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SYNTHESIS AND ANTIMICROBIAL SCREENING OF NOVEL MONO AND TRI SCHIFF BASES OF THIAZOLE DERIVATIVES

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ABSTRACT

This present work deals with the synthesis, characterization and biological screening of some novel Schiff bases of thiazole derivatives[1,2,4]. Ethyl-2(2-amino thiazole-4 yl) glyoxylate (I) react with 2, 5-dimethyl tetrahydro furan gave N-pyrol derivatives (II). Equal mole of (II) and hydrazine hydrate were heated for 10 minutes. It gave mono hydrazine derivatives (III) and when 1 mole of (II) and 2 mole of hydrazine hydrate were refluxed for 3 hours, it gave dihydrazine derivatives (IV). Equal mole of mono hydrazine derivatives (III) and aromatic aldehyde (one mole of dihydrazine derivatives (IV) and one mole of aromatic aldehyde) are refluxed for 10 minutes, it gave pale yellow mono and tri Schiff base derivatives. When (I) was directly reacted with hydrazine hydrate it gave (V). Compound (V) contains both 2-thiazole amine and hydrazine active sites for Schiff base formation. But when (V) was treated with aromatic aldehyde, hydrazine active site form solid Schiff base very fast, because in low temperature 2-thiazole amine get stable by amine emine tautomerism. This is conformed by H-NMR (Ar-NH_2 proton peak is single let only). The chemical structures of synthesized compounds were conformed by MASS, IR and H-NMR spectral studies. The synthesized compounds were (25, 50 and 100 µg/mL) screened for antimicrobial activity by paper disc diffusion method.

Key words: Thiazole schiff bases, Tautomerism, N-Pyrrole derivatives.

INTRODUCTION

Thiazole is one such important hetrocyclic system with pronounced pharmacological activities[1,2,4]. This present work deals with the synthesis, characterization and biological screening of some novel Schiff bases of thiazole derivatives.

Objective

1. Synthesis of novel thiazole Schiff bases.
2. Characterization of structures by MASS, IR and H NMR spectral studies.
3. Screened for anti microbial activity by paper disc diffusion method.

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EXPERIMENTAL

All the chemicals used for the synthesis are received from the Orchid R & D centre, Chennai.

The IR spectra – Perkin Elmer FTIR paragon 1000 using potassium bromide pellets.

H NMR - Bruker avance 400 MHZ using DMSO and $CDCl_3$.

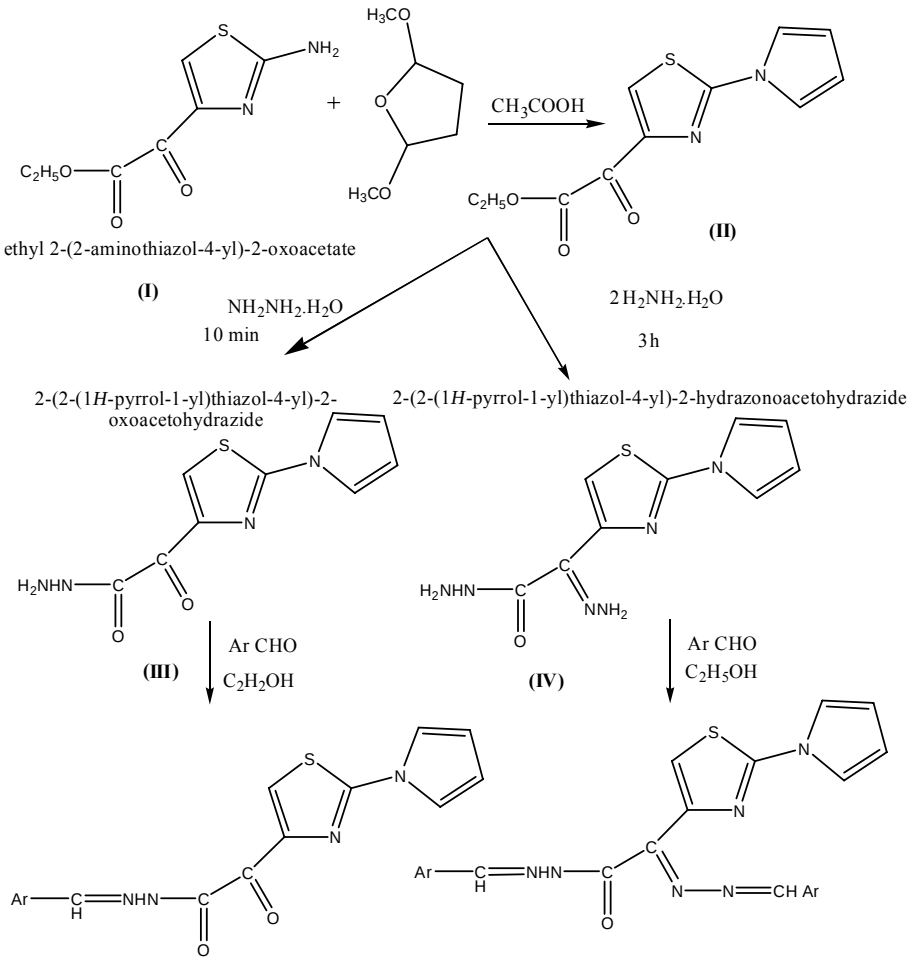
MASS - LCMS D Agilent Technology.

Method of synthesis

Preparation of N-pyrrole derivatives[6]

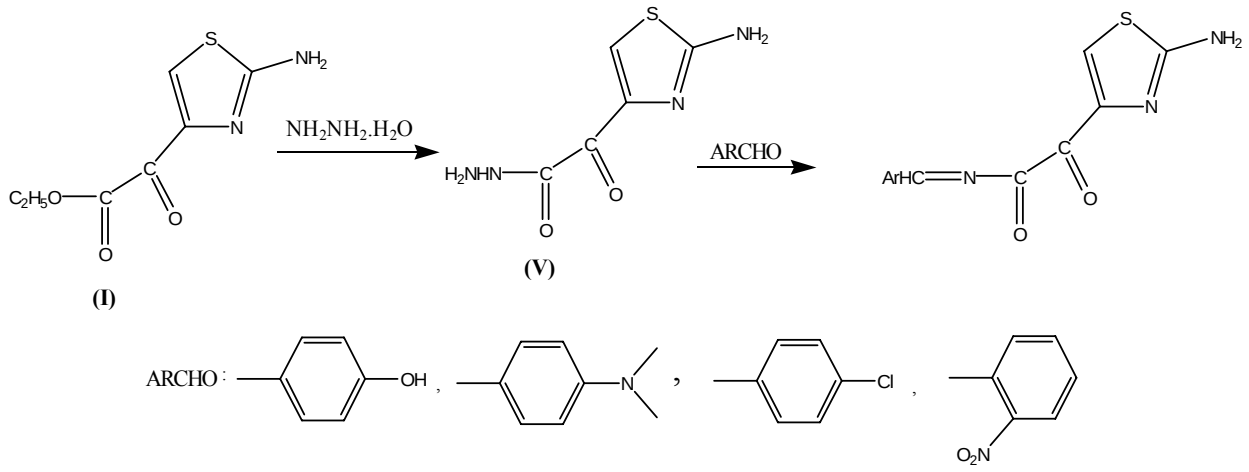
In a dry 150 mL RB flask 5 g (0.025 mol) of ethyl-2(2-amino thiazole-4 yl) glyoxylate and 3.2 mL (3.3 g, 0.25 mol) of 2,5-dimethoxy tetrahydro furan were taken. 100 mL of acetic acid was added to it. This content was refluxed for 1 hr at 118ºC in an oil bath using magnetic stirrer. The reaction mixture was cooled and poured in 1000 mL of cold water. The precipitate (brown colour) was filtered and recrystalized from cyclohexane to get pale yellow coloured needle like crystals.

Preparation of mono hydrazine derivatives[11,12]



Scheme 1

In a 150 mL RB flask a mixture of ethanol 100 mL, 5 g (0.02 mol) of A and 1 g (0.97 mL, 0.02 mol) of hydrazine hydrate was charged and heated gently for 10 min in a water bath under magnetic stirrer. White coloured solid obtained was filtered and dried.



Scheme 2

In a 150 mL RB flask a mixture of Ethanol 100 mL, 5 g (0.026 mol) of B and 1.3 g (01.27 mL, 0.26 mol) of Hydrazine hydrate was charged and heated gently for 10 min in a water bath under magnetic stirrer. White coloured solid obtained was filtered and dried.

In a 150 mL RB flask a mixture of 5 g (0.025 mol) of C and 1.25 g (1.21 mL, 0.025 mol) of hydrazine hydrate and 100 mL of Ethanol were taken. It was heated gently for 10 min in a water bath under magnetic stirrer. White coloured solid obtained was filtered and dried.

Preparation of di hydrazine derivatives[13,14]

In a 150 mL RB flask 5 g (0.02 mol) of A, 100 mL of ethanol and 2 g (1.94 mL, 0.02 mol) of hydrazine hydrate were taken. It was refluxed for 3 hr in a water bath and cooled. The yellowish ash coloured solid obtained was filtered and dried.

Preparation of Schiff's base

General method[1,2,4]

In our starting material contain both 2-thiazolamine and hydrazine active sites for Schiff's base formation.

When we refluxed the compound with aromatic aldehyde, hydrazine active sites, only formed solid Schiff's base very fastly. Compared to hydrazine active site, thiazolamine active site required more heat and time for formation of Schiff's base.

In low temperature 2-thiazolamine form the tautamerism of amine and emine so this 2-thiazolamine getting stable by tautamerism. It required more heat and time of Schiff's base formation compared to hydrazine active site. All the 2-thiazolamine active site Schiff's base derivatives are oily in nature.

This is confirmed by NMR because aryl NH_2 proton peak was obtained as singlet only.

General procedure[7]

Equal molar quantity of single hydrazine derivative and aromatic aldehyde (1 mol dihydrazine derivative and 2 mol aromatic aldehyde) were refluxed in a water bath for 10 min in 10 fold ethanol with few drops of glacial acetic acid. The pale yellow coloured product was obtained. The separated product was filtered out, washed and recrystallised by ethanol.

Eight different Schiff's bases were obtained similarly by changing the calculated quantity respective starting material and aromatic aldehyde.

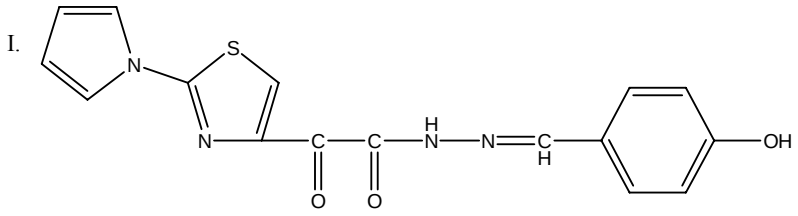
The synthesized Schiff's bases were confirmed by Mass, PNMR and IR Spectral studies.

Experimental data

(I) 2 (2-(1H-Pyrrol-1-yl) thiazole-4 yl)-N (4-hydroxy benzylidene)-2-oxoaceto hydrazine

This compound was obtained as a pale yellow coloured powder (60%), m.p.: 336°C; ^{1}H NMR: δ 9.95 (–NHN=), 8.58 (-N=CH-), 5.7 (Ar-OH); IR: ν 3518 (-OH), 3412 (-NH), 3079 (Ar-CH), 1655 (C=O), 1593 (C=N), 1130 (C-S) cm^{-1}.

I.

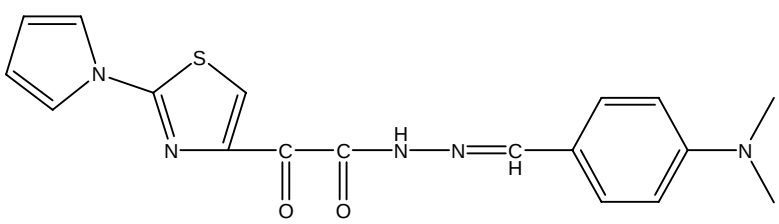


2-(2-(1H-pyrrol-1-yl)thiazol-4-yl)-N'-(4-hydroxybenzylidene)-2-oxoacetohydrazide

(II) 2 (2-(1H-Pyrrol-1-yl) thiazole-4 yl)-N (4 dimethylamino benzylidene)-2-Oxoaceto hydrazine

This compound was obtained as a pale yellow cloured powder (70%), m.p.: 324ºC; ^{1}H NMR: δ 9.90 (-NHN=), 8.50 (-N=CH-), 2.97 (N $(CH_3)_2$); IR: ν 3432 (-NH), 3089 (Ar-CH), 2892 (-CH_3), 1653 (C=O), 1592 (C=N), 1130 (C-S) cm^{-1}.

II

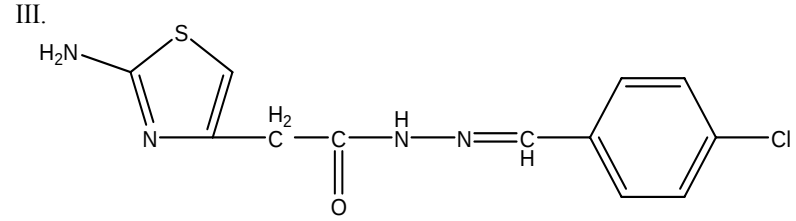


2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-(dimethylamino)benzylidene)-2-oxoacetohydrazide

(III) N′–(4-chlorobenzylidene)-2-(2-aminothi azol-4-yl) acetohydrazide.

This compound was obtained as a pale yellow coloured powder (62%), m.p.: 328ºC; ^{1}H NMR: δ 9.95 (–NHN=), 8.7 (-N=CH-), 4.5 (Ar-NH_2), 2.9 (-CH_2-), IR: ν 3396 (-NH), 3058 (Ar-CH), 2915 (-CH_3), 1675 (C=O), 1607 (C=N), 1130 (C-S), 826 (Ar-Cl) cm^{-1}.

III.

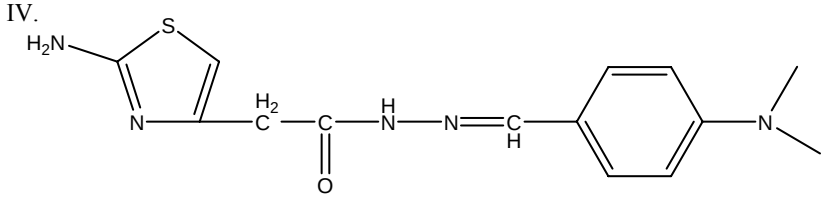


N'-(4-chlorobenzylidene)-2-(2-aminothiazol-4-yl)acetohydrazide

(IV) N′-(4-(dimethylamino)benzylidene)-2-(2-aminothiazol-4-yl)acetohydrazide

This compound was obtained as a pale yellow coloured powder (82%), mp: 342ºC; ^{1}H NMR: δ 9.7 (-NHN=), 8.72 (-N=CH-), 4.5(Ar-NH_2), 3 ($N(CH_3)_2$), 3.34 (-CH_2-); IR: ν 3338 (-NH), 3072 (Ar-CH), 2891 (-CH_3), 1661 (C=O), 1610 (C=N), 1130 (C-S) cm^{-1}.

IV.

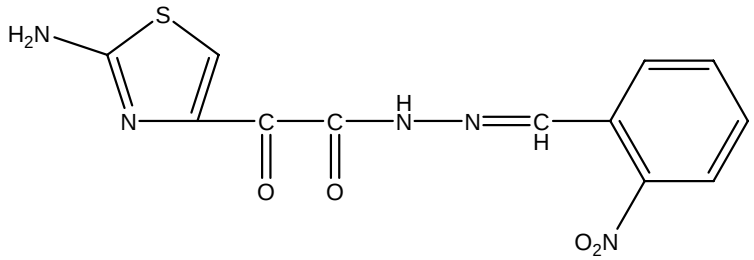


N'-(4-(dimethylamino)benzylidene)-2-(2-aminothiazol-4-yl)acetohydrazide

(V) N′-(2-nitrobenzylidene)-2-(2-aminothiaz ol -4-yl)-2-oxoacetohydrazide

This compound was obtained as a pale yellow coloured powder (70%), m.p.: 322ºC; ^{1}H NMR: δ 9.92 (–NHN=), 8.7 (-N=CH-), 4.56 (Ar-NH_2); IR: ν 3308 (-NH), 3045 (Ar-CH), 1706 (C=O), 1604 (C=N), 1114 (C-S), 1345 (-NO_2) cm^{-1}.

V.

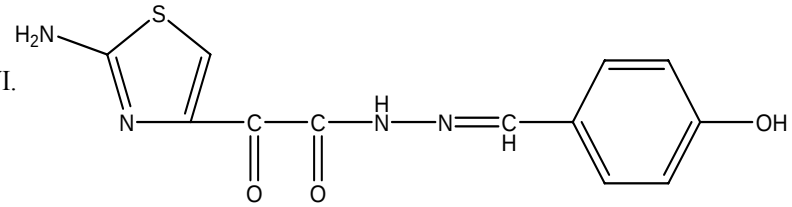


N'-(2-nitrobenzylidene)-2-(2-aminothiazol-4-yl)-2-oxoacetohydrazide

(VI) N′-(4-hydroxybenzylidene)-2-(2-amino thiazol-4-yl)-2-oxoacetohydrazide

This compound was obtained as a pale yellow coloured powder (60%), m.p.: 335ºC; ^{1}H NMR: δ 9.7 (–NHN=), 8.7 (-N=CH-), 4.55 (Ar-NH_2) 5.6 (Ar-OH); IR: ν 3522 (-OH), 3328 (-NH), 3074 (Ar-CH), 1662 (C=O), 1609 (C=N), 1130 (C-S) cm^{-1}.

VI.

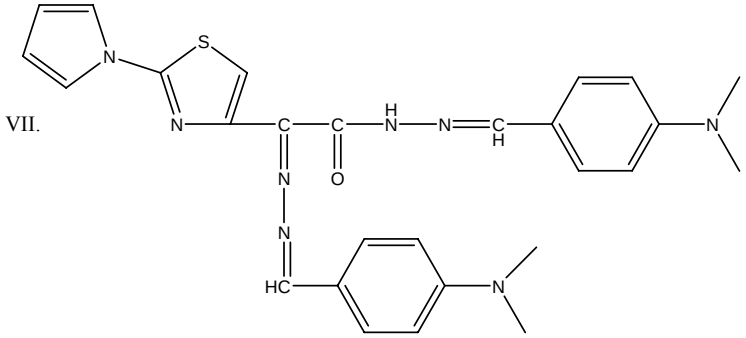


N'-(4-hydroxybenzylidene)-2-(2-aminothiazol-4-yl)-2-oxoacetohydrazide

(VII) (E)-2-(2-(1H-pyrrol-1-yl)thiazol-4-yl)-N′-(4-(dimethylamino)benzylidene) hydrazono) acetohydrazide

This compound was obtained as a pale yellow coloured powder (80%), m.p.: 350ºC; ^{1}H NMR: δ 9.90 (–NHN=), 8.49, 7.9 (-N=CH-), 2.8-3.0 ($N(CH_3)_2$); IR: ν 3412 (-NH), 3090 (Ar-CH), 2890 ($-CH_3$), 1652 (C=O), 1592 (C=N), 1130 (C-S) cm^{-1}.

VII.

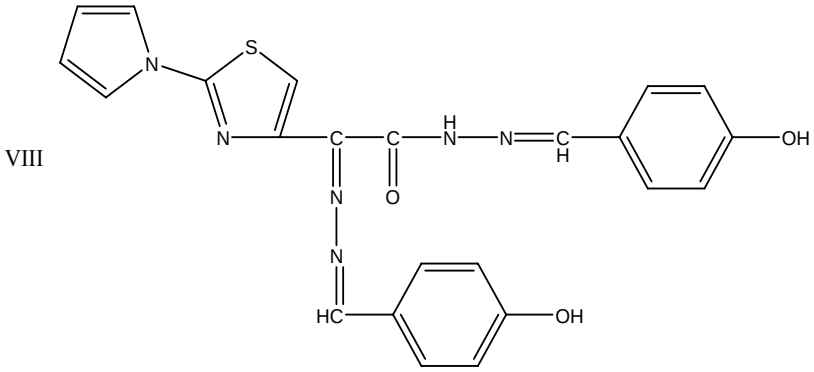


2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-(dimethylamino)benzylidene)-2-(2-(4-(dimethylamino)benzylidene)hydrazono)acetohydrazide

(VIII) (E)-2-(2-(1H-pyrrol-1-yl)thiazol-4-yl)-N′-(4-(hydroxybenzylidene)-2-(2-(4-hydroxybenzylidene) hydrazono) acetohydrazide

This compound was obtained as a pale yellow coloured powder (64%), m.p.: 344ºC; ^{1}H NMR: δ 8.4 - 7.9 (-N=CH-), 5.4, 5.21 (Ar-OH); IR: ν 3514 (-OH), 3304 (-NH), 3024 (Ar-CH), 1667 (C=O), 1608 (C=N), 1107 (C-S) cm^{-1}.

VIII



2-(2-(1*H*-pyrrol-1-yl)thiazol-4-yl)-*N*'-(4-hydroxybenzylidene)-2-(2-(4-hydroxybenzylidene)hydrazono)acetohydrazide

Screening of anti-microbial activity

Paper disc diffusion method[9,10]

The sterilized (autoclaved at 120°C for 30 min) medium (40-50°C) was inoculated (1 mL/100 mL of medium) with the suspension (10^5 CFU/mL) of the micro-organism (matched to McFarland barium sulfate standard) and poured into a Petri dish to give a depth of 3-4 mm. The paper impregnated with the test compounds (25, 50 and 100 µg/mL in dimethyl formamide) was placed on the solidified medium. The plates were pre-incubated for 1 hr at RT and incubated at 37°C for 24 hr for anti-bacterial activities[8]. Ciprofloxacin (100 µg/disc) was used as standard for anti-bacterial activities. The observed zone of inhibition is presented in the Table 1.

Table 1: Anti-microbial activity of the synthesized compounds

Compounds	Zone of inhibition (in mm)											
	Bacteria											
	S.aureus			***S.epidermidis***			***E.coli***			***K.pneumoniac***		
	Concentration (µg/mL)											
	25	50	100	25	50	100	25	50	100	25	50	100
I	12	15	19	14	17	20	11	15	19	11	14	17
II	13	14	22	14	16	21	12	15	17	11	15	18
III	11	17	21	11	13	17	13	16	19	12	15	17
IV	13	16	21	12	15	19	12	15	18	11	13	16
V	12	15	17	11	14	17	12	16	18	13	16	18
VI	15	17	20	12	15	18	14	16	19	14	16	19
VII	16	20	25	13	16	22	14	17	23	9	15	21
VIII	15	18	21	12	14	17	11	15	20	13	18	22
Ciprofloxacin (100 µg/mL)	26			28			27			23		
Control	-			-			-			-		

Determination of minimum inhibitory concentration (MIC)

Agar streak dilution method[5]

MIC of the synthesized compound was determined by agar streak dilution method. A stock solution of the synthesized compound (100 µg mL^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for anti-bacterial activity). A specified quantity of the medium (40-50°C) containing the compound was poured into a petri dish to give a depth of 3-4 mm and allowed to solidify. Suspension of the micro-organism was prepared to contain approximately 10^5 CFU/mL and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37°C for 24 hr for bacteria. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate. The observed MIC[3] is presented in the Table 2.

Table 2: MIC of the synthesized compounds

Compounds	Minimum inhibitory concentration (µg/mL)			
	Bacteria			
	S.aureus	***S.epidermidis***	***E.coli***	***K.pneumoniae***
I	15	16.5	16	16.5
II	12	11	13	12.5
III	13.5	16	14	18
IV	14	12	15	15

Cont…

Compounds	Minimum inhibitory concentration (µg/mL)			
	Bacteria			
	S.aureus	***S.epidermidis***	***E.coli***	***K.pneumoniae***
V	14.5	13	13	15.5
VI	12.5	14	19	14.5
VII	10	12.5	10.5	11.5
VIII	13	14	12	12

RESULTS AND DISCUSSION

The synthesized compounds were (25, 50 and 100 µg per mL) screened for anti microbial activity by paper disc diffusion method. Compared to standard drug (Ciprofloxacin) compound P7, P2, and P8 were found to exhibit good anti microbial activity.

Compounds were active against all the tested micro organisms with rang of MIC values for *S. aureus* (10-15 µg/mL), *S. epidermidis* (11-16.5 µg/mL), *E.coli* (10.5-16.5 µg/mL), *K. pneumoniae* (11.5-16.5 µg/mL).

CONCLUSION

In conclusion, the present study highlights the importance of thiazole Schiff basses to obtain clinically useful entities for the new millennium.

ACKNOWLEDGEMENT

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