+H]^+$ (100%), 469 $[M+2+H]^+$ (35%). Anal. Calcd for $C_{25}H_{39}ClN_2O_2S$: C, 64.28; H, 8.42; N, 6.00. Found: C, 64.39; H, 8.51; N, 6.07.

*3.2.14. 2-(4-Bromophenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3n**)*

Yield: 86%; m.p.: 92–94 °C; IR (KBr, cm^{-1}): 3340 (N–H), 2916 (C–H), 1642 (C═O), 1555 (N–H), 1465 (CH_2), 1090 (Ar–Cl), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.16 (s, 1H, NH), 5.98 (s, 1H, S–CH–N), 7.60–7.35 (m, 4H, ArH), 2.71 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.70–1.72 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.24–1.38 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 513 $[M+H]^+$ (100%), 515 $[M+2+H]^+$ (98%). Anal. Calcd for $C_{25}H_{39}BrN_2O_2S$: C, 58.70; H, 7.68; N, 5.48. Found: C, 58.79; H, 7.51; N, 5.59.

*3.2.15. 2-(4-Fluorophenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3o**)*

Yield: 82%; m.p.: 77–79 °C; IR (KBr, cm^{-1}): 3345 (N–H), 2916 (C–H), 1645 (C═O), 1553 (N–H), 1465 (CH_2), 1235 (Ar–F), 830 (*p*-disubstituted benzene), 720 (CH_2); ^{1}H NMR (DMSO-d_6): δ (ppm) 8.15 (s, 1H, NH), 5.97 (s, 1H, S–CH–N), 7.63–7.03 (m, 4H, ArH), 2.75 (s, 2H, S–CH_2–C), 2.25 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.68–1.70 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.25–139 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.86 (t, 3H, CH_3); MS, *m*/*z* (%): 451 $[M+H]^+$ (100%), 453 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{25}H_{39}FN_2O_2S$: C, 66.63; H, 8.72; N, 6.22. Found: C, 66.53; H, 8.80; N, 6.31.

Table 1 *In vitro* antibacterial activity of the title compounds (**3a**–**p**).

Compound	Minimum inhibitory concentration (μg/ml)			
	B. subtilis (MTCC 121)	*S. aureus* (MTCC 96)	*E. coli* (MTCC 40)	*P. aeruginosa* (MTCC 2453)
3a	0.75	0.80	0.65	0.70
3b	0.75	0.80	0.65	0.70
3c	0.80	0.85	0.65	0.70
3d	0.65	0.70	0.60	0.65
3e	0.60	0.60	0.35	0.35
3f	0.60	0.60	0.35	0.35
3g	0.60	0.60	0.35	0.35
3h	0.60	0.60	0.35	0.35
3i	0.75	0.80	0.65	0.65
3j	0.75	0.80	0.65	0.65
3k	0.80	0.85	0.70	0.75
3l	0.70	0.70	0.60	0.65
3m	0.60	0.60	0.35	0.35
3n	0.60	0.60	0.35	0.35
3o	0.60	0.60	0.35	0.35
3p	0.60	0.60	0.35	0.35
Ciprofloxacin (standard drug)	0.12	0.15	0.01	0.25

*3.2.16. 2-(4-Nitrophenyl)-3-hexadecanamido-4H-thiazolidin-4-one (**3p**)*

Yield: 81%; m.p.: 112–114 °C; IR (KBr, cm^{-1}): 3340 (N–H), 2917 (C–H), 1648 (C═O), 1557 (N–H), 1465 (CH_2), 1520 & 1340 (NO2), 830 (*p*-disubstituted benzene), 720 (CH_2);^{1}H NMR (DMSO-d_6): δ (ppm) 8.17 (s, 1H, NH), 5.94 (s, 1H, S–CH–N), 7.95–7.55 (m, 4H, ArH), 2.76 (s, 2H, S–CH_2–C), 2.26 [t, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.69–1.71 [m, 2H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 1.24–1.36 [m, 24H, CO–CH_2–CH_2–$(CH_2)_{12}$–CH_3], 0.87 (t, 3H, CH_3); MS, *m*/*z* (%): 478 $[M+H]^+$ (100%), 480 $[M+2+H]^+$ (4%). Anal. Calcd for $C_{25}H_{39}N_3O_4S$: C, 62.86; H, 8.23; N, 8.80. Found: C, 62.77; H, 8.31; N, 8.88.

3.3. Antibacterial activity

All the title compounds were screened for their *in vitro* antibacterial activity against two Gram positive strains, i.e., *B. subtilis* (MTCC 121) and *S. aureus* (MTCC 96) and two Gram negative strains, i.e., *E. coli* (MTCC 40) and *P. aeruginosa* (MTCC 2453), respectively. Ciprofloxacin was used as the standard drug for the present study. Serial two-fold dilution technique was used for the study of antibacterial activity (Cappucino and Sherman, 1999). A stock solution (10 μg/ml) of all the title compounds and standard drug was prepared in dimethyl sulfoxide. Sterilized double strength nutrient broth (DSNB) was used as a growth media. The stock solution was serially diluted by DSNB aseptically to give concentrations of 5.0–0.01 μg/ml into a series of sterilized culture tubes. All the tubes were inoculated by bacterial strain. The inoculum's size was approximately 10^6 colony forming units (CFU/ml). The inoculated tubes were incubated for 24 h at 37(±1) °C. After 24 h, the inoculated culture tubes were macroscopically examined for turbidity. The culture tube showing turbidity (lower concentration) and the culture tube showing no turbidity (higher concentration) gave the minimum inhibitory concentration (MIC) for the compound. The MIC for the title compounds and the standard drug, i.e., ciprofloxacin is presented in Table 1.

4. Conclusion

Present study describes the synthesis of a series of 2-aryl-3-alkanamido-4*H*-thiazolidin-4-ones starting from the hydrazides of the long chain fatty acids. The compounds were characterized by modern analytical techniques, such as CHN analyses, IR, Mass and proton NMR spectra. All the title compounds were screened for their *in vitro* antibacterial activity against *B. subtilis*, *S. aureus* (Gram positive) and *E. coli*, *P. aeruginosa* (Gram negative) and their minimum inhibitory concentration (MIC) were determined. The results of antibacterial activity showed that compounds containing electron withdrawing groups, e.g., chloro, bromo, fluoro or nitro were found to be more active than the compounds containing electron releasing groups such as methyl, methoxyl or hydroxyl. These results suggest that some more compounds using different aromatic or hetero-aromatic aldehydes and fatty acids should be synthesized and screened for their antibacterial activity to explore the possibility of 2-aryl-3-alkanamido-4*H*-thiazolidin-4-ones as a novel series of antibacterials.

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