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Synthesis and Biological Investigations of Some New Thiazolidinone Derivatives As Anti-Tubercular Agents

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ABSTRACT

To synthesize and characterize novel thiazolidinone derivatives and screen them for anti tubercular activity. A series of ten 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) were synthesized from 1-acetyl naphthalene. The synthesized compound, characterized on the basis of satisfactory analytical and spectral (IR, H^1NMR, Mass and elemental) data. Studies were carried out for the synthesized compounds which were also evaluated for anti-tubercular activity by using Lowenstein-Jensen (LJ) acid medium and screening by Cup plate method. Rifampicin (Lupin) is used as standard antitubercular agents. The synthesized compounds showed good anti tubercular activity, compared to standard drugs. Two of the compounds TM_1 (Ar = 4-nitrophenyl) and TM_6 (Ar = 3-fluorophenyl) exhibited significant anti-tubercular activity, as compared to standard drug Rifampicin. We report the successful synthesis of novel thiazolidinones, as well as their spectral characterization, and anti tubercular activity which, for some, is superior to currently used anti-tubercular agents.

Keywords: Anti-tubercular activity, 1-Acetylnaphthalene, Thiazoles, Thiazolidinones

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INTRODUCTION

The steady growth of interest in the synthesis of heterocyclic compounds is connected with their raised biological activity and also with the fact that these compounds make possible the development of novel materials of unique properties. Thiazolidinone are an important group of heterocyclic compounds containing sulphur and nitrogen in a five member ring. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities[1,2].

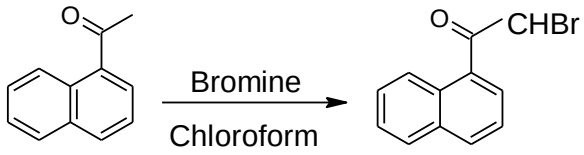
Literature survey reveals that 4-thiazolidinones are usually synthesized starting from thiourea[3-5], thiosemicarbazides[6] and azomethines[7]. Thiazolidinones have been synthesized and screened for possible antimicrobial activity[8-12] moreover; thiazolidinones have a broad spectrum of pharmacological properties like anti HIV[13], antipshychotic[14], anti convulsant[15] and antitubercular[16] activity.

The β-lactams also serve as synthons for many biologically important classes for many biologically important classes of organic compounds [17]. Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists.

Method of Synthesis:

Synthesis of 1-bromoacetyl naphthalene (Scheme-1):

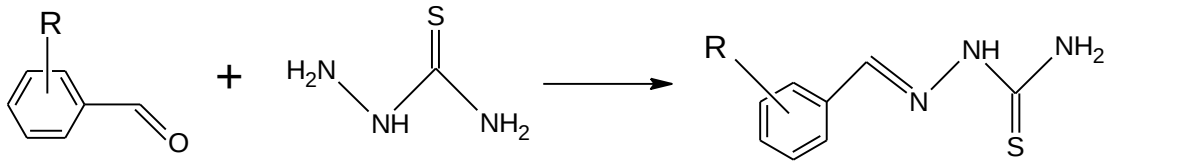
1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to flask containing 1-acetylnaphthalene solution, drop wise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene yielding 1-bromoacetyl naphthalene.



(Scheme -1)

Synthesis of substituted thiosemicarbazone (Scheme-2):

A solution of 0.05 mol. Substituted benzaldehyde in warm alcohol (300 ml) and a solution of 0.05 mol thiosemicarbazide in 300 ml water were mixed slowly. The product, which separated, was filtered off after cooling and recrystallised from ethanol. Other thiosemicarbazones were prepared in the same way.

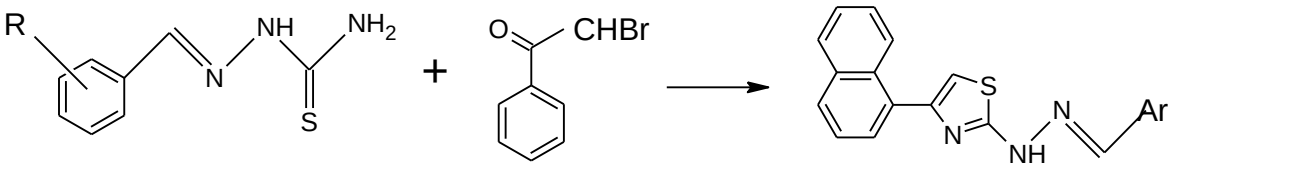


Substituted Benzaldehyde Thiosemicarbazide Substituted benzaldehyde thiosemicarbazo

(**Scheme-2)**

Synthesis of 4-naphthalen-1-yl-2-{2-[(substituted phenyl) methyl idene] hydrazino}-1, 3-thiazole(Scheme-3):

Equimolar quantities (0.01 mole) of 1- bromoacetylnaphthalene and substituted benzaldehyde thiosemicarbazones were dissolved in 50 mL of ethanol in a 100 mL round bottom flask. The reaction mixture was refluxed for 1-2 h. A solid was separated during refluxing which was hot filtered, dried and recrystallized from ethanol yielding 4-naphthalen-1-yl-2-{ 2 - [(substituted phenyl) methylidene] hydrazine }- 1,3-thiazole.

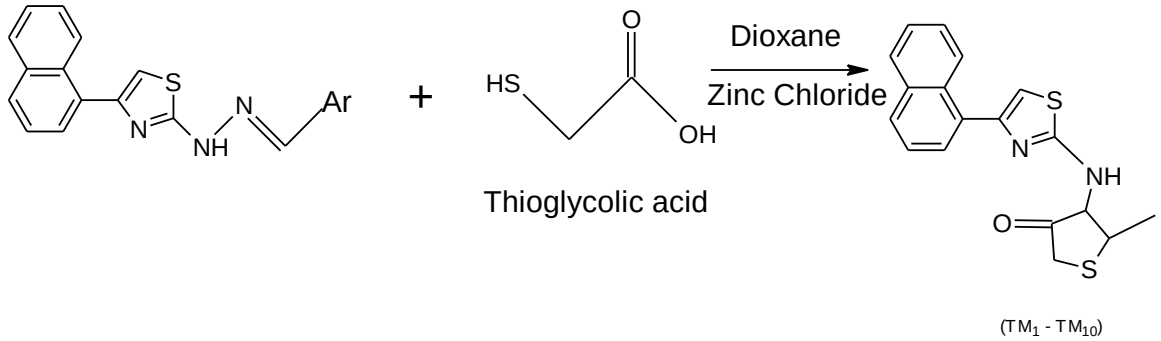


Substituted benzaldehyde thiosemicarbazone 1-Bromoacetyl napthalene 4-Naphthalene-1-yl-2-{[(substituted phenyl methylidene] hydrazino}-1,3-thiazole

(**Scheme-3)**

Synthesis of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1-TM_{10}) (Scheme-4):

A mixture of respective thiazole derivative (0.01 mole) and thiomalic acid (0.015 mole) in 25 mL of dioxane was taken in a 100 mL round bottom flask. To this solution 25 mg of $ZnCl_2$ was added and the reaction mixture was refluxed for 6-10 h. The mixture was then poured on crushed ice and solid so obtained was filtered, washed with water, dried and recrystallized from dioxane. The purity of the compounds was established on the basis of TLC.



Thioglycolic acid

(TM_1 - TM_{10})

(**Scheme-4)**

General Procedures:

Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}HNMR spectra were recorded on Bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million (ppm). Splitting patterns are designated as follows: S-Singlet, d-doublet, t-triplet, q-quartet and m-multiplet. Mass spectra (MS) were recorded on Shimadzu GC-MS operating at 70eV. All the synthesized compounds were purified by recrystallization. The reaction were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultra violet light.

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the basis of their IR, ^{1}H NMR, Mass and elemental analysis. The study was aimed at evaluating the anticonvulsant effect of compounds on mice.

Compound [TM_1]:

Preparation of 2-(4-nitrophenyl)-3-[(4-(1naphthyl) -1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-one. **IR Spectra:** 3243.54 (N-H), 1697.68 (C=O), 1613.32 (C=N), 1543.84 (C=C), 1512.04, 1441.30 and 1042.02 (Characteristic of thiazole nucleus). **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.45 (s, 1H, -N-CH-), 7.35 (s, 1H, Ar-H), 7.42 (d, J=12Hz, 2H, Ar-H), 7.56 (m, 2H, Ar-H), 7.67 (m, 4H, Ar-H), 7.97 (d, J=12Hz, 1H, Ar-H), 8.07 (d, J=12Hz, 1H, Ar-H), 8.21 (d, J=12Hz, 1H, Ar-H), 8.92 (s, 1H, NH). **Mass (m/z):** 462 (M^+, $C_{23}H_{18}N_4O_3S_2$), 181 (100%, $C_7H_5N_2O_2S$), 154 ($C_{11}H_8N$), 70 (C_3H_4NO), 57 (C_3H_5O).

Compound [TM_2]:

Preparation of 2-(3-chlorophenyl)-3-[{4-(1naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-one **IR Spectra:** 3251.03 (N-H), 1696.48 (C=O), 1617.56 (C=N), 1539.30 (C=C). 1516.60. 1440.04 and 1037.94. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3) 4.79 (q, 1H, -CH-S-), 6.69 (s, 1H. -N-CH-), 7.24 (m, 4H, Ar-H), 7.66 (m, 5H, Ar-H), 7.94 (d, J=12Hz, 1H, Ar-H), 8.11 (d, J=12Hz, 1H, Ar-H), 8.21 (d, J=12Hz, 1H, Ar-H), 8.97 (s, 1H, NH).

Compound [TM_3]:

Preparation of 2-(4-chlorophenyl)-3-[{4-(1naphthyl)-1,3-thiazol-2-yl} amino]-5-methyl-1,3-thiazolidin-4-one **IR Spectra:** 3252.84 (N-H), 1700.02 (C=O), 1613.66 (C=N), 1541.92 (C=C), 1515.15, 1452.48 and 1040. 10. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 4.78 (q, 1H, -CH-

S-), 6.45 (s, 1H, -N-CH-), 7.28 (m, 5H, Ar-H), 7.59 (m, 4H, Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.11 (d, J=12Hz, 1H, Ar-H), 8.22 (d, J=12Hz, 1H, Ar-H), 8.90 (s, 1H, NH). **Mass (m/z):** 452 ($M^{+,}$ $C_{23}H_{18}N_3S_2OCl$), 453 (M^+ +1), 170 (100%, C_7H_5NSCl), 155 (C_7H_4SCl), 127 ($C_{10}H_7$), 99 ($C_3H_3N_2S$).

Compound [TM_4]:

Preparation of 2-(2, 4-dichlorophenyl)-3-[{4- (1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1,3-thiazolidin-4-one. **IR Spectra:** 3248.44 (N-H), 1694.06 (C=O), 1617.74 (C=N), 1542.92 (C=C), 1515.16, 1452.78 and 1038.66. **^{1}HNMR [δ ppm]:** 1.36 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.75 (s, IH, -N-CH-), 7.08 (d, J-12Hz, 2H, Ar-H), 7.33 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.58(m, 4H, Ar-H), 7.92 (d, J=12Hz, 1H, Ar-H), 8.12 (d, J=12Hz, 1H, Ar-H), 8.22 (d, J=12Hz, 1H, Ar-H), 8.96 (s. 1H, NH).

Compound [TM_5]:

Preparation of 2-(2, 6-dichloro phenyl)-3-[{4- (1 -naphthyl) - 1, 3-thiazol-2-yl} amino] -5 -methyl – 1, 3-thiazolidin-4-one. **IR Spectra:** 3248.04 (14-H), 1693.88 (C=O), 1610.65 (C=N), 1541.06 (C=C), 1515.15, 1438.64 and 1040.25 **^{1}HNMR [δ ppm]**: 1.36 (d, J=8Hz, 3H, CH_3), 4.76 (q, 1H, -CH-S-), 6.77 (s, 1H. -N-CH-), 7.54 (m, 8H, Ar-H), 7.95 (d. J=12Hz, 1H, Ar-H), 8.12 (d, J=12Hz, 1H, Ar-H), 5.24 (d, J=12Hz, 1H, Ar-H), 8.95 (s, 1H, NH).

Compound [TM_6]:

Preparation of 2-(3-fluorophenyl)-3-[{4-(1-naphthyl)-1,3-thiazol.-2-yl} amino], -5-methyl-1, 3-thiazolidin-4-one. **IR Spectra:** 3251.66 (N-H), 1694.83 (C=O), 1615.18 (C=N), 1542.56 (C=C), 1514.20, 1451.92 and 1039.08. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.50 (s, 1H, -N-CH-), 6.89 (s, 1H, Ar-H), 7.16 (m, 2H, Ar-H), 7.32 (s, 1H, Ar-H), 7.62 (m, 5H, Ar-H), 7.96 (d, J= 12Hz, 1H, Ar-H), 8.08 (d, J= 12Hz, 1H, Ar-H), 8.23 (d, J=12Hz, 1H, Ar-H), 8.92 (s, 1H, NH).

Compound [TM_7]:

Preparation of 2-(2-hydroxy-4-bromophenyl) - 3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl- 1,3-thiazolidin-4-one. **IR Spectra:** 3418.44 (O-H), 3239.96 (N-H), 1697.82 (C=0), 1616.38 (C=N), 1543.72 (C=C), 1515.15, 1440.02 and 1043.82. **^{1}HNMR [δ ppm]:** 1.34 (d, J=8Hz, 3H, CH_3), 4.79 (q, 1H, -CH-S-), 6.53 (s. 1H, -N-CH-), 7.12 (m, 3H, Ar-H), 7.33 (s, 1H, Ar-H), 7.59 (m, 4H, Ar-H), 7.97 (d, J=12Hz, lH, Ar-H), 8.13 (d, J=12Hz, 1H, Ar-H), 8.24 (d., J=12Hz, 1H, Ar-H), 8.97 (s, 1H, NH), 10.98 (s, 1H, OH). **Mass (m/z):** 512 ($M^{+,}$ $C_{23}H_{18}N_3S_2O_2Br$), 514(M^- +2), 287 ($C_{10}H_9NO_2SBr$), 259 (C_9H_9NOBrS), 215 (C_7H_5NSBr), 57 (C_3H_5O).

Compound [TM_8]:

Preparation of **2**-(2-hydroxy-4-chlorophenyl) - 3-[{14-(1-naphthyl)-1,3-thiazol-2-yl}amino]-5-methyl-1,3-thiazolidin-4-one. **IR Spectra:** 3418.06 (O-H), 3249.50 (N-H). 1798.02 (C=0), 1616.20 (C=N), 1538.93 (C=C). 1509.48, 1436.88 and 1040.10. **^{1}HNMR [δ ppm]:** 1.37 (d. J=8Hz, 3H, CH_3), 4.77 (q, 1H, -CH-S-), 6.53 (s, 1H, -N-CH-), 6.98 (m, 3H, Ar-H), 7.35 (s, 1H, Ar-H), 7.62 (m, 4H, Ar-H), 7.95 (d, J=12Hz- 1H, Ar-H), 8.09 (d, J=12Hz, 1H, Ar-H), 8.23 (d. J=12Hz, 1H, Ar-H), 8.99 (s, 1H, NH), 10.97 (s, 1H, OH).

Compound [TM_9]:

Preparation of 2-(4-dimethylaminophenyl)-3- [{4-(1-naphthyl)-I, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-one. **IR Spectra:** 3247.88 (N-H), 1698.04 (C=0), 1616.42 (C=N), 1543.30 (C=C), 1515.15, 1440.80 and 1043.76. **^{1}HNMR [δ ppm]:** 1.33 (d. J=8Hz, 3H, CH_3), 3.01 (s, 6H, CH_3), 4.79 (q. 1H, -CH-S-), 6.39 (s, 3H, Ar-H, -N-CH-), 7.10 (d, J=12Hz, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 7.62 (m, 4H, Ar-H), 7.95 (d, J=12Hz, 1H, Ar-H), 8.08 (d, J=12Hz, 1H, Ar-H), 8.26 (d, J= I 2Hz, 1H, Ar-H), 8.93 (s, 1H, NH). **Mass (m/z):** 460 (M^+, $C_{25}H_{24}N_4OS_2$), 164 ($C_9H_{10}NS$), 154 (100%, $C_{11}H_8N$), 120 ($C_8H_{10}N$), 88 (C_3H_6NS), 44 (C_2H_6N).

Compound [TM_{10}]:

Preparation of 2-(4-methoxyphenyl) - 3 - [{ 4 - (1-naphthyl)-1,3-thiazol-2-yl}amino]-5-methyl-1,3- thiazolidin-4-one. **IR Spectra:** 3247.72 (N-H), 1697.42 (C=O). 1613.82 (C=N), 1548.50 (C=C), 1515.13, 1441.35 and 1040.10. **^{1}HNMR [δ ppm]**: 1.34 (d, J=8Hz, 3H, CH_3), 1.65 (s, 3H, OCH_3), 4.80 (q, 1H, -CH-S-), 6.44 (s, 1H, -N-CH-), 7.24 (m, 5H, Ar-H), 7.58 (m, 4H, Ar-H), 7.93 (d, J=12Hz, 1H, Ar-H), 8.09 (d, J=12Hz, 1H, Ar-H), 8.25 (d, J= 12Hz, 1H, Ar-H), 8.95 (s, 1H, NH).

PHARMACOLOGICAL STUDIES

Anti-tubercular Activity

Lowenstein-Jensen (LJ) acid medium:

For the preparation of medium eggs were washed and immersed in 70% v/v alcohol. The eggs were broken and homogenised. Then strained the mixture through sterile gauge into a sterile container. Then hydrochloric acid, salt glycerol solution, malachite green and Penicillin G were mixed. The pH was adjusted between 6.4 and 6.8.It was then inspissated at 80° C for about one hour[18].

Preparation of standard discs:

The drug Rifampicin (Lupin) was taken as a standard drug.

Screening of antitubercular activity:

Cup plate method:

Micro wells were made on culture media in 6 mm in diameter with the help of gel puncture machine. The micro wells were filled with 100 µl from different concentration of test solutions and standard drug (Rifampicin). The Petri dishes used for antitubercular screening were incubated at 37^0 C for 3-4 weeks. The activity was measured in terms of diameter of zone of inhibition appearing around the micro- wells[19].

Table: 1 Anti-tubercular activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1&TM_6)

Compound Name	Zone of Inhibition (mm)
TM_1 400µg/ml	23
TM_6 400µg/ml	17
TM_1 200µg/ml	11
TM_6 200µg/ml	12
TM_1 100µg/ml	0
TM_6 100µg/ml	0
Standard Drug (Rifampicin) 100µg/ml	18

Micro-organism = *Mycobacterium tuberculosis* 25177(h37Ra)

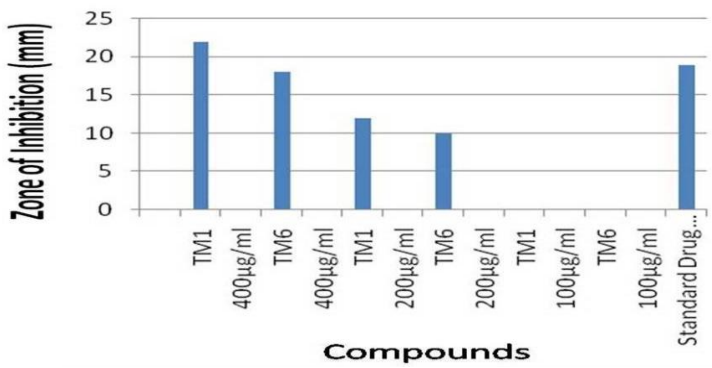


Figure: 1 Anti-tubercular activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1 & TM_6)

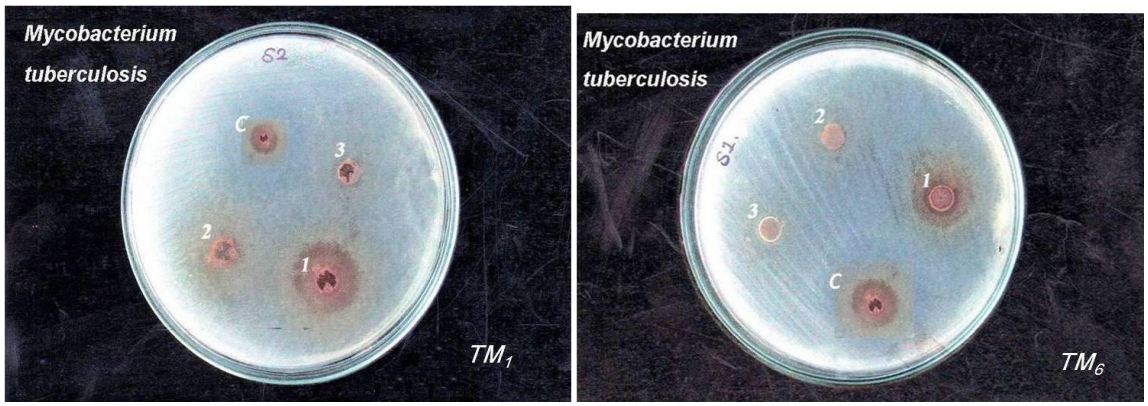


Figure: 2 Anti-tubercular activity of 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino]-5-methyl-1, 3-thiazolidin-4-ones (TM_1&TM_6)

CONCLUSION

Clinical study for antitubercular activity for the synthesized 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3- thiazol-2-yl) amino] -5-methyl- 1, 3 -thiazolidin-4-ones (TM_1-TM_{10}) revealed that the compounds TM_1 (Ar = 4-nitrophenyl) and TM_6 (Ar = 3-fluorophenyl) exhibited significant anti-tubercular activity, as compared to standard drug Rifampicin. From the above result it has been concluded that 2-(substituted phenyl)-3-[{4-(1-naphthyl) - 1, 3 -thiazo 1-2 –yl} amino] - 5 -methyl- 1, 3-thiazolidin-4 -ones (TM_1-TM_{10}) may be used as lead compounds for anti-inflammatory activity and may further be evaluated for toxicological profile.

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