SYNTHESIS OF SOME NEW SUBSTITUTED 4-THIAZOLIDINONES BEARING BROMO VANILLIN MOIETY AS ANTIBACTERIAL AGENTS

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ABSTRACT

Some new substituted 4-Thiazolidinones II(a-j) have been prepared from substituted Schiff Bases I(a-j) by the action of mercaptoacetic acid in dioxane solvent containing a pinch of anhydrous Zncl$_2$ by conventional method. The structure of substituted 4-Thiazolidinones have been characterized by using IR, ^{1}HNMR and Mass spectral data. All synthesized compounds have been screened for their antibacterial activity. Some of these compounds showed potential antibacterial activity.

***Keywords:**, Schiff bases, Thiazolidinones, Thioglycolic acid, Spectral studies, Antibacterial activity.*

Introduction

There are many biologically active molecules that contain various heteroatoms such as nitrogen, sulfur, and oxygen, which have always attracted the attention of chemists for years, mainly due to their biological importance. Thiazolidinone, a saturated form of thiazole with a carbonyl group on the fourth carbon, is thought to be a magic nucleus, involved in almost all biological activities. It belongs to an important group of heterocyclic compounds containing sulfur and nitrogen in a five-member ring[1]. This biologically active scaffold has sparked interest in synthesizing many new compounds using multiple substitutions in different locations associated with 4-thiazolidinone moieties. Substitution may be varied in 2nd, 3rd and 5th positions. But the largest difference in structure and properties is imposed by the group attached to the carbon atom in the 2-position[2]. The tetrahydro derivative of thiazole is called thiazolidine and the oxo derivative of thiazolidine is called thiazolidinone.

However, its derivatives are the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature. Thiazolidin-4-ones scaffolding is very versatile and has been depicted in many clinically used .drugs. They have been used as antibacterial[3], antitubercular[4], anti-inflammatory[5] and antiviral agents, especially anti-HIV agents[6]. 4-Thiazolidinones play an important role due to their extensive biological activity and industrial significance. 4-Thiazolidinones have always been attractive to researchers due to their potential for various medicinal drug uses. The global population is under threat due to the prevalence of infectious diseases. Although the infection has been seen as a pathogen for years, it is still important due to its multidrug resistance[7]. The R-*N* group at the 3-position of thiazolidin-4-ones may be varied to be alkyl, aryl, heterocyclic groups etc. It is also well known that thiazole is important moiety for biological activity[8-11]. The chemical alteration of the bioactive component is one of the most common approaches in drug discovery, with enhanced therapeutic effects[12] and the wide incidence of the heterocyclic moieties in bioactive natural products and pharmaceuticals has made them as central synthetic targets. A small ring containing heterocyclic atoms such as nitrogen, sulfur and oxygen has long been considered for its important properties due to its medicinal properties and has also been given to society from a biological and industrial perspective to help understand life processes[13]. They are seen as integral components in the bacterial peptidoglycan biosynthesis, a novel inhibitor of the Mur B enzyme at low micro-molar levels[14]. Shivaji Chavan *et al.*[15] have synthesized new class of 4-thiazolidinones by cyclocondensation reaction of imines with thioglycolic acid afforded 4-thiazolidinones, using both conventional as well as microwave irradiation (MWI) technique. Some of the newly synthesized derivatives showed effective antimicrobial activity against tested microbes.

Subhash B Junne *et al.*[16] had reported the synthesis of Schiff bases by treating dioxane

with mercaptoacetic acid to give 4-thiazolidinones (2a-m) and screened for their antibacterial activity using *Escherichia coli*, *Xanthomonas citri*, *Erwinia carotovara* and *Bacillus substilis* as bacteria. Mudassar Sayyed *et al.*[17] had carried out the synthesis of some new 2,3-diaryl-1,3-thiazolidin-4-ones as antibacterial agents. The synthesis of the new 2,3-diaryl-1,3-thiazolidin-4-ones was carried out by reacting various substituted benzylidene-aniline derivatives with mercapto-acetic acid in the presence of zinc chloride. Upon screening for antibacterial activity some of them proved to have potent antibacterial activity and the results confirmed that the antibacterial activity was strongly dependent on the nature of the substituent's at C-2 and N-3 of the thiazolidinone ring.

Thiazolidinones, an important group of heterocyclic compounds, are widely recognized for their application in the field of medicine. 4-Thiazolidinones play an important role due to their extensive biological activity and industrial significance. 4-Thiazolidinones have always been attractive to researchers due to their potential for various medicinal drug uses. The global population is under threat due to the prevalence of infectious diseases. Although the infection has been seen as a pathogen for years, it is still important due to its multidrug resistance. An increase in multi-drug resistance (MDR) is a major problem, making the disease costly and insurmountable, especially in immune affected subjects such as AIDS patients. These researches have encouraged us to synthesize various derivatives of 4-thiazolidinone to investigate the antimicrobial activity profile. From this point of view, the aim of the present work is to synthesize new compounds containing the novel 4-thiazolidinone nucleus. These synthesized heterocycles were screened for their antibacterial activity against *Xanthomanas citri, Erwinia carotovara, Escherichia coli, Bacillus subtilis* using penicillin as a standard for comparison. Further the structures of synthesized compounds were confirmed by spectral data (IR, 1H NMR and Mass).

Experimental

Melting points are taken in open capillary tube. The purity of compounds was checked by T.L.C. The IR spectra were recorded in KBr on Perkin-Elmer 157 Spectrophotometer (_max in cm-1) and 1H NMR spectra were recorded on Bruker Advanced Spectrophotometer 300 MHz NMR instrument using DMSOd6 instrument using TMS as an internal standard (chemical shift are given in δ ppm). The Mass spectra were recorded on a FT-VC-7070 and Mass Spectrometer using the EI technique at 70 ev.

General Procedure

A mixture of Schiff base and mercaptoacetic acid in dioxane containing a pinch of anhydrous $ZnCl_2$ was refluxed for 8 hrs. The reaction mixture was cooled and poured in ice cold water. The solid, thus obtained was treated with saturated solution of sodium bicarbonate to eliminate the excess of mercaptoacetic acid. The separated solid was filtered, washed with cold water and recrystallised from 1-4 dioxane. The purity of synthesized 4-thiazolidinones was checked by TLC. The structure of 4-thiazolidinone were assigned by spectral data (I.R. ^{1}H NMR, and Mass).

Synthesis of 2-(3-bromo-4-hydroxy-5-methoxyphenyl)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-1,3-thiazolidin-4-one (IIh)

A mixture of 4-{[(1*E*)-(3-bromo-4-hydroxy-5-methoxyphenyl)methylidene]amino}-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (0.01 mmole) dissolved in 1,4 dioxane (50 mL) and thioglycolic acid (0.01 mmole) was refluxed for 8 hrs. The content were then cooled and poured into sodium bicarbonate, solution (4N) to remove the excess of mercaptoacetic acid. The resultant solid was filtered, washed with cold water and recrystallized from ethanol: 1-4dioxane to give **IIh**

Yield : 60%

M.P. : 258° C

IR: ν_{max} :3321 (Ph-OH), 3041 (Ar-C-H), 2960 (C-H of R-CH_3), 2924 (C-H of R_2-CH_2), 2851 (C-H of R_3-CH), 2871 (C-H of R-CH_3), 2851 (C-H of R_2-CH_2), 1674 (C=O), 1590, 1501, 1462, 1423 (Aromatic ring), 1408 (Ph-OH), 1354 (C-N of $(C)_3N$), 1292 (Ph-O-C), 1161 (C-N of Ph-N-$(R)_2$), 972, (Ph-C-H), 1045 (Ph-O-C), 677 (Aromatic ring), 532 (C-Br)

^{1}H NMR : ^{1}HNMR:DMSO: δ2.43 (3H, S, CH_3), 3.15 (3H, S, N-CH_3), 3.34 (2H, S, Thiazole ring), 3.89 (3H, S, O-CH_3), 7.35 (1H, S, Thiazole ring), 7.38-7.60 (7H, m, Ar-H), 9.98 (1H, S, Ar-OH).

MS: m/z : Mass Spectrum shows the formation of molecular ion peak (M+1) at m/z = 491.40 which is equal to the calculated molecular weight 490.37

Synthesis of 3-(5-bromo-1,3-benzothiazol-2-yl)-2-(3-bromo-4-hydroxy-5-methoxyphenyl)-1,3-thiazolidin-4-one (IIi)

A mixture of 2-bromo-4-{(*E*)-[(5-bromo-1,3-benzothiazol-2-yl)imino]methyl}-6-methoxyphenol (0.01 mmole) dissolved in 1,4 dioxane (50 mL) and thioglycolic acid (0.01 mmole) was refluxed for 8 hrs. The content were then cooled and poured into sodium bicarbonate, solution (4N) to remove the excess of mercaptoacetic acid. The resultant solid was filtered, washed with cold water and recrystallized from ethanol: 1-4dioxane to give **IIi**

Yield : 68%

M.P. : 125° C

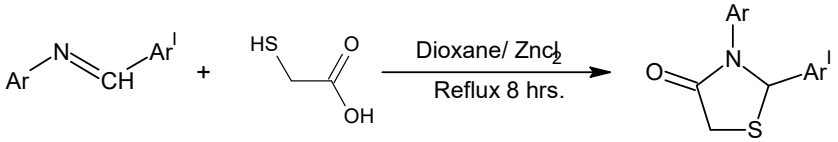
IR: ν_{max} : 3298 (Ph-OH), 3101 (Ar-C-H), 2960 (C-H of R-CH_3), 2970 (C-H of R-CH_3), 2936 (C-H of R_2-CH_2), 2900 (C-H of $(R)_3$-CH), 2845 (C-H of R_2-CH_2), 2700 (C-H of R-CH_3), 1675 (C=O), 1653, 1591, 1539, 1499 (Aromatic ring), 1456 (C-H of R_2-CH_2), 1423 (C-H of R-CH_3), 1354 (C-N of $(C)_3N$), 1291 (Ph-O-C), 1158 (Ph-C-H), 1045, 854 (Ph-O-C), 970 (Ph-C-H), 584 (C-Br)

^{1}H NMR : ^{1}HNMR: DMSO: 3.61 (1H, d, Thiazole ring), 3.85 (3H, S, OCH_3), 3.79-3.80 (1H, d, Thiazole ring), 6.96 (1H, S, Thiazole ring), 7.21-7.80 (5H, m, Ar-H), 9.89 (1H,S, Ar-OH).

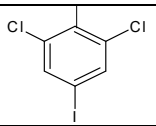
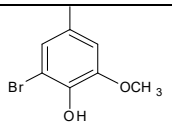
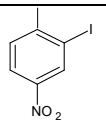
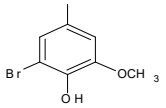
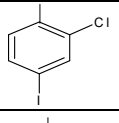
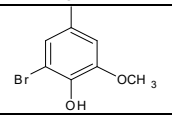
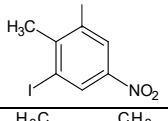
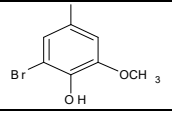
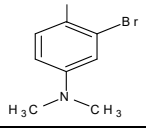
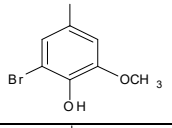
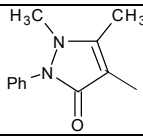
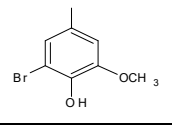
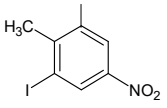
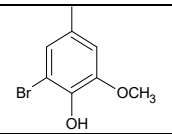
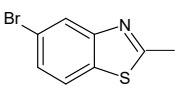
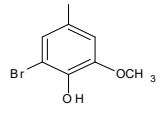
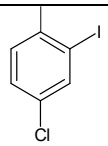
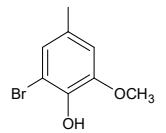
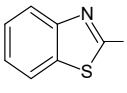
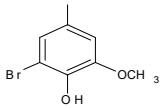
MS: m/z : Mass Spectrum shows the formation of molecular ion peak (M+1) at m/z = 515.80 which is equal to the calculated molecular weight 516.22.

Similarly, other compounds of series were prepared by the same procedure. The physical data of characterization of compounds are listed in Table-I

Scheme-I



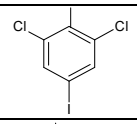
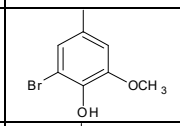
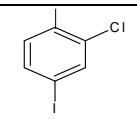
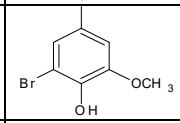
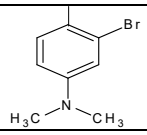
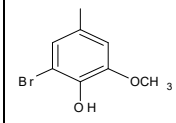
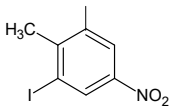
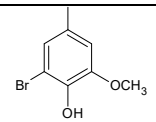
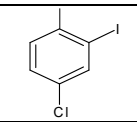
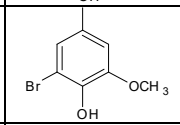
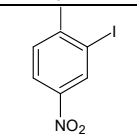
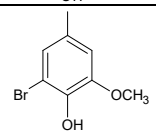
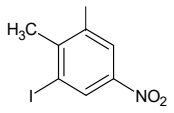
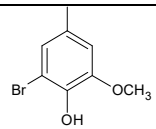
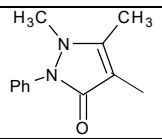
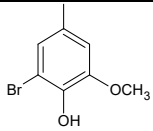
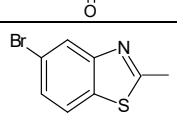
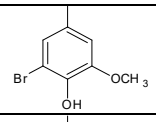
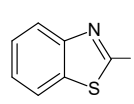
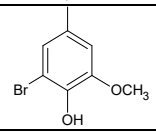
I(a-j) **TGA** **II(a-j)**

Comp. code	Ar	Ar^I	Comp. code	Ar	Ar^I
IIa			IIf		
IIb			IIg		
IIc			IIh		
IId			IIi		
IIe			IIj		

Result and Discussion

Structures of compounds synthesized have been elucidated by spectral data. IR spectra of 4-thiazoidinone derivatives showed characteristics band at near region 3490-3290 cm^{-1} due to -OH stretching vibrations of Ph-OH. A strong sharp band in the region 1680-1610 cm^{-1} is observed due to C=O stretching vibration and band around 1765-1420 cm^{-1} due to aromatic ring stretching. The characteristic vibrations have been recorded in the region of 1295 to 1230 due to Ph-O-C stretching. The characteristic vibrations were observed for C-N stretching around 1360-1160 cm^{-1}. The presence of halogen group C-X has been confirmed due to characteristic stretching vibration peaks in the region of 620-520. ^{1}H NMR spectra of 4-thiazolidinones studied in DMSO showed multiplet in the region δ 7.0 - 7.9 due to aromatic proton. The protons of methyl group showed singlet peaks in the region 2.30 – 3.90 δppm. The singlets at δ 2.65 due (-OH). All aromatic protons showed multiplet in the region δ 6.11 – 7.61. Mass spectroscopy is important tool in determining the molecular mass of the unknown compounds. Mass spectra of 4-thiazolidinones of some representative members of the series wherein good agreement with their suggested structures is presented here.

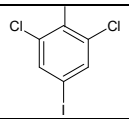
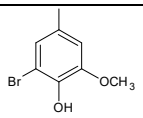
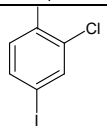
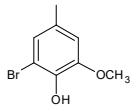
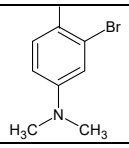
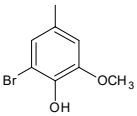
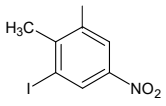
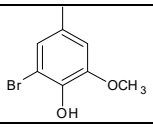
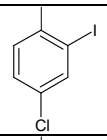
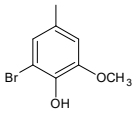
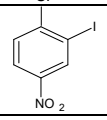
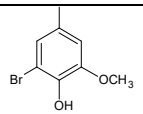
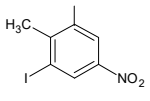
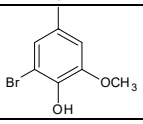
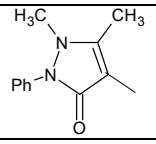
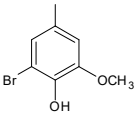
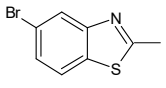
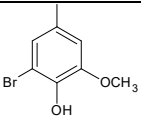
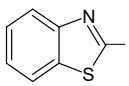
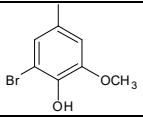
Table I: Physical data of characterization of compounds – II (a-j)

	Ar	Ar^{I}	Molecular Formula	Molecular Weight	Melting point	Yield
IIa			$C_{16}H_{11}BrCl_2INO_3S$	575.04	135°C	75%
IIb			$C_{16}H_{12}BrClINO_3S$	540.59	285°C	80%
IIc			$C_{18}H_{18}Br_2N_2O_3S$	502.22	220°C	78%
IId			$C_{17}H_{13}BrINO_5S$	550.16	198°C	60%
IIe			$C_{16}H_{12}BrClINO_3S$	540.59	222°C	70%
IIf			$C_{16}H_{12}BrIN_2O_5S$	551.15	240°C	65%
IIg			$C_{17}H_{14}BrIN_2O_5S$	565.17	245°C	56%
IIh			$C_{21}H_{20}BrN_3O_4S$	490.37	165°C	70%
IIi			$C_{17}H_{12}Br_2N_2O_3S_2$	516.22	125°C	68%
IIj			$C_{17}H_{13}BrN_2O_3S_2$	437.33	160°C	68%

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity using *Eschericha coli (E. coli.), Xanthomonas citri (X.c.), Erwina carotovora (E.c.) and Bacillus substills (B.s.)* as bacteria. The activities of these compounds were tested using disc diffusion method[18-19] at 200 ppm concentration using 5 mm filter paper disc. Penicillin antibiotics were used as standards for comparison. The zone of inhibition was measured for compounds IId (21mm), IIi (23mm), IIj (22mm) emerged out to be more stronger and (IIg), (IIe), (IIf), showed good antibacterial activity. Remaining while other compounds showed moderate to less activity.

Table II : Antibacterial activities of substituted 4-Thiazolidinones II(a-j)

Compounds	Ar	Ar^{I}	Zone of Inhibition in Millimetre (in mm)			
			Xc	E. coli	Ec	Bs
IIa			06	12	10	03
IIb			09	18	15	05
IIc			14	16	10	09
IId			21	24	22	10
IIe			17	14	12	08
IIf			12	15	14	02
IIg			09	11	9	05
IIh			10	10	8	02
IIi			23	21	23	05
IIj			22	19	21	08
Penicillin			21	22	19	23
Control(DMF)			00	00	00	00

Xc = Xanthomonas citri, E. coli = Escherichia coli, Ec = Erwinia carotovara, Bs = Bacillus subtilis

Conclusion

The series of newly synthesized substituted 4-thiazolidinone derivatives **II (a-j)** were obtained by reacting substituted Schiff Bases **I (a-j)** with thioglycolic acid in Dioxane/$ZnCl_2$ by conventional method. **II (a-j)** new 4-Thiazolidinone derivatives were synthesized as per **Scheme I** and were evaluated for antibacterial activity. The antibacterial activity results revealed that all tested compounds showed good activity against bacteria *Xanthomanas citri, Escherichia coli* and *Enterobacter cloacae* but very few compounds showed weak and most of the compounds showed negligible activity against *Bacillus subtilis* as compared to standard drug Penicillin. Amongst these compound IIi (23mm), IId (21mm), IIj (22mm) emerged out to be more stronger and (IIg), (IIe), (IIf), showed good antibacterial activity. Remaining while other compounds showed moderate to less activity.

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