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Synthesis and biological evalution of some thiazolidinone derivatives of acyclic and cyclic ketones as antibacterial agents

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ABSTRACT

Thiosemicarbazone and 4-thiazolidinone derivatives were synthesized in one and two step, respectively from thiosemicarbazide, in satisfactory yields. The structure of the compounds were elucidated by Elemental, IR, and NMR spectral data. The antibacterial activity of these compounds was tested by disc diffusion assay against two Gram-positive and two Gram-negative bacterie. The results showed that acyclic and cyclic 4-thiazolidinone derivatives are better in inhibiting the growth of both types of bacteria. Compounds 4e and 7b were found to be most potent compared to standard drug Norfloxacin.

Key words: Acyclic and cyclic ketones, Thiosemicarbazones, Thiazolidinone derivatives, Antibacterial activity.

INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem. The search of novel antimicrobial agents is a field of current and growing interest. Many compounds have been synthesized with this aim; their clinical use has been limited by their relatively high risk of toxicity, bacterial resistance and/or pharmacokinetic deficiencies. A major research emphasis to counter this growing problem is the development of antimicrobials structurally unrelated to the existing molecules. One possibility to achieve this goal is the combination of a steroid molecule with structural elements possessing appropriate biological activities[1-5]. According to the literature, thiosemicarbazones as a class of compounds which have the 4-thiazolidinone ring are reported to possess various biological activities such as tranquilizing, muscle relaxant, antidepressant, antibacterial, antifungal analgesic and anti-inflammatory properties[6-12]. Biological activities of these thiosemicarbazones are related to their abilities to form complex with metal cations, by bonding through the sulphur and azomethine nitrogen atoms[13]. As a part of our continuing interest, we have investigated for the first time cyclic and acyclic ketones of thiazolidinone derivatives with an acetic acid group. In the present investigation, we utilized a thia-Micheal addition reaction with the employment of maleic anhydride as the acceptor of Michael addition[14]. The reaction was carried out in dry toluene and DMF. The activities of these compounds were screened *in vitro* against bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae* and *Escherichia coli.*

MATERIAL AND METHODS

All the chemicals were purchased from s.d.fine chem. limited (India) and were used as such without further purification. Melting points were

determined by open capillary method and are uncorrected. Infrared (IR) spectra were recorded on AVATAR-330 FT-IR Spectrometer. Nuclear Magnetic Resonance spectra were measured with BRUCKER DRX 500MHz Spectrometer in DMSO. The following abbreviations were used to indicate the peak multiplicity s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, dd- doublet of doublet.

EXPERIMENTAL

Compounds **3a-e** and **6a-b** were prepared according to the procedure described earlier[15].

General procedure for the synthesis of thiazolidinone

A mixture of 3a-e/6a-b (0.0078mol) and maleic anhydride (0.0352mol) in 50mL of dried toluene and 2mL of DMF was refluxed with stirring for 6-10hours. After the removal of solvent in reduced pressure the crude product was extracted with ethyl acetate twice. The organic layer was dried over anhydrous sodium sulphate and evaporated. The product obtained was purified by recrystallization from MeOH.

2-[2-(1-methylethylidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (4a)

Yield:82%; M.p.110-112° Spectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3156(NH), 1708 (C=O, COOH), 1672 (C=O, lactam), 1633(C=N), 1356(NCS), 1275(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.7 (br, s, 1H, CO_2H), 11.75 (s, 1H, NH), 4.30 (dd, 1H, CH), 2.97 (dd, 1H, CH_2), 2.84 (dd, 1H, CH_2), 2.01 (s, 3H, CH_3), 1.91, (s, 3H, CH_3); ^{13}C NMR: 175.1 (CO_2H), 172.1 (C=O), 166.4 (C=N), 158.1 (C=N), 44.0 (CH), 37.1 (CH_2), 25.2 (CH_3), 16.7 (CH_3). Anal calcd. for $C_8H_{11}N\text{-}_3SO_3$ (M_r =229.48) C: 41.90, H: 4.80, N: 18.34% found: C: 41.45, H: 4.92, N: 18.12%

2-[2-(1-methylpropylidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (4b)

Yield: 86% M.p.98-100°C Spectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3158(NH), 1718 (C=O, COOH), 1684 (C=O, lactam), 1649(C=N), 1343(NCS), 1295(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.8 (br, s, 1H, CO_2H), 11.90 (s, 1H, NH), 4.24 (dd, 1H, CH), 2.98- 2.94 (dd, 1H, CH_2), 2.78-2.83 (dd, 1H, CH_2), 2.23-2.28 (dd, 2H, CH_2) 1.91 (s, 3H, CH_3), 1.01, (t, 3H, CH_3); ^{13}C NMR: 174.5 (CO_2H), 171.1 (C=O), 166.1 (C=N), 159.8 (C=N), 42.32 (CH), 36.1 (CH_2), 30.38 (CH_2), 16.2 (CH_3), 9.81 (CH_3). Anal calcd. for $C_9H_{13}N\text{-}_3SO_3$ (M_r =243.72) C: 44.44, H: 5.35, N: 17.28% found: C: 44.70, H: 5.02, N: 17.12%

2-[2-(1-methylbutylidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (4c)

Yield: 85% M.p.110-112°C Spectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3158(NH), 1707 (C=O, COOH), 1670 (C=O, lactam), 1626(C=N), 1355(NCS), 1253(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.66 (br, s, 1H, CO_2H), 11.75 (s, 1H, NH), 4.32-4.34 (dd, 1H, CH), 2.94- 2.98 (dd, 1H, CH_2), 2.81-2.87 (dd, 1H, CH_2), 2.30 (t, 2H, CH_2) 2.01 (s, 3H, CH_3), 1.61, (m, 2H, CH_2), 0.96 (t, 3H, CH_3); ^{13}C NMR: 174.6 (CO_2H), 171.6 (C=O), 165.9 (C=N), 157.8 (C=N), 43.52 (CH), 36.6 (CH_2), 32.18 (CH_2), 22.96 (CH_2), 18.8 (CH_3), 13.56 (CH_3). Anal calcd. for $C_{10}H_{15}N\text{-}_3SO_3$ (M_r =257.25) C: 46.64, H: 5.85, N: 16.34% found: C: 46.19, H: 5.24, N: 16.72%

2-[2-(1-ethylpropylidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (4d)

Yield: 83% M.p.120-122°C Spectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3094(NH), 1729 (C=O, COOH), 1690 (C=O, lactam), 1609(C=N), 1351(NCS), 1263(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.66 (br, s, 1H, CO_2H), 11.75 (s, 1H, NH), 4.29-4.34 (dd, 1H, CH), 2.94- 2.98 (dd, 1H, CH_2), 2.81-2.87 (dd, 1H, CH_2), 2.15 (s, 2H, CH_2) 1.85 (s, 3H, CH_3), 1.51, (s, 2H, CH_2), 0.88 (s, 3H, CH_3); ^{13}C NMR: 174.6 (CO_2H), 171.6 (C=O), 165.9 (C=N), 157.8 (C=N), 43.52 (CH), 36.6 (CH_2), 32.18 (CH_2), 22.96 (CH_2), 18.8 (CH_3), 14.06 (CH_3). Anal calcd. for $C_{10}H_{15}N\text{-}_3SO_3$ (M_r =257.25) C: 46.64, H: 5.85, N: 16.34% found: C: 46.99, H: 5.71, N: 16.52%

2-[2-(1,2-dimethylpropylidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (4e)

Yield: 80% M.p.130-132° Spectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3143(NH), 1708 (C=O, COOH), 1669 (C=O, lactam), 1629(C=N), 1356(NCS), 1253(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.61 (br, s, 1H, CO_2H), 11.75 (s, 1H, NH), 4.29-4.32 (dd, 1H, CH), 2.94- 2.98 (dd, 1H, CH_2), 2.81-2.87 (dd, 1H, CH_2), 2.11 (s, 1H, CH), 2.05 (s, 2H, CH_2) 1.84 (s, 3H, CH_3), 0.83 (s, 6H, $[CH_3]_2$); ^{13}C NMR: 175.1 (CO_2H), 172.1 (C=O), 164.9

(C=N), 158.1 (C=N), 47.2 (CH), 44.0 (CH) 36.6 (CH_2), 32.18 (CH_2), 22.5 [$(CH_3)]_2$, 16.02 (CH_3). Anal calcd. for $C_{11}H_{17}N\text{-}_3SO_3$ (M_r =271.54) C: 48.71, H: 6.27, N: 15.50% found: C: 48.99, H: 6.01, N: 15.82%

2-[(2-cyclopentylidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (7a)

Yield: 90% M.p.154-156°CSpectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3178(NH), 1728 (C=O, COOH), 1654 (C=O, lactam), 1614(C=N), 1346(NCS), 1250(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.12 (br, s, 1H, CO_2H), 4.23-4.26 (dd, 1H, CH), 2.97- 2.99 (dd, 1H, CH_2), 2.91-2.94 (dd, 1H, CH_2), 2.33-2.38 (m, 4H, $[CH_2]_2$), 1.67-1.73 (m, 4H, $[CH_2]_2$); ^{13}C NMR: 175.7 (CO_2H), 172.6 (C=O), 170.0 (C=N), 160.1 (C=N), 43.0 (CH) 36.8 (CH_2), 29.8 (CH_2), 24.5 (CH_2). Anal calcd. for $C_{10}H_{13}N\text{-}_3SO_3$ (M_r =255.34) C: 47.06, H: 5.09, N: 16.47% found: C: 47.36, H: 5.21, N: 16.12%

2-[(2-cyclohexlidene)hydrazono]-4-oxo-1,3-thiazolan-5-yl-acetic acid (7b)

Yield: 83% M.p.170-172°C Spectroscopic analysis : IR (KBr) ν_{max}/cm^{-1}: 3161(NH), 1727 (C=O, COOH), 1624 (C=O, lactam), 1632(C=N), 1336(NCS), 1262(N-N=C); ^{1}H NMR (DMSO, 500 MHz, δ ppm): 12.60 (br, s, 1H, CO_2H), 11.75 (s, 1H, NH), 4.29-4.36 (dd, 1H, CH), 2.97- 2.99 (dd, 1H, CH_2), 2.81-2.86 (dd, 1H, CH_2), 2.28 (s, 4H, $[CH_2]_2$), 1.68 (s, 6H, $[CH_2]_3$); ^{13}C NMR: 175.1 (CO_2H), 172.1 (C=O), 170.0 (C=N), 158.1 (C=N), 44.0 (CH) 37.1 (CH_2), 25.9 (CH_2), 18.4 (CH_2). Anal calcd. for $C_{11}H_{15}N\text{-}_3SO_3$ (M_r =269.57) C: 49.06, H: 5.59, N: 15.61% found: C: 49.52, H: 5.27, N: 15.72%

Antibacterial activity

The compounds 4a-e, and 7a-b were tested for their antibacterial activity by disc-diffusion method using nutrient broth medium [contained {g/L}: beef extract 3g; peptone 5g; pH7.0]. The Gram-positive bacteria and Gram-negative bacteria utilized in this study consisted of *Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae* and *Escherichia coli.* In the disc-diffusion method, sterile paper discs (05mm) impregnated with compound dissolved in dimethylsulfoxide (DMSO) at concentration 100µg/mL were used. Then, the paper disc impregnated with the solution of the compound tested was placed on the surface of the media inoculated with the microorganism. The plates were incubated at 37°C for 24h. After incubation, the zone inhibitions were noted and the results are given in Table 1.

Table 1: Antibacterial activities of compounds 4a-e and 7a-b. (Diameter of the zone of inhibition in mm)

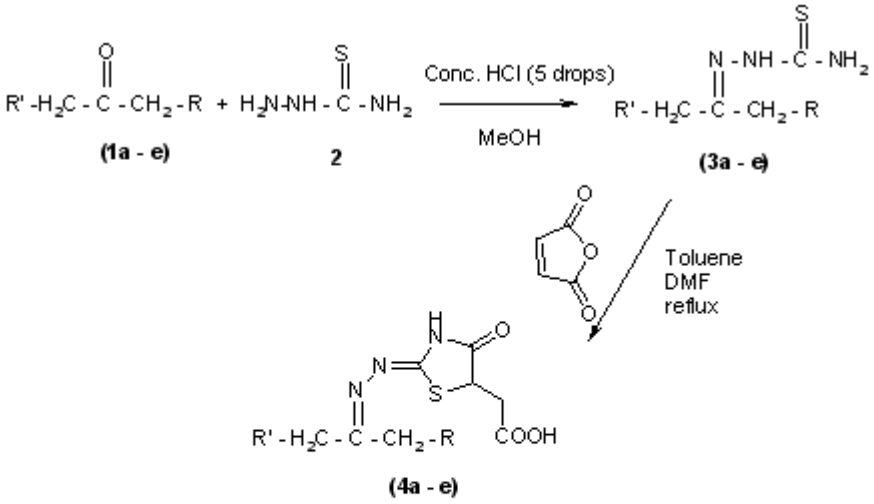
Compound	Gram-positive		Gram-negative	
	A	B	C	D
4a	8.0	8.3	8.1	8.2
4b	9.8	9.5	9.9	10.0
4c	12.0	11.9	12.3	12.5
4d	13.1	12.9	13.6	13.7
4e	15.3	15.9	16.2	15.8
7a	13.8	14.1	13.7	13.9
7b	16.2	16.4	15.9	16.3
Norfloxacin	24.0	23.0	24.0	26.0
DMSO	-	-	-	-

A - *Staphylococcus aureus* ; B - *Bacillus subtilis* ;
C - *Klebsiella pneumoniae*
D- *Escherichia coli.* Reference Compound: Norfloxacin
Inactive < 8mm; Moderate < 8-12 mm; Active > 12mm.

Of the compounds tested, 4e and 7b inhibit the growth of tested bacteria at a minimum concentration of 25 µg/mL. 4c, 4d and 7a showed activity at higher concentrations ranging from 50 to 200 µg/mL. 4a and 4b showed moderate activity at 200 µg/mL when compared to the standard Norfloxacin.

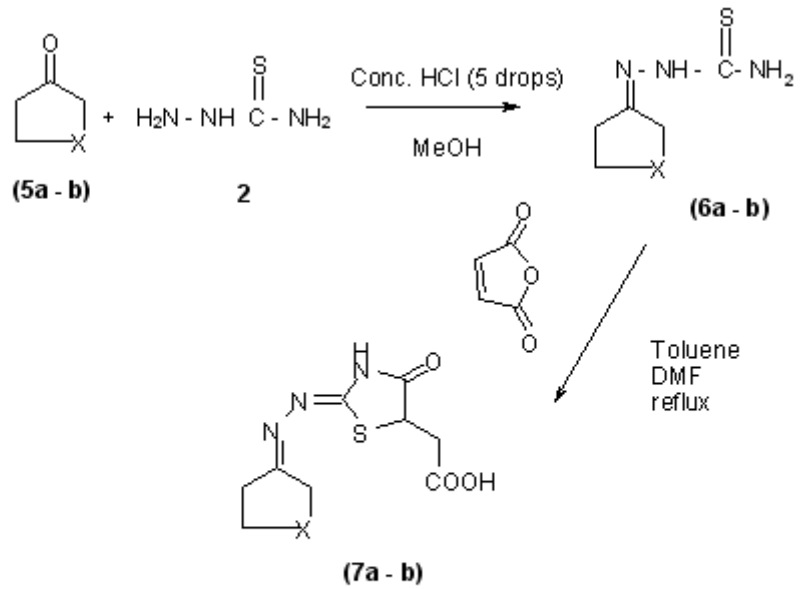
RESULTS AND DISCUSSION

The IR spectra of the 4-thiazolidinones 4a-e and 7a-b showed absorption bands at about 1728-1708cm^{-1} characteristic for C=O stretching vibration of acid group and 1684-1623cm^{-1} associated with C=O amide group. Absorption bands around 1356-1343cm^{-1} characteristic for NCS bending vibration. In addition, absorption bands at 1275-1250cm^{-1} for N-N=C vibration provided confirmatory evidence for ring closure. Further support was obtained from the ^{1}H NMR spectra, resonance assigned to the SCH



(1a - e) 2 (3a - e) (4a - e)

	R'	R
1a : 3a : 4a	H	H
1b : 3b : 4b	CH_3	H
1c : 3c : 4c	C_2H_5	H
1d : 3d : 4d	CH_3	CH_3
1e : 3e : 4e	$CH(CH_3)_2$	H



(5a - b) 2 (6a - b) (7a - b)

5a : 6a : 7a $X = CH_2$

5b : 6b : 7b $X = (CH_2)_2$

Scheme 1

group of the thiazolidinone ring appearing as doublet of doublet at 4.32 ppm due to the interaction with methylene protons of the acid group. Similarly the methylene protons appearing as doublet of doublet at δ 2.97 and 2.84. The peaks resonated at δ 12.83 (COOH) and 11.75 (NH), provide the additional support. ^{13}C NMR spectra peaks resonated in the range of 175.1, 172.1, 166.4, 158.1, 44.0 and 37.1 assigned for COOH, CO, CN, CN, CH and CH_2 moieties.

CONCLUSION

The biological behavior of these compounds revealed that Compounds 4e and 7b showed better antibacterial activity than their respective analogues.

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