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SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4 - THIADIAZOLE DERIVATIVES FOR THEIR ANTITUBERCULAR ACTIVITY

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Abstract

In the present study, novel 134 Thiadiazoles derivatives were synthesized by reaction of various aromatic acid with thiosemicarbazide and then diazotized to synthesize 5-phenyl-1,3,4-thiadiazol-2-amine diazoamino derivatives (A series) and .From these compounds various derivatives of 1,3,4-Thiadiazole have been synthesized. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H NMR, and MASS Spectra. These compounds were screened for anti-tubercular activity using H37 Rv strains and anti-cancer activity against Lung cancer cell lines.

Keywords: 1,3,4-Thiadiazole, Synthesis, Anti tubercular, NMR.

Introduction [1-8]

The research and development in cancer therapy plays an important role in worldwide scientific research. The frequency of cancer disease is progressively increasing all over the world and causes major health and medical complications. The currently available methods for cancer treatment are surgical procedures, nonselective chemotherapy, radiotherapy and hormonal therapy. Many normal tissues and rapidly growing cells such as the epithelial cells, gametocytes and lymphatic cells are severely affected by the non-selective chemotherapy. Radiotherapy also exhibits toxic effects on many healthy tissues. The treatment approach for cancer should be directed towards eradication of only cancer cells selectively. There has been always a constant struggle in search of novel anti-cancer drugs with specific and selective mechanism of action. This can be successfully obtained by the discovery of new scaffolds with potent anti-cancer activity.

Some types of cancers like breast, lungs, liver, and colorectal cancers are the most common cause of deaths due to cancer each year. The lung cancer in men and breast cancer in women is the most commonly recorded cancer disease globally. The use of tobacco and cigarettes causes around 70% lung cancer death globally. Many chemotherapeutic agents are always important even now clinically for cancer treatment, despite of radiation therapy and surgical procedures. But the level of toxicity produced by the chemotherapy drugs and the cellular drug resistance causes main considerable difficulty in drug based chemotherapy.

Tuberculosis (TB) caused by Mycobacterium tuberculosis infects more than 30 % of the world wide population. Nearly two million people die with a global case fatality rate of 23 % and reaching more than 50 % in some African countries. Tuberculosis (TB) claims 1.8 million lives each year, and it is estimated that one-third of the global population is latently infected by the bacilli Mycobacterium tuberculosis (MTB). The spread of multidrug-resistant tuberculosis (MDR-TB) and the emergence of extensively drug-resistant tuberculosis (XDR-TB) pose a challenge for the treatment and control of this devastating disease, one of the leading causes of death in the world. Nearly 1.6 million people died of this disease during 2006 and 98% are from developing countries. Also with HIV infected people with less and impaired immune system, TB is the most leading disease causing many deaths among the AIDS patients. This becomes further more dangerous due to incurable extensive drug resistant TB and multi drug resistant TB which causes serious mortality. The MDR and XDR strains which are resistant are unresponsive to the presently available drugs representing a serious medical problem. Despite of many drugs available for the treatment of TB, A compound with novel and potent mechanism of action is still not available. No new TB drugs are developed for nearly 35 years since the introduction of rifampicin. It is thus important to search for new and more potent compound with novel mode of action to reduce the emergence of drug resistance against *mycobacterium tuberculosis.*

In the last few decades owing to their pharmacological and synthetic applications, the five membered heterocyclic rings with two or three hetero atoms have received more considerable attention. Derivatives of 1,3,4 – thiadiazoles have been found to possess a wide spectrum of biological activity.

The pharmacological profile of thiadiazoles and their derivatives are interesting and extensive. The biological activities of 1,3,4-thiadiazole derivatives is probably by virtue of toxophoric -N=C-S- grouping. The reported

biological activities of 1,3,4-thiadiazoles include antiinflammatory, antiviral, leishmenicidal, adenosine receptor antagonist, diuretic activity, antihypertensive, anthelmintic, antifungal, antimicrobial and analgesic activity. As a result, many new substituted 1,3,4-thiadiazole derivatives were developed. The synthesis and studies on the anti-microbial properties of several compounds containing substituted 1,3,4-thiadiazoles have been described previously , Prompted and interested by these findings, the attention has been focused on the synthesis of a series of novel 1,3,4-thiadiazole derivatives, which are expected to show antimicrobial activity.

Materials and Method

All chemicals used in this study were purchase from Aldrich Chemicals and were used without further purification. All melting points were taken in open capillary tube and are uncorrected. The purity of the compounds was checked by TLC on pre-coated SiO2 gel (HF254, 200 mesh) aluminum plates (E Merk) using Butanol: Acetic acid: water (4:1:5) visualized in iodine chamber. FTIR spectra were recorded with Perkin Elmer spectrophotometer. The 1HNMR spectra were determined with Brucker 400 MHz FTNMR spectrometer.

Step 1: General Procedure for Synthesis of 2-Amino 5-Aryl -1, 3, 4- Thiadiazole [9-11]

A mixture of thiosemicarbazide (0.1mole), aryl carboxylic acid (0.1 mole), & Conc Sulphuric acid (10 drops) in 30 mL ethanol was refluxed for 1 hr & poured onto crushed ice. The solid separated out was filtered, washed with water & recrystallized from ethanol.

Step 2: General Procedure for Synthesis of Substituted Diazoaminobenzene 1 3 4 Thiadiazole Derivatives

2-Amino- 5 – Aryl 1 3 4 Thiadiazole derivatives (0.01 mol) and Conc. HCl (10ml) was taken in 250ml Erlenmeyer Flask containing 40ml of water and stirred vigoursly to make a homogeneous solution by adding 25gm of crushed ice. Then added slowly 2.6gm of sodium nitrite solution in 6 ml of water with constant stirring for 10-15 min, allowing the flask to stand for 10min. Sodium acetate (10.5gm) in 20ml of water was added during a period of 5 min. A yellow precipitate of diazoamino thiadiazole derivatives was filtered and washed with cold water. Recrystallized from ethanol.

Step 3: General Procedure for Synthesis of Substituted P-Aminoazobenzene Thiadiazoles

Diazoaminobenzene 1,3,4-thiadiazole derivatives from previous step (0.01mole) was taken in 100 ml Erlenmeyer Flask containing different substituted aniline (0.01 mol). To the solution 1.3gm of finely powdered

aniline hydrochloride was added and heated the mixture at 40-45^{0}C for 1hr on a water bath with occasional shaking. Allowed to stand for 15min at room temperature. Then 1ml glacial acetic acid was added with shaking thoroughly to remove excess aniline as aniline acetate. Allowed the mixture to stand for 15 min. Filtered the solid on Buchner funnel and wash with water. Recrystallized from carbon tetrachloride.

Step 4: General Procedure for 2-Isopropyl-5-Methyl-4-(2-Nitroazobenzyl) Diazenyl Phenol

p-Aminoazobenzene thiadiazoles derivatives (0.01 mol) was mixed with conc. HCl (2.5 cm3). To the resultant suspension crushed ice (25 gm) and $NaNO_2$ (2.5 cm3, 4N) was added with stirring. Diazotization was carried over 0.5 hr. at 5^{0}C and then diazonium salt solution was added drop wise at 5 – 10^{0}C to the alkaline solution of various phenollic compounds. The coupling reaction was stirred for 0.5 hr. and the pH of the resultant mixture was adjusted to pH 7. The formed dye was filtered, washed with water and dried. Crude products were recrystalised with ethanol (Table-I).

Compound A- Series

1. A1-Yield(2.93g,90%),m.p168-170°C.IR(KBr,ύcm-1):3251, 3143NH, 3062 (CH,aromatic), 2968(CH,aliphatic),1707 (C=O), 1616(C=N), 1531(C=C).1H NMR (300 MHz, DMSO-*d*6)δ ppm 5.06 (s,2H, NCH2), 7.16-7.68 (m, 9H,Ar-H,), 8.21 (s, 1H,C2 Thiadiazole), 9.71 (s, 1H, NH, D2Oexchangeable), 9.76 (s, 1H, NH, D2Oexchangeable), 10.50 (s, 1H, NH, D2O-exchangeable); MS :*m*/*z*(%) 325 (M+).
2. A3 -Yield (3.84 g, 95 %), m.p. 177-180°C. IR (KBr, ύ cm-1): 3233, 3170, NH, 3060 (CH aromatic), 2973(CH aliphatic), 1702 (C=O), 1630(C=N), 1568 (C=C),1490 (C-N); 1H NMR (300 MHz, DMSO-*d*6): δppm 5.81 (s,2H, NCH2), 7.24-7.70 (m, 8H,Ar-H,), 8.20 (s, 1H,C2 Thiadiazole), 9.77 (s, 1H, NH, D2Oexchangeable), 10.65 (s, 1H, NH, D2O-exchangeable), 11.17 (s, 1H, NH, D2O-exchangeable) ; MS: *m*/*z*(%) 405 (3.2)M++1, 404 (3.85)M+,165(21.22),80(100).
3. A6 -Yield (3.84 g, 95 %), m.p. 177-180°C. IR (KBr, ύ cm-1): 3233, 3170, NH, 3060 (CH aromatic), 2973(CH aliphatic), 1702 (C=O), 1630(C=N), 1568 (C=C),1490 (C-N); 1H NMR (300 MHz, DMSO-*d*6): δppm 5.81 (s,2H, NCH2), 7.24-7.70 (m, 8H,Ar-H,), 8.20 (s, 1H,C2 Thiadiazole), 9.77 (

s, 1H, NH, D2Oexchangeable), 10.65 (s, 1H, NH, D2O-exchangeable), 11.17 (s, 1H, NH, D2O-exchangeable) ; MS: *m*/*z*(%) 405 (3.2)M++1, 404 (3.85)M+,165(21.22),80(100).

4. A7 - Yield (3.41 g, 96 %), m.p. 175-177 °C. IR (KBr, ύ cm-1): 3181, 3101, NH, 3050 (CH aromatic), 2956(CH aliphatic), 1703(C=O), 1633(C=N), 1576(C=C),1468 (C-N) ; 1H NMR (300 MHz, DMSO-*d*6): δ ppm 3.68(s,3H, OCH3), 5.81 (s,2H, NCH2), 7.21-7.70 (m, 8H,Ar-H,), 8.37 (s, 1H,C2 Thiadiazole), 9.77 (s, 1H, NH, D2Oexchangeable), 10.65 (s, 1H, NH, D2O-exchangeable),11.17 (s, 1H, NH, D2O-exchangeable); MS : *m*/*z*(%) 356(0.13) M++1, 355(0.25)M+.
5. A9 -Yield (2.8 g, 68 %), m.p. > 300 °C. IR (KBr, ύ cm-1): 3263 NH,3049(CH aromatic),2850(CH aliphatic) , 1600(C=N), 1506(C=C) ,1448(C-N) . 1H NMR (300 MHz, DMSO-*d*6) δ ppm : 6.14 (s,2H, NCH2), 7.48-8.04 (m, 9H,Ar-H,), 9.75 (s, 1H,C2 Thiadiazole), 10.56 (s, 1H, NH, D2O-exchangeable); MS : *m*/*z*(%) 307 (2.3)M+ , 118 (100),77(24),63(59.8)
6. A10 -Yield (2.8 g, 73 %), m.p. 118-120 °C. IR (KBr, ύ cm-1): 3239, NH,3034 (CH aromatic) ,2851(CH aliphatic) , 1611(C=N), 1546(C=C) ,1497(C-N) . 1H NMR (300 MHz, DMSO-*d*6) δppm: 6.03 (s,2H, NCH2), 7.44-7.87 (m, 8H,Ar-H,), 9.23 (s, 1H,C2 Thiadiazole), 10.81 (s, 1H, NH, D2O-exchangeable); MS : *m*/*z*(%) 387 (46.10)M++1, 386(38.96) M+,378(50.60).
7. A12 -Yield (2.4 g, 71 %), m.p. 256-258 °C. IR (KBr, ύ cm-1): 3241, NH,3042 (CH aromatic),2851(CH aliphatic) , 1610(C=N), 1549(C=C),1493 (C-N). 1H NMR (300 MHz, DMSO-*d*6) δppm: 3.68(s,3H, OCH3), 6.07 (s,2H, NCH2), 6.91-7.88 (m, 8H,Ar-H,), 9.59 (s, 1H,C2 Thiadiazole), 10.31 (s, 1H, NH, D2O-exchangeable); MS : *m*/*z(%)* 338 (0.27)M++1, 337(0.76) M+,336 (0.59).
8. A13 - Yield (2.24 g, 77 %), m.p. 245-247 °C. IR (KBr, ύ cm-1): 3251 NH,3077(CH aromatic) ,2932(CH aliphatic) , 1626(C=N), 1570(C=C),1495 (C-N) ;1H NMR (300 MHz, DMSO-*d*6) δ ppm:5.81 (s,2H, NCH2), 6.94-7.71 (m, 9H,Ar-H,), 8.41 (s, 1H,C2 Thiadiazole), 10.46 (s, 1H, NH, D2O-exchangeable); MS: *m*/*z*(%) 292 (38.5)M++ 1 , 291 (50.8)M+
9. A14 - Yield (2.81 g, 76 %), m.p. 118-120 °C. IR (KBr, ύ cm-1): 3252, NH, 3050 (CH aromatic), 2975(CH aliphatic), 1632(C=N), 1571(C=C), 1491 (C-N); 1H NMR (300 MHz, DMSO-*d*6) δ ppm:

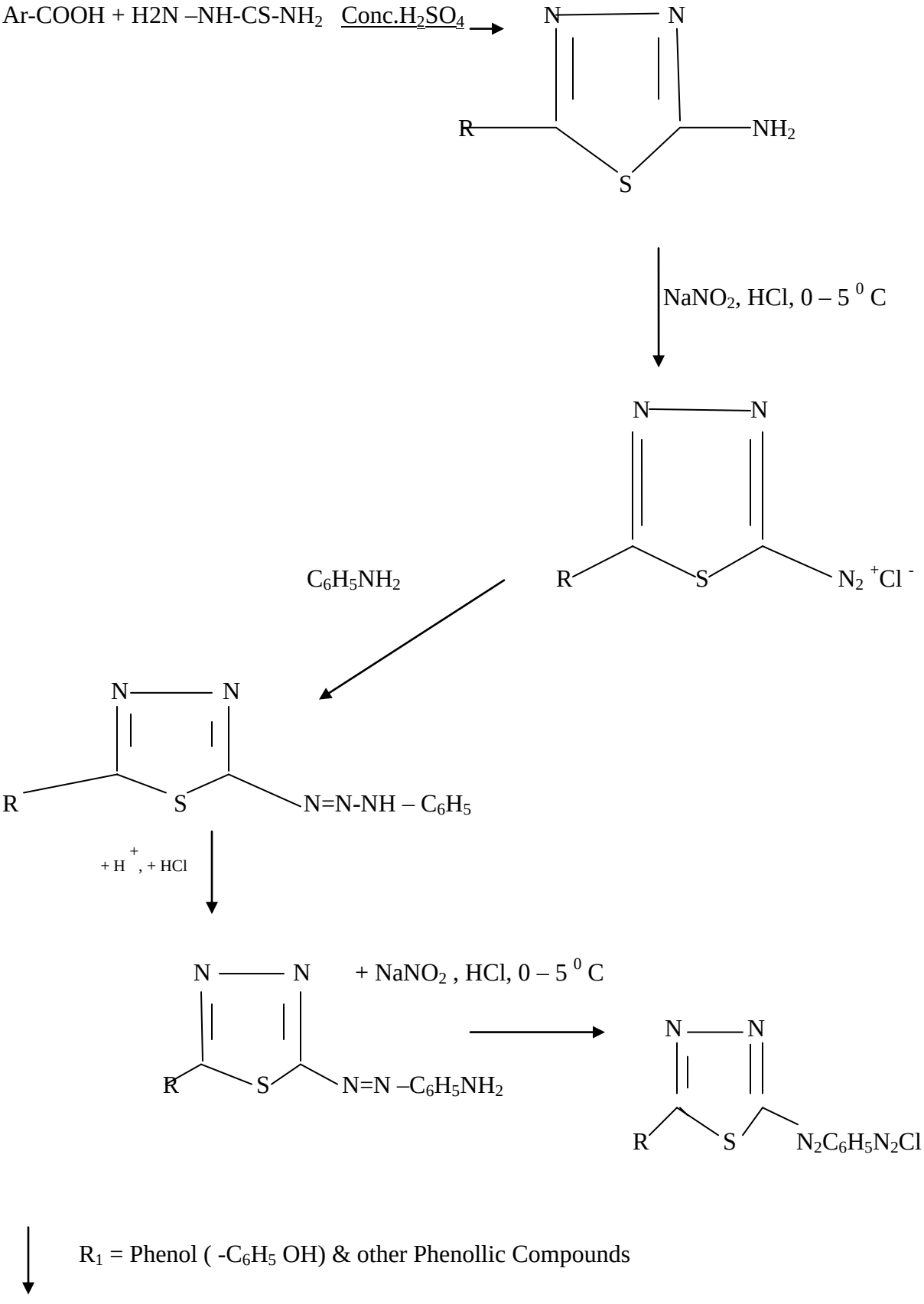
5.81 (s,2H, NCH2), 7.24-7.70 (m, 8H,Ar-H,), 8.36 (s, 1H,C2 Thiadiazole), 10.64 (s, 1H, NH, D2O-exchangeable); MS :*m*/*z(%)* 370 (20.36)M+.

10. A15 - Yield (2.41 g, 75 %), m.p. 214-216 °C. IR ύ cm-1): (KBr, 3264, NH, 3051(CH aromatic), 2947 (CH aliphatic), 1636(C=N), 1579(C=C), 1463 (C-N); 1H NMR (300 MHz, DMSO-*d*6)δ ppm :3.70(s,3H, OCH3), 5.78 (s,2H, NCH2), 6.87-7.70 (m, 8H,Ar-H,), 8.36 (s, 1H,C2 Thiadiazole), 10.22 (s, 1H, NH, D2O-exchangeable); MS :*m*/*z*(%) 321 (100)M+, 320 (14.57).
11. A17 - Yield (2.7 g, 89%), m.p. 243-245 °C. IR (KBr, ύ cm-1): 3145 NH, 3051(CH aromatic) ,2935(CH aliphatic), 2746 (SH), 1614(C=N), 1579 (C=C), 1462(C-N). 1H NMR (300 MHz, DMSO-*d*6) δ ppm 5.48 (s, 2H, NCH2), 7.19-7.62 (m, 9H, Ar-H), 7.68 (s, 1H, C2 Thiadiazole), 13.98 (s, 1H, NH ,D2O-exchangeable).MS : *m*/*z(%)* 307 (100) M+,306(67.5),118(76).
12. A20 - Yield (2.97 g, 77 %), m. p. 172-174 °C. (KBr, ύ cm-1): 3439 NH, 3060(CH aromatic),2926(CH aliphatic), , 1633(C=N), 1484 (C=C) , 1426 (C-N). 1H NMR (300 MHz, DMSO-*d*6)δppm :5.48 (s,2H, NCH2), 7.18-7.71 (m, 8H,Ar-H,), 7.78 (s, 1H,C2 imidazole), 13.96 (s, 1H, NH, D2O-exchangeable); MS : *m*/*z(%)* 387(97.25)M++1, 386(38.34)M+,385(93.02%).
13. A23 - Yield (2.80 g, 83 %), m.p. 261-263 °C. (KBr, ύ cm-1): 3210 NH, 3057(CH aromatic) ,2995(CH aliphatic), 1607(C=N), 1552(C=C) , 1455 (C-N).1H NMR (300 MHz, DMSO-*d*6) δ ppm: 3.81(s,3H, OCH3), 5.84 (s,2H, NCH2), 6.80-7.71 (m, 8H,Ar-H,), 8.76 (s, 1H,C2 Thiadiazole), 13.98 (s, 1H, NH, D2O-exchangeable). 13C NMR(DMSO-d6) ,δppm 40.22, 55.31 , 110.69 , 113.87 , 119.19, 121.47 , 122.14 , 128.51 , 133.45, 143.07, 146.25 , 158.54 . MS:*m*/*z*(%)338,(7.3)M++1 ,337(7.87)M+, 118(100).
14. A30 - Yield (2.66 g, 83 %), m.p. 154-156 °C. IR (KBr, ύ cm-1): 3080 (CH aromatic) ,2950(CH aliphtic) ,1625(C=N), 1523(C=C) , 1496(C-N). 1H NMR (300 MHz, DMSO-*d*6)δ ppm : 2.54 (s, 3H, SCH3), 5.58 (s, 2H, NCH2), 7.16-7.57 (m, 9H, Ar-H), 7.59 (s, 1H, C2 Thiadiazole)
15. A33 - Yield (2.85 g, 85 %), m.p. 85-87 °C. IR (KBr, ύ cm-1): 3095 (CH aromatic) ,2976 (CH aliphatic) ,1616(C=N), 1521 (C=C) , 1460 (C-N). 1H NMR (300 MHz, DMSO-*d*6) δppm: 1.21-1.24

(t, 3H, CH3), 3.02-3.06 (q, 2H, CH2), 5.59 (s, 2H, NCH2), 7.16-7.57 (m, 9H, Ar-H), 7.61 (s, 1H,C2

Thiadiazole); MS : *m*/*z* (%)336 (18) M++1,217(78.8), 77(100).

Reactions Involved



R_1 = Phenol (-C_6H_5 OH) & other Phenollic Compounds

A SERIES

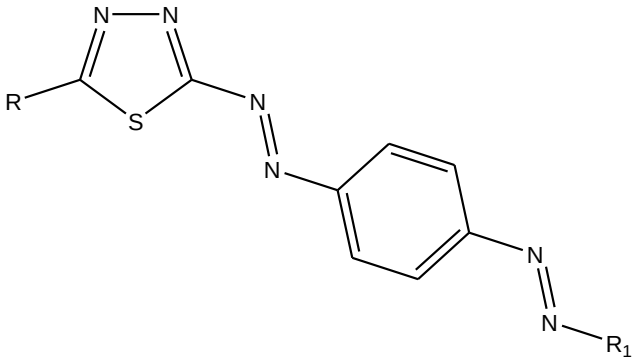


Table-1: 1,3,4-thiadiazole diazo derivatives derivatives of a series.

COMPOUND CODE	R	R1	
A Series with phenyl group (Benzoic acid)	Phenyl (C6H5-)	A1	4-Hydroxy Phenyl
		A3	4-Hydroxy-3-Methyl Phenyl
		A6	4-Hydroxy – 2 Methyl Phenyl
		A7	3,5-Dimethyl-4-Hydroxy Phenyl
		A9	3-Isopropyl-4-Hydroxy-6-Methyl Phenyl
		A10	1-Napthyl Phenyl
		A12	2-Napthyl Phenyl
		A13	3-Isopropyl-4-Hydroxy-6-Methyl Cyclohexyl
		A14	2-Hydroxy-3-Methoxy-5-Vinyl Phenyl
		A15	3-Acetyl Phenyl
A series with p – Hydroxy Phenyl Group (p –Hydroxy Benzoic Acid)	p-Hydroxy Phenyl	A17	4-Hydroxy Phenyl
		A20	4-Hydroxy-3-Methyl Phenyl
		A23	4-Hydroxy – 2 Methyl Phenyl
		A30	3-Isopropyl-4-Hydroxy-6-Methyl Phenyl
		A33	1-Napthyl Phenyl

Anti-Tb Activity Using Alamar Blue Dye [12-13]

Procedure:

The anti-mycobacterial activity of compounds were assessed against M. tuberculosis using microplate Alamar Blue assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink. Standard Strain used: ***Mycobacteria tuberculosis*** (Vaccine strain, H37 RV strain): ATCC No- 27294. ***Standard values*** for the Anti-Tb test which was performed. Pyrazinamide- 3.125µg/ml Ciprofloxacin-3.125µg/ml Streptomycin-6.25µg/ml.

Standard Drug Photograph

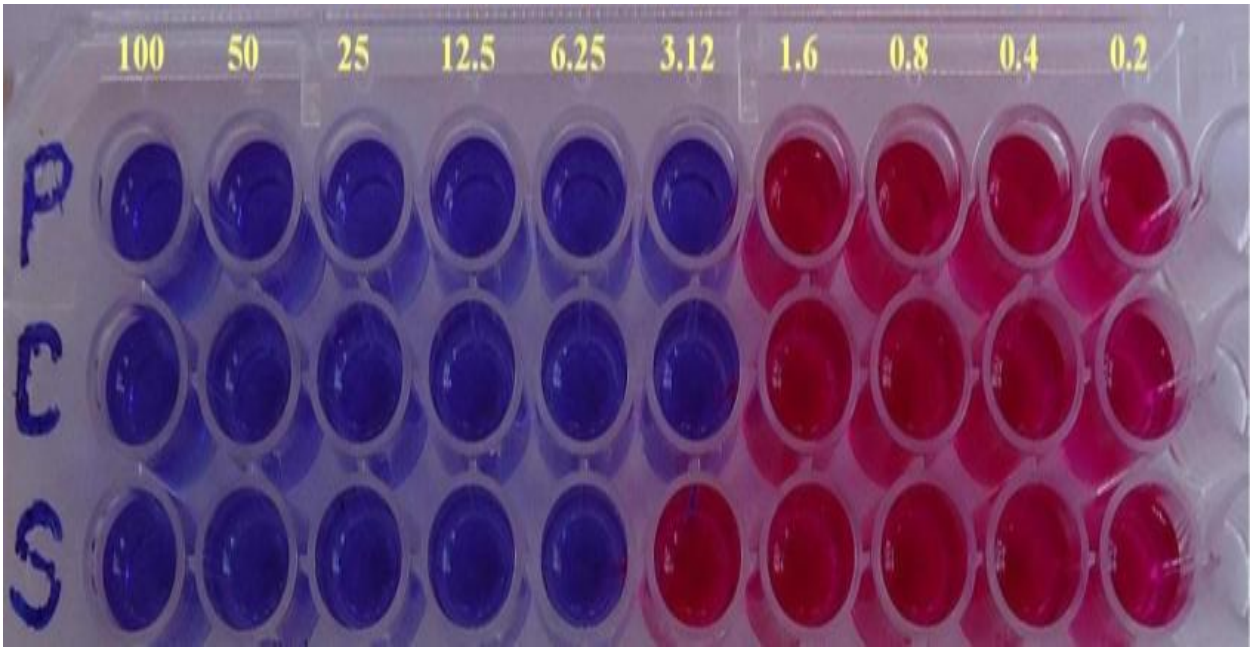
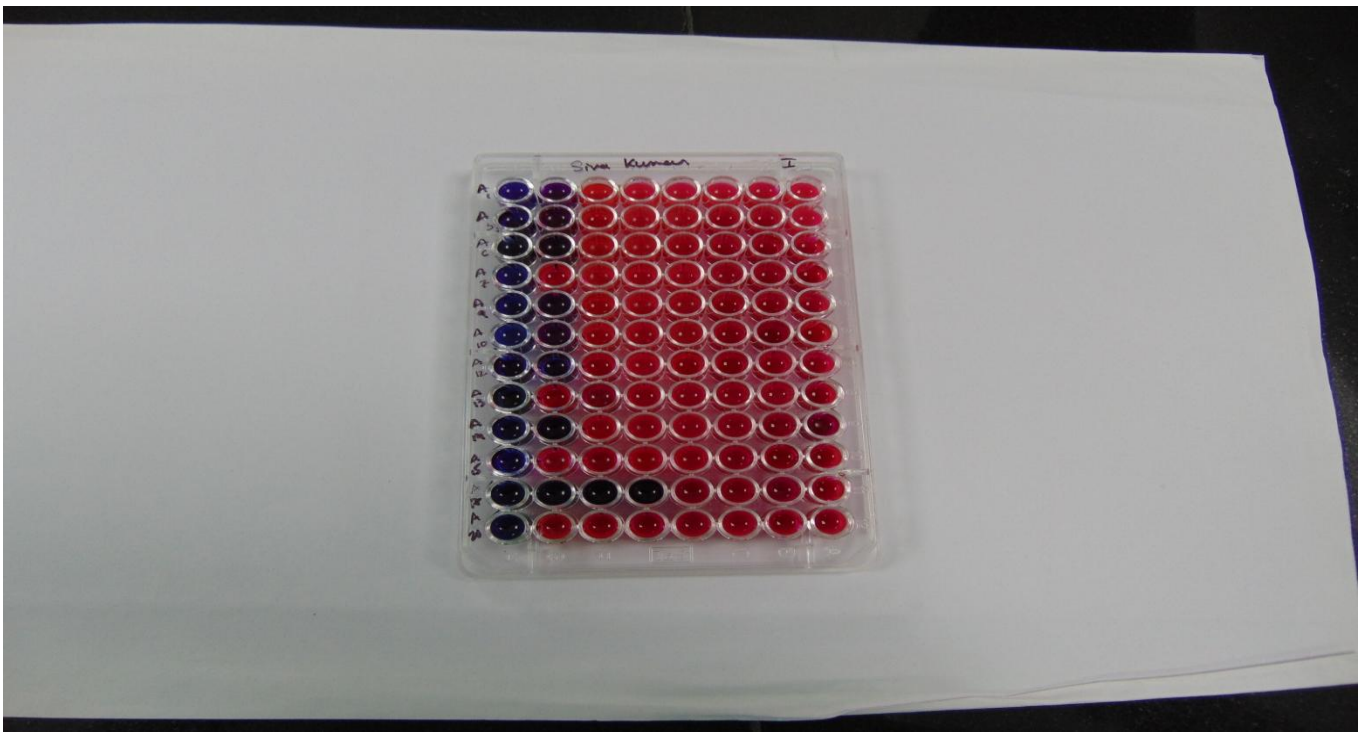


Table-2: Anti-tubercular activities of 'A' series against *M. Tuberculosis* H_{37} RV strain.

Sl. No.	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
01	A-01	S	S	R	R	R	R	R	R
02	A-03	S	S	R	R	R	R	R	R
03	A-06	S	S	R	R	R	R	R	R
04	A-07	S	R	R	R	R	R	R	R
05	A-09	S	S	R	R	R	R	R	R
06	A-10	S	S	R	R	R	R	R	R
07	A-12	S	S	R	R	R	R	R	R
08	A-13	S	R	R	R	R	R	R	R
09	A-14	S	S	R	R	R	R	R	R
10	A-15	S	R	R	R	R	R	R	R
11	A-17	S	S	S	S	R	R	R	R
12	A-20	S	R	R	R	R	R	R	R
13	A-23	S	S	S	R	R	R	R	R
14	A-30	S	S	S	R	R	R	R	R
15	A-33	S	S	S	S	R	R	R	R

NOTE: S - Sensitive R- Resistant



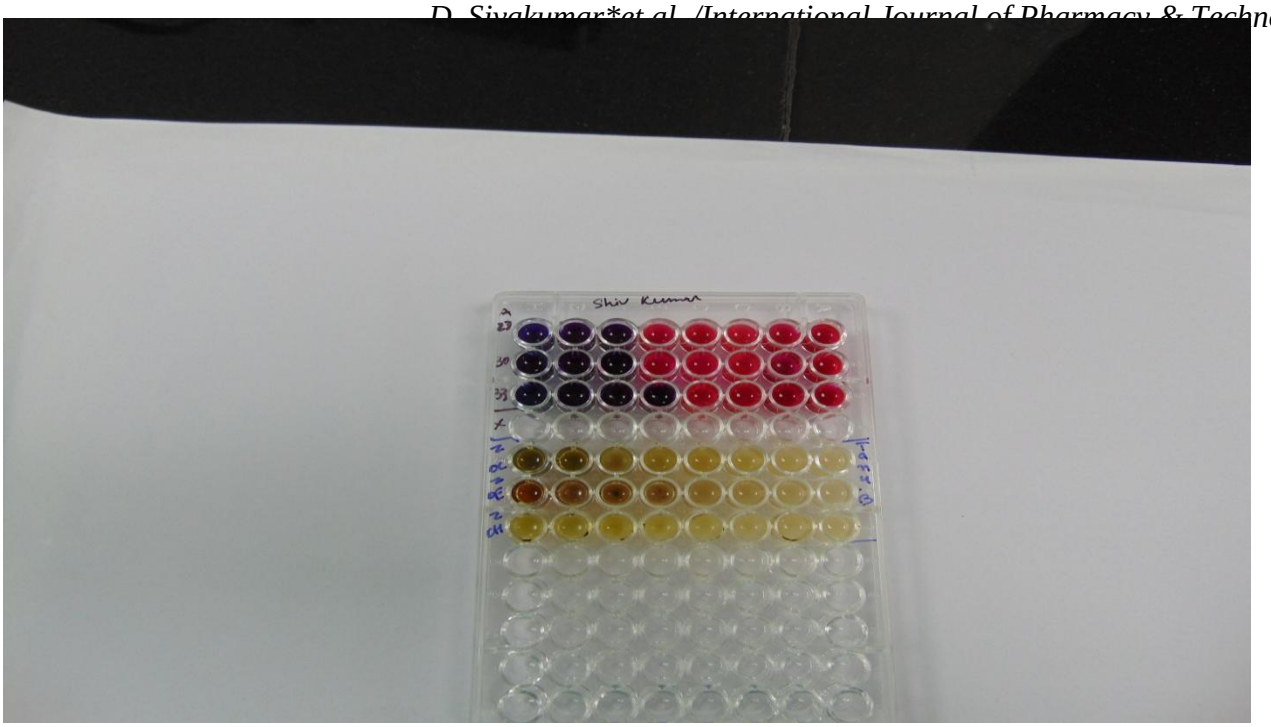


Figure-2: photograph of test drug 'A' series and solvent used.

Results and Discussion

In this present communication, synthesis and antitubercular activity of some new p-amino azobenzene with 1 3 4 thiadiazole moiety is reported from corresponding from different substituted aromatic acids. Initially different 2- Amino -5 –substituted 134 thiadiazole derivatives were prepared from different aromatic acids and thiosemicarbazides. Then, substituted diazoaminobenzene thiadiazoles derivatives were prepared. These, Thiadiazole substituted diazoaminobenzene were treated with Aniline chloride in presence of 1:1 glacial acetic acid condition for 15 min to furnish the corresponding substituted p-Aminobenzene thiadiazoles derivatives, which on diazotization and coupling with Thymol predicts 2-isopropyl-5-methyl-4-(Substituted azothiadiazolyl) diazenyl phenol, the final product. The newly synthesized compounds were established on the basis of IR, ^{1}H NMR and MASS spectroscopic method. The IR spectra of the compounds showed the presence of primary amine group and absence of primary amine group as well presence of hydroxyl group at 3517.36 cm-1 indicating the formation of product. In ^{1}H NMR spectra, a broad peak due to presence of –OH is observed at 5.69 ppm. While in Thymol, aromatic proton near azo group is observed at 6.70 ppm and other present near –OH and Methyl group is appear at 7.20 ppm. Proved the structure of the products. While other aromatic and aliphatic protons were observed at excepted regions. The mass spectra of the thiadiazoles substituted p-

aminoazobenzene with thymol moiety were showed molecular ion peak corresponding to their molecular formula. The compound shows [M+] and [M+ +2] peak at 437.09 and 439.09 showing presence of hydroxyl group similarly peak at 79 and 81 confirms presence of methyl group. The results of the antitubercular activity data are given in Table-2. The investigation of antimicrobial screening data revealed that the tested compounds were showed moderate to good activity. In comparison with standard drugs, the *M.Tuberculosis* H37 RV strains were sensitive to all the compounds at a concentration of 100mcg/ml. A blue colour in the well was interpreted as no bacterial growth (Sensitive) and a pink colour was scored as bacterial growth (resistant). The bacteria are sensitive towards the compounds A33 and A17 at concentrations 100, 50, 25, and 12.5mcg/ml. All the other compounds inhibited the bacterial growth at 100 and 50 mcg/ml concentration.

Conclusion

In summary, an operationally simple, inexpensive, efficient, environment benign protocol in synthesis of p-aminoazobenzene with thiadiazole moiety by the simple diazotization and coupling method was developed. Further these compounds were evaluated for their antitubercular activity. Some of the compounds showed good activity against *M.Tuberculosis* H37 RV strains.

The merits of the current work are:

a) The reaction is conducted under solvent free condition.

b) The reaction is carried out without using any catalyst.

c) The reaction proceeds at low temp. (0-5^{0}C).

d) The uses of hazardous chemicals are avoided.

e) The reaction time is short.

f) Work up is very simple and operable on large scale.

g) Yields are excellent.

Conflict of Interest: We declared that this review does not have any conflict of interest.

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