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RESEARCH ARTICLE

SYNTHESIS OF NOVEL THIAZOLIDINONES AND THEIR BIOLOGICAL ACTIVITIES

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Abstract

Various Novel 2-(Substitutedphenyl) -3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl)-2-phenylthiazolidin-4-one (2b) were prepared by refluxing with Schiff bases (2a) in presence of thioglycolic acid in benzene. The Schiff bases were prepared by condensation of various Aryl Aldehydes with 1-[2-amino-1-(3-methoxyphenyl)ethyl]cyclohexanol. The titled Compounds were characterized by TLC and spectral analysis. Some of the synthesized compounds showed potential antibacterial and antifungal activity.

INTRODUCTION

The great expansion in medicinal research in the field of various heterocyclic compounds has contributed much to the unparallel progress of medicine and benefited numerous chemists and researchers. The Human immune system has long being implicated in the body's defence against various diseases. There is a constant requirement in the research of New drugs to overcome the increasing diseases and emerging anti drug resistant microbes Today a large number of diseases are cured or at least controlled by drug therapy.

4-Thiazolidinones is a core of various pharmacological agents. The Magical moiety of 4-Thiazolidinones have a broad spectrum of biological activities such as, Anti-inflammatory [1][2], Anti-tubercular [3][4], Anti-Histamic [5][6], Anti-Convulsant[7][8], Anti-microbial[9], Anti HIV[10], Anti-viral[11], Antimycobacterial[12], cardiovascular effects[13]. Compound containing thiazolidinone moiety have been found to exhibit broad spectrum Anti-microbial activity[14].

4-Thiazolidinone derivatives play a vital role in many biological processes and synthetic drugs. They also play a vital role owing to their wide range of pharmacological activities and industrial importance as stabilizers for polymeric materials. Substituent in the 2, 3 and 5 position may be varied, but the greatest difference in structure and properties is exerted by groups attached to carbon atom at the 2 position and to nitrogen atom at the 3 position. Infections caused by multidrug resistant gram-positive organisms pose a serious challenge to the scientific community and the need for an effective therapy has led to a search for novel antibacterial agents[15].

From above data and reasoning we have directed our work to synthesize new derivatives consisting of 4-thiazolidinones. The aim of the present paper is to synthesize 4-thiazolidinones derivatives depicting favourable biological activities.

2. Experimental

2. 1. General

All chemicals used in the synthesis of the titled compounds were of analytical grade. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was determined by thin layer chromatography (TLC) plates using Toluene-Ethyl Acetate (7.5: 2.5, 9:1) solutions. The spots were observed by exposure to iodine vapours or by UV light. The IR spectra were obtained on SHIMADZU, Model: FTIR 8400S With DRS. The 1H-NMR were recorded on a BRUKER NMR spectrometer (300 MHz) in DMSO. The results of particular Elemental analysis of all the compounds were in good agreement with the calculated values.

2.1 Materials: Aryl Aldehydes, MeOH, Acetic Acid, 1-[2-amino-1-(3-)ethyl] cyclohexanol , Thioglycolic acid, Benzene.

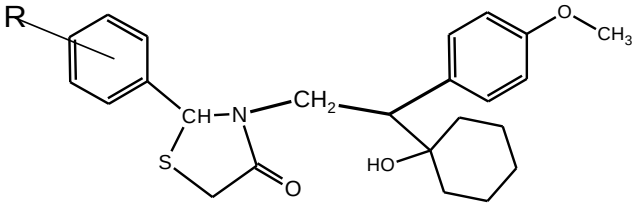
2.2 Synthesis of 2-(Substitutedphenyl) -3-(2-(1-hydroxycyclohexyl)thiazolidin-4-one (2b)

GENERAL PROCEDURE :

A mixture of aryl aldehydes (0.01 M) and 1-[2-amino-1-(3-)ethyl]cyclohexanol(0.01 M) in Methanol was refluxed on water bath for 6-7 hours. Excess of Methanol was then distilled off and resulting product was kept in dark for 1 day, resulting solid was washed with DIPE(Diisopropyl Ether) and recrystallised with a suitable solvent.

Schiff base and and thioglycolic acid (0.012 M) in dry benzene (50 ml) were refluxed on waterbath using Dean-Stark water-separator for 10-12 hours. Excess of benzene was then distilled off and the resulting viscous liquid was washed with 10% NaHCO3 solution to remove any unreacted Thioglycolic acid. The resulting product separated was washed with water dried and recrystallised from Methanol.

Materials and Methods



(2b)

Where R= Substituted Phenyls

2b-1

2-(3,4-dihydroxy-5-nitrophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl)thiazolidin-4-one

Brown solid, M.P. 225-227 °C, yield: 80%; IR (KBr) ν cm-1: 1672 (C=O), 1265 (C-N).

1H NMR (DMSO): δ 3.66 (s, 2H, S-CH_2), 3.77(d, 2H, -N-CH_2-)3.72 (s, 3H,-OCH_3), 3.42 (t, 1H, -CH<), 4.18 (s, 1H, N-CH-Ar), 6.77-7.65 (m, 8H, Ar-H), 1.08-1.62 (m, 10H, Cyclohexane); *m/z*: 487(M+1)

Elemental analyses of $C_{24}H_{28}N_2O_7S$; M.WT:488.55

Calculated: C-58.99; H-5.71; N-5.73; found C-58.94; H-5.69; N-5.70.

2b-2

2-(4-hydroxyphenyl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl)thiazolidin-4-one

Brown solid, M.P. 115-118°C, yield:74 %; IR (KBr) cm-1: 1675 (C=O), 1259 (C-N).

H1 NMR (CDCl3): δ 1H NMR (DMSO): δ 3.59 (s, 2H, S-CH_2), 3.82(d, 2H, -N-CH_2-)3.72 (s, 3H,-OCH_3), 3.28 (t, 1H, -CH<), 5.55 (s, 1H, N-CH-Ar), 6.89-8.07 (m, 8H, Ar-H), 1.27-1.95 (m, 10H, Cyclohexane); *m/z*:426.30(M+1)

Elemental analyses of $C_{24}H_{29}NO_4S$; M.WT.: 427.55;

Calculated C-67.41; H-6.83; N-3.27;found C-67.38; H-6.80; N-3.24.

2b-3

2-(p-tolyl)-3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylthiazolidin-4-one

Brown solid, M.P. 118-122°C, yield: 65%; IR (KBr) ν cm-1: 1666 (C=O),1252 (C-N).

1H NMR (DMSO): δ 1H NMR (DMSO): δ 3.54 (s, 2H, S-CH_2), 3.80(d, 2H, -N-CH_2-)3.69 (s, 3H,-OCH_3), 3.39 (t, 1H, -CH<), 5.10 (s, 1H, N-CH-Ar), 6.90-7.61 (m, 8H, Ar-H), 1.02-1.51 (m, 10H, Cyclohexane); *m/z*: 424.29(M+1).

Elemental analyses of $C_{23}H_{31}NO_3S$; M.WT.:425.58;

Calculated C-64.91; H-7.34; N-3.29;found C-64.87; H-7.31; N-3.26.

2b-4

2-(phenyl)- 3-(2-(1-hydroxycyclohexyl)-2-(3-methoxyphenyl)ethyl) thiazolidin-4-one

Brown solid, M.P. 145-148°C, yield: 85%; IR (KBr) ν cm-1: 1678 (C=O),1259 (C-N).
1H NMR (DMSO): δ 1H NMR (DMSO): δ 3.60 (s, 2H, S-CH_2), 3.71(d, 2H, -N-CH_2-)3.79 (s, 3H,-OCH_3), 3.39 (t, 1H, -CH<), 4.45 (s, 1H, N-CH-Ar), 6.80-7.60 (m, 8H, Ar-H), 1.10-1.52 (m, 10H, Cyclohexane); *m/z*:410.01(M+1).
Elemental analyses of $C_{24}H_{29}NO_3S$; M.WT: 411.55;
Calculated C-70.03; H-7.59; N-3.40; found C-70.00; H-7.55; N-3.38

2b-5

2-(2-chlorophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(3-methoxyphenyl)ethyl)thiazolidin-4-one

Brown solid, M.P. 126-129°C, yield: 81 %; IR (KBr) ν cm-1: 1685 (C=O),1256 (C-N).
1H NMR (DMSO): δ 1H NMR (DMSO): δ 3.58 (s, 2H, S-CH_2), 3.73(d, 2H, -N-CH_2-)3.70 (s, 3H,-OCH_3), 3.46 (t, 1H, -CH<), 4.77 (s, 1H, N-CH-Ar), 6.90-7.75 (m, 8H, Ar-H), 1.21-1.83 (m, 10H, Cyclohexane).
Elemental analyses of $C_{24}H_{28}ClNO_3S$; M.WT.: 446.002;
Calculated C-64.62; H-6.32; N-3.41;found C-64.60; H-6.29; N-3.39

2b-6

2-(2-fluorophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(3-methoxyphenyl)ethyl)thiazolidin-4-one

Brown solid, M.P. 169-171°C, yield: 70 %; IR (KBr) ν cm-1: 1689 (C=O),1260 (C-N).
1H NMR (DMSO): δ 1H NMR (DMSO): δ 3.70(s, 2H, S-CH_2), 3.79(d, 2H, -N-CH_2-)3.70 (s, 3H,-OCH_3), 3.49 (t, 1H, -CH<), 5.25 (s, 1H, N-CH-Ar), 7.18-8.10 (m, 8H, Ar-H), 1.18-1.68 (m, 10H, Cyclohexane).
Elemental analyses of $C_{24}H_{28}FNO_3S$; M.WT.: 429.54;
Calculated C-67.10; H-6.57; N-3.26; found C-67.05; H-6.52; N-3.24

2b-7

2-(4-hydroxy-3-methoxyphenyl)-3-(2-(1-hydroxycyclohexyl)-2-(3-methoxyphenyl)ethyl)thiazolidin-4-one

Brown solid, M.P. 153-156°C, yield: 72%; IR (KBr) ν cm-1: 1653 (C=O),1251 (C-N).
1H NMR (DMSO): δ 1H NMR (DMSO): δ 3.64 (s, 2H, S-CH_2), 3.80 (d, 2H, -N-CH_2-)3.75 (s, 3H,-OCH_3), 3.50 (t, 1H, -CH<), 5.00 (s, 1H, N-CH-Ar), 6.97-7.85 (m, 8H, Ar-H), 1.13-1.68 (m, 10H, Cyclohexane).
Elemental analyses of $C_{25}H_{31}NO_5S$; M.WT.: 457.582;
Calculated C-65.61; H-6.82; N-3.06; found C-65.58; H-6.80; N-3.02.

2b-8

2-(4-hydroxy-3-methoxy-5-nitrophenyl)-3-(2-(1-hydroxycyclohexyl)-2-(3-methoxyphenyl)ethyl)thiazolidin-4-one

Brown solid, M.P. 110-113°C, yield: 47%; IR (KBr) ν cm-1: 1690 (C=O),1270 (C-N).
1H NMR (DMSO): δ 1H NMR (DMSO): δ 3.71 (s, 2H, S-CH2), 3.79(d, 2H, -N-CH2-)3.69 (s, 3H,-OCH3), 3.48 (t, 1H, -CH<), 5.45 (s, 1H, N-CH-Ar), 7.20-8.05 (m, 8H, Ar-H), 1.08-1.70 (m, 10H, Cyclohexane).
Elemental analyses of $C_{25}H_{30}N_2O_7S$; M.WT.: 502.579;
Calculated C-59.74; H-6.61; N-5.57; found C-59.70; H-6.58; N-5.52.

2b-9

3-(2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl) ethyl)-2-(4-methoxyphenyl)thiazolidin-4-one

Brown solid, M.P. 178-180°C, yield: 58 %; IR (KBr) ν cm^{-1}: 1690 (C=O),1259 (C-N).
1H NMR (DMSO): δ 3.66 (s, 2H, S-CH_2), 3.77(d, 2H, -N-CH_2-)3.72 (s, 3H,-OCH_3), 3.42 (t, 1H, -CH<), 4.18 (s, 1H, N-CH-Ar), 6.77-7.65 (m, 8H, Ar-H), 1.08-1.62 (m, 10H, Cyclohexane); m/z: 440.45(M+1)
Elemental analyses of $C_{25}H_{31}NO_4S$; M.WT: 441.58;
Calculated C-67.99; H-7.07; N-3.17; found C-67.95; H-7.01; N-3.15.

2b-10

2-(4-amino-2,3-dimethylphenyl)-3-(2-(1-hydroxycyclohexyl)-2-(3-methoxyphenyl)ethyl)thiazolidin-4-one

Brown solid, M.P. 220-223°C, yield: 52%; IR (KBr) ν cm^{-1}: 1712 (C=O),1328 (C-N).
1H MR (DMSO): δ 3.70 (s, 2H, S-CH_2), 3.81(d, 2H, -N-CH_2-)3.65 (s, 3H,-OCH_3), 3.39 (t, 1H, -CH<), 5.20 (s, 1H, N-CH-Ar), 7.10-8.15 (m, 8H, Ar-H), 1.10-1.83(m, 10H, Cyclohexane).
Elemental analyses of $C_{26}H_{34}N_2O_3S$; M.WT. : 454.624;
Calculated C, 72.05; H, 6.05; N, 4.94; found C, 72.02; H, 6.00; N, 4.89.

3. Results and Discussion

The 4-thiazolidinones are synthesised from Schiff bases containing different Aryl Aldehydes . When Schiff base was treated with thioglycolic acid in benzene, 4-thiazolidinones are formed. All the synthesized compounds are confirmed from their characteristic IR, 1H NMR spectroscopic data and elemental analysis as described above. The structures of the synthesized compounds (2-(1-10) b) were supported by spectral analysis. In IR spectra >C=O of thiazolidinone observed at 1653-1690 cm^{-1}. Another C-N stretching found at 1251-1270 cm-1. The 1H-NMR signals of cyclized thiazolidinones were observed at 3.54-3.71 corresponding to S-CH2– in the ring. From the above spectral discussions, the structure of thiazolidinone in synthesised compounds is confirmed.

TABLE – 1

Sr. No.	R	**M.F** M.Wt. (g/mol)	**Yield %**	**M.P**˚C	**Elemental analysis**		
					%C (Found)	**%H (Found)**	**%N (Found)**
2-1b	3,4-dihydroxy-5-nitrobenzaldehyde	$C_{24}H_{28}N_2O_7S$ 488.55	80	225-227	58.99 (58.94)	5.71 (5.69)	5.73 (5.70)
2-2b	4-Hydroxybenzaldehyde	$C_{24}H_{29}NO_4S$ 427.55	74	115-118	67.41 (67.38)	6.83 (6.80)	3.27 (3.24)
2-3b	4-Methylbenzaldehyde	$C_{23}H_{31}NO_3S$ 425.58	65	118-122	64.91 (64.87)	7.34 (7.31)	3.29 (3.26)
2-4b	Benzaldehyde	$C_{24}H_{29}NO_3S$ 411.55	85	145-148	70.03 (70.00)	7.59 (7.55)	3.40 (3.38)
2-5b	2-Chlorobenzaldehyde	$C_{24}H_{28}ClNO_3S$ 446.00	81	126-129	64.62 (64.60)	6.32 (6.29)	3.41 (3.39)
2-6b	2-Fluorobenzaldehyde	$C_{24}H_{28}FNO_3S$ 429.54	70	169-171	67.10 (67.05)	6.57 (6.52)	3.26 (3.24)
2-7b	4-Hydroxy-3-methoxybenzaldehyde	$C_{25}H_{31}NO_5S$ 457.58	72	153-156	65.61 (65.58)	6.82 (6.80)	3.06 (3.02)
2-8b	4-Hydroxy-3-methoxy-5-nitrobenzaldehyde	$C_{25}H_{30}N_2O_7S$ 502.57	80	110-113	59.74 (59.70)	6.61 (6.58)	5.57 (5.52)
2-9b	4-Methoxybenzaldehyde	$C_{25}H_{31}NO_4S$ 441.58	77	178-180	67.99 (67.95)	7.07 (7.04)	3.17 (3.15)
2-10b	2,3-dimethyl-4-aminobenzaldehyde	$C_{26}H_{34}N_2O_3S$ 454.62	83	220-223	68.68 (68.66)	7.53 (7.50)	6.16 (6.14)

TABLE 2

SERIES 2 - ANTIBACTERIAL ACTIVITY TABLE					
Sr.No.	R	MINIMAL INHIBITION CONCENTRATION			
		Gram negative		Gram positive	
		E.COLI	**K.PNEUMONIAE**	**S.AUREUS**	**S.PYOGENUS**
		MTCC 443	**MTCC 109**	**MTCC 96**	**MTCC 442**
1b	3,4-dihydroxy-5-nitro vanillin	125	200	250	250
2b	4-hydroxy benzaldehyde	200	250	100	50
3b	4-methyl benzaldehyde	250	125	500	500
4b	Benzaldehyde	250	100	250	250
5b	2-chlorobenzaldehydel	500	500	62.5	125
6b	2-flourobenzaldehyde	500	500	125	125
7b	4-Hydroxy-3-methoxybenzaldehyde	250	125	250	250
8b	4-Hydroxy-3-methoxy-5-nitrobenzaldehyde	100	62.5	250	100
9b	4-methoxy benzaldehyde	200	125	500	250
10b	2,3-dimethyl-4-amino benzaldehyde	62.5	100	500	100
STANDARD DRUGS		**MICROGRAMME/ML**			
1.	GENTAMYCIN	0.05	1	0.25	0.5
2.	AMPICILLIN	100	--	250	100
3.	CHLORAMPHENICOL	50	50	50	50
4.	CIPROFLOXACIN	25	25	50	50
5.	NORFLOXACIN	10	10	10	10

3.2 Antimicrobial activity

All compounds given in Table-1 were tested in vitro for their antimicrobial activity. The products are screened for their antimicrobial activity using Broth dilution method by measuring the Minimum inhibition concentration (MIC) of compounds 2b (1-10) against gram positive strains of S. aureus and S. pyogenus and gram negative strains of E-coli and K. Pneumoniae bacteria.

From the antibacterial results of the series presented, compound 2b showed high activity and 5b showed good activity against gram positive organisms whereas compounds 8b and 10b showed good activity against gram negative organisms. Rest of compounds showed good to moderate activity.

Gentamycin, Ampiciline, Chloramphenicol, Ciprofloxacin and Norfloxacin are used as the standard antibacterial drugs.

All the synthesized compounds have been screened against fungal strains C. albicans, A.clavatus and A. niger. Compounds 4b and 9b are the most active against both the fungal species. Remaining compounds showed the moderate activity. Nystatin and Greseofulvin are used as the standard antifungal drugs.

TABLE 3

SERIES 2 - ANTIFUNGAL ACTIVITY TABLE				
Sr.No.	R	MINIMAL FUNGICIDAL CONCENTRATION		
		C.ALBICANS	**A.NIGER**	**A.CLAVATUS**
		MTCC 227	**MTCC 282**	**MTCC 1323**
1b	3,4-dihydroxy-5-nitro vanillin	500	>1000	>1000
2b	4-hydroxy benzaldehyde	1000	>1000	>1000
3b	4-methyl benzaldehyde	1000	>1000	>1000
4b	Benzaldehyde	250	500	500
5b	2-chlorobenzaldehydel	250	>1000	>1000
6b	2-flourobenzaldehyde	>1000	>1000	>1000
7b	Vanillin	500	1000	1000
8b	5-Nitrovanillin	100	>1000	>1000
9b	4-methoxy benzaldehyde	250	500	500
10b	2,3-dimethyl-4-amino benzaldehyde	500	500	500
STANDARD DRUGS		**MICROGRAMME/ML**		
1.	NYSTATIN	100	100	100
2.	GRESEOFULVIN	500	100	100

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