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SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL SCREENING OF NOVEL THIAZOLIDINO-FUSED COMPOUNDS

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ABSTRACT

4-Thiazolidinones **(III a-e)**, which are hetarylsubstituted at the 2-position were prepared by the reaction of mercaptoacetic acid with aldimines **(II a-e)** which were prepared by the condensation of 2-amino benzothiazole **(I)** with different substituted aryl aldehyde. After their benzylidene derivatives **(IV a-e)** were obtained, We synthesized pyrazolinothiazolidine **(V a-e)** by using phenyl hydrazine in the presence of sodium acetate. All mentioned compounds have been characterized by spectral data and screened for their antimicrobial activity. Some of them exhibit appreciable activity with known standard drugs at same concentration.

Key words : Benzothiazole, Thiazolidine-4-one, Benzylidene derivatives, Pyrazolinothiazolidine and Antimicrobial activity.

INTRODUCTION

Aldimines have been generally used as substrates in the formation of a large number of industrial compounds *via* cycloaddition, ring closure, replacement reactions, etc.[1, 2]. In addition, the aldimines of heterocyclic compound, which are widely used in the production of pharmaceuticals, have taken an important place among the compounds of biological interest because of the conjugation and the groups that they contain within their molecules. Furthermore, most of the 4-thiazolidinones and their benzylidene derivatives display a large variety of activities such as antibiotic, diuretic, organoleptic,

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tuberculostatic, antileukemik and antiparasitical[3, 4]. To our knowledge, little is known about fused thiazolidines known to possess such activities[5]. Moreover, little attention has been directed to the behavior of this class of compounds towards phenylhydrazine under varied conditions to determine their cyclization reactions for possible biological activities of new compounds[6, 7].

For a long time, imines have been used successfully in the synthesis of nitrogen containing heterocycles[8]. As part of ongoing project aimed at the discovery of bioactive 4-thiazolidinones, We employed the Schiff bases, **II a-e** toward their synthesis. These azomethines have been obtained by the reaction of 2-amino benzothiazole with different substituted aromatic aldehydes in refluxing dry ethanol or dry benzene[9]. First, We obtained the new 3-(benzothiazol-2-yl)-2-substituted aryl-4-thiazolidinones, **III a-e** in good yields by refluxing equimolar amounts of the Schiff's base **II a-e** and thioglycollic acid in DMF. Then compounds **III a-e** reacted with benzaldehyde in the presence of anhyd. sodium acetate to afford benzylidene derivatives **IV a-e**. These were condensed with phenyl hydrazine in glacial acetic acid in the presence of sodium acetate. They underwent subsequent cyclization to give 2-substituted phenyl-6, 7-diphenyl-3-benzothiazol-2-yl-pyrazolino-(3, 4-d)thiazolidines **V a-e**. The structures of the new compounds were firmly established on the basis of their IR, ^{1}H NMR analysis and screened for their antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open glass and are uncorrected. The purity of the compounds was ascertained by TLC on silica gel-G plate. Characterization of synthesized compounds were done by spectral studies. IR spectra were taken in KBr on a THERMONICOLET NEXUS-670 Spectrophotometer. ^{1}H NMR spectra were recorded on AVANCE-300MHZ Spectrophotometer in DMSO-d6 with TMS as internal standard. The chemical shift values are in delta (ppm). Physical data and antimicrobial activities of synthesized compounds are recorded in Tables 1 and 2, respectively.

Preparation of II a-e

Equimolar (0.01 mol) quantity of 2 - aminobenzothiazole and substituted benzaldehyde dissolved in absolute ethanol (50 mL) and few drops of acetic acid was heated on steam bath for 2 hrs. After standing for 24 hrs at room temperature, the product was filtered, dried and recrystallized from warm absolute alcohol.

IIa: ^{1}H NMR (DMSO-d6) : 7.23-7.96 (m, Ar-H, benzothiazole-H), 8.7 (s, 1H,

N=CH).

IIb: ^{1}H NMR (DMSO-d6) : 7.19-7.9 (m, Ar-H, benzothiazole-H), 5.4 (s, phenolic-OH), 8.5 (s, 1H, N=CH).

IIc: ^{1}H NMR (DMSO-d6) : 7.19-7.71 (m, Ar-H, benzothiazole-H), 8.6 (s, 1H, N=CH), 5.1 (s, phenolic-OH), 3.0 (s, O-CH_3).

IId: ^{1}H NMR (DMSO-d6) : 7.2-7.8 (m, Ar-H), 7.8 (s, 1H, N=CH), 6.7-7.2 (m, furan-H).

IIe: ^{1}H NMR (DMSO-d6) : 7.2-7.9 (m, Ar-H, benzothiazole-H), 8.5 (s, 1H, N=CH).

Preparation of IIIa-e

A mixture of Schiff's base (0.01 mol) and mercapto acetic acid (0.01 mol) dissolved in DMF (30 mL) containing a pinch of anhydrous $ZnCl_2$ (0.5 mg) was refluxed for 8 hrs. The reaction mixture was cooled and the resulting solid was washed with sodium bicarbonate solution and recrystallized from absolute alcohol.

IIIa : IR (KBr) : 2924.6 cm^{-1} (Ar-H), 1601.68 cm^{-1} (C=O), 695.4 cm^{-1} (C-S-C)

^{1}H NMR (DMSO-d6) : 7.0-8.28 (m, Ar-H, benzothiazole-H), 5.86 (s, N-CH-S), 3.91 (s, S-CH_2-).

IIIb : IR (KBr) : 3059.78 cm^{-1} (Ar-H), 1742 cm^{-1} (C=O), 3454 cm^{-1} (OH), 694.4 cm^{-1} (C-S-C)

^{1}H NMR (DMSO-d6) : 6.5-7.9 (m, Ar-H, benzothiazole-H), 5.85 (s, N-CH-S), 3.5(s, S-CH_2-), 5.3 (s, Phenolic-OH).

IIIc : IR (KBr) : 2925.05 cm^{-1} (Ar-H), 1655.08 cm^{-1} (C=O), 3245cm^{-1} (-OH), 693.08 cm^{-1} (C-S-C)

^{1}H NMR (DMSO-d6) : 7.2-7.9 (m, benzothiazole-H), 6.2-6.9 (m, Ar-H), 5.9 (s, N-CH-S), 3.4 (s, S-CH_2-), 3.8 (s, O-CH_3), 5.4 (s, Phenolic-OH).

IIId : IR (KBr) : 2921.33 cm^{-1} (Ar-H), 1638.93 cm^{-1} (C=O), 636.86 cm^{-1} (C-S-C)

^{1}H NMR (DMSO-d6) : 7.2-7.9 (m, benzothiazole-H), 6.5-6.7 (m, furan-H), 6.3 (s, N-CH-S), 3.5 (s, S-CH_2-).

IIIe : IR (KBr) : 2922.19 cm^{-1} (Ar-H), 1638.78 cm^{-1} (C=O), 694.09 cm^{-1} (C-S-C)

^{1}H NMR (DMSO-d6) : 7.3-7.9 (m, Ar-H, benzothiazole-H), 5.86 (s, N-CH-S), 3.32

(s, S-CH_2-).

Preparation of IVa-e

A mixture of **IIIa-e** (0.005 mol), benzaldehyde (0.005 mol) and anhydrous sodium acetate (0.005 mol) in glacial acetic acid (50 mL) was refluxed on a heating mantle for 3 hours. The reaction mixture was concentrated, cooled and poured into ice cold water. The solid thus obtained was filtered, washed with water and recrystallized from ethanol to give crystals.

IVa : IR (KBr) : 2925.6 cm^{-1} (Ar-H), 1602.68 cm^{-1} (C=O), 1670 cm^{-1} (C=CH).

^{1}H NMR (DMSO-d6) : 6.0-8.28 (m, Ar-H, benzothiazole-H, benzylidene-H), 5.76 (s, N-CH-S).

IVb : IR (KBr) : 3049.78 cm^{-1} (Ar-H), 1642 cm^{-1} (C=O), 1674.96 cm^{-1} (C=CH), 3454 cm^{-1} (OH)

^{1}H NMR (DMSO-d6) : 6.0-7.9 (m, Ar-H, benzothiazole-H, benzylidene-H), 5.75 (s, N-CH-S), 5.4 (s, Phenolic-OH).

IVc : IR (KBr) : 2927.05 cm^{-1} (Ar-H), 1657.08 cm^{-1} (C=O), 1671.95cm^{-1} (C=CH), 3255cm^{-1} (-OH)

^{1}H NMR (DMSO-d6) : 6.2-7.9 (m, Ar-H, benzothiazole-H, benzylidene-H), 5.7 (s, N-CH-S), 3.5 (s, O-CH_3), 5.1 (s, Phenolic-OH).

IVd : IR (KBr) : 2926.33 cm^{-1} (Ar-H), 1648.93 cm^{-1} (C=O), 1673.66 cm^{-1} (C=CH)

^{1}H NMR (DMSO-d6) : 6.2-8.4 (m, furan-H, benzothiazole-H, benzylidene-H), 6.0 (s, N-CH-S).

IVe : IR (KBr) : 2923.19 cm^{-1} (Ar-H), 1640.78 cm^{-1} (C=O), 1674.28 cm^{-1} (C=CH).

^{1}H NMR (DMSO-d6) : 7.0-8.2 (m, Ar-H, benzothiazole-H, benzylidene- H), 5.7 (s, N-CH-S).

Preparation of V a-e

A mixture of **IVa-e** (0.0025 mol), phenyl hydrazine (0.005 mol) and anhydrous sodium acetate (0.005 mol) in glacial acetic acid (50 mL) was refluxed on a heating mantle for 5 hours. The reaction mixture was concentrated, cooled and poured into ice cold water. The solid thus obtained was filtered, washed with water and recrystallized from ethanol to

give crystals.

Va : IR (KBr) : 2934.6 cm^{-1} (Ar-H), 1575.68 cm^{-1} (C=N).

^{1}H NMR (DMSO-d6) : 6.0-8.28 (m, Ar-H, benzothiazole-H, pyrazole-H), 5.66 (s, N-CH-S), 7.4 (d, 1H, 3'a-CH), 8.7 (d, 1H, 3'-CH).

Vb : IR (KBr) : 3039.78 cm^{-1} (Ar-H), 1542 cm^{-1} (C=N), 3464 cm^{-1} (OH)

^{1}H NMR (DMSO-d6) : 6.8-7.9 (m, Ar-H, benzothiazole-H, pyrazole-H), 5.85 (s, N-CH-S), 5.3 (s, Phenolic-OH), 7.5 (d, 1H, 3'a-CH), 8.80 (d, 1H, 3'-CH).

Vc : IR (KBr) : 2935.05 cm^{-1} (Ar-H), 1559.08 cm^{-1} (C=N), 3246cm^{-1} (-OH)

^{1}H NMR (DMSO-d6) : 6.3-7.8 (m, Ar-H, benzothiazole-H, pyrazole-H), 5.7 (s, N-CH-S), 3.74 (s, O-CH_3), 5.6 (s, Phenolic-OH), 7.50 (d, 1H, 3'a-CH), 8.76 (d, 1H, 3'-CH).

Vd : IR (KBr) : 2931.33 cm^{-1} (Ar-H), 1578.93 cm^{-1} (C=N).

^{1}H NMR (DMSO-d6) : 6.0-8.4 (m, furan-H, benzothiazole-H, pyrazole-H), 6.4 (s, N-CH-S), 7.34 (d, 1H, 3'a-CH), 8.6 (d, 1H, 3'-CH).

Ve : IR (KBr) : 2932.19 cm^{-1} (Ar-H), 1570.78 cm^{-1} (C=N).

^{1}H NMR (DMSO-d6) : 6.9-7.9 (m, Ar-H benzothiazole-H, pyrazole- H), 5.76 (s, N-CH-S), 7.45 (d, 1H, 3'a-CH), 8.75 (d, 1H, 3'-CH).

Antibacterial activity

All the compounds were tested for their antibacterial activity against *Bacillus Cereus* NCCS 2106*, Staphylococcus aureous* NCCS 2079 (Gram +ve), *Escherichia Coli* NCCS 2065 (Gram -ve) using disc diffusion method[10, 11]. DMF was run as a control and test was performed at different concentrations using a solvent DMF. Ciprofloxacin was used as a standard drug. All the pyrazolinothiazolidine derivatives **(Va-e)** showed antibacterial activity.

Antifungal activity

All the compounds were tested for their antifungal activity against *Candida albicans* NCCS 3471 and *Aspergillus niger* NCCS 1196 by disc diffusion method [10, 11]. DMF was run as a control and test was performed at different concentrations using a solvent DMF. Ketoconazole was used as a standard drug. All the compounds **(Va-e)** showed antifungal activity.

Table 1 : Physical data of compounds

Compound	R	m. p (^{o} C)	Yield (%)	Molecular formula
Va	Phenyl	220 – 223	62	$C_{29}H_{22}N_4S_2$
Vb	2-Hydroxyphenyl	234 – 237	58	$C_{29}H_{22}N_4S_2O$
Vc	4-Hydroxy, 3-methoxy phenyl	216 – 220	60	$C_{30}H_{24}N_4S_2O_2$
Vd	Furan	228 – 230	64	$C_{27}H_{20}N_4S_2O$
Ve	2 – Chlorophenyl	225 – 228	66	$C_{29}H_{21}N_4S_2Cl$

Table 2 : Anti-microbial activity data

Comp. (50µg/mL)	Antibacterial activity Zone of inhibition in (mm)			Antifungal activity Zone of inhibition in (mm)	
	***Bacillus Cereus* NCCS 2106**	***Staphylococcus aureus* NCCS 2079**	***Escherichia coli* mutant NCCS 2065**	***Candida albicans* NCCS 3471**	***Aspergillus niger* NCCS 1196**
Va	18	19	17	17	15
Vb	21	20	19	18	14
Vc	22	21	21	19	16
Vd	19	19	18	16	13
Ve	16	17	17	13	13
Standard	33	29	31	33	28
Control DMF	-	-	-	-	-

RESULTS AND DISCUSSION

The structures of the new compounds were firmly established on the basis of their IR and ^{1}H NMR analysis. Compounds **Va-e** showed two doublets at δ 7.4 ppm and 8.70 ppm, respectively for the protons at 3'a and 3' positions, which corroborates the cyclic

structure and cis configuration. In the IR spectra of the thiazolidinones, the characteristic C=O bands appeared in the region of 1680-1660 cm^{-1}. The strong sharp bands at 1620-1610 cm^{-1} corresponding to initial azomethines were absent, which was the most characteristic evidence of the cyclocondensation. In compounds **V a-e,** amide carbonyl band was absent, which clearly confirmed that a cyclocondensation with phenylhydrazine had taken place. In general, all the compounds showed antibacterial and antifungal activity. The maximum activity was obtained when R was substituted by a hydroxyl, methoxy group in the phenyl ring of thiazolidine nucleus (22 mm). The thiazolidine derivatives having chlorine atom showed minimum activity (16 mm). Rest of the compounds showed moderate activity. It was found that the compounds possessing electron releasing groups considerably enhanced the antimicrobial activity when compared to the electron withdrawing substituents on the phenyl ring. In summary, we have prepared a new series of potentially bioactive substituted pyrazole with the thiazolidinyl moieties.

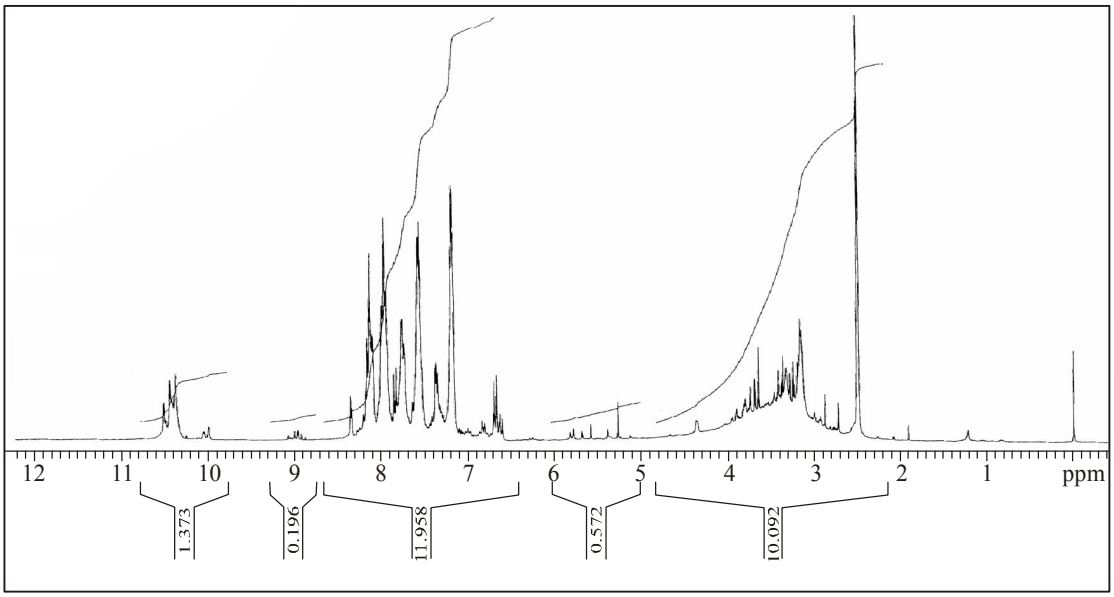


Fig. 1: NMR spectrum of compound Va

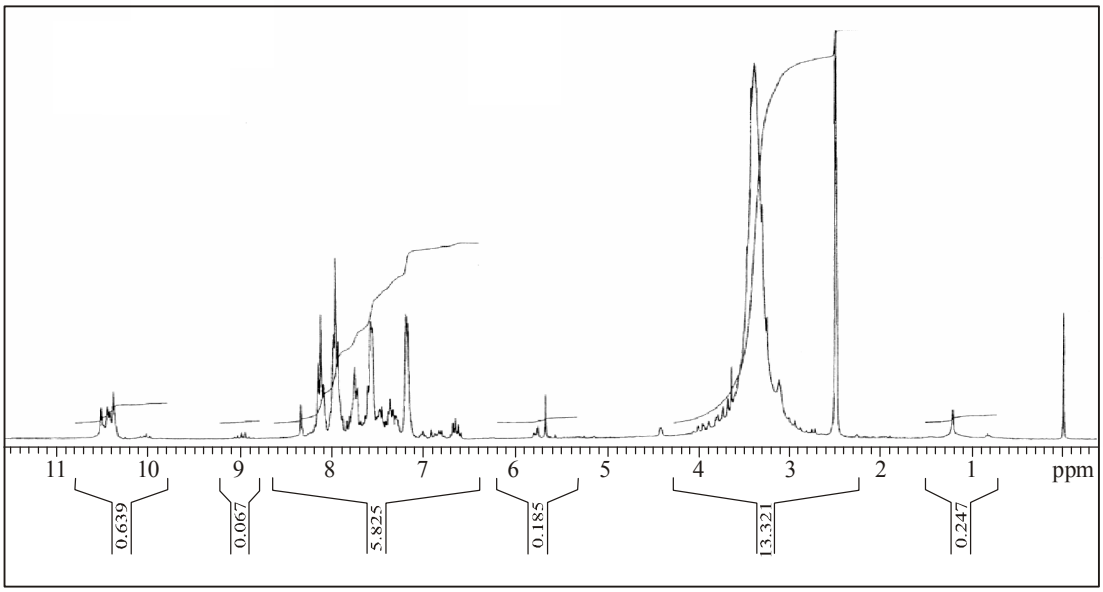


Fig. 2: NMR spectrum of compound Vb

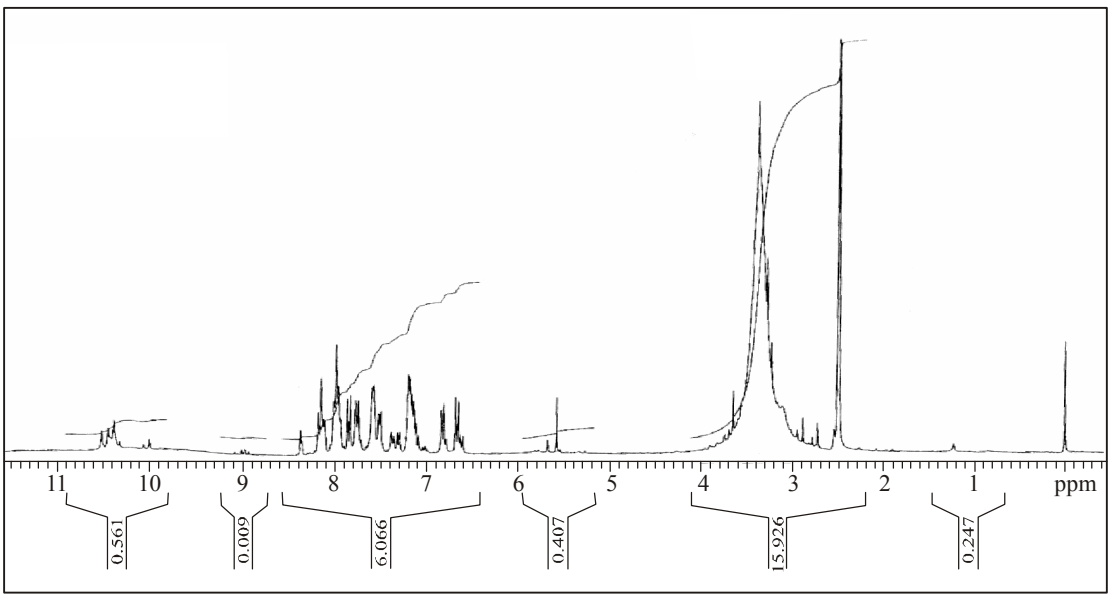


Fig. 3: NMR spectrum of compound Vc

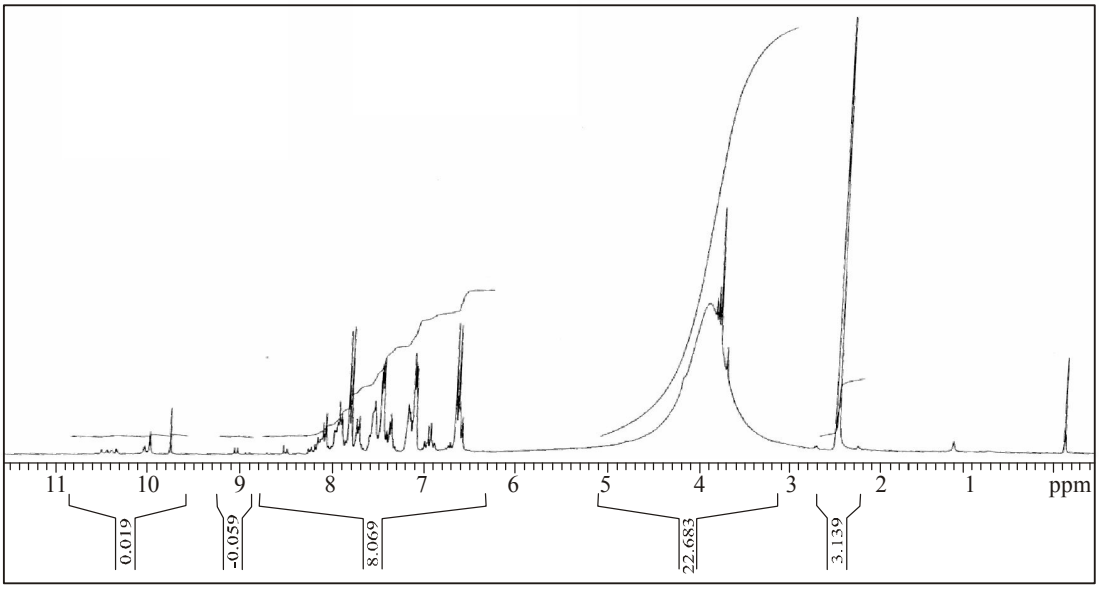


Fig. 4: NMR spectrum of compound Vd

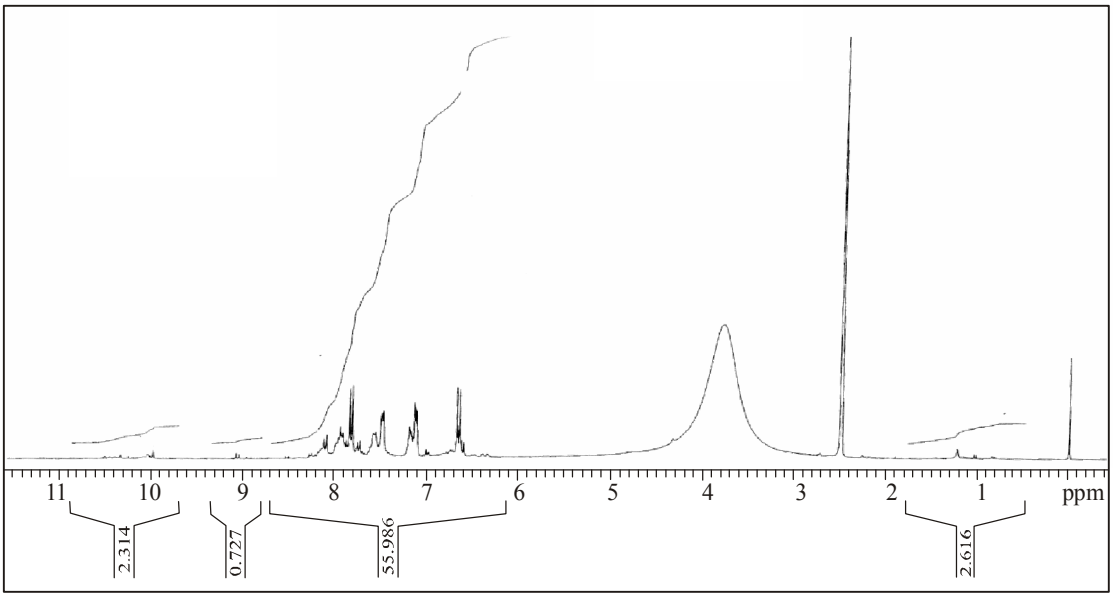
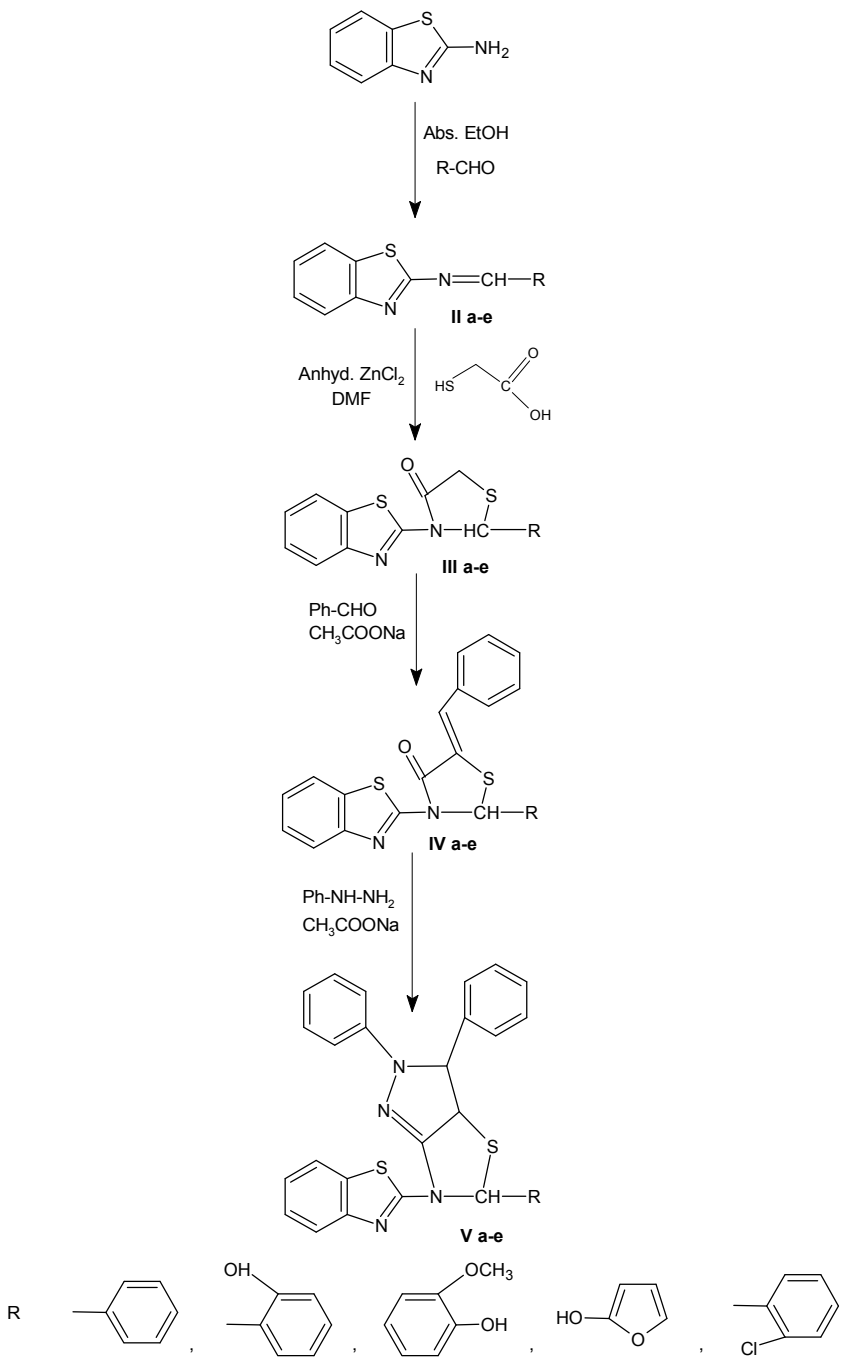


Fig. 5: NMR spectrum of compound Ve


NH2
Abs. EtOH
R-CHO
N=CH—R
II a-e
Anhyd. ZnCl2
DMF
HS
OH
HC—R
III a-e
Ph-CHO
CH3COONa
IV a-e
Ph-NH-NH2
CH3COONa
V a-e
R
OH
OCH3
OH
HO
Cl

Scheme

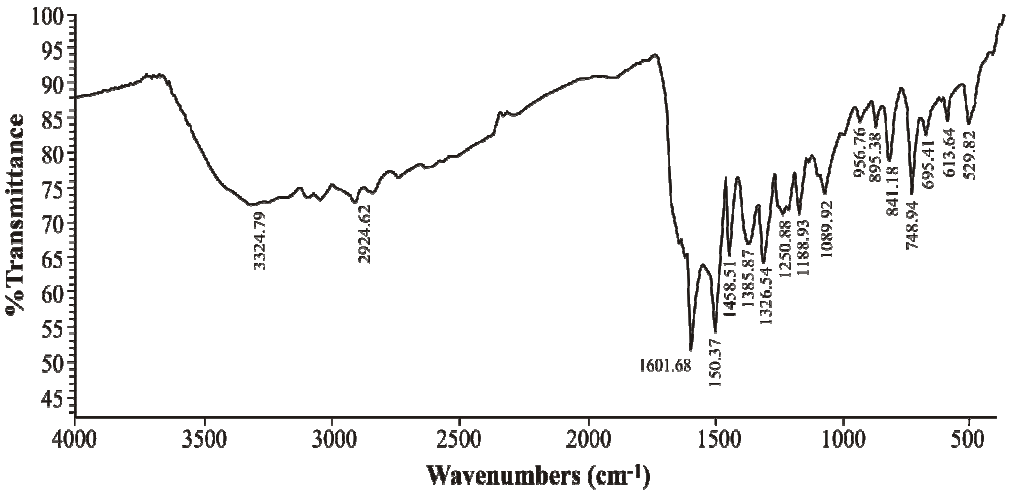


Fig. 6: IR spectrum of compound Va

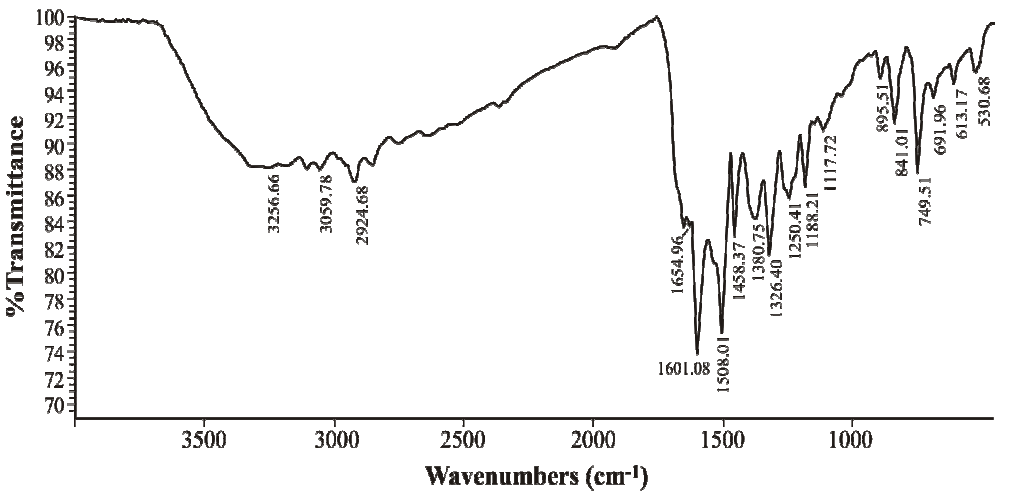


Fig. 7: IR spectrum of compound Vb

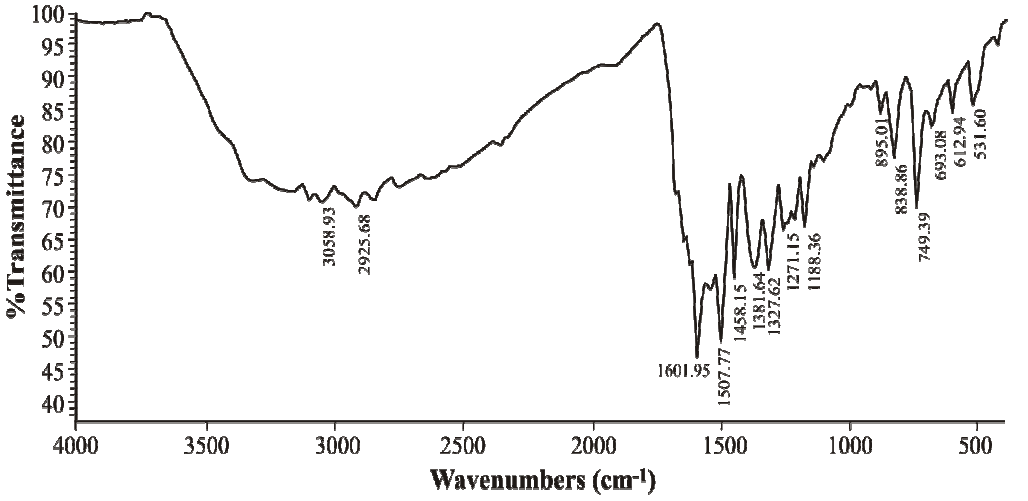


Fig. 8: IR spectrum of compound Vc

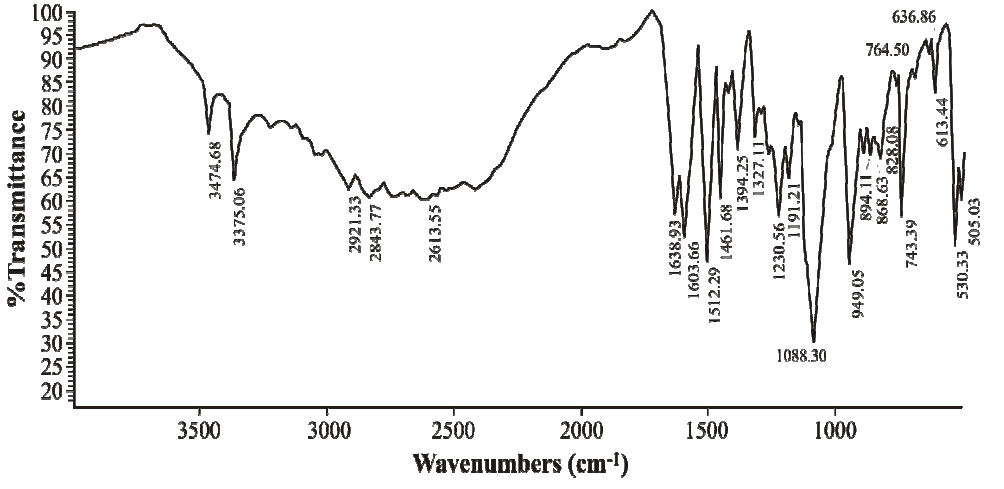


Fig. 9: IR spectrum of compound Vd

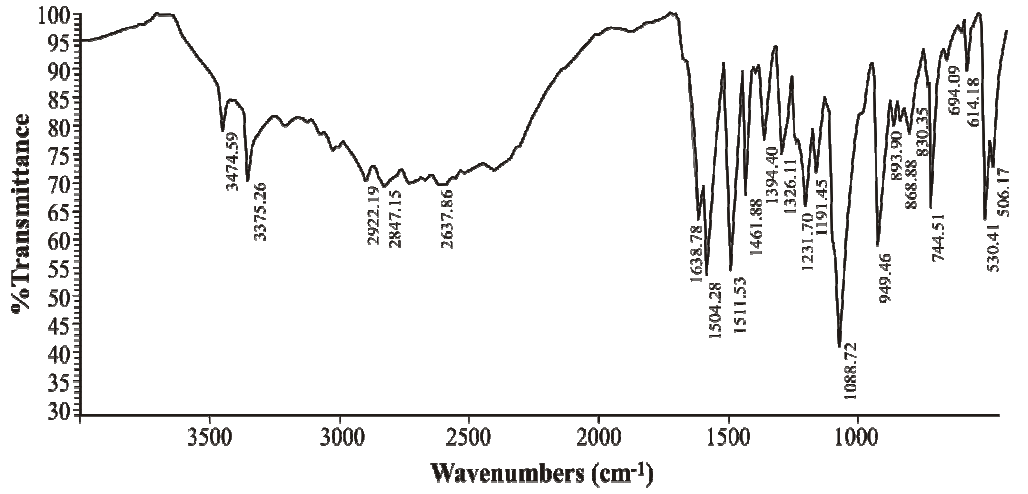
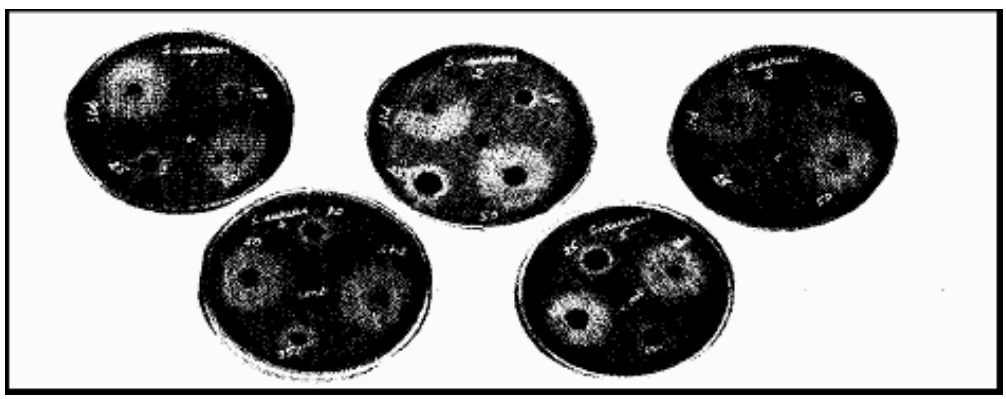


Fig. 10: IR spectrum of compound Ve

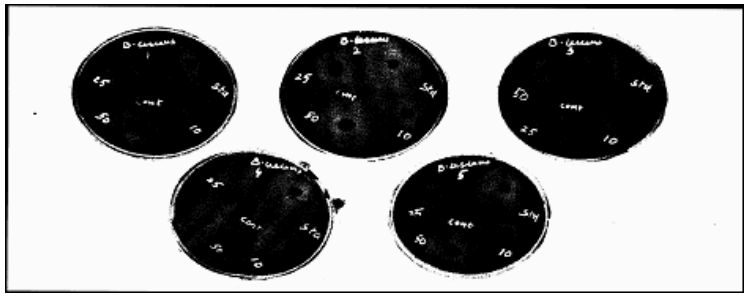


Concentration : 10, 25 and 50 μg/mL

Standard : Ciprofloxacin (50 μg/mL)

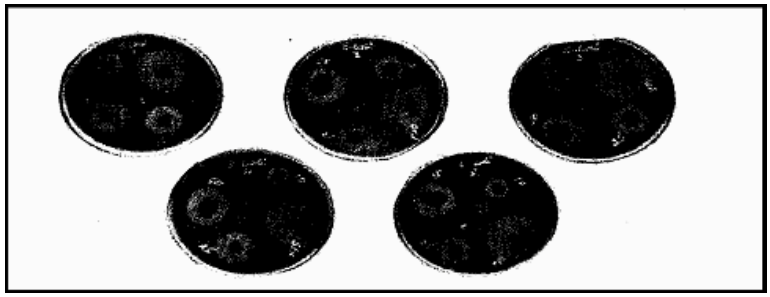
Control : DMF

Fig. 11: Antibacterial activity of compounds Va-e against *B. cereus*



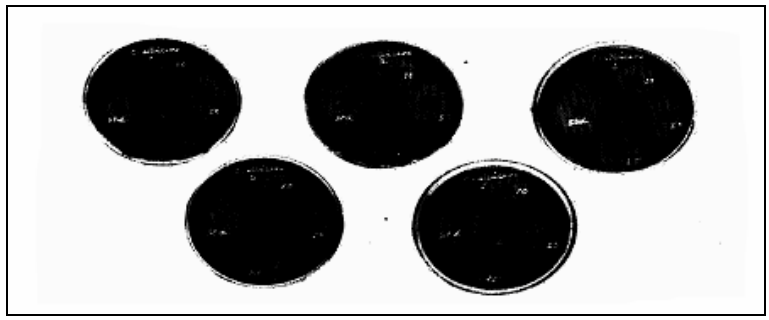
Concentration : 10, 25 and 50 μg/mL
Standard : Ciprofloxacin (50 μγ/mL) Control : DMF

Fig. 12: Antibacterial activity of compounds Va-e against *S. aureus*



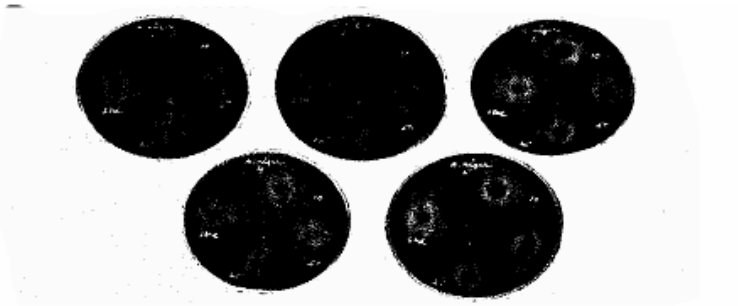
Concentration : 10, 25 and 50 μg/mL
Standard : Ciprofloxacin (50 μg/mL) Control : DMF

Fig. 13: Antibacterial activity of compounds Va-e against *E. coli*



Concentration : 10, 25 and 50 μg/mL
Standard : Ciprofloxacin (50 μg/mL) Control : DMF

Fig. 14: Antibacterial activity of compounds Va-e against *C. albicans*



Concentration : 10, 25 and 50 μg/mL

Standard : Ciprofloxacin (50 μg/mL)

Control : DMF

Fig. 15: Antibacterial activity of compounds Va-e against *A. niger*

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