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SYNTHESIS AND INVITRO ANTIMICROBIAL STUDY OF SOME 4-THIAZOLIDINONES CONTAINING PIPERAZINE MOEITY

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ABSTRACT:

*Substituted Schiff bases**(2a-j)** were prepared by treatment of 4-(4-ethylpiperazine-1-yl)benzenamine**(1)** with different aromatic aldehydes. These Schiff base on cyclocondensation with thioglycolic acid in 1,4-dioxane gave desired thiazolidinones **(3a-j).** The structures of the newly synthesized compounds were assigned on the basis of elemental and spectral analysis. These compounds were evaluated for their in vitro growth inhibiting activity against various microbes.*

Keywords:Antibacterial Activity,Antifungal Activity, Piperazine, Schiff Base,Thaizolidinone,

1. INTRODUCTION

Thiazolidinones are the derivatives of thiazolidinone which belong to an important group of heterocyclic compounds containing sulphur and nitrogen in a five member ring. 4-thiazolidinones are derivatives of thiazolidinone with a carbonyl group at the 4th position[1]. Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which possesses almost all types of biological activities. This diversity in the biological response profile and easy synthetic routes for synthesis has attracted the attention of many researchers to explore this skeleton to its multiple potential against various activities. The presence of N-C-S linkage in these compounds has been shown to have anti-HIV[2.3,4,5], local[6] and spinal anaesthetic[7],antifungal[8,9,10], anti-tubercular[11,12], CNS stimulant[13], anti-convulsant[14], antimicrobial[15,16], anti-inflammatory[17,18],anti-cancer[19] activities, etc.

Piperazine is an interesting heterocyclic moiety as constituent of several biologically active molecules. The polar nitrogen atoms in the piperazine ring confer bioactivity to molecules and enhance favourable interaction with macromolecules[20]. Some piperazine derivatives possess high biological activities for multidrug

resistance in cancer[21] and malaria[22]. Piperazine derivatives containing tetrazole nucleus have been reported as antifungal agents[23]. Several quinolone drugs like norfloxacin and ciprofloxacin having piperazine nucleus have shown broad spectrum activity against respiratory, urinary gastrointestinal tract and soft tissue infection caused by bacteria[24]. Various cyclopiperazine derivatives have been known for their use in the synthesis of pharmaceutical intermediates, peptide analogues and antibacterial drugs[25-28].

Keeping in view, the diverse therapeutic activities of 4-thiazolidinones and piperazine nucleus, it was contemplated to synthesize a series of 4-thiazolidinones containing piperazine nucleus and screen them for their *in-vitro* microbial activities.

In the present study, we have synthesized ten newer 4-thiazolidinones **(3a-3j)** by cyclocondensation of various Schiff bases **(2a-2j)** with thioglycolic acid in dioxane. The structures for the newly synthesised compounds were elucidated on the basis of elemental and spectral analysis and were screened for their antibacterial and antifungal activities.

2. MATERIALS AND METHODS

All chemicals used were of Sigma Aldrich, Merck and Fluka make. Solvents used were of analytical grade. All reactions were routinely checked by TLC. TLC was performed on aluminum-backed silica gel plates (silica gel 60 F254 grade, Merck DC) with spots visualized by UV light. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 8400S FTIR spectrophotometer. ^{1}H NMRspectra were recorded on a Hitachi 300 MHz using TMS as an internal standard and elemental analysis had been carried out on Perkin-Elmer CHNS-2400.

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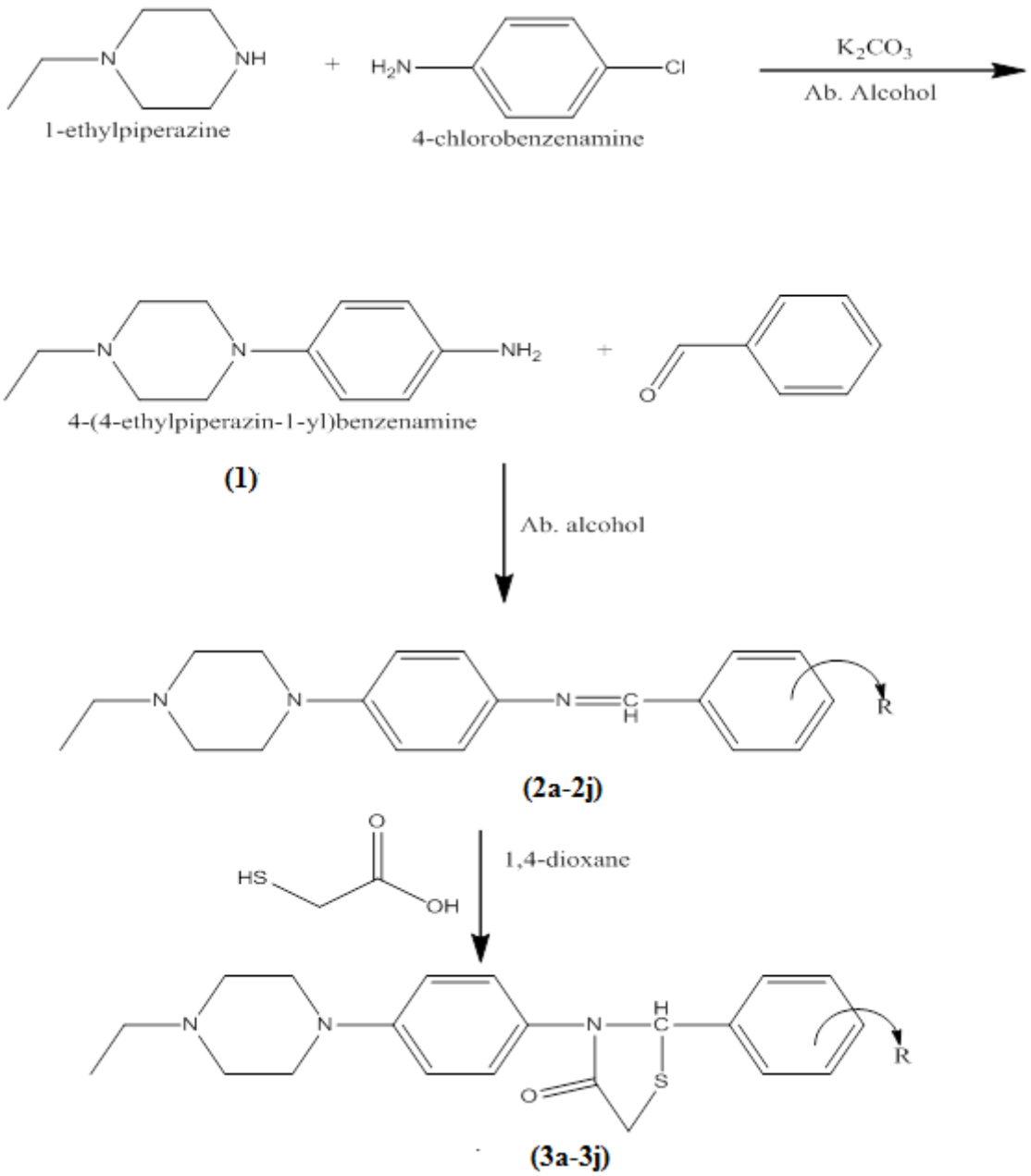

Substituents of compounds **3a-3j**

R = 3 a. H,3 b. 4-Cl,3 c. 4-OCH_3 ,3 d. 3-NO_2 ,3 e. 3-OCH_3 ,3f. 4-OH,3 g. 2-Cl ,

3 h. 2-OH,3 i. 3,4,5-OCH_3, 3 j. 3,4-OCH_3

. **Scheme: Synthetic rout for 4-thiazolidinone derivatives (3a-3j**

3. EXPERIMENTAL

3.1.1. Preparation of 4-(4-ethylpiperazin-1-yl) benzamine (1)

A mixture of 1-ethylpiperazine **(**0.1 mole) and 4-chloroaniline **(**0.1 mole) and anhydrous K_2CO_3 in absolute alcohol (20 ml) was refluxed for 4 hrs.The resultant mixture was cooled to room temperature and poured into ice-cold water with stirring. The separated solid was filtered, washed with water and recrystalized from ethanol.

3.1.2. Preparation of N-substitutedbenzylidene-4-(4-ethylpiperazin-1-yl)benzamine (2a-2j)

A mixture of 4-(4-ethylpiperazin-1-yl)benzenamine**(1)**(0.01 mole), aromatic aldehyde (0.01 mole) and 2-3 drops of glacial acetic acid in absolute alcohol (30 ml) was refluxed for 2 hrs. After the completion of reaction, it was poured into ice-cold water with stirring.The solid product obtained was filtered, washed with water and recrystalized from ethanol to give compounds **2a-2j.**

3.1.3.Preparation of 2-(sustitutedphenyl)-3-(4-(4-ethylpiperazin-1-yl) phenyl) thiazolidin-4-one (3a-3j)

A mixture of compound **3a** (0.01 mole) and thioglycolic acid (0.02 mole) was refluxed in the presence of 1,4-dioxane for 12 hrs. The completion of reaction was monitored by TLC (toluene: acetone, 5.0:5.0). After completion of reaction the resulting liquid was treated with saturated sodium bicarbonate solution to remove unreacted thioglycolic acid.The separated solid was washed with water, dried and recrystallized from ethanol. Similarly, other compounds of the series were prepared by the above procedure.

The characterization data and spectral data for the synthesized compounds are presented in Table-1 and Table-2 respectively.

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Table- 1: Characterization data of 3a-3j

Compound No.	R	Molecular Formula	M.P. (°C)	Yield (%)	Elemental analysis (%)					
					C		H		N	
					Calcd	*Found*	*Calcd*	*Found*	*Calcd*	*Found*
3a	H	$C_{21}H_{25}N_3OS$	96-97 °C	58%	68.63	68.64	6.86	6.88	11.43	11.45
3b	4-Cl	$C_{21}H_{24}ClN_3OS$	280 °C	50%	62.75	62.76	6.02	6.03	10.45	10.47
3c	4-OCH_3	$C_{22}H_{27}N_3O_2S$	80-85 °C	53%	66.47	66.48	6.85	6.87	10.57	10.59
3d	3-NO_2	$C_{21}H_{24}N_4O_3S$	>300°C	59%	61.14	61.16	5.86	5.88	13.58	13.59
3e	3-OCH3	$C_{22}H_{27}N_3O_2S$	65-70 °C	52%	66.47	66.49	6.85	6.87	10.57	10.57
3f	4-OH	$C_{21}H_{25}N_3O_2S$	80-90 °C	55%	65.77	65.79	6.57	6.59	10.96	10.97
3g	2-Cl	$C_{21}H_{24}ClN_3OS$	70-75 °C	54%	62.75	62.77	6.02	6.03	10.45	10.47
3h	2-OH	$C_{21}H_{25}N_3O_2S$	140-145 °C	60%	65.77	65.78	6.57	6.59	10.96	10.97
3i	3,4,5-OCH_3	$C_{24}H_{31}N_3O_4S$	55 °C	60%	63.00	63.02	6.83	6.84	9.18	9.19
3j	3,4-OCH_3	$C_{23}H_{29}N_3O_3S$	130-135°C	61%	64.61	64.63	6.84	6.85	9.83	9.84

Table-2: Spectral Data of Synthesized compounds 3a-3j

Compound No.	IR (KBr, cm-1)	^{1}H NMR(δ ppm)
3a	622 (C-S-C), 835 (Aromatic -CH), 1730(C=O thiazolidinone), 2900 (N-CH_2-CH_3), 3350 (NH_2), 3450 (NH), 3500 (NH-CH_3)	1.35 (t, 3H), 1.98 (q, 2H),3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3b	620 (C-S-C), 836 (Aromatic -CH), 1740(C=O thiazolidinone), 2910 (N-CH_2-CH_3), 3348 (NH_2), 3448 (NH), 3510 (NH-CH_3)	1.30 (t, 3H), 2.11 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3c	624 (C-S-C), 833 (Aromatic -CH), 1770(C=O thiazolidinone), 2890 (N-CH_2-CH_3), 3352 (NH_2), 3445 (NH), 3495 (NH-CH_3)	1.32 (t, 3H), 1.99 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94

		(1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3d	630 (C-S-C), 832 (Aromatic -CH), 1772(C=O thiazolidinone), 2895 (N-CH_2-CH_3), 3360 (NH_2), 3455 (NH), 3525 (NH-CH_3)	1.34 (t, 3H), 2.10 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3e	626 (C-S-C), 834 (Aromatic -CH), 1745(C=O thiazolidinone), 2910 (N-CH_2-CH_3), 3347 (NH_2), 3452 (NH), 3530 (NH-CH_3)	1.31 (t, 3H), 2.10 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3f	620 (C-S-C), 835 (Aromatic -CH), 1747(C=O thiazolidinone), 2915 (N-CH_2-CH_3), 3335 (NH_2), 3447 (NH), 3520 (NH-CH_3)	1.32 (t, 3H), 1.99 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3g	622 (C-S-C), 836 (Aromatic -CH), 1769(C=O thiazolidinone), 2920 (N-CH_2-CH_3), 3360 (NH_2), 3454 (NH), 3526 (NH-CH_3)	1.33 (t, 3H), 1.96 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3h	628 (C-S-C), 840 (Aromatic -CH), 1750(C=O thiazolidinone), 2925 (N-CH_2-CH_3), 3347 (NH_2), 3455(NH), 3514 (NH-CH_3)	1.34 (t, 3H), 1.98 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3i	626 (C-S-C), 842 (Aromatic -CH), 1745(C=O thiazolidinone), 2900 (N-CH_2-CH_3), 3335 (NH_2), 3449 (NH), 3522 (NH-CH_3)	1.34 (t, 3H), 2.11 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),
3j	630 (C-S-C), 835 (Aromatic -CH), 1767(C=O thiazolidinone), 2905 (N-CH_2-CH_3), 3340 (NH_2), 3452 (NH), 3534 (NH-CH_3)	1.35 (t, 3H), 1.98 (q, 2H), 3.52 (br s, 4H, piperazine), 3.72 (br s, 4H, piperazine) 3.81(1H, S–CH2), 3.94 (1H, S–CH2), 6.26 (s, 1H, S–CH–N), 6.75 – 8.12 (m,9H, Ar–H),

4. ANTIMICROBIAL ACTIVITY

The *in vitro* results of antimicrobial activity of the newly synthesized compounds,**3a**-**3j** are presented in Table-3 as a minimal inhibitory concentration (MIC).The antimicrobial activity of synthesized analogs has been carried out against two Gram-positive bacteria (*S. Aureus* ATCC 6538P and *S. Pyrogenus* ATCC 8668), two Gram-negative bacteria (*E. Coli.* ATCC 8739 and *P.Aeruginosa*ATCC 9027) and against three fungal species (*C. Albicans* ATCC 10231, *A. Niger* ATCC16404 and *A. Clavatus*ATCC 9600). Here, ampicillin, chloramphenicol, ciprofloxacin (100 µg/disk) were used as control drugs forantibacterial activity while nystatin and griesofulvin for antifungal activity**.**

Table-3: *In-vitro* antibacterial and antifungal activity of compounds 3a-3j

Compound No.	R	Minimum Inhibitory Concentrations (µg/mL)				Minimum Inhibitory Concentrations (µg/mL)		
		Gram positive bacteria		Gram negative bacteria		Fungus		
		S.aereus ATCC 6538P	*S. pyogenus* ATCC8668	*E. coli* ATCC 8739	*P.aeruginosa* ATCC 9027	*C.albicans* ATCC 10231	*A. niger* ATCC 16404	*A.clavatus* ATCC 9600
3a	H	512	512	512	512	256	512	256
3b	4-Cl	512	512	128	128	256	256	128
3c	4-OCH_3	256	512	512	128	256	256	128
3d	3-NO_2	128	256	128	128	256	128	256
3e	3-OCH3	256	128	256	256	256	512	256
3f	4-OH	32	32	64	256	256	512	256
3g	2-Cl	256	512	512	512	512	512	512
3h	2-OH	64	128	128	128	128	256	256
3i	3,4,5-OCH_3	128	128	512	256	256	256	256
3j	3,4-OCH_3	128	128	512	256	512	512	512
Ampicilin	-	250	100	100	100	-	-	-
Chloramphenicol	-	50	50	50	50	-	-	-
Ciprofloxacin	-	50	50	25	25	-	-	-
Norfloxacin	-	10	10	10	10	-	-	-
Nystatin	-	-	-	-	-	100	100	100
Griesofulvin	-	-	-	-	-	500	100	100

5. CONCLUSIONS

5.1Antibacterial activity

Antibacterial activities have been studied for 2-(substituted phenyl)-3-(4-(4-ethylpiperazin-1-yl) phenyl)thiazolidin-4-one compounds **(3a-3j)**.

Compounds **3c, 3e** and**3g** containing 4-methoxy, 3-methoxy and 2-chloro substituents possessed moderate activity (MIC 236 µg/mL) whereas compounds **3d, 3i** and **3j** having 3-nitro, 3,4,3-tri methoxy and

3,4-dimethoxy substituents showed good activity (MIC 128 µg/mL) against *S. aureus* when compared with ampicillin. Compound **3h** having 2-hydroxy substituents showed very good activity (MIC 64 µg/mL) against *S. aureus*when compared with ampicillin. Compound **3h** having 2-hydroxy substituents showed moderate activity (MIC 64 µg/mL) against *S. aureus* when compared with chloramphenicol.

Compounds **3e, 3h, 3i** and **3j** having 3-methoxy, 2-hydroxy, 3, 4, 3-trimethoxy and 3, 4-dimethoxy substituents respectively showed good activity (MIC 128 µg/mL) against *S. pyogenus* when compared with Ampicillin.

Compounds **3b, 3d** and **3h** having 4-chloro, 3-nitro and 2-hydroxy substituents respectively showed good activity (MIC 128 µg/mL) against *E. Coli* compared with ampicillin and moderate with chloramphenicol. Compounds **3f** having 4-hydroxy substituent showed better activity (MIC 64 µg/mL) against *E. Coli.* when compared with Ampicillin, good activity with chloramphenicol and moderate with ciprofloxacin.

Compounds **3b, 3c, 3d** and **3h** having 4-chloro, 4-methoxy, 3-nitro and 2-hydroxy substituents displayed good activity (MIC128 µg/mL) against *P.aeroginosa*when compared with ampicillin.

5.2 Antifungal activity

Compounds**3a, 3b, 3c, 3d, 3e, 3f,** and **3i** having H,4-chloro,4-methoxy,3-nitro,3-methoxy,4-hydroxy and 3,4,3-trimethoxy substituents exhibited good activity (MIC 236 µg/mL) against *C. albicans* when compare with griseofulvin. Compound **3h** having 2-hydroxy substituent exhibited better activity (MIC 128 µg/mL) against *C. albicans* when compare with griseofulvin and moderate activity when compare with nystain.

Compounds**3b** and **3c** having 4-chloro and 4-methoxy substituents exhibited moderate33 activity (MIC 128µg/mL) against *A. clavatus* when compared with griseofulvin. Compound **3b** and **3c** having 4-chloro and 4-methoxy substituents exhibited moderateactivity (MIC 128µg/mL) against *A. niger* when compare with griseofulvin.

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