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Synthesis and antimicrobial activity of some novel thiazolidinone derivatives

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ABSTRACT

Ethylchloroacetate and hydrazine hydrate were reacted with substituted aldehydes to get the corresponding substituted N-benzylidine-2-chloro acetohydrazides, which were further condensed with succinimide to get corresponding subsituted N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl) acetohydrazides. These compounds were cyclized with thioglycollic acid to get the corresponding thiazolidinone derivatives, which have been evaluated for their antimicrobial activity.

Keywords: Thiazolidinone derivatives, N-benzylidine-2-chloro acetohydrazides, N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl)acetohydrazides, Antimicrobial activity.

INTRODUCTION

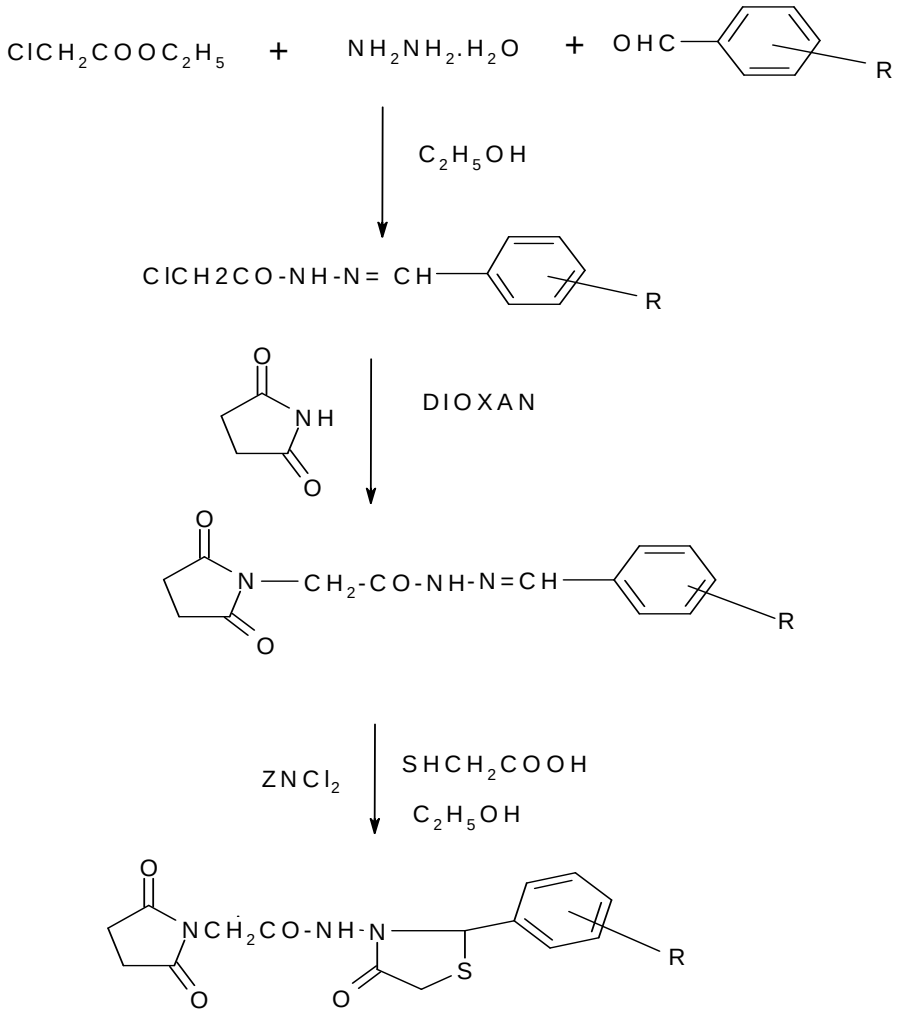
1,3-Thiazolidines are the new class of antimicrobial agents with activity against broad spectrum of Gram-positive pathogens including Staphylococci, Streptococci and Entercocci[1]. 4-oxo-thiazolidine have been extensively investigated due to their various types of pharmacological activities such as antimicrobial[2], anasthetic[3], antidiabetic[4], anti-inflammatory[5] etc. The structural and therapeutic diversity coupled with commercial viability of these small heterocyclic molecules has fascinated organic and medicinal chemists. Many 4-Thiazolidinones inhibit the bacterial enzyme muramin B. Their activity profile also includes COX inhibition, non nucleoside inhibition of HIV-RT and Histamine antagonism[6].

MATERIALS AND METHODS

The chemicals and reagents used in the present project were of AR and LR grade, procured from Aldrich, Hi-media, Merck, Ranbaxy, sigma and S.D-Fine Chem Ltd. Melting points of the synthesized compounds were determined by open capillary method and are uncorrected.

The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (8400S, Shimadzu) at M.S. Ramaiah college of pharmacy, Bangalore. ^{1}H NMR spectra were recorded on NMR spectrometer (AMX-400, Bruker) at Indian Institute of Science Bangalore using DMSO and chemical shifts (δ) are reported in parts per million downfield from internal reference Tetramethylsilane (TMS). Mass spectra were recorded on Mass spectrophotometer (LCMS-2010 A, Shimadzu) at Uwin Global Services and Quest Bangalore.

Scheme for synthetic methodlogy:



SNo.	Compounds	R
1	CHSVR-RAVI-03A	H
2	CHSVR-RAVI-03B	$N(CH_3)_2$
3	CHSVR-RAVI-03C	3-OCH_3,4-OH
4	CHSVR-RAVI-03D	2-OH
5	CHSVR-RAVI-03E	2,4 Cl
6	CHSVR-RAVI-03F	2-NO_2
7	CHSVR-RAVI-03G	4-Cl
8	CHSVR-RAVI-03H	3-OCH_3

Synthesis of N-benzylidine-2-chloro acetohydrazide [01A-H] [7]

It is a Mannich type reaction. First ethylchloroacetate (0.05mol) and hydrazine hydrate (0.05mol) were mixed together in 250ml beaker to which substituted benzaldeydes (0.05 mol) in 30ml ethanol was added drop wise with vigorous shaking for 30 mins at 60˚C. Then the mixture was refluxed for appropriate time at 70˚C, cooled and poured into ice-cold water. The product was filtered, dried and recrystallized from ethanol. The yields of the products were between 56-82%. The physical and spectral data of synthesized compounds are given in Table-I and II respectively.

Synthesis of N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl)acetohydrazide [02A-H] [7]

0.01mol of succinimide and 0.01mol of N-substituted benzylidine-2-chloro aceto hydrazides were mixed together in 30ml of dioxan in 250ml round bottomed flask and refluxed for appropriate time at 70˚C. Soft solid mass had appeared which was filtered, dried and recrystallized with ethanol. The yields of the products ranged from 58-72%. The physical and spectral data of synthesized compounds are given in Table-I and II respectively.

Table-I : Physical Data of Synthesized Compound

Fig. No.	Compound	Chemical Name	Mol. Formula	Mol. Wt. (g)	m.p (ºC)	% Yield
01	01A	N-benzylidine-2-chloro acetohydrazide	$C_9H_9N_2OCl$	196.6	84-86	69.89
02	02A	N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl)acetohydrazide	$C_{13}H_{13}O_3N_3$	259.3	123-125	57.6
03	03A	N-benzylidine-4-oxo-1,3-thiazolidine succinimido acetohydrazide	$C_{15}H_{15}N_3O_4S$	333.7	67-69	70.0
04	01B	p-dimethyl amino-N-benzylidine-2-chloro acetohydrazide	$C_{11}H_{14}N_3OCl$	239.7	167-169	72.92
05	02B	p-dimethylamino-N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl) acetohydrazide	$C_{15}H_{18}N_4O_3$	302.3	199-201	66.2
06	03B	3-[2-(4-N-dimethylaminophenyl)-4-oxo-1,3-thiazolidine] acetamido succinimide	$C_{17}H_{20}O_4N_4S$	376.44	229-231	74.4
07	01C	3-methoxy-4-hydroxy-N-benzylidine-2-chloro acetohydrazide	$C_{10}H_{11}O_3N_2Cl$	242.66	183-184	82.6
08	02C	3-methoxy-4-hydroxy-N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl) acetohydrazide	$C_{14}H_{15}O_5N_3$	305.3	147-149	66.6
09	03C	3-[2-(3-methoxy-4-hydroxyphenyl)-4-oxo-1,3-	$C_{16}H_{17}O_6N_3S$	379.39	137-139	50.0

		thiazolidine]acetamido succinimide				
10	01D	2-hydroxy-N-benzylidine-2-chloro acetohydrazide	$C_9H_9O_2N_2Cl$	212.6	124-126	56.7
11	02D	2-hydroxy-N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl)acetohydrazide	$C_{13}H_{13}O_4N_3$	275.26	111-113	74.1
12	03D	3-[2-(2-hydroxy phenyl) 4-oxo-1,3-thiazolidine] acetamido succinimide	$C_{15}H_{15}O_5N_3S$	349.37	94-96	55.5
13	01E	2,4-dichloro-N-benzylidine-2-chloro acetohydrazide	$C_9H_7ON_2Cl_3$	265.5	145-147	75.19
14	02E	2,4-dichloro-N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl) acetohydrazide	$C_{13}H_{11}O_3N_3Cl_2$	328.15	131-133	72.2
15	03E	3-[2-(2, 4-dichloro phenyl) 4-oxo-1, 3-thiazolidine] acetamido succinimide	$C_{15}H_{13}O_4N_3Cl_2S$	401.2	109-111	63.0
16	01F	2-nitro-N-benzylidine-2-chloro acetohydrazide	$C_9H_8O_3N_3Cl$	241.63	245-247	81.97
17	02F	2-nitro-N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl) acetohydrazide	$C_{13}H_{12}O_5N_4$	304.26	214-216	66.67
18	03F	3-[2-(2-nitro phenyl) 4-oxo-1, 3-thiazolidine] acetamido suucinimide	$C_{15}H_{14}O_6N_4S$	378.37	189-191	78.9
19	01G	4-chloro-N-benzylidine-2-chloro acetohydrazide	$C_9H_8ON_2Cl_2$	231.08	149-151	78.26
20	02G	4-chloro N-benzylidine-2-(2,5-dioxo pyrrolidin-1-yl) acetohydrazide	$C_{13}H_{12}O_3N_3Cl$	293.71	134-136	68.9
21	03G	3-[2-(4-chloro phenyl)4-oxo-1,3-thiazolidine] acetamido succnimide	$C_{15}H_{14}O_4N_3S$	367.81	119-121	66.6
22	01H	3-methoxy-N-benzylidine-2-chloro acetohyrdazide	$C_{10}H_{11}O_2N_2Cl$	226.6	197-199	79.82
23	02H	3-methoxy-N-benzylidine-2-(2,5-dioxopyrrolidin-1-yl) acetohyrdazide	$C_{14}H_{15}O_4N_3$	289.29	184-186	68.9
24	03H	3-[2-(3-methoxy phenyl) 4-oxo-1,3-thiazolidine] acetamido succinimide	$C_{16}H_{17}O_5N_3S$	363.39	169-171	66.67

Synthesis of N-benzylidine-4-oxo-1,3-thiazolidine succinimido acetohydrazide [03A -H] [7]
N-substituted benzylidine-2-(2,5-dioxo pyrrolidin-1-yl)acetohydrazides (0.01mol) were taken in round bottomed flask and thioglycollic acid (0.01mol) was added to it. To this mixture a pinch of anhydrous zinc chloride, 2-3 drops of conc sulphuric acid and ethanol (60 ml) were added. This mixture was refluxed for appropriate time at 70˚C and allowed to cool. The filtered and dried product was recrystallized from chloroform. The yields of the products ranged from 50-79%. The physical and spectral data of synthesized compounds are given in Table-I and II respectively.

Table-II : Spectral Data of Synthesized Compounds

Table-(IIA) IR Spectral Data

Sr. No.	Compound	IR Spectral Data ν_{max} (cm^{-1})
1	01A	3363(N-H str), 3060(Ar ,C-H str), 1272(C0-NH str), 1704,1649 (C=O str), 2985 (alkenes), 817(C-Cl, Al str)
2	02A	3213(N-H str), 3045 (Ar, C-H str), 2979 (alkenes), 1670, 1650 (C=O), 1701 (CO-NH str), 1244 (C=O)
3	03A	3334 (N-H str), 3043 (Ar, C-H str), 2995,2983 (alkenes), 1704,1683,1643 (C=O str), 1232 (C0-NH str), 690(C-S str), 1404(C-N str)
4	03B	3201(N-H str), 2981(Ar, C-H str), 2912 (alkenes), 1701,1608, 1670(C=O str), 1255(C0-NH str), 615(C-S str), 1415(C-N str)
5	03C	3226 (N-H str), 3082(Ar, C-H str), 2983 (alkenes), 3483(O-H str), 1259(C0-NH str),1691,1660,1622(C=O str),642(C-S str), 1429(C-N str)
6	03D	3215(N-H str), 3082 (Ar, C-H str), 2979 (alkenes), 3473(O-H str), 1606,1668,1697(C=O str), 1249 (CO-NH str), 1396 (C-N str), 640 (C-S str)
7	03E	3311 (N-H str), 3055 (Ar, C-H str),2923(alkenes),1701,1643,1629 (C=O str), 1259 (CO-NH str), 1400(C-N str), 671(C-S str), 1067(C-Cl Ar str)
8	03F	3326 (N-H str), 3056 (Ar, C-H str), 2966 (alkenes), 1703,1643,1629 (C=O str), 1247(C0-NH str), 1394(C-N str)669(C-S str), 1506(N=O str).
9	03G	3203(N-H str), 3049 (Ar, C-H str), 2979(alkenes),1714,1699,1668(C=O), 1244 (C0-NH str), 1394(C-N str), 659(C-S str).1053(C-Cl, Ar str)
10	03H	3257 (N-H str), 3062 (Ar, C-H str), 2983 (alkenes), 1704,1660,1625 (C=O str), 1261(CO-NH str), 1392 (C-N str), 665 (C-S str).

Table-(IIB) ^{1}HNMR and Mass Spectral Data

Fig. No.	Compound	^{1}HNMR Spectral Data δ (ppm)	Peaks Observed
1	01A	8.5 (1H, CH), 4.2 (2H, CH_2)11.1 (1H, NH), 7.5-7.8 (5H, Ar)	196 (M^+), 194(M-2)
2	02A	8.3 (1H, CH), 11.1 (1H, NH), 2.62 (4H,CH2),2.27(2H, CH2)7.5-7.8 (5H, Ar)	259(M^+) and other important peaks are 203, 189
3	03A	5.9 (1H, CH), 11.1 (1H, NH), 2.3(2H,CH2),2.6(4H,CH2),3.9 (2H, CH2),7.5-7.8 (5H, Ar)	334(M^+)
4	03B	5.9 (1H, CH),11.1 (1H, NH), 2.6(4H,CH2), 2.3(2H,CH2), 3.9(2H, CH2), 7.5-7.8 (4H,Ar), 3.06(6H,CH3)7.5-7.8 (4H, Ar), 3.06(6H,CH3)	376(M^+) and other important peaks are 233

5	03C	5.9 (1H, CH), 11.1 (1H, NH), 2.62 (4H,CH2), 2.27(2H,CH2),3.96(2H, CH2),9.63(1H, OH), 3.83(3H, CH3),7.5-7.8 (3H, Ar)	379(M^+) and other important peaks are 325, 253
6	03D	5.9 (1H, CH),11.1 (1H, NH), 2.62 (4H,CH2), 2.27(2H,CH2), 3.96(2H, CH2),9.63(1H, OH),7.5-7.8 (4H, Ar)	350(M + 1)
7	03E	5.9 (1H, CH),11.1 (1H, NH), 2.62 (4H,CH2), 2.27(2H, CH2),3.96(2H, CH2),7.5-7.8 (3H, Ar)	401(M^+) and other important peaks are 263, 228
8	03F	5.9 (1H, CH),11.1 (1H, NH), 2.62 (4H,CH2), 2.27(2H, CH2),3.96(2H, CH2),7.5-7.8 (4H, Ar)	378(M^+), 379(M+1) and other important peaks are 226, 194
9	03G	5.9 (1H, CH),11.1 (1H, NH), 2.62 (4H,CH2), 2.27(2H, CH2),3.96(2H, CH2),7.5-7.8 (4H, Ar)	367(M^+) and other important peaks are 227, 211, 195
10	03H	5.9 (1H, CH),11.1 (1H, NH), 2.62 (4H,CH2), 2.27(2H, CH2),3.96(2H, CH2),7.5-7.8 (4H, Ar), 3.83(3H, CH3)	365(M+2) and other important peaks are 350, 210, 209

RESULT AND DISCUSSION

Antibacterial activity

Staphylococcus aureus and Enterococci (gram-positive)

The zone of inhibition exhibited by 50µg of the compound 3-[2-(2,4-dichloro phenyl)4-oxo-1,3-thiazolidine] acetamido succinimide [03E] against *Staphylococcus aureus* (16mm) is significant but is less than the inhibition shown by 10ug and 5ug of standards Norfloxacin and Gatifloxacin (19.3mm and 23.3mm respectively).

The zone of inhibition exhibited by 50µg of the compound 3-[2-(2, 4-dichloro phenyl) 4-oxo-1, 3-thiazolidine] acetamido succinimide [03E] against *Enterococci* (13mm) is significant but is less than the inhibition shown by 10ug and 5ug of standards Norfloxacin and Gatifloxacin (13.7mm and 16.3mm respectively).

The 2,4-dichloro substituted derivative of thiazolidinone has shown better activity against both ***Staphylococcus aureus*** *and* ***Enterococci*** among the newly synthesized compounds.

All compounds have shown antibacterial activity against gram-positive bacteria namely

Staphylococcus aureus *and* ***Enterococci.***

The order of the antimicrobial activity for the synthesized compounds is as follows:

For *Staphylococcus aureus*

03E (16mm) > 03G (15mm) > 03F (14mm) > 03C (13.3mm) > 03D (12.3mm) > 03H (12mm) > 03B (10.3mm) > 03A (9.7mm).

For *Enterococci*

03E (13mm) > 03D (12.7mm) > 03G (12mm) > 03H (12mm) > 03C(11mm) > 03F (11mm) > 03A (8mm) > 03B (7.3mm)

Escherichia coli and Pseudomonas aerugenosa (gram-negative)
The zone of inhibition exhibited by 50µg of the compound 3-[2-(2-nitro phenyl) 4-oxo-1,3-thiazolidine]acetamido succinimide [03F] against *Escherichia coli* (19.3mm) is significant but is less than the inhibition shown by 10ug and 5ug of standards Norfloxacin and Gatifloxacin (25.7mm and 27.3mm respectively).

The zone of inhibition exhibited by 50µg of the compound 3-[2-(4-chloro phenyl)4-oxo-1,3-thiazolidine] acetamido succnimide [03G] against *Psuedomonas aerogenosa* (11.7 mm) is significant but is less than the inhibition shown by 10ug and 5ug of standards Norfloxacin and Gatifloxacin (13mm and 14.3mm respectively).

The substiution of 2-nitro or 2-chloro group on thiazolidinone derivatives has shown activity against both *Escherichia coli and Psuedomonas aerugenosa* respectively *among* the newly synthesized compounds.

All compounds have shown antibacterial activity against gram-negative bacteria,

Escherichia coli *and* ***Psuedomonas aerugenosa***.
The order of the antimicrobial activity for the synthesized compounds is as follows.
For *Psuedomonas aerugenosa*.
03G (11.7mm) > 03B (10mm) > 03C (9mm) > 03H (9mm) > 03E (9mm) > 03F (7.7mm) > 03A (7mm) > 03D (6mm).

For *Escherichia coli*
03F (19.3mm) > 03C (18.7mm) > 03G (14.3mm) > 03A (13.7mm) > 03D (12.3mm) > 03B (11.7mm) > 03E (10.3mm) > 03H (10.3mm).

Antifungal activity
Aspergillus niger and Aspergillus flavus
The antifungal activity of newly synthesized thiazolidinone derivatives has been evaluated against *Aspergillus niger and Aspergillus flavus* the standards used is Clotrimazole and Amphotericin B.
The zone of inhibition exhibited by 50µg of the compound 3-[2-(3-methoxy phenyl) 4-oxo-1,3-thiazolidine]acetamido succinimide [03H] against *Aspergillus niger* (13.3mm) is significant but is less than the inhibition shown by 10ug and 100units of standards Clotrimazole and Amphotericin B (14.33mm and 16mm respectively).

The zone of inhibition exhibited by 50µg of the compound 3-[2-(2-hydroxy phenyl) 4-oxo-1,3-thiazolidine] acetamido succinimide and 3-[2-(3-methoxy phenyl) 4-oxo-1,3-thiazolidine] acetamido succinimide [03D] and [03H] against *Aspergillus flavus* (13mm respectively) is significant but is less than the inhibition shown by 10ug and 100units of standards Clotrimazole and Amphotericin B (16mm).

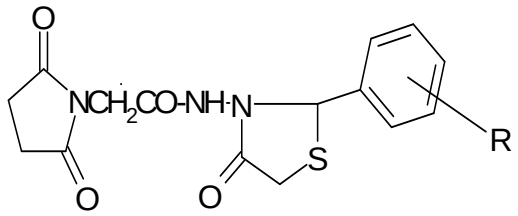
All compounds have shown antifungal activity against ***Aspergillus flavus*** *and* ***Aspergillus niger.***
The order of the antifungal activity for the synthesized compounds is as follows,

For *Aspergillus niger*
03H (13.3mm) >03F (11mm) >03B (10.7mm) >03D (10.7mm) >03C (10.3mm) >03A (9.3mm) >03G (8mm) > 03E (7mm).

For *Aspergillus flavus*
03D (13mm) >03H (13mm) >03C (11.7mm) >03B (11.3mm) >03E (11.3mm) >03 (11mm) >03F (10.3mm) >03G (9.7mm).

Antimicrobial activity:

Table – II (A) : Results Of Antibacterial Activity



Compounds	R	Zone of Inhibition (mm)			
		S.aureus	***Enterococci***	***E.coli***	***Pseudo. aeroginosa***
03A	H	9.7	08	13.7	07
03B	$N(CH_3)_2$	10.3	7.3	11.7	10
03C	$3\text{-}OCH_3$,4-OH	13.3	11	18.7	09
03D	2-OH	12.3	12.7	12.3	06
03E	2,4 Cl	16	13	10.3	09
03F	$2\text{-}NO_2$	14	11	19.3	7.7
03G	4-Cl	15	12	14.3	11.7
03H	$3\text{-}OCH_3$	12	12	10.3	09
Norfloxacin	……..	19.3	13.7	25.7	13
Gatifloxacin	……..	23.7	16.3	27.3	14.3
Control(DMF)	……..	NI	NI	NI	NI

Table –II (B) : Results of Antifungal Activity

Compounds	R	Zone of Inhibition (mm)	
		Aspergillus flavus	***Aspergillus niger***
03A	H	11	9.3
03B	$N(CH_3)_2$	11.3	10.7
03C	3-OCH_3,4-OH	11.7	10.3
03D	2-OH	13	10.7
03E	2,4 Cl	11.3	8
03F	2-NO_2	10.3	11
03G	4-Cl	9.7	7
03H	3-OCH_3	13	13.3
Clotrimazole	……..	16	14.3
Amphotericin B	……..	16	16
Control (DMF)	……..	NI	NI

NOTE:- Average Zone diameter of triplicates in mm
NI :- No Inhibition

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