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# SYNTHESIS, CHARECTERIZATION AND EVALUATION OF *IN-VITRO* ANTI-TUBERCULAR ACTIVITY OF NOVEL SUBSTITUTED TRIAZOLE DERIVATIVES

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## ABSTRACT

Ethyl Palmitate **(i)** was prepared by the reaction of Palmitic acid with absolute ethanol in the presence of concentrated sulphuric acid by refluxing. Ethanolic solution of Ethyl Palmitate **(i)** treated with Hydrazine hydrate and refluxed to yield Palmitohydrazide **(ii)**. 5-pentadecyl-1,3,4-oxadiazole-2(3*H*)-thione **(iii)** was prepared by treating Palmitohydrazide **(ii)** with solution of Potassium hydroxide then Carbon disulfide was added, refluxed, cooled, Hydrochloric acid was added to neutralise, the solid filtered and recrystallized. 4-amino-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol **(iv)** was synthesized by an Ethanolic solution of 5-pentadecyl-1,3,4-oxadiazole-2(3*H*)-thione **(iii)** and Hydrazine hydrate heated for 3hrs and poured in ice, filtered and recrystallized. 4-amino-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol **(iv)** upon treatment with different substituted aldehydes in Ethanol followed by addition of few drops of Sulphuric acid was refluxed for an appropriate time, resulted in the formation of above titled compounds **[NT-(a-d)].** All the synthesized compounds were characterized on the bases of its TLC, physical constant, spectral studies. Further these compounds were evaluated for their anti-microbial and anti-tubercular activities.

**KEYWORDS**: Anti-tubercular, Substituted Triazole, Microplate Alamar Blue Assay, Antimicrobial.

## INTRODUCTION

Tuberculosis (TB)[1-2] is an infection caused by the *Mycobacterium tuberculosis*. TB most commonly occurs in the lungs but can sometimes also affect other organs, including the skin, bones, lymph nodes, liver, digestive tract and central nervous system (brain and spinal cord). Tissue response in tuberculosis is classical example of chronic granulomatous inflammation in humans. Emergence of various forms of resistant strains of *Mycobacterium tuberculosis* led to the exploration of drugs with novel mechanism of action.

Triazole is a five-member heterocyclic ring containing two carbon and three nitrogen atoms with molecular formula $C_2H_3N_3$. And it is found in two isomeric forms, 1,2,3-triazole and 1,2,4-triazole, which are also known as Pyrrodiazole.[3]

1*H*-1,2,3-triazole 2*H*-1,2,3-triazole 1*H*-1,2,4-triazole 4*H*-1,2,4-triazole

1,2,3-triazole 1,2,4-triazole

### Different isomers of Triazole

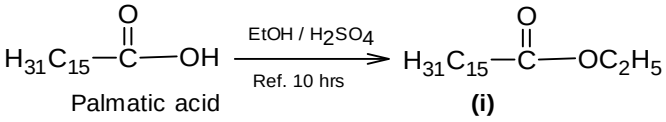
Substituted Triazole have received considerable attention during the last two decades as they are endowed with a variety of biological activities and have a wide range of therapeutic properties. Triazole moiety is one of the most significant five-member heterocyclic compound which is a quality of natural and synthetic compounds. There are two probable isomers of Triazole depending on the location of nitrogen atom in the moiety.[4] Triazoles including 1,2,3-triazole and 1,2,4-triazole are one of the most important classes of nitrogen containing heterocycles that exhibited various biological activities.[5] Triazole is a building block of great value in drug candidates and a large number of ring systems containing this heterocyclic core have been incorporated into a wide variety of therapeutically interesting drug compounds.[6]

## MATERIAL AND METHOD

Chemicals and reagents were procured commercially from Sigma, NR Chem, S.D.Fine Chem.Ltd and Merck, of AR grade and LR grade, used after purification. Melting point were

checked in open capillaries and are uncorrected. All the compounds were crystallized using suitable solvents. I.R spectra was recorded on KBr beam splitter in DTGS KBr detector on Thermo Nicolet Nexus 670 Spectrophotometer with resolution of 4000-500 cm-1. The $^{1}H$ NMR Spectra were reported on AVANCE 300 MHz NMR Spectrophotometer using DMSO as solvent & frequencies were recorded in wave numbers. Mass spectra was done by LC-MS technique, and elemental analysis were done with a flash EA 1112 series CHN report thermo finnigan Silica gel Merck (60-120 mesh).

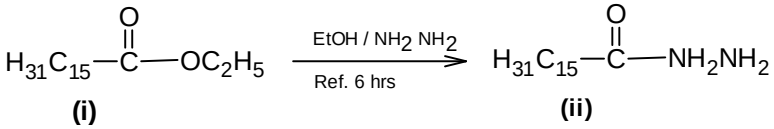
**Synthesis of Ethyl Palmitate (i)**




Palmatic acid (i)

A mixture of Palmitic acid (2.6 g, 0.01 mol), absolute ethanol (50 ml) and few drops of conc. sulphuric acid (0.5 ml) was refluxed for 10 hrs in a round bottom flask and then cooled to $5^{0}C$. The liquid product was separated from reaction mixture by using ether on the basis of density and then purified.

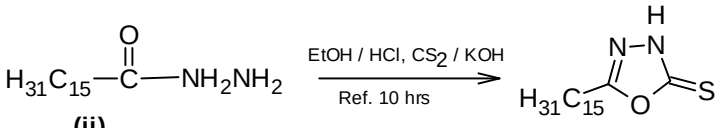
**Synthesis of Palmitohydrazide (ii)**




(i) (ii)

To a solution of Ethyl palmitate (Int-i, 2.8 g, 0.01 mol) in absolute ethanol (30 ml), Hydrazine hydrate (0.64 g,0.02 mol) was added and refluxed for 6 h and then left to cool. The solid product was collected by filtration and recrystallized from Ethanol.

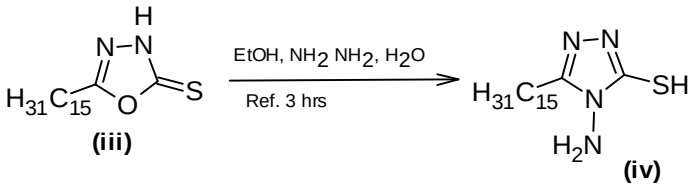
**Synthesis of 5-pentadecyl-1,3,4-oxadiazole-2(3*H*)-thione (iii)**




(ii) (iii)

Palmitohydrazide (Int-ii, 3.12 g, 0.01 mol) dissolved in the solution of Potassium hydroxide (1.12 g, 0.02 mol) in Ethanol (30 ml) and then (0.76 g, 0.01 mol) Carbon disulfide was added slowly in the reaction mixture. Then reaction mixture was refluxed for 10–12 hrs, then cooled at room temperature followed by addition of Hydrochloric acid for neutralization of product. The precipitated solid was filtered, washed and dried then recrystallized from Ethanol.

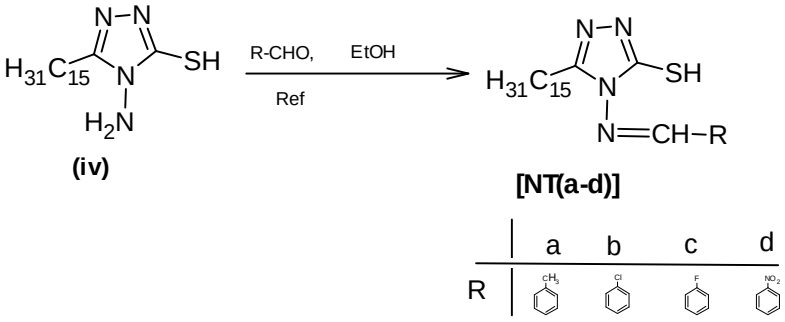
**Synthesis of 4-amino-5-pentadecyl-4H-1,2,4-triazole-3-thiol (iv).**




An Ethanolic (30 ml) solution of 5-pentadecyl-1,3,4-oxadiazole-2(3H)-thione (Int-iii, 3.26 g, 0.01 mol) and Hydrazine hydrate (0.38 g, 0.01 mol) was heated under reflux for 3hrs and then solution was poured in ice. The resulting product was filtered, washed and recrystallized from Ethanol.

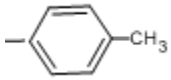
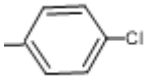
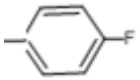
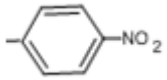
**Synthesis of Substituted 1,2,4-triazole derivatives [NT-(a-d)]**

**General procedure**




The reaction mixture of 4-amino-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol (Int-iv, 3.26 g,0.01 mol) and different substituted Aldehydes (0.01 mol) in Ethanol followed by addition of few drops of Sulphuric acid was refluxed for an appropriate time. The reaction was monitored by thin layer chromatography. After completion of reaction, the product was poured in ice and filtered, then wash and finally solid products were collected and recrystallized from Ethanol.

**Table-1. Physical Characterization Data of Synthesized Compounds (i-iv) & [NT(a-d)]**

| Compound Code | R | Molecular Formula | Molecular Weight | m. p ($^0$C) | Yield (%) | Rf value | S | Elemental Analysis Found(calculated)% | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H | N |
| i | - | $C_{18}H_{36}O_2$ | 284 | - | 62.0 | 0.37 | - | 76.00(76.02) | 12.76(12.73) | - |
| ii | - | $C_{16}H_{35}N_2O$ | 271 | 103-105 | 68.0 | 0.45 | E | 70.79(70.80) | 13.00(13.03) | 10.32(1034) |
| iii | - | $C_{17}H_{32}N_2OS$ | 312 | 156 | 58.0 | 0.40 | E | 65.34(65.32) | 10.32(10.35) | 8.96(8.92) |
| iv | - | $C_{17}H_{34}N_4S$ | 326 | 177-179 | 66.0 | 0.59 | E | 62.53(62.55) | 10.49(10.44) | 17.16(17.12) |
| NT-a |  | $C_{25}H_{40}N_4S$ | 428 | 192-193 | 74.0 | 0.52 | E | 70.05(70.03) | 9.41(9.43) | 13.07(13.09) |
| NT-b |  | $C_{24}H_{37}ClN_4S$ | 449 | 205-208 | 78.0 | 0.65 | E | 64.19(64.21) | 8.30(8.29) | 12.48(12.50) |
| NT-c |  | $C_{24}H_{37}FN_4S$ | 432 | 181-184 | 65.9 | 0.73 | E | 66.63(66.61) | 8.62(8.65) | 12.95(12.92) |
| NT-d |  | $C_{24}H_{37}N_5O_2S$ | 459 | 195-198 | 90.0 | 0.68 | E | 62.71(62.73) | 8.11(8.09) | 15.24(15.21) |

S= Solvent for crystallization, E=Ethanol

**Spectral Characterization of Synthesized Compounds. [NT-(a-d)]**

**4-[(4-methylbenzylidene)amino]-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol (NT-a)**

**IR (KBr) cm$^{-1}$**: 3293(NH, str), 3114(Ar, C-H), 3051(N=C-H), 1668(C=N), 1586(Ar, C=C), 2784(S-H str),2360(C-$CH_3$ Substituted Ar.) **MS (m/z):** Exhibited a molecular ion peak at m/z 428, corresponds to molecular weight compound.

**4-[(4-chlorobenzylidene)amino]-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol (NT-b)**

**IR (KBr) cm$^{-1}$**: 3256(NH,str), 3086(Ar,C-H), 2944(Ali,CH), 3144(N=CH), 1649(C=N), 1445(Ar, C=C), 2627(S-H str), 750(C-Cl). **MS(m/z):** Showed its molecular ion peak at m/z 449, agree with the molecular weight of compound 449.

**4-[(4-fluorobenzylidene)amino]-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol (NT-c)**

**IR (KBr) cm$^{-1}$**: 3274(NH,str), 3122(Ar,C-H), 3043(Ali,CH), 3013(N=CH), 1649(C=N), 1536(Ar, C=C), 2836(S-H str), 1407(C-F). **MS(m/z):** Showed its molecular ion peak at m/z 432, correlate to its molecular weight of compound 432.

**4-[(4-nitrobenzylidene)amino]-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol (NT-d)**

**IR (KBr) cm$^{-1}$**: N-H stretching vibration at the region 3276 cm$^{-1}$ and peak, stable in the spectrum and are distinct band occurs and C-H aromatic stretching vibration shows moderately weak peak and their frequency observed at 3120 cm$^{-1}$ and C-H aliphatic stretching occurs at 2905 cm$^{-1}$ and C=N stretching occurs at 1695 cm$^{-1}$ and C=C aromatic stretching vibration occurs at 1450 cm$^{-1}$ showed moderately weak peak, the $NO_2$ stretching vibration showed strong peak at 1545 cm$^{-1}$ and S-H stretching showed moderately weak peak at 2721 cm$^{-1}$.**$^1$H NMR (DMSO-d6):** 13.51 [s, H -SH(mercapto group or Aromatic C-SH)], 9.26 (s, H, N=CH), 8.09-8.33( m, 4H Ar-H), 2.87( t, 2H -$CH_2$), 1.26-1.33[(m, 24H (-$CH_2$)$_{12}$], 0.88 (t, 3H, -$CH_3$). **MS(m/z):** showed molecular ion peak at 459.4 as (M+), which is in agreement with the molecular weight of the compound 459.

**Determination of Minimum Inhibitory Concentration (MIC) by Broth dilution method**

MIC was determined by Broth dilution method for each of the test organism. To 0.5 ml of varying concentrations of the compounds (0-200 µg/ml for bacterial strains and 0-200 µg/ml for fungal strains), 2ml of nutrient broth was added and then a loopful of test organism was introduced into the tubes. The procedures were repeated on the test organisms using standard Ciprofloxacin and Griseofulvin. A tube containing nutrient broth only seeded with the test organisms served as control. Tubes containing bacterial cultures were then incubated at 37 $^0$C

for 24 hours for bacteria and 30 $^{0}$C for 72 hours for fungal spores. After incubation the tubes were examined for microbial growth by observing the turbidity through spectroscopic method.

**Table-2: MIC of synthesized compounds for bacterial strains.[NT(a-d)]**

| Compound code | *S. aureus* | *B. subtilis* | *E. coli* | *P. aeruginosa* |
|---|---|---|---|---|
| NT-a | 15 | 20 | 25 | 20 |
| NT-b | 20 | 25 | 30 | 22 |
| NT-c | 10 | 30 | 20 | 15 |
| NT-d | 15 | 12 | 10 | 20 |
| Ciprofloxacin | 40 | 60 | 50 | 30 |

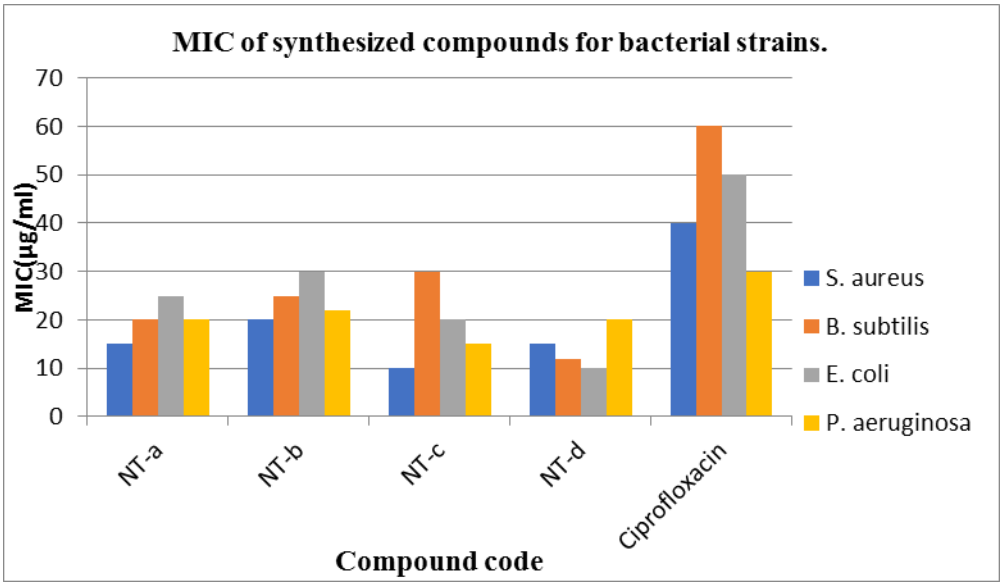



**Fig-1: Graphical representation of Minimum inhibitory concentration (µg/ml).**

**Table -3: MIC of Synthesized compounds for fungal strains.**

| Compound code | *A. niger* | *C.albicans* |
|---|---|---|
| NT-a | 30 | 25 |
| NT-b | 20 | 20 |
| NT-c | 20 | 25 |
| NT-d | 20 | 15 |
| Griseofulvin | 40 | 30 |

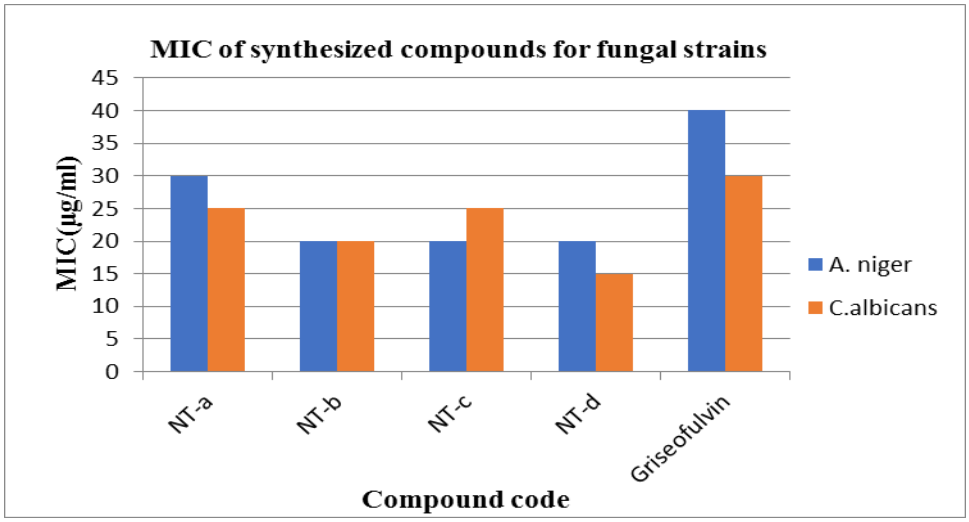



**Fig-2: Graphical representation of Minimum inhibitory concentration (µg/ml).**

## BIOLOGICAL EVALUATION

### Antibacterial and Antifungal Evaluation

### Preparation of test solution

The stock solution was prepared by dissolving 10 mg of each test compound in 10 ml of DMF(Dimethyl formamide) in serial and suitably labelled sterile test tubes, to get concentration of 100 µg/ 0.1ml.

### Preparation of standard antibiotic solution

Ciprofloxacin and Gresiofulvin was used as standard antibacterial and antifungal agent respectively for comparison and solution was prepared by using DMF. 10 mg of Ciprofloxacin and Gresiofulvin was dissolved in 10 ml of DMF(Dimethyl formamide) to get final concentration of 100 µg/0.1ml.

### Preparation of disc

Disc of 6 mm in diameter were punched from no.1 Whatman filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at $130^0$C for one hour. The standard and test solutions were added to each disc and are air dried.

### Test organisms

Bacterial strain, two from gram positive ***Staphylococcus aureus*** , ***Bacillus subtilis*** and two from gram negative ***Escherichia coli, Pseudomonas aeruginosa*** and two different fungal strains namely, ***Aspergillus niger,*** and ***Candida albicans*** were collected from Department of

Microbiology, M. R. Medical College, Gulbarga, India. The antibacterial and antifungal activity of the compounds was assessed by the Cup diffusion technique.

**Evaluation of antimicrobial activity**

The sterilised media was cooled to $45^0$C with gentle shaking to bring about uniform cooling and then inoculated with 24 hrs old culture under aseptic conditions. This was poured into sterile Petridis and allowed the medium to set. After solidification all the Petridis were transferred to laminar air flow. Then previously prepared discs were kept on the solidified media using sterilised forceps. These Petridis were kept aside for 60 min for diffusion at room temperature and then incubated for 24 hrs at $37^0$C in an incubator. The extent of diameter of zone of inhibition recorded as the zone of inhibition in millimetre. Zone of inhibition for DMF was done separately. The antibacterial activities of test compounds are discussed with comparison to Ciprofloxacin and the results were shown in Table-4.

**Table 4: Antibacterial activity of synthesized compounds.[NT(a-d)]**

| Compound code | Mean zone of inhibition in mm* | | | |
|---|---|---|---|---|
| | Gram-positive organisms | | Gram-negative organisms | |
| | ***S.aures*** | ***B. subtilis*** | ***E. coli*** | ***P.aeruginosa*** |
| NT-a | 13.42±0.06 | 12.02±0.55 | 11.55±0.66 | 14.00 ±0.22 |
| NT-b | 13.31±0.53 | 11.44±0.08 | 11.43±0.62 | 12.02±0.22 |
| NT-c | 17.00±0.17 | 12.20±0.34 | 12.10±0.01 | 13.21 ±0.36 |
| NT-d | 16.25± 0.20 | 12.44±0.08 | 12.55±0.01 | 16.65±0.00 |
| Ciprofloxacin | 22.05± 0.99 | 23.02±0.17 | 21.22± 0.14 | 23.13 ± 0.07 |
| Control | 6 | 6 | 6 | 6 |

***** Diameter of borer 6 mm.

Average of triplicate ± standard deviation

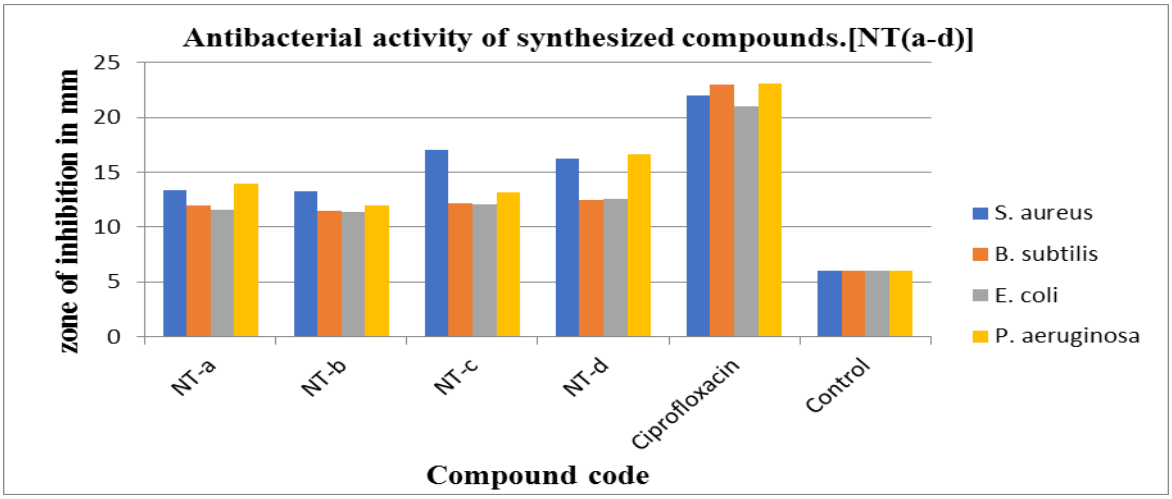



**Fig-3: Graphical representation of Antibacterial activity of compounds.[NT(a-d)]**

**Evaluation of antifungal activity**

A previously liquefied medium was inoculated appropriate to the assay with the requisite quantity of the suspension of the micro-organism between 40-50$^0$C and the inoculated medium was poured into Petridis to give a depth of 3-4 mm, ensure that the layers of the medium were uniform in thickness by placing the dishes on a level surface. The dishes thus prepared were stored in a manner so as to ensure that no significant growth or death of the test organisms occur before the dishes were used and the surface or the agar layer was dry at the time of use. With the help of the sterile cork borer, Four cups of each 6 mm diameter were punched and scooped out to set agar in each petridis (number the cups for the particular compounds and standard). Using sterile pipettes, standard and test solutions (0.1ml) of known concentration were fed into the borer cups. The dishes were left standing for two hrs at room temperature as a period of pre-incubation diffusion to minimise the effects of variation in time among the application of different solutions. These were then incubated for 24 hrs at 37$^0$C. The zone of inhibition developed, if any, was then accurately measured and recorded. Each zone of inhibition recorded was average of three measurements. The antifungal activity data were shown in Table-5.

**Table-5: Antifungal activity of synthesized compounds.[NT(a-d)]**

| Compound code | Mean zone of inhibition in mm* | |
|---|---|---|
| | ***A. niger*** | ***C.albicans*** |
| NT-a | 14.00±0.34 | 14.26±0.03 |
| NT-b | 16.44±0.22 | 17.64±0.12 |
| NT-c | 15.65±0.00 | 14.87±0.88 |
| NT-d | 18.45±0.88 | 12.24±076 |
| Griseofulvin | 25.13 ± 0.49 | 24.22±0.14 |
| Control | 6 | 6 |

***** Diameter of borer 6 mm.

Average of triplicate ± standard deviation.

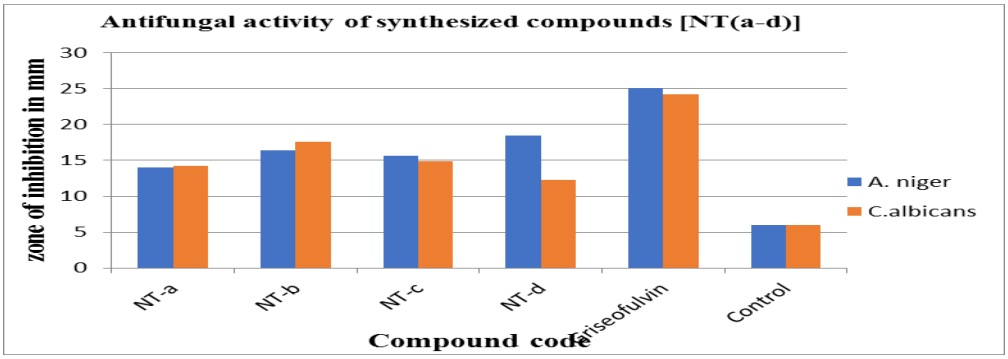



**Fig-4: Graphical representation of Antibacterial activity of compounds.[NT(a-d)]**

**ANTI-TUBERCULAR ACTIYITY.**

**Microplate Alamar Blue Assay (MABA)**

The reported compounds[NT-(a-d)] were evaluated for anti-tubercular activity using Microplate Alamar Blue Dye Assay (MABA) method[8] against *Mycobacterium tuberculi* strain $H_{37}$ Rv. The synthesized compounds were tested at a concentration of 0.2, 0.4, 0.8, 1.6, 3.12, 6.25, 12.5, 25, 50, 100 µg/ml using Isoniazid as reference standard. A blue colour in the well was interpreted as no bacterial growth, and pink colour was scored as growth. The MIC was defined as lowest drug concentration which prevented the colour change from blue to pink.

**Determination of MIC**

After overnight incubation, determine the MIC of organism for the compounds tested by visual inspiration. In the broth jars which is clear does not show the turbidity should be consider as a MIC value. If there is turbidity in both the tubes then the organism is highly resistant and the MIC value would be >100 µg/ml. If there is a clarity in both the jars, then the organism is highly sensitive and the MIC value would be < 25 µg/ml.

**Table-6: Anti-tubercular activity of synthesized compounds [NT-(a-d)]**

| Compds. code. | 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 | 0.4 µg/ml | 0.2 µg/ml |
|---|---|---|---|---|---|---|---|---|---|---|
| NT-a | R | R | R | R | R | R | R | R | R | R |
| NT-b | S | S | S | R | R | R | R | R | R | R |
| NT-c | S | S | S | S | S | R | R | R | R | R |
| NT-d | S | S | S | S | S | S | S | R | R | R |
| Isoniazid | S | S | S | S | S | S | S | S | S | S |

**S = Sensitive, R = Resistant**

**Table- 7: Anti-tubercular Evaluation Data of compounds [NT-(a-d)**

| Compound code | MABA I.C. (µg/ml) |
|---|---|
| NT-a | - |
| NT-b | 25 |
| NT-c | 6.25 |
| NT-d | 1.6 |

I.C-Inhibitory concentration

**RESULTS AND DISCUSSION**

Compounds[**NT(a-d**)] were evaluated for their antibacterial activity, reported values clearly showed that the compound **(NT-b)** and **(NT-c)** exhibited good antibacterial activity against ***E.coli*** & ***B.subtilis***. Other representative compounds of the series **(NT-a)** and **(NT-d)** possess

moderate to weak antibacterial activity against selected bacteria when compared to reference standard Ciprofloxacin. Antifungal activity data of the synthesized compounds[**NT(a-d**)] showed, compound**(NT-d)** good, compound**(NT-a), (NT-c)** moderate and compound**(NT-b)** weak antifungal activity against **A.niger** and ***C.albicans*** when compared to reference standard Gresiofulvin. Anti-tubercular activity of synthesized compounds were evaluated by using Microplate Alamar Blue Assay, compound **NT-c** and **NT-d** were exhibited significant activity against the mycobacterium tuberculiH37Rv. The compound **NT-b** were exhibited moderate activity against the mycobacterium tuberculi H37Rv. And the compound **NT-a** showed the no activity against the mycobacterium tuberculiH37Rv.

## CONCLUSION

The conclusion may be.

- Synthesized compounds were confirmed by physical characterization, spectral techniques like, IR, $^{1}$H-NMR and mass spectroscopy, and the spectral data's of compounds were in agreement with their structure.
- Our study investigated that certain new substituted triazole derivatives were displayed good to moderate anti-microbial and anti-tubercular activity in comparison with the reference standard.
- Thus the present work provides a new outline of the study of anti-microbial and anti-tubercular activity of substituted triazole.

The outcome of this work suggested that heterocyclic compounds containing triazole moiety with substituted aryl group are of interesting molecules. The study has proved that the efficacy of triazole derivatives when incorporated with substituted aromatic moieties produced useful therapeutic agents.Thus an attempt has been undertaken to study active molecules at different concentrations and the quest to explore many more modifications on triazole moiety needs to be continued.

## ACKNOWLEDGEMENT

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