HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (4), 2012, 429-436**

SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF SOME THIAZOLIDINONE DERIVATIVES INCORPORATING WITH PHENOTHIAZINE MOIETY

Nareshvarma Seelam[* a)], S. P. Shrivastava[b)], S. Prasanthi[a)]

[a)] Department of Chemistry, K. L. University, Vaddeswaram, Guntur, A.P-India-522502
[b)] Heterocyclic Research Laboratory, Department of Chemistry, Dr. H. S. Gour Central University, Sagar, M.P, India-470003
E-mail: utd_naresh@yahoo.co.in

ABSTRACT: A novel series of 4-thiazolidinone derivatives (5a-g) incorporating with Phenothiazine moiety via mannich reaction were synthesized by the reaction of 4-[Phenothiazin-10-ylmethyl)-amino]-benzoic acid benzylidene hydrazide (4a-g) with mercapto acetic acid in the presence of anhy., $ZnCl_2$. The chemical structures of newly synthesized compounds were elucidated by IR, ^1H NMR, ^{13}C NMR, Mass spectral data. The compounds (5a-g) were evaluated for their anti tubercular activity against M. Tuberculosis H37Rv. Some of the compounds were showed appreciable anti-tubercular activity comparing with standard drug. Furthermore the compounds (5a-g) were screened for their antimicrobial activity against various bacterial and fungal strains.

KEYWORDS: Thiazolidinones; Phenothiazines; anti-tubercular activity; antimicrobial activity.

INTRODUCTION: Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In addition, primary and opportunistic fungal infections continue to increase rapidly because of the increased number of immuno compromised patients. On the other hand, mycobacterium tuberculosis remains a dangerous cause of death in the world today. More over the development of drug resistant strains of mycobacterium species, has contributed to the in efficiency of the conventional anti tuberculosis therapy, thus it is still necessary to search for new anti microbial agents.

Thiazolidinones and their derivatives are an important group of heterocyclic compounds, which are having various biological activities in the areas of medicine and agriculture[i-ii]. The thiazolidinone nucleus also appears frequently in the structure of various natural products, notably thiamine compounds possessing cardiac and glycemic benefits such as triglitazone[iii]. Numerous thiazolidinone derivatives have shown significant bioactivities such as antidiarrhoeal [iv], anticonvulsant[v], anti-cancer[vi], antitubercular agents[vii-ix], COX-1 inhibitor[x], antihistamine[xi], antimicrobial[xii], antidiabetic[xiii], anti-HIV[xiv], Ca^{2+} channel blockers[xv], PAF antagonist[xvi], cardio protective[xvii], anti-ischemic agents[xviii].

More over, phenothiazine derivatives are an important class of bioactive molecules. Which exhibit significant activities such as anti-tubercular[xix], NMDA channel blockers[xx], antimicrobial agents[xxi]. In view of the above findings it was thought of interest to accommodate thiazolidinone derivatives with phenothiazine moiety in a single molecular frame work. In this article we wish to report the synthesis of a new class of N-(4-Oxo-2-phenyl-thiazolidin-3-yl)-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide derivatives **5a-g** (Scheme-I) from 4-[Phenothiazin-10-ylmethyl)-amino]-benzoic acid benzylidene hydrazide derivatives and evaluated their in-itro antitubercular and anti microbial activity.

EXPERIMENTAL SECTION

All melting points were measured on open capillary method. IR spectra were recorded for KBr disc on Schimadzu-8400 FTIR spectrophotometer. ^{1}H NMR, ^{13}C NMR spectra were measured on a Bruker Avance-II 400 spectrometer, operating at 400, 100.6 MHz respectively. Chemical shifts (δ) are reported in parts per million and TMS as an internal standard. Reactions were monitored by thin layer chromatography (TLC) on silica gel, plates were visualizing with ultraviolet light or iodine. Column chromatography was performed on silica gel 60(0.043-0.06mm) Merck..

General procedure for the synthesis of 4-[(Phenothiazin-10-ylmethyl)-amino]-benzoic acid ethyl ester II:

A mixture of phenothiazine **I** (0.01 mole), formaldehyde 2.0ml and dioxane (25ml) was stirred at room temperature for ½h followed by the addition of Benzocaine (0.01 mole) it was refluxed and stirred for 4 hr on a oil bath. The solid separated out was filtered and dried. The solid was recrystallized from ethanol, to afford pure compound 2. (yield 74%) as a brown colour solid; m.p. 121°-24°c, IR (KBr, νmax, cm^{-1}) 3087.11 (Ar-H) 3055.35 (C-H in hetero aromatic ring) 3340.68 (N-H),2943.18 (C-H in CH_3),2907.16 (C-H in CH_2),1307.73 (C-N), 697.12 (C-S); ^{1}H NMR (400 MHz, δppm, DMSO-d6) δ: 6.72 (m, 8H, Ar-H), 6.49 (d, J = 9.1 Hz, 2H, Ar-H), 7.01 (d, J = 9.1 Hz, 2H, Ar-H), 4.96(s,2H,N-CH_2), (t, 3H, CH_3) (q, 2H, CH_2), 5.1 (s,1H,N-H);^{13}C NMR (DMSO, 100MHz) δ;162.8 (C=0), 57.3 (CH_2), 16.2 (CH_3), 73.9(N-CH), 131.9 (Ar),112.4 (Ar)

General procedure for the synthesis of 4-[(Phenothiazin-10-ylmethyl)-amino]-benzoic acid hydrazide III.

A solution of the compound **II** (0.01 mole) in ethanol (25ml) and hydrazine hydrate (80% 0.01 mole) was added. The reaction mixture was refluxed for 4h and then cooled. The solid product so formed was filtered washed with ethanol, dried and recrystallized from a mixture of DMF/EtOH (1: 2) to give compound 3.

Pale yellow crystals; yield 81% ; m.p. 207°-209°c, IR (KBr, νmax, cm^{-1}) 3340.68 (N-H), 3089.27 (Ar-H), 3054.93 (C-H str,, in hetero aromatic ring), 2907.16 (C-H str,, in CH_2), 1685.81 (C=0), 697.27 (C-S), 1307.73 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d6) δ: 6.69 (m, 8H, Ar-H), 6.21 (d, J=8, 2H, Ar-H), 7.13 (d, J=8.6 Hz, 2H, Ar-H), 4.91 (s, 2H, N-CH_2), 5.12 (s, 1H, N-H), 8.4 (s, 1H, N-H).

General procudure for the synthesis of 4-[(Phenothiazin-10-ylmethyl)-amino]-benzoic acid benzylidene-hydrazide IVa-g:

A mixture of the compound **III** (0.01 mole) and an equimolar amount of the appropriate aromatic aldehydes in 30ml methanol was refluxed for 6h in the presence of few drops glacial acetic acid then left to cool to room temperature. The solid deposited was collected, and recrystallized from ethanol to give compounds 4a-g.

Yellow powder yield 71%; m.p. 260°-61°c, IR (KBr, νmax, cm^{-1}); 3087.21 (Ar-H), 3340.51 (N-H), 3054.27 (C-H in hetero aromatic ring), 2907.15 (C-H in CH_2), 1685.81 (C=O), 698.28 (C-S), 1307.16 (C-N), 1452.19 (C=N); ^{1}H NMR (400 MHz, δ ppm, DMSO–d6) δ: 6.69 (m, 12H, Ar-H), 5.17 (s, 2H, N-CH_2), 6.27 (d, J=8.1 Hz, 2H, Ar-H), 7.09 (d, J=8.1 J, 2H, Ar-H), 5.23 (s, 1H, N-H), 8.03 (5, 1H, N-H), 5.91 (5, 1H, =C-H), 3.25 (s, 6H, CH_3); ^{13}C NMR (DMSO, 100 MHz) δ; 165.6 (C=O), 130.8 (Ar-C-H), 73.1 (HN-CH_2), 66.3 (=CH), 107.8, 112.4, 127.9, 118.6, (Ar)

General Procedure for the synthesis of N-(4-Oxo-2-phenyl-thiazolidin-3-yl)-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide.Va-g:

A mixture of compound **IV** (0.01 ml) and thioglycolic acid (0.01 mol) was refluxed in methanol (40ml) for 8-10h in the presence of anhydrous, $ZnCl_2$. After completion of reaction excess methanol was evaporated in vacuo, the resulting residue was neutralized with saturated $NaHCO_3$ solution until CO_2 evolution ceased. The solid product was washed with water, dried and recrystallized from ethanol to obtain the desired compound.

N-[2-(4-Dimethylamino-phenyl)-4-oxo-2-thiazolidin-3-yl)]-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide Va:

This compound was obtained as dark yellow solid, m.p. 295°-97°c, IR (KBr, νmax, cm^{-1}) 3099.71 (Ar-H), 1685.84 (C=O), 3184.58 (N-H in O=C-N-H), 3342.75 (N-H str,,), 1305.85 (C-N str,, in amine), 1313.57 (C-N str,,, 3^0 amine); ^{1}H NMR (400 MHz, δ ppm, DMSO-d6) δ: 6.6-6.9 (m, 12H Ar-H), 7.8 (d, J = 9.0 Hz, 2H, Ar-H), 4.87 (s, 2H, N-CH_2), 3.7 (s, 2H, S-CH_2), 7.57 (d, J=9.0 Hz, 2H, Ar-H), 8.74 (s, 1H, N-H), 3.09 (s, 6H, N(CH_3)$_2$); ^{13}C NMR (DMSO, 100.6 MHz) δ:165.4 (C=O), 74.3 (CH_2), 69.6 (C-H in ring), 154.7 (C=O in ring), 51.5 (CH_2 in ring), 130.7, 127.3, 105.7 (Ar-H). TOF MS ES m/z (%):567.24(M^+, 100%),568.19(M^{+1},38.4%).

Physical and analytical data of synthesized compounds **5a-g** were depicted in **Table-1.**

N-[2-(4-Nitro-phenyl)-4-oxo-2-thiazolidin-3-yl)]-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide V**b**:

This compound was obtained as dark yellow solid; m.p. 248°-51°c, IR (KBr, νmax, cm^{-1}) 3098.29 (Ar-H), 1661.18 (C=O), 3186.53 (N-H in O=C-N-H), 3342.75 (N-H), 1305.88 (C-N str,, in amine), 1541.18 (N=O), 657.75 (C-S); ^{1}H NMR (400 MHz, δ ppm, DMSO-d6) δ: 6.71(m, 8H, Ar-H), 7.14 (m, 6H, Ar-H), 7-5 (d, J= 8.6Hz, 2H, Ar-H), 7.95 (s, 1H, N-H), 4.72 (s, 2H, N-CH_2), 3.68 (s, 2H, S-CH_2-C=O), 5.91 (s, 1H, C-H in thiazolidinone ring), ^{13}C NMR (DMSO, 100 MHz) δ:165.7 (C=O), 74.3 (CH_2), 69.0 (C-H in ring), 158 (C=O in ring), 51.5 (CH_2 in ring), 131.1, 126.7, 105.7 (Ar-H). TOF MS ES m/z(%):569.53(M^+,100%), 570.15(M^{+1},38.3%).

N-[2-(3, 4, 5-trimethoxy-phenyl)-4-oxo-2-thiazolidin-3-yl)]-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide Vc:

This compound was obtained as dark yellow solid; m.p.267°-68°c; yield 68%; (KBr, νmax, cm^{-1}) 3099.71 (Ar-H), 3340.82 (N-H), 1263.42 (C- O – C str,,), 2904.89 (C-H in CH_2), 1282.71 (C-N str,,), 1651.11 (C=O).

N-[2-(4-Methyl-phenyl)-4-oxo-2-thiazolidin-3-yl)]-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide Vd:

This compound was obtained as dark yellow solid; m.p. 250°-53°c; yield 71%; IR (KBr, νmax, cm^{-1}) 3099.71 (Ar-H), 1649.77 (C=O), 3342.75 (N-H str,, in amine), 3184.58 (N-H str,, in amide), 2904.89 (C-H str,, in CH_2), 1282.71 (C-N), 1415.80 (C-N str,,), 2941.54 (C-H str,, in CH_3).

N-[2-(2-Chloro-phenyl)-4-oxo-2-thiazolidin-3-yl)]-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide Ve:

This compound was obtained as dark yellow solid; m.p. 217°-20°c; yield 65%; IR (KBr, νmax, cm^{-1}) 3099.67 (Ar-H), 3341.23 (N-H), 3186.97 (N-H str,, in amide), 1091.08 (C-Cl) 1643.15 (C=O), 2904.87 (C-H in CH^2), 1282.66 (C-N); ^{1}H NMR (400 MHz, δ ppm, DMSO-d6) δ: 6.95 (m, 8H Ar-H), 7.25 (m, 6H, Ar-H), 7.81 (d, J= 7.6 MHz, 2H, Ar-H), 4.98 (s, 2H, N-CH_2), 8.1 (s, 1H, O=C-N-H), 4.25 (s, 2H, S-CH_2-C=O), 5.71 (s, 1H, C-H).

N-[2-(4-Methoxy-phenyl)-4-oxo-2-thiazolidin-3-yl)]-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide Vf:

This compound was obtained as dark yellow solid; m.p. 261°-63°c; yield 68% ;IR (KBr, νmax, cm^{-1}) 3099.71 (Ar-H), 3340.82 (N-H), 2904.89 (C-H str,, in CH_2), 1685.84 (C=O), 1263.42 (C-O-C in str,,), 1303.92 (C-N), 655.82 (C-S str,,); ^{1}H NMR (400 MHz, δ ppm, DMSO-d6) δ: 6.55 (m, 8H Ar-H), 6.86 (d, J= 7.6 MHz, 2H, Ar-H), 2.54 (s, 3H, OCH_3), 4.21 (s, 2H, SCH_2CO), 4.94 (s, 2H, NCH_2); ^{13}C NMR (DMSO, 100 MHz) δ: 164.8 (C=O), 74.6 (CH_2), 69.5 (C_2-H in ring), 53.7 (CH_2 in ring), 158.7 (C=O in ring), 131.1, 126.3, 107.6 (Ar-H).

N-(4-Oxo-2-phenyl-thiazolidin-3-yl)-4-[(phenothiazin-10-ylmethyl)-amino]-benzamide. Vg:

This compound was obtained as dark yellow solid, m.p. 275°-278°c, yield 71% (KBr, νmax, cm^{-1}), 3099.12 (Ar-H), 1641.16 (C=O), 3184.55 (N-H), 1305.83 (C-N), 2904.89 (C-H str,, in CH_2), 671.44 (C-S), 3342.21 (N-H).

Table-1: Physical and analytical data of synthesized compounds 5a-g.

Compound	R	Yield (%)	m.p (°c)	Molformula/m.wt	C calcd(found)	H calcd(found)	N calcd(found)
Va	-N $(CH_3)_2$	68	295-97	$C_{31}H_{29}N_5O_2S_2$(567.72)	65.58(65.55)	5.15(5.13)	12.34(12.29)
Vb	4-NO_2	62.5	248-51	$C_{29}H_{23}N_5O_4S_2$(569.95)	61.14(61.11)	4.07(4.03)	12.29(12.26)
Vc	3, 4, 5-OCH_3	68	267-68	$C_{32}H_{30}N_4O_5S_2$(614.73)	62.52(62.48)	4.92(4.89)	9.11(9.08)
Vd	4-CH_3	71	250-53	$C_{30}H_{26}N_4O_2S_2$(538.68)	66.89(66.86)	4.86(4.82)	10.40(10.37)
Ve	2-Cl	65	217-20	$C_{29}H_{23}ClN_4O_2S_2$(559.10)	62.30(62.27)	4.15(4.13)	10.02(10.00)
Vf	4-OCH_3	68	261-63	$C_{30}H_{26}N_4O_3S_2$(554.68)	64.96(64.93)	4.72(4.69)	10.10(10.06)
Vg	H	71	275-78	$C_{29}H_{24}N_4O_2S_2$(524.66)	66.39(66.36)	4.61(4.58)	10.68(10.64)

Results and Discussion:

Chemistry: The key intermediated 3 was required for the synthesis of title compounds and was prepared according to the procedure out lined in **Scheme-I**. Condensation of Phenothiazine I with benzocaine and formaldehyde gave 4-[(Phenothiazin-10-ylmethyl)-amino]-benzoic acid ethyl ester **II** with good yield. Compound **II** was then reacted with hydrazine hydrate to gave 4-[(Phenothiazin-10-ylmethyl)-amino]-benzoic acid hydrazide **III**. The synthesis of 4-[(Phenothiazin-10-ylmethyl)-amino]-benzoic acid benzylidene-hydrazide derivatives (**IVa-g**) were carried out by the condensation reaction between compound **III**, aromatic aldehydes under acidic conditions **(Scheme-I)**. Compounds **(IVa-g)** were then reacted with thioglycolic acid in the presence of anhydrous $Zncl_2$ to gave compounds **Va-g** in good to excellent yields. The structures of the synthesized compounds were confirmed by their IR, ^{1}H NMR, ^{13}CNMR, Mass spectral analysis.

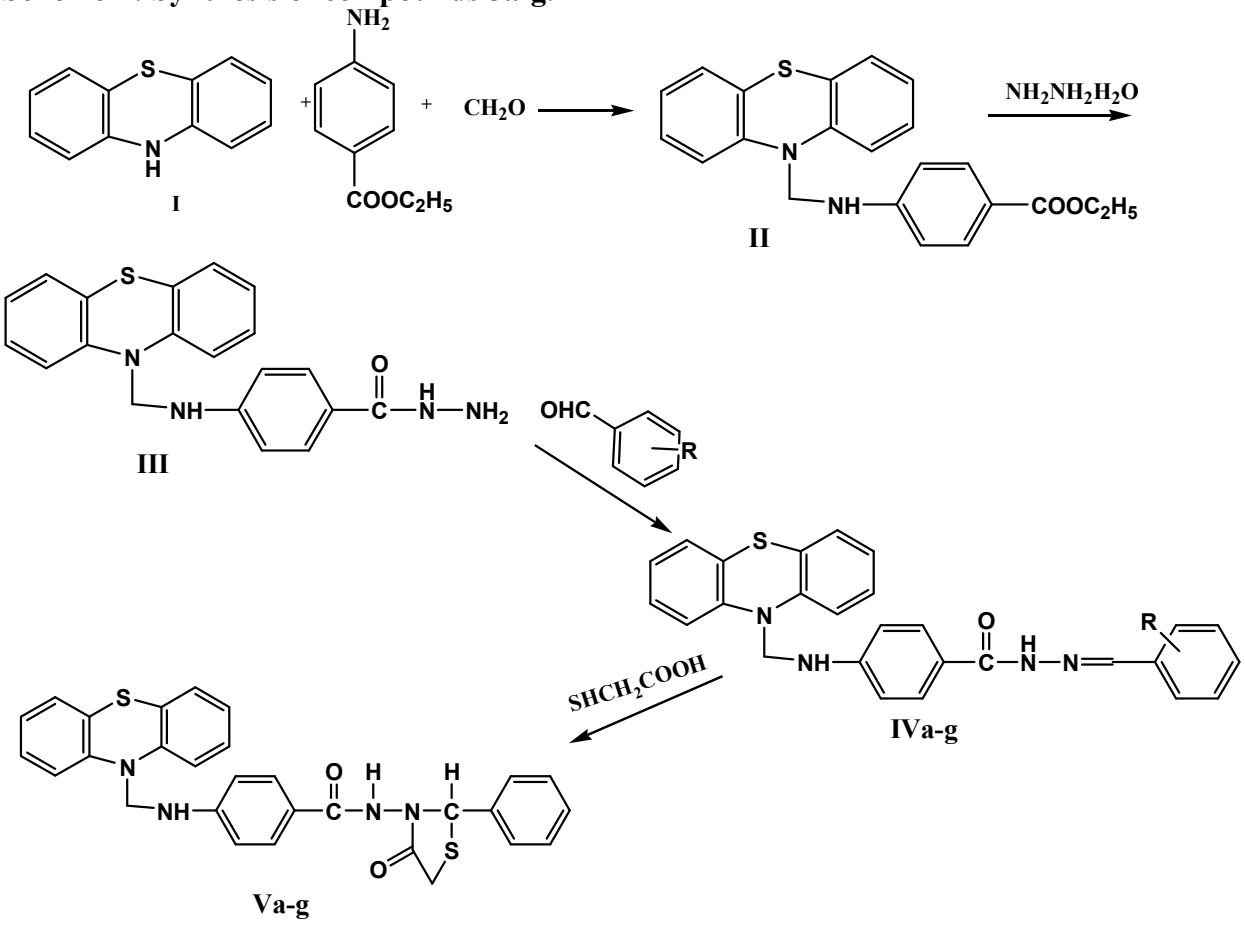
In the IR spectra of compounds **Va-g** disappearance of C=N absorption band at ~1452.19cm^{-1}, which was present in compound **IVa-g** confirmed the cyclization (or) involvement of α, β-unsaturated carbonyl system.

In the ^{1}H NMR spectra of compounds (**Va-g**) were recorded in DMSO–d6. The signal due to the presence of S-CH_2 group at 3.7ppm as a singlet along with N-CH_2 group at 4.87ppm as a singlet confirmed the cyclic system of thiazolidinone derivatives.

In the ^{13}C NMR spectra of compounds **Va-g** records in DMSO-d6. The signal due to C=O group of ring appeared at 158.7 ppm, as well as the disappearance of signal due to N=CH group appeared at 66.3 ppm which was present in compound **IVa-g** were confirmed the cyclic system of thiazolidinone system.

^{1}H-NMR, ^{13}C-NMR spectral data of these compounds are in good agreement with the formation of thiazolidinone ring. The mass spectra of compounds **Va-j** displayed M^{+}/M^{+1} peaks, in agreement with their molecular formula.

Scheme-1: Synthesis of compounds 5a-g.



Antimicrobial activity:

The newly prepared synthesized compounds **Va-g** were screened for their antibacterial activity against B. subtilis, B. thuringiensis, E. coli and P. aeruginosa strains. This activity was determined by the agar diffusion method and the compounds were dissolved in DMSO at concentration $lmgm^{-1}$. The activity was compared with streptomycin and chloramphenicol standard drugs.

The antibacterial screening data depicted in **Table-2** showed moderate activity of the test compounds, among the screened compound **Vb, Ve** in which thiazolidinone moieties bearing p-nitro phenyl and o-Cl phenyl nucleus on carbon respectively showed high degree of activity against all the microorganisms employed. The activities of these two compounds are equal to the standard drug Chloramphenicol against B.subtilis (MIC 6.25 µg/mL).

The antifungal screening data depicted in **Table-2** showed moderate activity of test compounds, among the screened **Vc, Vf** in which thiazolidinone derivatives bearing 3,4,5-trimethoxy phenyl, and p-methoxy phenyl nucleus on carbon respectively showed high degree activity against all the microorganisms employed.

In this view compound **Vc** was equipotent to Treflucan against F.oxysporum (MIC 3.125 µg/mL), while it's activity was 50% lower than Treflucan against B. fabae (MIC 6.25 µg/mL) and the compound **Vf** was 50% lower than Treflucan against B.fabae and F.oxysporum(MIC 6.25 µg/mL).

Table-2: Antimicrobial data of synthesized compounds 5a-g.

Compounds MIC in µg/mL. and zone of inhibition (mm)

Compound No.	Bacteria				Fungi	
	B.subtilis	B.Thuringiensis	E.Coli	P.aeruginosa	B.Fabae	F.oxysporum
Va	25(25-30)	12.5(31-36)	25(25-30)	50(19-24)	12.5(31-36)	25(25-30)
Vb	6.25(37-42)	6.25(37-42)	12.5(31-36)	25(25-30)	50(19-24)	50(19-24)
Vc	12.5(31-36)	25(25-30)	12.5(31-36)	25(25-30)	3.125(43-48)	3.125(43-48)
Vd	50(19-24)	50(19-24)	100(13-18)	50(19-24)	12.5(31-36)	25(25-30)
Ve	3.125(43-48)	6.25(37-42)	12.5(31-36)	12.5(31-36)	12.5(31-36)	25(25-30)
Vf	25(25-30)	25(25-30)	50(19-24)	25(25-30)	6.25(37-42)	12.5(31-36)
Vg	6.25(37-42)	12.5(31-36)	12.5(31-36)	25(25-30)	12.5(31-36)	12.5(31-36)
Streptonycin	3.125(43-48)	6.25(37-42)	6.25(37-42)	6.25(37-42)	-	-
Chloramphenicol	6.25(37-42)	6.25(37-42)	6.25(37-42)	6.25(37-42)	-	-
Treflucan	-	-	-	-	3.125	3.125

Evaluation of anti-tubercular screening

The synthesized compounds were evaluated for their anti tubercular activity. Drug susceptibility and determination of MIC of the test compounds against M.tuberculosis H_{37} R_V was performed by agar micro dilution (L-J) method. Where two fold dilutions of each test compound were added into 7H10 agars supplemented with OADC and organism. The testing tubes were incubated at 37^0c for 24h followed by streaking of M.tuberculosis H_{37}Rv (5x104 bacilli per tube). These cubes were then incubated at 37^0c Growth of bacilli was seen after 30 days of incubation. Tubes having the compounds were compared with control tubes where

medium alone was incubated with $H_{37}Rv$. The concentration takes as active concentration of test compounds. Isoniazid was used as standard drug. The MIC levels of some active compounds against anti-tuberculosis, as can be seen from the **Table-3** the results revealed that the compounds **Vb, Ve** showed broad spectrum anti tubercular profile against M. tuberculosis $H_{37}Rv$.

Table-3: Anti tuberculosis activity data of compounds 5a-g:

Compound	MIC (μg/ml)
Va	>25
Vb	3.125
Vc	>12.5
Vd	>25
Ve	>3.125
Vf	12.5
Vg	>6.25
Isoniazid	0.20

Conclusion: In conclusion our aim has been verified by the synthesis of thiazolidinones incorporating with phenothiazine moiety through various linkages of synergistic purpose. The obtained results clearly revealed that some of the compounds showed good activity against test bacterial and fungal organisms employed as well as some of the compounds showed promising activity against M.tuberculosis $H_{37}Rv$.

Acknowledgement:
We sincerely express our gratitude to Head, Biotechnology laboratory, Department of Botany, Dr. H. S. Gour Central University, Sagar for providing antimicrobial data. We are grateful to The Director, SAIF, Panjab University for providing spectral data and The Director Micro care laboratory Surat, for providing anti-mycobacterial data.

References:

i. M. G. Vigorita, R. Ottana, F. Monforte, R. Maccari, A.Trovato, M.T.Monforte, and M.F.Traviano, Bioorg.Med.Chem.Lett, 11, 2791 (2001).
ii. C. V. Kavitha, S. Basappa, N. Swamy, K. Mantelingu, S. Doreswamy, M. A. Sridhar, S. Prasad and K. S. Rangappa, Bioorg.Med.Chem,14, 2290 (2006).
iii. B. A. Sobin, J.Am.Chem.Soc,74, 2947 (1952).
iv. K. Badaoglu, M. A. Page, V. C. Jones, M. R. Mc. Neil, C. Dong, J. H. Nai smith and R. E. Lee, Bioorg.Med.Chem.lett,13, 3227 (2003).
v. N. Ergenc and G. Capan, Il Farmaco, 49, 133 (1994).
vi. J. J. Bhatt, B. R. Shah, H. P. Shah, P. B. Trivedi, N. K. Undavia and N. C. Desai, Indian J.Chem. 33B, 189 (1994).
vii. L. Bukowski, M. Janowiec, Z. Zwolska-Kwiek and Z. Andrezejczyk, Pharmazie, 53, 373 (1998).
viii. T. de Aquino, A. P. Liesen, R. E. A. da Silva, V. T. Lima, C. S. Carvalho, A. R. de Faria, J. M. de Arau´ jo, J. G. de Lima, A. J. Alves, E. J. T. de Melo and A. J. S. Go´ es, Bioorg. Med.Chem. 16, 446 (2008).

ix. A. Verma and S. K. Saraf, Eur. J. Med. Chem, 43, 2008, 897.
x. G. C. Look, J. R. Schullek, C. P. Homes, J. P. Chinn, E. M. Gordon and M. A. Gallop, Bioorg. Med. Chem. Lett, 6, 707 (1996).
xi. M. V. Diurno, O. Mazzoni, P. E. Calignano, F. Giordano and A. Bolognese, J. Med. Chem. 35, 2910 (1992).
xii. J. S. Viswajanani, S. Ajay, S. Smita, K. Seema, P. Manisha, B. Pragya, M. Tarun, R. Ashok, K. Jag Mohan and M. Anitha, ARKIVOC, 46 (2005).
xiii. H. Ueno, T. Oe, I. Snehiro and S. Nakamura, US Patent, 5594116 (1997).
xiv. R. K. Rawal, Y. S. Prabhakar, S. B. Katti and E. De Clercq, Bioorg. Med. Chem. 13, 6771 (2005).
xv. T. Kato, T. Ozaki and K. Tamura, J. Med. Chem. 42, 3134 (1999).
xvi. Y. Tanabe, G. Suzukamo, Y. Komuro, N. Imanishi, S. Morooka, M. Enomoto, A. Kojima, Y. Sanemitsu and M. Mizutani, Tetrahedron Lett. 32, 379 (1991).
xvii. T. Kato, T. Ozaki and N. Ohi, Tetrahedron Asymmetry, 10, 3963 (1999).
xviii. Y. Adachi, Y. Suzuki, N. Homma, M. Fukazawa, K. Tamura, I. Nishie and O. Kuromaru, Eur. J. Pharmacol. 367, 267 (1999).
xix. P. B. Madrid, W. E. Polgar, L. Toll and M. J. Tanga, Bioorg.Med.Chem.Lett, 17, 3014 (2007).
xx. H. Takayama, Y. Yaegashi, M. Kitajima, Xia Han, K. Nishimura, S. Okuyama and K. Igarashi, Bioorg. Med. Chem. Lett, 17, 4729 (2007).
xxi. Y. Zhang, C. E. Ballard, Shi-long Zheng, Xingming Gao, Ko-Chun Ko, H. Yang, G. Brandt, X. Lou, P. C. Tai, C-Dar Lu and B. Wang, Bioorg. Med. Lett., 17, 707 (2007).

Received on July 1, 2012.