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Synthesis and Antimicrobial Evaluation Of Some Novel Optically Active 4-Thiazolidinones Derivatives

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ABSTRACT

Various novel optically active substituted aryl-4-thiazolidinones 2a-j have been prepared from corresponding Schiff's bases 1a-j & thioglycolic acid in benzene using Dien and Stark apparatus. Structure of the synthesized compound was confirmed by Spectral data (IR, ^{1}H NMR) & elemental analysis. All the newly synthesized compounds were evaluated for their antimicrobial activities. Investigation of antimicrobial activities of compounds was done by Broth dilution method used for the determination of minimum inhibitory concentration.

Keywords: Schiff's base, 4-thiazolidinone, specific optical rotation, spectral studies, optically active.

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INTRODUCTION

A number of 4-thiazolidinone derivatives have been reported to possess diversified activities including hypoglycemic action [1]. With the discovery of 4-thiazolidinones as promising fungitoxic agents [2] medicinal chemists started working on this nucleus. 4-Thiazolidinone moieties are known to exhibit diverse bioactivities such as antitumor [3], anthelmintic [4], antibacterial[5-9], antifungal[10], CNS depressant & skeletal muscle relaxant activity[11], antitubercular [12-15], anti-inflammatory [16], anticonvulsant [17], analgesic[18], anti-HIV[19], antidiuretic [20]. 4-Thiazolidinone ring also plays important role in antidibetic activity of some drugs (pioglitazone, rosiglitazone).

For a long time we have described sets of Schiff's bases [21] (2-{4-[(S)-(4-chlorophenyl)(phenyl) methyl]-1-piperazinyl}-1-(4-{[aryl methylidene] amino}phenyl)ethanone) endowed with strong antimicrobial activity **(1a-j)**. The observed activity was clearly exceeding that of the starting optically active amine and aldehydes were surely active. Owing to this, we decide to extend our research to class analogs. Our analogs based design encompasses the synthesis of a series of novel optically active 4-thiazolidinone derivatives (scheme-I) to be tested for their antimicrobial properties.

All the newly synthesized compounds were evaluated for their antimicrobial activities. Investigation of antimicrobial activities of compounds was done by Broth dilution method used for the determination of minimum inhibitory concentration. The synthesize compounds were screened for antibacterial against gram-positive bacteria [*Staphylococcus aureus* (MTCC96), *Streptococcus pyogenes* (MTCC442)] & gram-negative bacteria [*Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC424)] & antifungal against *Candida alb cans* (MTCC227), *Aspergillus niger* (MTCC282) & *Aspergillus cravats* (MTCC1323).

MATERIALS AND METHODS

Experimental Section

All melting points were taken in open capillary tubes & are uncorrected. Purity of compound was checked by thin layer chromatography, performed on precoated TLC plates with silica gel (Merck 60 F_{254}) & detection was done by UV lamp (254 nm). Specific optical rotations (SOR) were taken in Jasco digital polarimeter. The IR spectra were obtained on a Perkin-Elmer BX series FTIR-5000 spectrophotometer using KBr pellets. The ^{1}H NMR spectra in DMSO-d_6 or $CDCl_3$ were recorded on Bruker WM 400FT MHz spectrometer & chemical shift were reported as parts per million (δ ppm) down field using TMS as internal standard. The antimicrobial activities were carried out at Microcare Laboratory, Surat.

General Procedure for Synthesis

A mixture of 2-{4-[(*S*)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[substituted methylidene] amino} phenyl) ethanone (0.01mole) & thioglycolic acid (0.01 mole) in benzene

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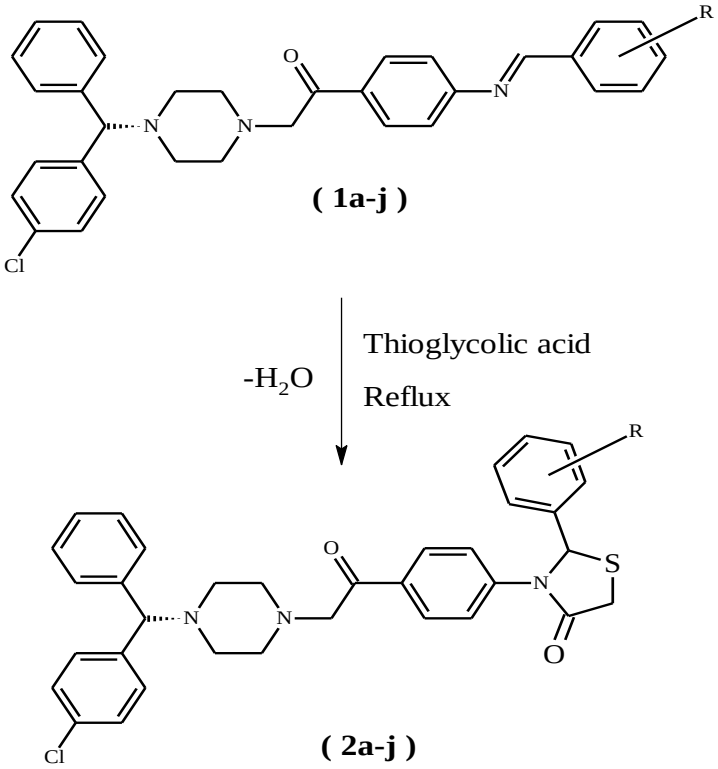
(30 ml) was refluxed for 6 hours. The water formed during the reaction was removed azeotropically by Dean and Stark apparatus. After the completion of the reaction, the solvent was removed & the product was isolated and recrystalised in methylene chloride. The remaining compounds 2a-j was synthesized by using appropriate substituted Schiff's base similarly. Their characterization data were recorded in Table-1.



Where, R=H, 2-Cl, 3-Cl, 2-OCH_3, 4-OCH_3, 4-CH_3, 3-NO_2, 2-NO_2, 4-OH-3-Br, 2-OH

Scheme1: Synthetic scheme for the title compound

3-[4-({4-[(*S*)-(4-chlorophenyl) (phenyl) methyl]-1-piperazinyl} acetyl) phenyl]-2- phenyl -1, 3-thiazolidin-4-one (2a):

IR [ν, cm^{-1}, KBr]: 1712 (C=O), 702 (C-S-C), 2956 (CH_2). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.83 (2H, s, –$COCH_2$), 3.99 (2H, s, –CH_2-S), 6.41 (1H, s, –CH-S), 5.46 (1H, s, –CH-N), 2.61-4.08 (8H, m, CH_2 piperazine), 7.05-8.15 (18H, m, Ar-H).

2-(2-chlorophenyl)-3-[4-({4-[(*S*)-(4-chlorophenyl) (phenyl) methyl] -1- piperazinyl} acetyl) phenyl] -1, 3-thiazolidin-4-one (2b):

IR [ν, cm^{-1}, KBr]: 1696 (C=O), 715 (C-S-C), 2945 (CH_2). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.89 (2H, s, –$COCH_2$), 3.97 (2H, s, –CH_2-S), 6.40 (1H, s, –CH-S), 5.40 (1H, s, –CH-N), 2.56-4.14 (8H, m, CH_2 piperazine), 7.0-8.18 (17H, m, Ar-H).

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2-(4-chlorophenyl)-3-[4-({4-[(*S*)-(4-chlorophenyl)(phenyl)methyl]-1- piperazinyl} acetyl) phenyl]-1,3-thiazolidin-4-one (2c):

IR [ν, cm^{-1}, KBr]: 1702 (C=O), 754 (C-S-C), 2961 (CH_2). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.84 (3H, s, –OCH_3), 3.88 (2H, s,–$COCH_2$), 4.01 (2H, s, –CH_2-S), 6.04 (1H, s, –CH-S), 5.38 (1H, s, –CH-N), 2.54-4.18 (8H, m, CH_2 piperazine), 7.10-8.19 (17H, m, Ar-H).

3-[4-({4-[(*S*)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}acetyl)phenyl]-2-(2-methoxy phenyl)-1,3-thiazolidin-4-one (2d):

IR [ν, cm^{-1}, KBr]: 1701 (C=O), 748 (C-S-C), 2975 (CH_2), 2866 (Ar-OCH_3). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.91 (3H, s, –OCH_3), 3.89 (2H, s,–$COCH_2$), 4.04 (2H, s, –CH_2-S), 6.14 (1H, s, –CH-S), 5.52 (1H, s, –CH-N), 2.65-4.11 (8H, m, CH_2 piperazine), 6.98-8.15 (17H, m, Ar-H).

3-[4-({4-[(*S*)-(4-chlorophenyl) (phenyl)methyl]-1-piperazinyl}acetyl)phenyl]-2-(4-methoxy phenyl)-1, 3-thiazolidin-4-one (2e):

IR [ν, cm^{-1}, KBr]: 1708 (C=O), 766 (C-S-C), 2975 (CH_2), 2861 (Ar-OCH_3). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.96 (3H, s, –OCH_3), 3.85 (2H, s,–$COCH_2$), 4.0 (2H, s, –CH_2-S), 6.24 (1H, s, –CH-S), 5.41 (1H, s, –CH-N), 2.58-4.05 (8H, m, CH_2 piperazine), 6.96-8.18 (17H, m, Ar-H).

3-[4-({4-[(*S*)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}acetyl)phenyl]-2-(4-methyl phenyl)-1,3-thiazolidin-4-one (2f):

IR [ν, cm^{-1}, KBr]: 1712 (C=O), 748 (C-S-C), 2942 (CH_2), 1345 (Ar-CH_3). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 2.33 (3H, s, –CH_3), 3.91 (2H, s,–$COCH_2$), 4.02 (2H, s, –CH_2-S), 6.20 (1H, s, –CH-S), 5.60 (1H, s, –CH-N), 2.54-4.11 (8H, m, CH_2 piperazine), 6.97-8.22 (17H, m, Ar-H).

3-[4-({4- [(*S*)-(4-chlorophenyl) (phenyl) methyl]-1-piperazinyl}acetyl) phenyl]-2-(3-nitro phenyl)-1,3-thiazolidin-4-one (2g):

IR [ν, cm^{-1}, KBr]: 1698 (C=O), 736 (C-S-C), 2949 (CH_2), 1514 (Ar-NO_2). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.97 (2H, s, –$COCH_2$), 4.1 (2H, s, –CH_2-S), 6.01 (1H, s, –CH-S), 5.58 (1H, s, –CH-N), 2.63-4.19 (8H, m, CH_2 piperazine), 6.96-8.09 (17H, m, Ar-H).

3-[4-({4- [(*S*)-(4-chlorophenyl) (phenyl) methyl]-1-piperazinyl} acetyl) phenyl]-2-(2-nitro phenyl)-1, 3-thiazolidin-4-one (2h):

IR [ν, cm^{-1}, KBr]: 1704 (C=O), 766 (C-S-C), 2968 (CH_2), 1518 (Ar-NO_2). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.79 (2H, s, –$COCH_2$), 4.06 (2H, s, –CH_2-S), 6.11 (1H, s, –CH-S), 5.68 (1H, s, –CH-N), 2.51-4.17 (8H, m, CH_2 piperazine), 6.95-8.19 (17H, m, Ar-H).

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2-(3-bromo-4-hydroxyphenyl)-3-[4-({4-[(*S*)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl} acetyl)phenyl]-1,3-thiazolidin-4-one (2i):

IR [ν, cm^{-1}, KBr]: 1706 (C=O), 758 (C-S-C), 3361 (OH), 2955 (CH_2), 691 (C-Br). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.96 (2H, s, –$COCH_2$), 3.98 (2H, s,–CH_2-S), 6.08 (1H, s, –CH-S), 4.35 (1H, s, –OH), 5.59 (1H, s, –CH-N), 2.62-4.23 (8H, m, CH_2 piperazine), 6.90-8.15 (16H, m, Ar-H).

3-[4-({4- [(*S*)-(4-chlorophenyl) (phenyl) methyl]-1-piperazinyl} acetyl) phenyl]-2-(2-hydroxyphenyl)-1, 3-thiazolidin-4-one (2j):

IR [ν, cm^{-1}, KBr]: 1699 (C=O), 726 (C-S-C), 3369 (OH), 2962 (CH_2). ^{1}H NMR [400MHz, δ, ppm, DMSO]: 3.90 (2H, s, –$COCH_2$), 4.02 (2H, s, –CH_2-S), 6.14 (1H, s, –CH-S), 5.71 (1H, s, –CH-N), 2.53-4.05 (8H, m, CH_2 piperazine), 6.89-8.17 (17H, m, Ar-H).

TABLE 1: THE PHYSICAL AND ANALYTICAL DATA OF (2a-j)

Comp. No.	R	Molecular Formula (M.wt.)	MR °C	SOR $[\alpha]_d^{28}$ °	Yield %	Elementary Analysis % Found (Calculated)		
						% C	% H	% N
2a	H	$C_{34}H_{32}ClN_3O_2S$ (582)	122-123	-1.98	78	70.12 (70.15)	5.51 (5.54)	7.20 (7.22)
2b	2 - Cl	$C_{34}H_{31}Cl_2N_3O_2S$ (616)	178-180	-1.39	75	66.19 (66.23)	5.05 (5.07)	6.80 (6.81)
2c	4 - Cl	$C_{34}H_{31}Cl_2N_3O_2S$ (616)	172-173	-1.45	79	66.22 (66.23)	5.01 (5.07)	6.83 (6.81)
2d	2 - OCH_3	$C_{35}H_{34}ClN_3O_3S$ (612)	195-196	-1.84	81	68.65 (68.67)	5.55 (5.60)	6.84 (6.86)
2e	4 - OCH_3	$C_{35}H_{34}ClN_3O_3S$ (612)	187-188	-1.56	76	68.61 (68.67)	5.58 (5.60)	6.80 (6.86)
2f	4 - CH_3	$C_{35}H_{34}ClN_3O_2S$ (596)	118-120	-1.14	70	70.50 (70.51)	5.73 (5.75)	7.00 (7.05)
2g	3 - NO_2	$C_{34}H_{31}ClN_4O_4S$ (627)	128-129	-1.89	71	65.09 (65.11)	4.99 (4.98)	8.90 (8.93)
2h	2 - NO_2	$C_{34}H_{31}ClN_4O_4S$ (627)	199-200	-1.52	83	65.10 (65.11)	4.94 (4.98)	8.92 (8.93)
2i	4 - OH 3 - Br	$C_{34}H_{31}BrClN_3O_3S$ (677)	99-100	-1.76	69	60.30 (60.32)	4.59 (4.62)	6.17 (6.21)
2j	2 - OH	$C_{34}H_{32}ClN_3O_3S$ (598)	121-122	-1.78	74	68.24 (68.27)	5.36 (5.39)	7.04 (7.02)

Antibacterial Activity

Antibacterial activities of all the compounds were studied against gram-positive bacteria [*Staphylococcus Aureus* (MTCC96), *Streptococcus pyogenes* (MTCC442)] & gram-negative bacteria [*Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC424)] by the broth dilution method. Stock solutions of the series of compounds were prepared in DMSO. Each synthesized drug was diluted obtaining 2000 microgram/ml concentration, as a stock solution.

Serial dilutions were prepared in primary & secondary screening. In primary screening 500 micro/ml, 250 micro/ml, & 125 micro/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, 6.250 micro/ml, 3.125 micro/ml & 1.5625 micro/ml concentrations. Under similar condition using Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin & Norfloxacin as a standard for comparison control experiment was carried out.

Antifungal Activity

The compounds 2a-j were also screened for their antifungal activity against *Candida albicans* (MTCC227), *Aspergillus niger* (MTCC282) & *Aspergillus clavatus* (MTCC1323) at 2000µg/ml concentration using agar cup plate method. The antifungal activity was compared with the known standard drugs Griseofulvin, Nystatin & the results were presented in Table-2.

RESULTS AND DISCUSSION

New series of compounds namely aryl-4-thiazolidinones 2a-j have been synthesized by using experimental protocol as shown in Scheme 1. All the derivatives were supported by spectral data. The structures of substituted aryl-4-thiazolidinone 2a-j were prepared by refluxing aryl Schiff's base with thioglycolic acid in benzene. The water formed during the reaction was removed azeotropically by Dean and Stark apparatus. The compound was confirmed by elemental analysis & IR spectra, showed (C=O) stretching absorption band at 1725-1660 cm^{-1}, (C-S-C) stretching absorption band at 800-600 cm^{-1} & ^{1}H NMR spectrum displayed signals for the presence of two proton of thiazolidinone ring (-CH_2-S) at 3.99 ppm (2H, s), one proton of thiazolidinone ring (-CH-S) at 6.01ppm (1H, s), ketone group (-CO-CH_2) at 2.63 ppm (2H, s) & aromatic ring proton (Ar-H) at 7.05-8.15 ppm (m).

CONCLUSION

New series of compounds namely substituted thiazolidinones 2a-j have been synthesized by using experimental protocol as shown in Scheme-1. All the derivatives were supported by spectral data. The result of the antimicrobial activities summarized in Table-2, indicated that the prepared compounds were toxic against the bacteria & showed better activity among the tested compounds. The screening data revealed that most of the tested compounds showed good bacterial inhibition. The compounds 2c, 2e & 2j were highly active against all four organisms employed. The compounds 2a, 2b, 2d, 2f & 2i were highly active against *Escherichia coli* (MTCC443) & *Staphylococcus aureus* (MTCC96).

The comparison of the antibacterial activity of these compounds with standard drugs show that the presence of methoxy, hydroxyl, halogen & nitro group in the phenyl ring increases the activity. As shown in Table-2, all the compounds were less active against *Candida albicans*, *Aspergillus niger* & *Aspergillus clavatus.*

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TABLE-2: ANTIMICROBIAL ACTIVITY OF COMPOUNDS (2a-j)

Comp.	Antibacterial activity				Antifungal activity		
	Minimum bactericidal concentration µg/ml				Minimum fungicidal concentration µg/ml		
	S.a[a]	S.p[b]	E.c[c]	P.a[d]	C.a[g]	A.n[e]	A.c[f]
2a	25	250	62.5	125	500	>1000	500
2b	50	500	50	125	>1000	1000	1000
2c	12.5	50	25	50	1000	1000	1000
2d	50	250	25	250	500	>1000	>1000
2e	25	25	50	50	1000	1000	500
2f	62.5	50	25	100	>1000	1000	1000
2g	50	250	250	500	500	500	500
2h	250	500	100	250	1000	500	1000
2i	12.5	250	50	125	1000	>1000	>1000
2j	25	12.5	12.5	50	>1000	500	500
Gentamycin	0.05	1	0.25	0.5	-	-	-
Ampicillin	100	100	250	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	25	25	50	50	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

S.a[a] - *Staphylococcus aureus*(MTCC96), S.p[b]- *Streptococcus pyogenes* (MTCC442), E.c[c]- *Escherichia coli*(MTCC443), P.a[d]- *Pseudomonas aeruginosa*(MTCC441), A.n[e]- *Aspergillus niger* (MTCC282),A.c[f]- *Aspergillus clavatus* (MTCC1323),
C.a[g]- *Candida albicans* (MTCC227).

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