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ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (4): 1650-1656

(International Peer Reviewed Journal)

Synthesis of Substituted 2-(3-(4-Chlorobenzamido)-2-(aryl)-4-oxo thiazolidine 5-yl)acetic acid Derivatives and their Biological Activities

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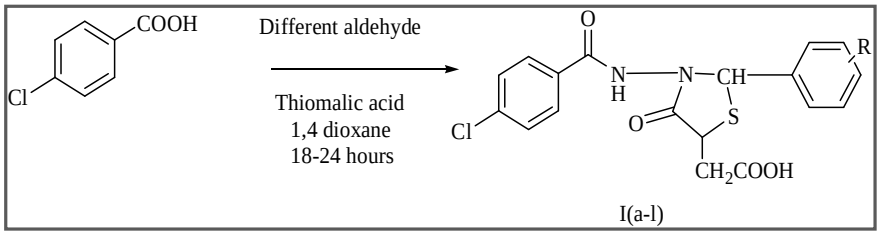
Accepted on 10th June, 2019

ABSTRACT

A series of 2-(3-(4-Chlorobenzamido)-2-(aryl)-4-oxo-thiazolidine5-yl) acetic acid derivatives were prepared by treating substituted 4-chlorobenzohydrazidewith thiomalic acid. The newly synthesized compounds were analyzed by IR, ^{1}H-NMR and Mass spectral analysis. The entire structure series of synthesized compounds was evaluated for their biological activities.

Graphical Abstract



General scheme for the synthesis of final compounds

Keywords: Thiazolidinone derivatives, Schiff base, Thiomalicacid, Biological activities, MIC.

INTRODUCTION

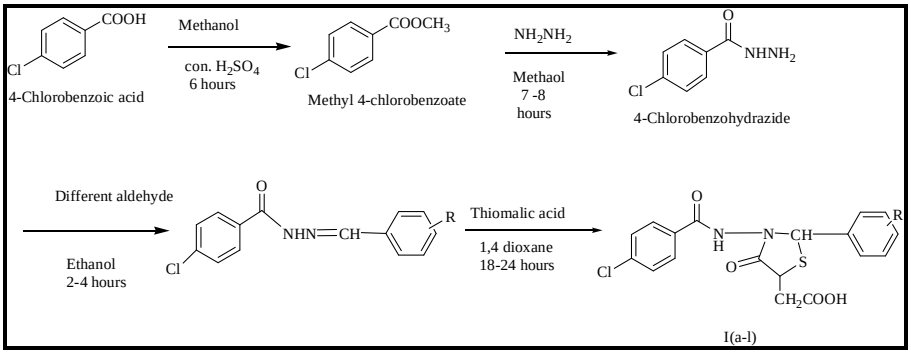
Heterocyclic compound is an important class of bioactive compounds. They are making up more than half of all known organic compounds. They are very widely distributed in nature and are particularly important because of the wide variety of pharmacological activities. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at 4-position. Substituent in the 3 and 5 positions may be varied, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2nd position. 4-Thiazolidinones derivatives play an important role in many biological processes.4-Thiazolidinones derivatives has a broad spectrum of biological activities such as, anti-fungal [**1**], anti-cancer [**2, 3**], anti-tubercular [**4**], anti-bacterial [**5-7**], anti-viral [**8-11**], anti-microbial [**12-14**] etc. Some thiazoli dinones derivatives are recently reported as novel inhibitors of mycobacterial rhamnose synthetic enzymes [**15**].

Hydrazides and their hetrocyclised derivatives also found to passes an important role in biological activities. Thiazolidinones derivatives [**16-18**] showed good pharmacological properties.

On the basis and literature study the objective of the present work was to prepare new derivatives of hydrazide containing thiazolidine moiety. In the present work we have prepared 12 novel thiazolidinones derivatives. The structures of newly synthesized compounds were evaluated by IR, ^{1}H-NMR, Mass spectral analysis and screened for their biological activities like anti-bacterial against (two gram positive and two gram negative bacteria) and anti-fungal activities.

MATERIALS AND METHODS

General: All chemicals used in the synthesis of the titled compounds were of analytical grade. Melting points were reported by the open capillary tube method and are uncorrected .Merck Kieselgel 60 F254 plates were used for TLC using mobile phase ethylacetate: chloroform (4:1). IR spectra were recorded on SHIMADZU FT-IR 8400 using potassium bromide pallets. The ^{1}H NMR spectra were recorded in DMSO d_6 solution in 5 mm tubes at room temperature, on a BRUKER 400 MHz FT-NMR, with TMS as internal standard. Mass spectra were recorded on SHIMADZU QP-2010. The antimicrobial activity was carried out using broth dilution method to determine minimum inhibitory concentration (MIC).



Scheme 1. Reaction scheme for the synthesis of the compounds I(a-l).

Synthesis of methyl 4-chloro benzoate: 4-chlorobenzoic acid (0.26 mol) was taken in a round bottom flask with 25 mL methanol and then sulfuric acid was added drop-wise through a dropping funnel. The solution was heated to reflux for 6 h. It was then cooled to room temperature and poured into ice of cold water and to form product methyl 4-chloro benzoate. The product was re-crystallized from ethanol and the progress and completion of the reaction was confirmed by TLC.

Synthesis of 4-chlorobenzohydrazide: A mixture of 4-chloro methyl benzoate (0.22 mol) and hydrazine hydrate (0.22 mol) in methanol was heated in a round bottom flask for 7-8 h. The reaction mixture was cooled to room temperature. A white precipitates obtained to form 4-chlorobenzo hydrazide obtained. Finally the product was re-crystallized from ethanol and confirmed by TLC.

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General procedure for the schiff bases: In a round bottom flask equimolar quantities of different aromatic benzaldehyde (0.1 mol) and 4-chlorobenzo hydrazide(0.1 mol) were dissolved in ethanol and refluxed for 2-4 h and Solid product obtained are respectively schiff base.

Finally the products were re-crystallized from ethanol or methanol and the progress and completion of the reaction was confirmed by TLC.

General Procedure for the preparation of I(a-l): A mixture of schiff bases (0.01 mol) and thiomalic acid (0.01 mol) were taken in round bottom flask followed by the addition of 1,4-dioxane and a pinch

of powder anhydrous $ZnCl_2$ was added to it. The reaction mass was heated for 18-24 h. The reaction mixture was poured into ice cold water with constant stirring. It was filtered then washed with sodium bicarbonate and to get the final product **I(a-l)**. Finally the products were re-crystallized from ethanol or methanol and the progress and completion of the reaction was confirmed by TLC.

Spectral data of some of the synthesized compounds:

Synthesis of 2-(3-(4-chlorobenzamido) 2-(4-formylphenyl)-4-oxo-2-phenylthiazolidine-5-yl) acetic acid (Ia): IR(cm^{-1}, KBr):837(C-Cl Stretching), 1555(N-H bending, CONH), 1647 (C=O Thiazolidine ring), 694(C-S-C Thiazolidine ring),1487(R-COOH), **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 3.1(2H,s), 6.8(1H,s), 3.57(1H,s), 7.3(1H,s), 7.6(2H,s), 7.5(2H,d), 7.9(2H,s), 7.99(2H,s), 8.6(1H,), 11.9(1H,s), Mass (m/z):390.

Synthesis of 2-(3-(4-Chlorobenzamido)-2-(3-nitrophenyl)-4 oxo-thiazolidine-5-yl)-acetic acid (Ib): IR (cm^{-1}, KBr): 844(C-Cl Stretching), 1562((N-H bending, CONH), 1612(C=O Thiazolidine ring), 1535(C-NO_2), 734(C-S-C Thiazolidine ring), 1490(R-COOH). **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 2.09(3H, s), 6.53(1H,s), 7.6(2H,s), 7.7(1H,d), 7.9(2H, s), 8.1(1H,d), 8.2(2H, s) 8.5(1H,s), 12.2(1H,s), Mass (m/z):435.

Synthesis of 2-(3-(4-Chlorobenzamido)-2-(3-chlorophenyl)-4 oxo-thiazolidine-5-yl)-acetic acid (Ic): IR (cm^{-1}, KBr): 843 (C-Cl Stretching), 1552 (N-H bending, CONH), 1658 (C=O Thiazolidine ring), 1523 (C-NO_2), 752 (C-S-C Thiazolidine ring), 1483 (R-COOH). **^{1}H NMR** (DMSO, 400MHz) (δ ppm)**:** 3.1(3H, s), 6.5(1H, s), 7.6(2H, s), 7.7(1H, s), 7.9(2H, s), 8.1(1H,d), 8.2(2H, s) 8.5(1H, s), 12.2(1H, s), Mass (m/z):424.

Synthesis of 2-(3-(4-chlorobenzamido)-2-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl)-acetic acid (Id): IR(cm^{-1},KBr): 762(C-Cl Stretching), 1558(N-H bending, CONH), 1616 (C=O Thiazolidine ring), 6845(C-S-C Thiazolidine ring),1489(R –COOH), 3059 (Ar-OH), **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 3.2(3H,s), 6.4(1H, s), 7.6(2H,s),7.7(1H,s), 7.9(2H,s), 8.1(1H,d), 8.2(2H, s) 8.39(1H, s),11.5(1H, s), Mass (m/z):406.

Synthesis of 2-(3-(4-chlorobenzamido)-2-(2-hydroxyphenyl)-4-oxothiazolidin-5-yl)-acetic acid (Ie): IR (cm^{-1}, KBr):843(C-Cl Stretching), 1564(N-H bending, CONH), 1624 (C=O Thiazolidine ring), 741(C-S-C Thiazolidine ring), 1465(R-COOH),3056 (Ar-OH), **^{1}H NMR:** 3.4(2H, s), 6.94(1H, s), 3.57(2H,s), 6.96(1H, s), 7.3(1H, s),7.5(2H,d) ,7.9(2H, s), 7.99(2H,s) 8.6(1H,s),12.2(1H,s), Mass (m/z):406.

Synthesis of 2-(3-(4-chlorobenzamido)-2-(4-metoxyphenyl)-4-oxothiazolidin-5-yl)-acetic acid (If): IR (cm^{-1}, KBr):744 (C-Cl Stretching), 1564(N-H bending, CONH), 1606 (C=O Thiazolidine ring), 641(C-S-C Thiazolidine ring), 1425 (R-COOH), 2845 (OCH_3), **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 3.4 (3H,s), 6.94(1H,s),6.97(2H,s),7.7(2H,t),7.9(3H,s),8.1(2H,d), 8.2(2H,d) 8.5(1H,s), 12.2(1H,s), Mass (m/z): 420.

Synthesis of 2-(3-(4-chlorobenzamido)-2-cinnamyl-4-oxothiazolidin-5-yl)-acetic acid (Ig): IR (cm^{-1}, KBr): 845 (C-Cl Stretching), 1560 (N-H bending, CONH), 162. (C=O Thiazolidine ring), 748(C-S-C Thiazolidine ring),1449 (R-COOH),1597(C=C Stretching), 3022(CH-Ar). **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.4(3H,s), 6.94(1H,s),6.97(2H,s),7.7(2H,t),7.9(3H,s),7.93(2H,d), 8.2(2H,s) 8.4(1H,s), 12.2(1H,s), Mass (m/z):416.

Synthesis of 2-(3-(4-chlorobenzamido)-2-(4-dimethylaminophenyl)-4-oxothiazolidin-5-yl)-acetic acid (Ih): IR(cm^{-1}, KBr):843(C-Cl Stretching), 1568(N-H bending, CONH), 1657(C=O Thiazolidine ring), 745(C-S-C Thiazolidine ring),1433.11 (R-COOH),2808.36 (N-CH_3). **^{1}H NMR:** (DMSO,

400MHz) (δ ppm)**:** 3.4(6H,s), 6.94(1H,s), 6.97(2H,s), 7.7(2H,t),7.9(3H,s), 8.1(2H,d), 8.2(2H,s) 8.5(1H,s), 12.2(1H,s), Mass (m/z):433.

Synthesis of 2-(3-(4-chlorobenzamido)-2-(3,4-dimethoxyphenyl)-4-oxothiazolidin-5-yl)-acetic acid (Ii): IR(cm^{-1}, KBr): 750 (C-Cl), 1604(N-H bending, CONH), 1652(C=O Thiazolidine ring), 643 (C-S-C Thiazolidine ring),1422 (R –COOH), 2804 (OCH_3). **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 3.3(6H,s), 6.4(1H,s),6.97(2H,s),7.7(2H,t),7.9(2H,s),8.1(2H,d), 8.29(2H,s) 8.5(1H,s),11.2(1H,s), Mass (m/z):450.

Synthesis of 2-(3-(4-chlorobenzamido)-2-(2 chlorophenyl)-4-oxothiazolidin-5-yl)acetic acid (Ij): IR(cm^{-1}, KBr): 846, (C-Cl),1558(N-H bending, CONH), 1647 (C=O Thiazolidine ring),632(C-S-C Thiazolidine ring), 1469 (R –COOH). **^{1}HNMR:**(DMSO,400MHz(δ ppm)**:**2.09(2H,s), 3.3(1H,s), 6.53(1H,s), 7.6(2H,s), 7.7(1H,s),7.9(2H,s),8.1(1H,d),8.2(2H,s) 8.5(1H,s),11.5(1H,s), Mass (m/z):424.

Synthesis of 2-(3-(4-Chlorobenzamido)-2-(2-nitrophenyl)-4 oxo-thiazolidine-5-yl)-acetic acid (Ik): IR (cm^{-1}, KBr): 843 (C-Cl Stretching), 1552 (N-H bending, CONH), 1658 (C=O Thiazolidine ring), 1523 (C-NO_2), 752 (C-S-C Thiazolidine ring), 1487 (R-COOH), **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 2.09(2H,s), 3.1(1H,s), 6.5(1H,s),7.6(2H,s), 7.7(1H,s), 7.9(2H,s), 8.1(1H,d), 8.2(2H,s) 8.5(1H,s),12.2(1H,s), Mass (m/z):435.

Synthesis of 2-(3-(4-Chlorobenzamido)-2-(3 methoxy,4-hydroxyphenyl)-4 oxo-thiazolidine-5-yl)-acetic acid (Il): IR (cm^{-1},KBr): 836 (C-Cl Stretching), 1554(N-H bending, CONH), 1650(C=O Thiazolidine ring), 1523 (C-NO_2), 752 (C-S-C Thiazolidine ring), 1489(R-COOH). **^{1}H NMR:**(DMSO, 400MHz) (δ ppm)**:** 3.1(3H,s), 6.94(1H,s), 7.6(2H,s), 7.7(2H,t),7.9(3H,s), 8.1(2H,d), 8.2(2H,s) 8.5(1H,s), 12.2(1H,s), Mass (m/z):436.

Table 1..Physical properties of the synthesized compounds

S.No.	Compound Id	R	Molecular Formula	M.W. gm $mole^{-1}$
1	Ia	-CHO	$C_{18}H_{15}ClSN_2O_4$	390.84
2	Ib	-3 NO_2	$C_{18}H_{14}ClSN_3O_6$	435.84
3	Ic	-4-Cl	$C_{18}H_{14}Cl_2SN_2O_4$	424.29
4	Id	-4-OH	$C_{18}H_{15}ClSN_2O_5$	406.84
5	Ie	-2-OH	$C_{18}H_{15}ClSN_2O_5$	406.84
6	If	-4-OCH_3	$C_{19}H_{17}ClSN_2O_5$	420.87
7	Ig	-4-C_8H_7	$C_{20}H_{17}ClSN_2O_5$	416.06
8	Ih	-$N(CH_3)_2$	$C_{20}H_{20}ClSN_3O_4$	433.91
9	Ii	-3,4-$(OCH_3)_2$	$C_{20}H_{19}ClSN_2O_6$	450.89
10	Ij	-2-Cl	$C_{18}H_{14}Cl_2SN_2O_4$	424.29
11	Ik	-2-NO_2	$C_{19}H_{14}ClSN_3O_6$	435.84
12	Il	-3-OCH_3,4-OH	$C_{19}H_{17}ClSN_2O_6$	436.87

RESULTS AND DISCUSSION

In the present work we have prepared a new series of thiazolidines derivatives. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis. Compound **Ib** showed strong absorption at 1612 cm^{-1} due to carbonyl group and C-Cl stretching at 844 cm^{-1}. Compound **Id** showed very strong absorption at 2845 cm^{-1}due to R-COOH for O-H stretching. The compound **Ib** showed singlet at 2.09 δ ppm to three protons and one hydrogen at 6.53 ppm for thiazolidine ring (Figure 2).

The mass spectrum of compound **Ib** showed the molecular ion peak at m/z = 435corresponding to the molecular formula $C_{18}H_{14}ClSN_3O_6$ (Figure 3).

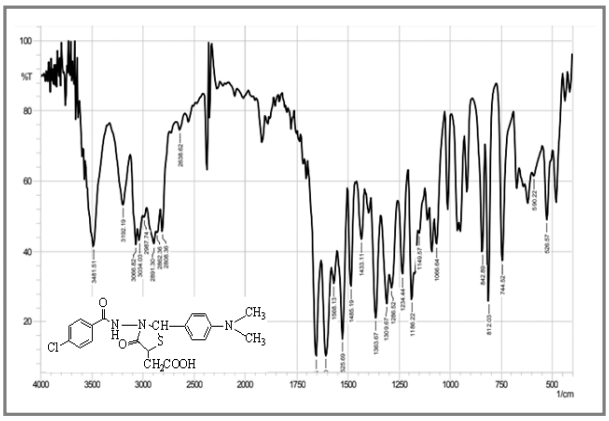

Figure 1. IR spectrum of compound Ih.

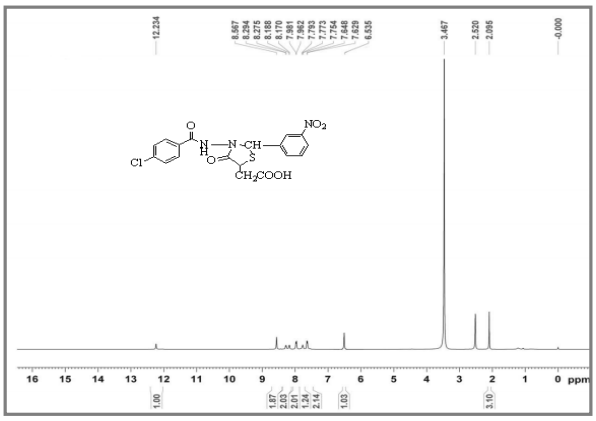

Figure 2. NMR spectrum of compound Ib.

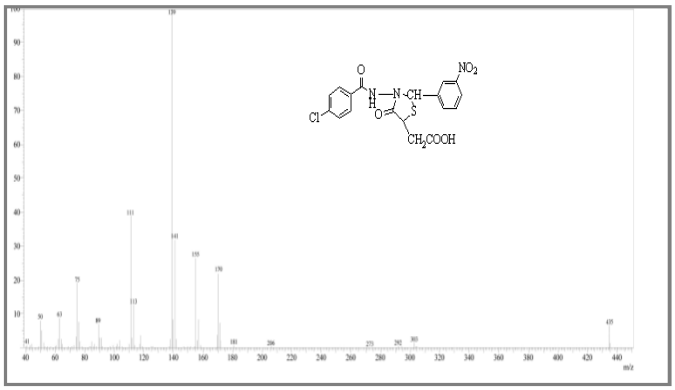

Figure 3. Mass spectrum of compound Ib.

Table 2. Biological activities in the terms of the MIC of synthesized Compounds.

S. No.	Compound Id	Anti-bacterial Activity				Anti-fungal activity
		Minimum inhibitory concentration (MIC) (µg mL^{-1})				Minimum inhibitory concentration (MIC) (µg mL^{-1})
		Gram Positives bacteria		Gram Negative bacteria		Fungus
		Bacillus Cereus MTCC 430	*S.aureus* MTCC 737	*E.coli* MTCC 1687	*P.Seudomonas* MTCC 1688	*Aspergillus-niger* ATCC 16404
1	Ia	1024	>1024	>1024	128	>1024
2	Ib	>1024	512	512	256	>1024
3	Ic	16	16	16	16	8
4	Id	1024	>1024	>1024	>1024	>1024
5	Ie	>1024	512	>1024	>1024	>1024
6	If	16	16	16	256	4
7	Ig	128	16	16	16	32
8	Ih	16	16	16	16	16
9	Ii	16	16	1024	16	12
10	Ij	16	16	16	16	8
11	Ik	>1024	512	512	256	>1024
12	Il	>1024	>1024	512	256	16
	Ampicilline	10.0	12	2.0	8.0	-
	Amphotericin B	-	-	-	-	0.05

All the synthesized compounds were screened for antibacterial and antifungal activities by broth dilution method. From the study of the biological activity data in reference to Standard drug

Ampicillin and Amphotericin B (Table 1). Now, we found that compound **Ic**, **If**, **Ih**, **Ij** and **Ii** exhibited good activity against *B.Cereus*. Compound **Ic**, **If**, **Ig**, **Ih**, **Ii** and **Ij** exhibited good activity against *S.aureus*. Compounds **Ic**, **Ig**, **Ih**, and **Ij** showed good activity against *E.coli* and *P.Seudomonas*. Compounds **Ia**, **Ib**, **Id**, **Ie**, **Ik** and **Il** exhibited moderate activity against *S.aureus*, *B.Cereus*, *E.coli* and *P.Seudomonas*. Compounds **Ia**, **Ib**, **Id**, **Ie** and **Ik** exhibited moderate activity against *A. niger (*Figure 4).

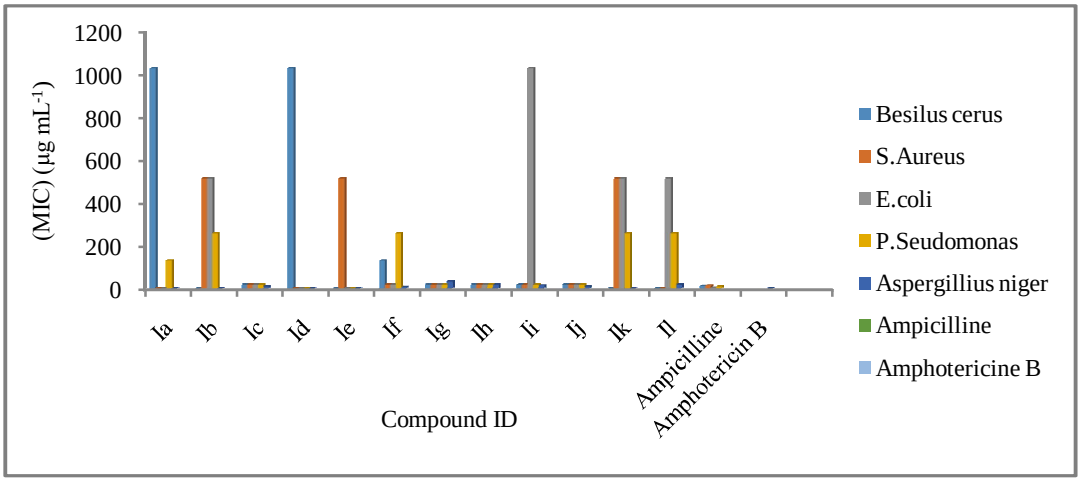

Figure 4. Biological activities of all the synthesized compounds I(a-l).

APPLICATION

In the present study thiazolidine derivatives synthesized in the present work were screen for their antibacterial and antifungal activities. Some of the compounds are found to possess good biological activity. They are hopeful as active pharmacophore. Further work on these compounds will help for invention of lead molecule in future.

CONCLUSION

From the present study it was observed that thiazolidinone moiety can be considered as promising pharmacophore for better antibacterial activities. It was found that varying the substitution in the final structure affect the biological activities. Final compounds with chloro, hydroxy, nitro and methoxy were found to posses good antibacterial activity and some of the compounds for example **Ic, If** and **Ij** showed moderate activity against *Aspergillius niger*.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the former Principal Fr. (Dr) Robert Arockiasamy and Principal Fr.Lancelot D'cruze St. Xavier's College (Autonomous) (Affiliated to Gujarat University), Ahmedabad, for providing necessary laboratory and library facilities. The authors also wish to thank the staff of Chemistry Department for especially support and help during the course of the work.

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