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RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF METHYLENE-BASED THIAZOLIDINONE DERIVATIVES

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ABSTRACT

Thiazolidinone derivatives have been synthesized by reacting various Schiff base with thioglycolic acid by using catalyst $ZnCl_2$ in 1,4-dioxane at room temperature. The structure of title compounds were established by elemental, IR and ^{1}H NMR spectral data. All the synthesized compounds were screened for in vitro antibacterial and antifungal activities on *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes*, *C. albicans*, *S. cervecieaceae* and *A. clavatus*.

INTRODUCTION

The newly synthesized different Schiff's bases after purification and characterization by physical and spectral methods reacted with 1,4-dioxane in presence of $ZnCl_2$ to yield thiazolidinones corresponding to them. Sulphur-nitrogen containing heterocycles have wide application in medicinal chemistry. thiazolidinones are associated with anticancer (Pawar *et al*., 1999) and versatile pharmacological activities (Thore *et al*., 1996; Jaish *et al*., 2001) like anti-inflammatory (Kumar *et al*., 2009; Sondhi *et al*., 2006), anti-HIV (Chen *et al*., 2009), anti-viral (Masoud *et al*., 2013), antitumor (Kamel *et al*., 2010) and antitubercular (Mistry *et al*., 2013) etc. Based on the results, we have designed and synthesized a series of 3,3'-(4,4'-methylene bis (2,5-dimethyl-4, 1-phenylene))bis (2-substituted phenylthiazolidin-4-one) (5a-j). The condensation of 2,5-dimethyl aniline (1) and formaldehyde (2) in presence of hydrochloric acid at 60 ^{0}C gives 4,4'-methylene bis (2,5-dimethyl aniline) (3), which when reacted with various substituted aromatic aldehydes yielded Schiff bases 4,4'-methylene bis (N-substituted benzylidine-2,5-dimethyl aniline) (4a- j).

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Then further it produced Compound (4a- j) which on condensed with mercaptoacetic acid in the presence of 1,4-dioxane gave 3,3'-(4,4'-methylene bis (2,5-dimethyl-4, 1- phenylene))bis (2-substituted phenylthiazolidin-4-one) (5a-j). The purity of the compounds was checked by TLC and elemental analysis. Based on these studies, the structural assignment of the products was based on their IR, ^{1}H NMR spectral data. The title compounds were screened for their antibacterial and antifungal activity on different strains of bacteria and fungi. Thiazolidinones are the important compound owing to their large range of biological activities and industrial applications.

RESULTS AND DISCUSSION

All the synthesized compounds were characterised on the basis of their FTIR and ^{1}H NMR spectra data. Methyl and methylene C-H stretching vibrations observed near 2926 cm^{-1} and 2853 cm^{-1}. Broad absorption bands observed in the region between 3080-3030 cm^{-1} and 1620-1480 cm^{-1} indicates the presence of C-H stretching and C=C stretching of aromatic ring. The position of various absorption bands in the spectrum is in each part. Examination of IR spectra reveals that all the band observed in the region of 1760-1655 cm^{-1} and 700-600 cm^{-1} indicate the presence of C=O stretching and C-S-N stretching of thiazolidine ring. The ^{1}H NMR spectra of the synthesized

compound showed chemical shifts, which are characteristics of the anticipated structure of compounds. A singlet observed at δ 3.84 attributed to the -CH_2-, δ 3.59 for the -CH_2-S and δ 5.88 for the –N-CH-S- of cyclic thiazolidinone observed in ^{1}H NMR.

Experimental

Synthesis of 4,4'-methylene bis (2, 5-dimethyl aniline) (3)

4-4'-Methylene bis (2,5-dimethyl aniline) (3) was synthesized by the method described in the literature (Patel *et al*., 2014).

General preparation of the compounds (4a- j)

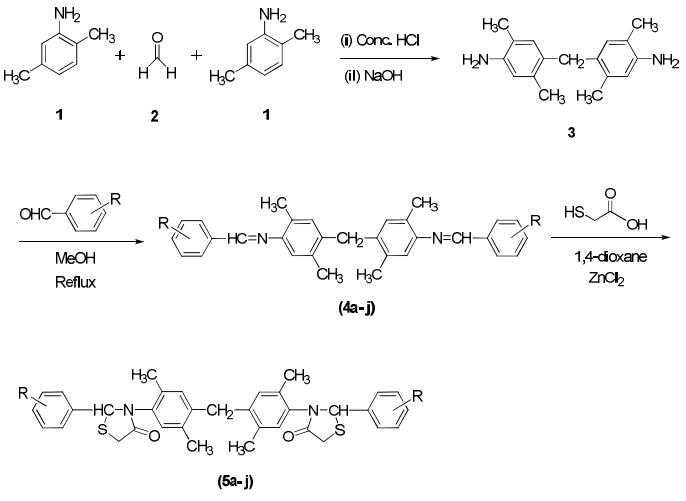
A mixture of 4,4'-methylene bis (2,5-dimethyl aniline) (2.54 g., 0.01 mol) and various substituted aromatic aldehyde (0.02 mol) was taken in absolute ethanol and few drops of glacial acetic acid were added. Then, the mixture was refluxed for 4-6 h on water bath. The completion of reaction was monitored by TLC (toluene: acetone, 5.0: 5.0). The excess solvent was distilled off, and then remaining residue was poured into ice cold water. The separated solid was filtered, washed and recrystalized from ethanol to give product 4a- j. (Patel *et al*., 2014).

General synthesis of the compounds (5a- j)

A mixture of compound (4a– j) (0.01 mol) and mercaptoacetic acid (0.02 mol) in the presence of $ZnCl_2$ and solvent 1,4-dioxane was refluxed for 12–14 h. The completion of reaction was monitored by TLC (toluene: acetone, 5.0: 5.0) and reaction mass was dumped in ice cold water. The resulting product was washed with 5 % sodium bicarbonate solution to remove unreacted traces of thioglycolic acid. The separated solid was washed with water, dried and recrystallized from absolute ethanol to give product 5a- j. (Nandagokula *et al*., 2013).

Scheme-1

Synthetic route for 3,3'-(4,4'-methylene bis (2,5-dimethyl-4, 1- phenylene))bis (2-substituted phenylthiazolidin-4-one) from 2,5-dimethyl aniline (5a- j).



Where, R = a. 2-F, b. 4-F, c. 4-OH, d. 2-OCH_3, e. 2,4-Cl, f. 4-Cl, g. 4-CH_3, h. 2-Cl, i. 4-OH, j. 2-NO_2.

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(2-fluorophenyl)thiazolidin-4-one) 5a

Brown colour solid powder, mp 108 ^{0}C, yield 70%; IR (KBr, cm^{-1}): 3035 (C-H stretching, aromatic), 2935, 2820 (C-H stretching, -CH_2- group), 2925, 2865 (C-H stretching, -CH_3), 1710 (C=O stretching, thiazolidinone), 1495 (C=C stretching, aromatic), 1470, 1390 (C-H bending, -CH_3 group), 1440 (C-H bending, -CH_2- group), 1100 (C-F stretching, Fluoro); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.27 (s, 12H, -CH_3), 3.79 (s, 2H, -CH_2-), 3.87 (s, 4H, -CH_2-S), 5.90 (s, 2H, -N-CH-S-), 6.88-7.71 (m, 12H, Ar-H); Anal. Calcd for: $C_{35}H_{32}F_2N_2O_2S_2$ (614.77); found (C, 68.44), requires (C, 68.38); found (H, 5.17), requires (H, 5.25); found (N, 4.51), requires (N, 4.56).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(4-fluorophenyl)thiazolidin-4-one) 5b

Brown colour solid powder, mp 99 ^{0}C, yield 65%; IR (KBr, cm^{-1}): 3030 (C-H stretching, aromatic), 2935, 2825 (C-H stretching, -CH_2- group), 2930, 2865 (C-H stretching, -CH_3), 1715 (C=O stretching, thiazolidinone), 1495 (C=C stretching, aromatic), 1475, 1390 (C-H bending, -CH_3 group), 1445 (C-H bending, -CH_2- group), 1100 (C-F stretching, Fluoro); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.25 (s, 12H, -CH_3), 3.79 (s, 2H,-CH_2-), 3.88 (s, 4H, -CH_2-S), 5.91 (s, 2H, -N-CH-S-), 6.88-7.71 (m, 12H, Ar-H); Anal. Calcd for: $C_{35}H_{32}F_2N_2O_2S_2$ (614.77); found (C, 68.31), requires (C, 68.38); found (H, 5.31), requires (H, 5.25); found (N, 4.49), requires (N, 4.56).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(2-hydroxyphenyl) thiazolidin- 4-one) 5c

Yellow colour solid powder, mp 101 ^{0}C, yield 67%; IR (KBr) cm^{-1}: 3400 (O-H stretching, Ar-OH), 3060 (C-H stretching, aromatic), 2935, 2850 (C-H stretching, -CH_2- group), 2920, 2870 (C-H stretching, -CH_3), 1705 (C=O stretching, thiazolidinone), 1505 (C=C stretching, aromatic), 1470, 1380 (C-H bending, -CH_3 group), 1430 (C-H bending, -CH_2- group), 1330 (O-H bending, Ar-OH); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.27 (s, 12H, -CH_3), 3.79 (s, 2H, -CH_2-), 3.85 (s, 4H, -CH_2-S), 5.88 (s, 2H, -N-CH-S-), 6.88-7.69 (m, 12H, Ar-H), 12.86 (s, 2H, OH); Anal. Calcd for: $C_{35}H_{34}N_2O_4S_2$ (610.79); found (C, 68.77), requires (C, 68.83); found (H, 5.66), requires (H, 5.61), found (N, 4.52), requires (N, 4.59).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(2-methoxyphenyl) thiazolidin-4-one) 5d

Yellow colour solid powder, mp 110 ^{0}C, yield 72%; IR (KBr) cm^{-1}: 3040 (C-H stretching, aromatic), 2925, 2850 (C-H stretching, -CH_2- group), 2925, 2875 (C-H stretching, -CH_3), 1710 (C=O stretching, thiazolidinone), 1510 (C=C stretching, aromatic), 1465, 1380 (C-H bending, -CH_3 group), 1435 (C-H bending, -CH_2- group); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.23 (s, 12H, -CH_3), 2.49 (s, 6H, -OCH_3), 3.80 (s, 2H, -CH_2-), 3.85 (s, 4H, -CH_2-S-), 5.90 (s, 2H, -N-CH-S-), 6.85-7.72 (m, 12H, Ar-H); Anal. Calcd for: $C_{37}H_{38}N_2O_4S_2$ (638.84); found

(C, 69.62), requires (C, 69.56); found (H, 6.09), requires (H, 6.00); found (N, 4.45), requires (N, 4.39).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(2,4-dichlorophenyl) thiazolidin -4-one) 5e

Light yellow colour solid powder, mp 115 ^{0}C, yield 70%; IR (KBr) cm^{-1}: 3030 (C-H stretching, aromatic), 2920, 2845 (C-H stretching, -CH_2- group), 2935, 2870 (C-H stretching, -CH_3), 1680 (C=O stretching, thiazolidinone), 1510 (C=C stretching, aromatic), 1465, 1380 (C-H bending, -CH_3 group), 1445 (C-H bending, -CH_2- group), 750 (C-Cl stretching, chloro); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.27 (s, 12H, -CH_3), 3.65 (s, 2H, -CH_2-), 3.80 (s, 4H, -CH_2-S-), 5.94 (s, 2H, -N-CH-S-), 6.70-7.90 (m, 10H, Ar-H); Anal. Calcd for: $C_{35}H_{30}Cl_4N_2O_2S_2$ (716.57); found (C, 58.73), requires (C, 58.67); found (H, 4.17), requires (H, 4.22); found (N, 3.97), requires (N, 3.91).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(4-chlorophenyl)thiazolidin-4-one) 5f

Light yellow colour solid powder, mp 137 ^{0}C, yield 68%; IR (KBr) cm^{-1}: 3050 (C-H stretching, aromatic), 2940, 2830 (C-H stretching, -CH_2- group), 2925, 2865 (C-H stretching, -CH_3), 1710 (C=O stretching, thiazolidinone), 1495 (C=C stretching, aromatic), 1470, 1390 (C-H bending, -CH_3 group), 1440 (C-H bending, -CH_2- group), 720 (C-Cl stretching, chloro); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.23 (s, 12H, -CH_3), 3.59 (s, 2H, -CH_2-), 3.84 (s, 4H, -CH_2-S-), 5.92 (s, 2H, -N-CH-S-), 6.76-7.95 (m, 12H, Ar-H); Anal. Calcd for: $C_{35}H_{32}Cl_2N_2O_2S_2$ (647.68); found (C, 64.95), requires (C, 64.90); found (H, 4.93), requires (H, 4.98); found (N, 4.28), requires (N, 4.33).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-p-tolythiazolidin-4-one) 5g

Yellow colour solid powder, mp 129 ^{0}C, yield 69%; IR (KBr) cm^{-1}: 3040 (C-H stretching, aromatic), 2925, 2850 (C-H stretching, -CH_2- group), 2925, 2875 (C-H stretching, -CH_3), 1690 (C=O stretching, thiazolidinone), 1520 (C=C stretching, aromatic), 1465, 1380 (C-H bending, -CH_3 group), 1435 (C-H bending, -CH_2- group); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.25 (s, 18H, -CH_3), 3.80 (s, 2H, -CH_2-), 3.87 (s, 4H, -CH_2-S-), 5.90 (s, 2H, -N-CH-S-), 6.88-7.72 (m, 12H, Ar-H); Anal. Calcd for: $C_{37}H_{38}N_2O_2S_2$ (606.84); found (C, 73.17), requires (C, 73.23); found (H, 6.26), requires (H, 6.31); found (N, 4.69), requires (N, 4.62).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(2-chlorophenyl)thiazolidin-4-one) 5h

Light yellow colour solid powder, mp 156 ^{0}C, yield 69%; IR (KBr) cm^{-1}: 3055 (C-H stretching, aromatic), 2950, 2830 (C-H stretching, -CH_2- group), 2935, 2860 (C-H stretching, -CH_3), 1675 (C=O stretching, thiazolidinone), 1490 (C=C stretching, aromatic), 1470, 1390 (C-H bending, -CH_3 group), 1440 (C-H bending, -CH_2- group), 730 (C-Cl stretching, chloro); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.25 (s, 12H, -CH_3), 3.60 (s, 2H, -CH_2-), 3.82 (s , 4H, -CH_2-S-), 5.94 (s, 2H, -N-CH-S-), 6.76-7.97 (m, 12H, Ar-H); Anal. Calcd for: $C_{35}H_{32}Cl_2N_2O_2S_2$ (647.68); found (C, 64.87), requires (C, 64.90); found (H, 4.93), requires (H, 4.98); found (N, 4.27), requires (N, 4.33).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(4-hydroxyphenyl) thiazolidin- 4-one) 5i

Yellow colour solid powder, mp 121 ^{0}C, yield 68%; IR (KBr) cm^{-1}: 3420 (O-H stretching, Ar-OH), 3065 (C-H stretching, aromatic), 2940, 2850 (C-H stretching, -CH_2- group), 2920, 2870 (C-H stretching, -CH_3), 1690 (C=O stretching, thiazolidinone), 1505 (C=C stretching, aromatic), 1470, 1380 (C-H bending, -CH_3 group), 1435 (C-H bending, -CH_2- group), 1330 (O-H bending, Ar-OH); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.27 (s, 12H, -CH_3), 3.79 (s, 2H, -CH_2-), 3.85 (s, 4H, -CH_2-S-), 5.88 (s, 2H, -N-CH-S-), 6.88-7.69 (m, 12H, Ar-H), 12.86 (s, 2H, OH); Anal. Calcd for: $C_{35}H_{34}N_2O_4S_2$ (610.79); found (C, 68.77), requires (C, 68.83); found (H, 5.66), requires (H, 5.61); found (N, 4.53), requires (N, 4.59).

3,3'-(4,4'-Methylene bis(2,5-dimethyl-4,1-phenylene))bis(2-(2-nitrophenyl)thiazolidin-4-one) 5j

Brown colour solid powder, mp 132 ^{0}C, yield 71%; IR (KBr) cm^{-1}: 3070 (C-H stretching, aromatic), 2945, 2830 (C-H stretching, -CH_2- group), 2940, 2860 (C-H stretching, -CH_3), 1695 (C=O stretching, thiazolidinone), 1550, 1360 (N=O stretching, Nitro), 1485 (C=C stretching, aromatic), 1475, 1395 (C-H bending, -CH_3 group), 1435 (C-H bending, -CH_2-group); ^{1}H NMR (400.1 MHz, DMSO): δ_H 2.23 (s, 12H, -CH_3), 3.62 (s, 2H, -CH_2-), 3.86 (s, 4H, -CH_2-S-), 5.92 (s, 2H, -N-CH-S-), 6.75-7.90 (m, 12H, Ar-H); Anal. Calcd for: $C_{35}H_{32}N_4O_6S_2$ (668.78); found (C, 62.81), requires (C, 62.86); found (H, 4.89), requires (H, 4.82); found (N, 8.44), requires (N, 8.38).

Antimicrobial activity

Methods

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh. Mueller–Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight. The tubes were then incubated overnight. The MICs of compounds were carried out by broth micro-dilution method as described by (Rattan *et al*., 2000). Antibacterial activity was screened against two gram positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenus* MTCC 443) and two gram negative (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 2488) bacteria, norfloxacin, ciprofloxacin and chloramphenicol were used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *S. cervecieaceae* MTCC

149 and *Aspergillus clavatus* MTCC 1323, Nystatin-B and gresiofulvin was used as a standard antifungal agent.

Antibacterial activity

The minimum Inhibitory concentrations (MIC) of the tested compounds 5a- j are shown in (Table 1). From the screening data, most of the compounds possessed very good antibacterial activity (MIC, 100–250 µg/ml) against *P. aeruginosa* and *S. aureus*; some of them possessed better activity compared to norfloxacin, ciprofloxacin and chloramphenicol. The thiazolidinones **5d**, **5h** and **5i** having 2-OCH_3, 4-Cl and 4-OH substituents showed better activity (125µg/ml) against *E. coli*. Compounds **5b** and **5j** having 4-F and 2-NO_2 substituent possessed higher activity (62.5-125 µg/ml) against *P. aeruginosa*. Compound **5b, 5g** and **5j** having 4-F, 4-CH_3 and 4-OH. Compounds **5b, 5g** and **5j** having 4-F, 4-CH_3 and 2-NO_2 substituent possessed higher activity (62.5-125 µg/ml) against *S. aureus*. Compound **5b** and **5f** having 4-F and 4-Cl substituents possessed better activity (125 µg/ml) against *S. pyogenus*.

Table 1. Antibacterial activity of compounds [5a to 5j]

Compound	Minimum Inhibitory Concentrations (µg/ml)			
	Gram negative bacteria		Gram positive bacteria	
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*
5a	250	500	250	250
5b	250	62.5	125	125
5c	250	500	250	250
5d	125	500	250	500
5e	250	500	1000	250
5f	250	500	250	125
5g	500	125	125	500
5h	125	250	250	250
5i	125	125	250	500
5j	125	250	62.5	250
Norfloxacin	50	50	50	50
Ciprofloxacin	50	50	50	50
Chloramphenicol	50	50	50	50

Antifungal activity

Most of the compounds possessed very good antifungal activity against *C. albicans*, their MIC values were in the range between 250 and 500 µg/ml. Thiazolidinone **5d** containing 2-OCH_3 substituent possessed good activity of (250µg/ml) against *C. albicans*.

Table 2. Antifungal activity of compounds [5a to 5j]

Compound	Minimum Inhibitory Concentrations (µg/ml)		
	Fungus		
	C. albicans	*S. cervecieaceae*	*A. clavatus*
5a	500	1000	500
5b	500	500	1000
5c	500	1000	1000
5d	250	500	250
5e	500	1000	1000
5f	1000	1000	1000
5g	500	1000	1000
5h	500	500	500
5i	500	1000	500
5j	1000	500	500
Nystatin-B	100	100	100
Gresiofulvin	100	100	100

Compound **5d** containing 2-OCH_3 substituent possessed better activity (250µg/ml) against *A. clavatus*. Whereas remaining compounds possessed weak activity against *C. albicans, S. cervecieaceae* and *A. clavatus*. MIC of compounds **5a- j** is summarized in (Table 2).

Conclusions

A variety of thiazolidinone have been successfully synthesized in excellent appreciable yields and screened in vitro for their antimicrobial activities against both strains of Gram-positive, Gram-negative bacteria and fungal strains. All spectral analysis data confirmed the proposed structures for these newly synthesized compounds.

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