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Mini Review

Design, Synthesis, Characterization and Antimicrobial Activity of Oxothiazolidin Derivatives

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ABSTRACT

The basic compound *N*-[2-(substituted phenyl)-4-oxo-1,3-thiazolidin-3-yl]-4-chloro-3-nitrobenzamide **(2 a-j)** have been synthesized by reaction of N'-[(substituted phenyl)methylidene]-4-chloro-3-nitrobenzohydrazide **(1a-j)** and aromatic aldehyde in presence of benzene, further react with thioglycolic acid.

The structural assignment of the compounds was based on elements analysis and Infrared Spectroscopy (IR), ^{1}H Nuclear Magnetic Resonance (NMR), ^{13}C Nuclear Magnetic Resonance (NMR) spectral data. All the synthesized compounds have been screened for their antimicrobial activity to gram-positive and gram-negative bacterial strains and antifungal activity. The antimicrobial activities of the synthesized compounds have been compared with standard antibiotic drugs like Gentamycin and K.Nystatin. Purity of synthesized compounds has been checked by Thin Layer Chromatography.

Keywords: Schiff base; Thiazolidinone; Anti-microbial activity

INTRODUCTION

Thiazolidinones, which belong to an important group of heterocyclic compounds, have extensively explored for their application in the field of medicine. Numerous reports have been appeared in the literature which highlights their chemistry and use. Cylcoadition reactions of schiff base with mercapto acetic acid result into the formation of thiazolidinones. Litrature survey reveales several substituted biologically active thiazolidinones compounds were prepared and found to have antibacterial and antifungal properties [1-7]. It has also been found to possess anti tubercular activity as well as anticancer, anti- inflammatory activity, analgesic, antioxidant, anti-viral, anti-HIV, anti-malarial activity [8-17]. Cu catalyzed synthesis of pyrrole bearing novel isoxazole derivatives via [3+2] cycloaddition reaction [18]. As a part of the surge of interest in heterocycles that have been explored for developing pharmaceutically important molecule, 1-acetyl-3,-5-diarylpyrazolines have played an important role in medicinal chemistry as they possess wide range of therapeutic activities. The preparation of novel thiazolidinone derivatives of type **(2a-j)** have been under taken by reaction of schiff base of type **(1a-j)** with thioglycolic acid in dry benzene.

LITERATURE REVIEW

Antimicrobial activity

The Minimal Inhibitor Concentration method (MIC) of synthesized compound was obtained against two representatives Gram positive organisms *viz. S.aureus* (MTCC 96), *S.pyogenus* (MTCC 442) and two Gram-negative organisms *viz. E.coli* (MTCC 443), *P.aeruginosa* (MTCC 1688) and evaluated for MIC against fungal strains *C.albicans* at a concentration of 6.25 µg/ml.by the broth dilution method recommended by National Committee for Clinical laboratory (NCCL) standards [19,20] and Dimethyl Sulfoxide (DMSO) was used as a solvent. The MIC values of synthesized compounds were compared with standard antibiotic drugs like Gentamycin and K.Nystatin. The minimal inhibitor concentrations (MIC) of synthesized compounds are represented in Table 1.

Experimental analysis

All the melting points were measured by open capillary method and are uncorrected. The IR absorption spectra (v max in cm^{-1}) were recorded on a Shimadzu FTIR 8400 Spectrophotometer, ^{1}H NMR (δ ppm) and ^{13}C NMR spectra were recorded on a BRUKER (300 MHz) Spectrometer using Tetramethylsilane (TMS) as internal standard (Figures 1-3).

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Table 1: Antibacterial and antifungal activities of *N*-[2-(3-bromo-4-ethoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl]-4-chloro-3-nitrobenzamide.

		Minimal Inhibition Concentrations (MIC) of bacterial strains in µg/ml				Minimal Inhibition Concentrations (MIC) of fungal strains in µg/ml
		Gram positive strains		Gram negative strains		
Sr. No.	R1	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*C. albicans* MTCC 227
2a	2-hydroxy-5-bromo	500	250	500	500	125
2b	2-methoxy-5-bromo	250	100	100	500	1000
2c	2-ethoxy-5-bromo	500	50	50	500	1000
2d	3-bromo-4-hydroxy	100	100	500	100	500
2e	3-bromo-4-methoxy	500	100	500	500	125
2f	3-bromo-4-ethoxy	100	25	25	50	1000
2g	3, 5 dibromo-4-hydroxy	25	25	250	250	1000
2h	5-bromo-3, 4 dimethoxy	100	50	50	500	100
2i	3-ethoxy-4-hydroxy-5-bromo	250	50	6.25	12.5	1000
2j	5-bromo-3, 4 diethoxy	100	100	12.5	12.5	250
Std.	Gentamycin	0.25	0.5	0.05	1	-
Drug	K.Nystatin	-	-	-	-	100

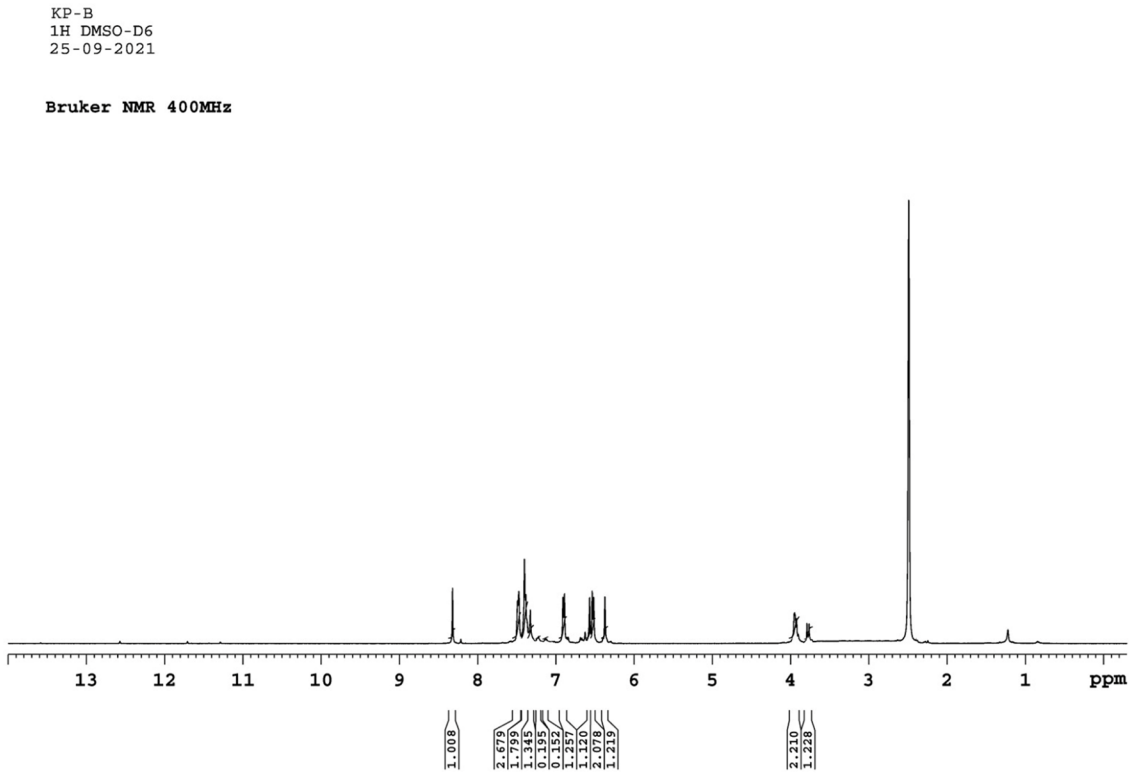


Figure 1: ^{1}H Spectra of N-(2-(2-bromo-6-methoxy phenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitrobenzamide**2b**.

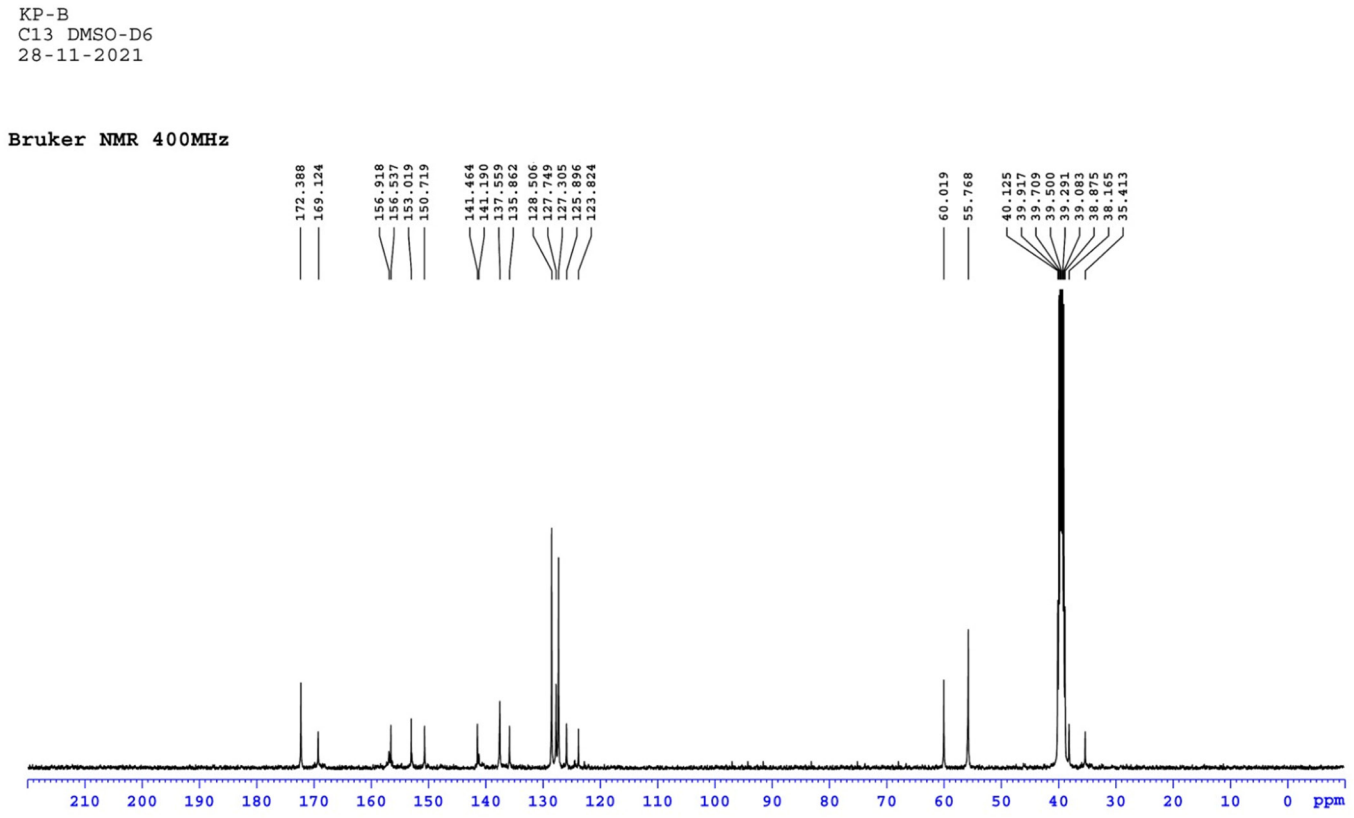


Figure 2: ^{13}C Spectra of *N*-(2-(2-bromo-6-methoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitrobenzamide**2b**.

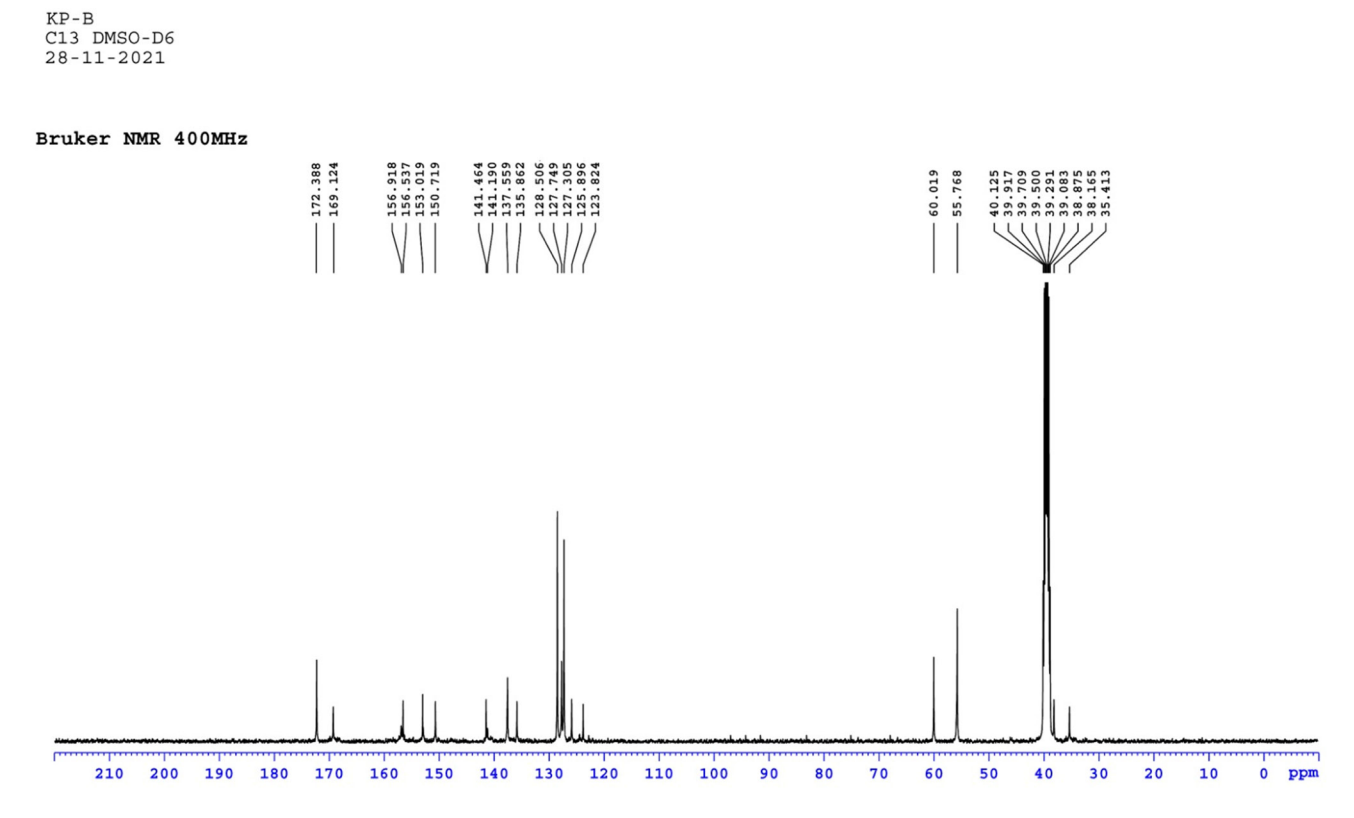


Figure 3: IR Spectra of *N*-(2-(2-bromo-6-methoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitrobenzamide**2b**.

General preparation of *N*-(2-(2-bromo-6-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitrobenzamide2a,(2 a-j)

A mixture of Schiff base (0.01 mole) and thioglycolic acid (0.015 mole) were dissolved in dry benzene (50 ml) and Dimethylformamide (DMF) (20 ml) were refluxed for 20-22 hours. Completion of the reaction was checked by TLC. Benzene was distilled out and then reaction mixture was cooled and poured in to ice cold water and stirred for 2 hrs. Further treated with 20% sodium bicarbonate solution, the product separated was filtered and washed with water and crystallized from ethanol (95%).

Similarly, other compound of this series **(2 a-j)** have been prepared. The physical constants are recorded below:

N-(2-(2-bromo-6-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide 2a:

White Creamish yellow solid,

Yield: 70%:

mp: 190-195°C;

Reaction time: 24 hrs:

Rf value: 0.45;

Molecular Weight: 472.69;

Anal. Calcd. For $C_{16}H_{11}BrClN_3O_5S$: C-40.65, H-2.35, X- 24.43, N-1.19, S-6.78;

Found: C-40.63, H-2.32, X- 24.44, N-1.21, S-6.80%.

IR (KBr) cm^{-1} 2a: 1662 (C=O str, thiazolidinone), 1178 (C-N str, thiazolidinone), 732 (C-S-C str., thiazolidinone), 1628(S-C=N str., thiazolidinone), 1511(NO2str. (asym.)), 1389 (NO2str. (sym.)) 1242 (C-O-C (sym)), 1058(C-O-C (asym)), 3321 (-NHstr.), 718 (C-Br str.), 604 (C-Cl str.).

N-(2-(2-bromo-6-methoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2b:

Light Creamish Yellow Solid,

Yield: 73%:

mp: 255-260°C;

Reaction time: 22 hrs:

Rf value: 0.37;

Molecular Weight: 486.72;

Anal. Calcd. for $C_{17}H_{13}BrClN_3O_5S$: C-41.95, H-2.69, X- 23.70, N-8.63, S-6.59;

Found: C-41.96, H-2.71, X- 23.74, N-8.60, S-6.61%;

N-(2-(2-bromo-6-ethoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2c:

Yellow Creamish solid,

Yield: 68%:

mp: 240-245°C;

Reaction time: 21hrs:

Rf value: 0.53;

Molecular Weight: 500.75;

Anal. Calcd. for $C_{18}H_{15}BrClN_3O_5S$: C-42.17, H-3.02, X- 23.04, N-8.39, S-6.40;

Found: C-42.19, H-3.05, X- 23.14, N-8.42, S-6.22%;

N-(2-(3-bromo-4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2d:

White Creamish solid,

Yield: 78%:

mp: 155-160°C;

Reaction time: 20 hrs:

Rf value: 0.32;

Molecular Weight: 472.69;

Anal. Calcd. for $C_{16}H_{11}BrClN_3O_5S$: C-40.65, H-2.35, X- 24.43, N-1.19, S-6.78;

Found: C-40.68, H-2.31, X- 24.44, N-1.16, S-6.77%.

^{1}H NMR (δ ppm) 2d: 3.771-3.781 (d, ^{1}H, CH_2 (thiazolidinone)), 3.914-3.993 (d, ^{1}H, CH_2(thiazolidinone), 6.37 (Singlet, ^{1}H, N-CH-S thiazolidinone)), 8.367 (Singlet, ^{1}H, N-H), 6.516 (s, ^{1}H, OH merged with Ar-H), 6.536-7.490 (Multiplet, 6H, Ar-H).

N-(2-(3-bromo-4-methoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2e:

Light white yellow solid,

Yield: 67%:

mp: 225°C-230°C;

Reaction time: 20 hrs:

Rf value: 0.54;

Molecular Weight: 486.72;

Anal. Calcd. for $C_{17}H_{13}BrClN_3O_5S$: C-41.95, H-2.69, X- 23.70, N-8.63, S-6.59;

Found: C-41.93, H-2.73, X- 23.71, N-8.66, S-6.62%.

^{13}C NMR ($CDCl_3$) δppm **2e**: 150.72(C-1), 135.86(C-2), 169.123(C-3, CO-CH_2-S), 172.388(C-4, CO-CH_2-S), 35.413(C-5, CO-CH_2-S), 60.018(C-6, N-CH-S), 141.19(C-7), 55.76(C-8,-OCH_3), 153.019(C-9).

N-(2-(3-bromo-4-ethoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2f:

Yellow Creamish solid,

Yield: 70%:

mp: 195°C-200°C;

Reaction time: 22 hrs:

Rf value: 0.56;

Molecular Weight: 500.75;

Anal. Calcd. for $C_{18}H_{15}BrClN_3O_5S$: C-42.17, H-3.02, X- 23.04, N-8.39, S-6.40;

Found: C-42.19, H-3.07, X- 23.11, N-8.44, S-6.42%.

4-chloro-*N*-(2-(3,5-dibromo-4-hydroxyphenyl)-4 oxothiazolidin-3-yl)-3-nitro benzamide2g:

Yellow Creamish solid,

Yield: 60%:

mp: 135°C-240°C;

Reaction time: 19 hrs:

Rf value: 0.55;

Molecular Weight: 551.59;

Anal. Calcd. for $C_{16}H_{10}Br2ClN_3O_5S$: C-34.84, H-1.83, X- 35.40, N-7.62, S-5.81;

Found: C-34.86, H-1.82, X- 35.45, N-7.60, S-5.80%;

N-(2-(3-bromo-4,5-dimethoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2h:

White Creamish yellow solid,

Yield: 65%:

mp: 265°C-270°C;

Reaction time: 22 hrs:

Rf value: 0.61;

Molecular Weight: 516.75;

Anal. Calcd. for $C_{18}H_{15}BrClN_3O_6S$: C-41.84, H-2.93, X- 22.32, N-8.13, S-6.21;

Found: C-41.82, H-2.91, X- 22.30, N-8.11, S-6.24%;

N-(2-(3-bromo-5-ethoxy-4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitrobenzamide2i:

Yellow Creamish solid,

Yield: 69%:

mp: 210°C-215°C;

Reaction time: 21 hrs:

Rf value: 0.38;

Molecular Weight: 516.75;

Anal. Calcd. for $C_{18}H_{15}BrClN_3O_6S$: C-41.84, H-2.93, X- 22.32, N-8.13, S-6.21;

Found: C-41.86, H-2.94, X- 22.30, N-8.10, S-6.20%;

N-(2-(3-bromo-4,5-diethoxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide2j:

Light Creamish yellow solid,

Yield: 72%:

mp: 120-125°C;

Reaction time: 24 hrs:

Rf value: 0.0.39;

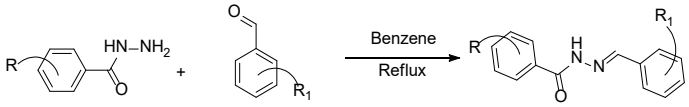
Molecular Weight: 544.80;

Anal. Calcd. for $C_{20}H_{19}BrClN_3O_6S$: C-44.09, H-3.52, X- 21.18, N-7.71, S-5.89;

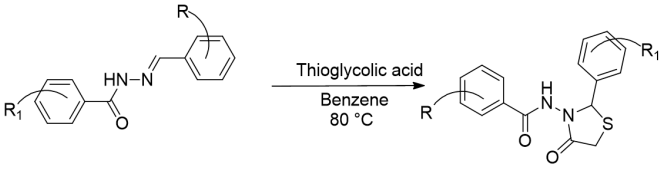
Found: C-44.11, H-3.53, X- 21.22, N-7.74, S-5.91%;

Reaction Scheme

Step-1: Synthesis of *(E)-N'*-(2-bromo-6-hydroxybenzylidene)-4-chloro-3-nitrobenzohydrazide **(1a-j)**:



Step-2: *N*-(2-(2-bromo-6-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide **(2a-j)**.



- Where, R=3-nitro4-chloro
- Where, R1= 2-hydroxy-5-bromo, 2-methoxy-5-bromo,2-ethoxy-5-bromo,3-bromo-4-hydroxy,3-bromo-4-methoxy,3-bromo-4-ethoxy,3, 5 dibromo-4-hydroxy,5-bromo-3, 4 dimethoxy,3-ethoxy-4-hydroxy-5-bromo,5-bromo-3, 4 diethoxy.

Spectral result and discussion

Thiazolidinone ring was characterized by several absorption peaks in the infrared spectrum. Spectra of **(2a)** showed absorption at 1628 cm^{-1}, which is a characteristic of S-C=N. It was also observed the stretching band of C-S-C of thiazolidinone ring at 732 cm^{-1}. C-N stretching band of thiazolidinone is exhibited 1178 cm^{-1}. Sharp absorption band appearing at 1662 cm^{-1} was attributed to carbonyl function of C=O. The band of secondary amine –NH observed at 3321 cm^{-1}.The symmetric and asymmetric bands of nitro group observed at 1389 $cm^{-1}$and 1511 cm^{-1}. C-Cl str. and C-Br str. band observed at 604 cm^{-1} and 718 cm^{-1}.respectively. ^{1}H NMR spectra of **(2d)** It was showed that magnetically non equivalent protones of thiazolidinone ring (–CH_2) attributed as two doublets at 3.771δppm-3.781 δppm and 3.914δppm-3.993δppm. Both the protons are well separated from each other, one hydrogen atom of each pair being above the phenyl ring in the shielding cone and the other one, outside of it. The diastereotopic hydrogen atoms are well separated. Singlet of-OH group appeared at 6.51 δppm which is merged with aromatic protons. The sharp singlet appeared at 6.37 δppm indicated presence of N-CH-S group of thiazolidinone nucleus. While the proton of secondary amine exhibited as sharp singlet at 8.36 δppm. In aromatic region, protons resonated in the range of, 6.536δ ppm-7.490 δppm. In ^{13}CNMR spectra of the compound **(2e)** carbons of the thiazolidinone were resonated at 60.018 δppm (C-10, N-CH-S). Ketone of thiazolidinone showed at 172.38 δppm (C-7, CO-CH_2-S). Carbon appeared at 35.41δppm confirms the presence of (C-9, CO-CH_2-S). The signal appeared at 55.76δppm (C-17, OCH_3) was assigned the presence of methoxyl carbon.

Biological result and discussion

The observation of inhibition data suggests that the only two compounds **2(i)** and **2(j)** have displayed excellent activity against gram negative bacterial strains *E.coli* and *P.aeruginosa* respectively. In addition compound **2(g)** have exhibited good activity against both gram positive bacterial strains. Compound **2(f)** have shown good activity against gram negative bacterial strain *E.coli* and gram positive bacterial strain *S.pyogenes* respectively. Compound **c** showed moderate activity against both gram negative strains. Compound **2(h)** exhibited moderate activity against gram negative bacterial strain *P.aeruginosa* and gram positive bacterial *S.pyogenes*.

The MIC values of screened compounds suggest that the test compound **2(h)** showed excellent activity against fungal strains comparable to reference agents K Nystatin. Compound **2(e)** have showed good activity against the tested organisms. While the other compounds showed poor or no activity even at concentration of 200 µg/ml. The overall results of anti-bacterial and antifungal activity are mentioned in Table 1.

CONCLUSION

In conclusion, we have synthesized a few novel hybrid molecules *N*-(2-(2-bromo-6-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-chloro-3-nitro benzamide **(2a-j)** neat reaction in microwave and also in presence of benzene. Only two compounds **2i** and **2j** have displayed excellent activity against gram negative bacterial strains *E.coli* and *P.aeruginosa* respectively. In addition compound **2g** have exhibited good activity against both gram positive bacterial strains. Compound **2f** have shown good activity against gram negative bacterial strain *E.coli* and gram positive bacterial strain *S.pyogenes* respectively. Compound **2c** showed moderate activity against both gram negative strains. Compound **2h** exhibited moderate activity against gram negative bacterial strain *P.aeruginosa* and gram positive bacterial *S.pyogenes*. The test compound **2h** showed excellent activity against fungal strains comparable to reference agents K Nystatin. Compound **2e** have showed good activity against the tested Organisms. While the other compounds showed poor or no activity even at concentration of 200 µg/ml. Research outcome of this study can be helpful for preparing new anti-bacterial molecules that is effective in numerous therapies for different Schiff base compounds.

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CONFLICT OF INTEREST

All authors agree for the publication. For all authors, there is no competing interests to declare.

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