



Received on 08 March, 2015; received in revised form, 18 April, 2015; accepted, 21 June, 2015; published 01 September, 2015

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 2-SUBSTITUTED BENZOTHAZOLE DITHIOMIDOCARBONATE DERIVATIVES

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Keywords:

Dibenzyl (1,3 benzothiazol-2yl) Dithioimidocarbonate, antimicrobial agent, Ciprofloxacin, Dipropyl (1,3 benzothiazol-2yl) Dithioimidocarbonate, antifungal agent

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ABSTRACT: A series of novel 2- substituted benzothiazole dithiomidocarbonate derivatives were synthesized by the reaction of 2-amino benzothiazole with various halides. The test compounds were screened for their antimicrobial activity (antibacterial and antifungal) by disc diffusion method and the results of the microbial activity indicates that the test compounds exhibited varying degree of antimicrobial activity. Among the substituents benzyl moiety exhibited the most potent activity and the compound Dibenzyl (1,3 benzothiazol-2yl) Dithioimidocarbonate(4T₁) emerged as the most active antimicrobial agent and it is equipotent when compared to the reference standard Ciprofloxacin. Among the substituents propyl moiety exhibited the most potent activity and the compound Dipropyl (1,3 benzothiazol-2yl) Dithioimidocarbonate (4T₃) emerged as the most active antifungal agent and it is equipotent when compared to the reference standard Fluconazole.

INTRODUCTION: Heterocyclic compound is a cyclic compound in which the ring atoms are of carbon and some others elements. The atoms of other elements (Nitrogen, Oxygen, Sulphur) are called as heteroatoms. Heterocyclic compounds are widely distributed in nature and plays a diverse and important role in the field of pharmaceutical chemistry. Heterocyclic compounds have a wide range of application in the field of pharmaceutical, agrochemical and veterinary products. They are also used as optical brightening agents, antioxidants, solvents, dye stuffs, and pigments. Heterocyclic compounds are also finding an increase use as intermediates in organic synthesis.

One such prominent heterocyclic system is benzothiazole with several of its derivatives exhibiting diversified biological activity.¹⁻⁸ Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activity they are widely found in bioorganic and medicinal chemistry with application in drug discovery.

Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial, anticancer, antihelminthic, anti-diabetic activities etc. They have also found application in industry as anti-oxidants, vulcanizations accelerators. Various benzothiazoles such as 2-substituted benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imaging agents, and anticancer agents. Benzothiazole is an aromatic heterocyclic compound with the chemical formula

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| <p>QUICK RESPONSE CODE</p>  | <p>DOI: 10.13040/IJPSR.0975-8232.6(9).4058-68</p> |
| <p>Article can be accessed online on: www.ijpsr.com</p> | |
| <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(9).4058-68</p> | |

C_7H_5NS . Benzothiazole consists of a 5-membered 1,3thiazole ring fused to a benzene ring.⁹⁻¹⁶

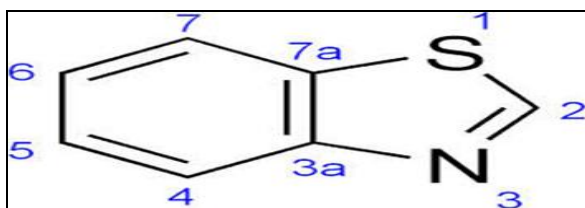


FIG.1: CHEMICAL STRUCTURE OF BENZOTHAZOLE

MATERIALS AND METHODS:

The following chemicals are used in the present work.

TABLE 1: LIST OF CHEMICALS

| S. No | Name | Grade | Company |
|-------|--------------------|-------|-------------------|
| 1. | Aniline | AR | Sd-fine Chemicals |
| 2. | Dimethyl formamide | AR | Sd-fine Chemicals |
| 3. | Carbondisulfide | AR | Sd-fine Chemicals |
| 4. | Methyl iodide | AR | Aldrich Chemicals |
| 5. | Aniline | AR | Sd-fine Chemicals |
| 6. | Ethanol | AR | MERCK |
| 7. | Benzyl chloride | AR | Sd-fine Chemicals |
| 8. | Sodium hydroxide | AR | Sd-fine Chemicals |
| 10. | Methanol | AR | Sd-fine Chemicals |
| 11. | Petroleum ether | AR | Sd-fine Chemicals |
| 12. | Ethyl acetate | AR | Sd-fine Chemicals |
| 13. | Chloroform | AR | Sd-fine Chemicals |
| 14. | Bromo Ethane | AR | Sd-fine Chemicals |
| 15. | Bromo propane | AR | Sd-fine Chemicals |

Chemistry:

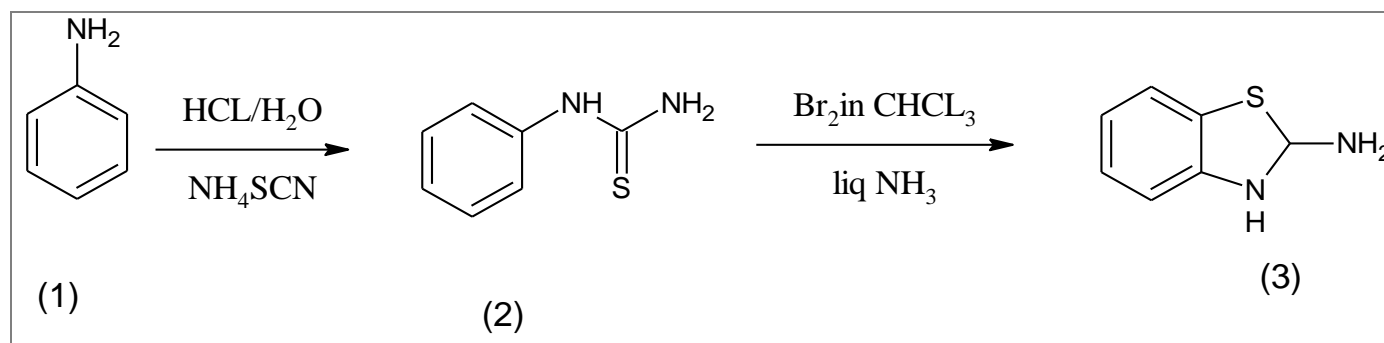
Reagent grade chemicals were used without further purification. All the melting points were taken in open capillary tubes and are uncorrected. The purity of the synthesized compounds was checked by Thin Layer Chromatography. IR spectra were scanned on Perkin Elmer Model 283B and Nicolet-740 F T-IR instruments and values are given in cm^{-1} . Each reaction was monitored by TLC by using appropriate solvent system, which was selected by trial and error method. Precoated TLC plates (0.25mm silica gel) were obtained from E. Merck. All solvents extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated at reduced pressures on Buchi-R-3000 rotary evaporator below $50^\circ C$.

Experimental Procedures:

Synthesis of 2-Aminobenzothiazole (3):

Aniline (0.1mol) was taken in a R.B.F. fitted with condenser & a mixture of HCl (9ml) & water (25ml) was added & then it was heated for about 30min. To the solution of aniline HCl obtained was cooled down to room temp & ammonium thiocyanate (0.1mol) was added. The reaction mixture was refluxed for 4 hr.

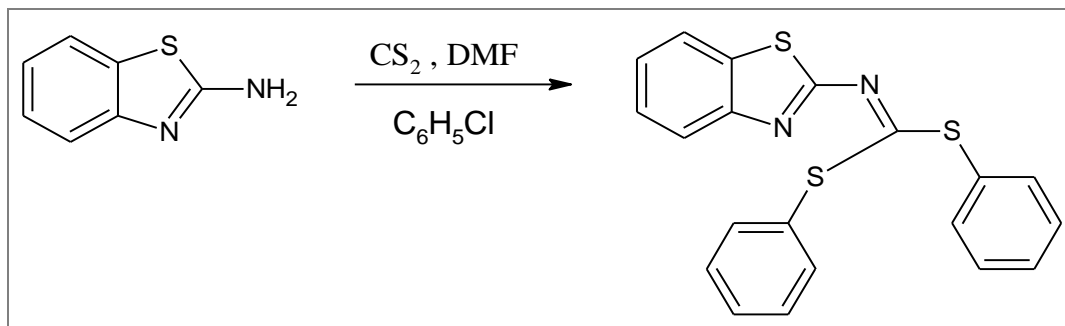
The solid separated out on cooling was filtered, washed with water, dried and crystallized from ethanol. To the solid product bromine in chloroform was added with continuous stirring. Later the solution was neutralized with ammonia. The formed solid product (3) was re crystallized with ethanol.



Molecular formula: $C_7H_8N_2S$; Molecular weight: 152;

Melting Point: $120-135^\circ C$; Solubility: Chloroform; R_f : 0.36; Percentage yield: 82%;

IR (KBr) cm^{-1} : 3420 N-H 1295 C-C (Aliphatic) 1611 C=C (Aromatic) 3181 C-H (Aromatic)

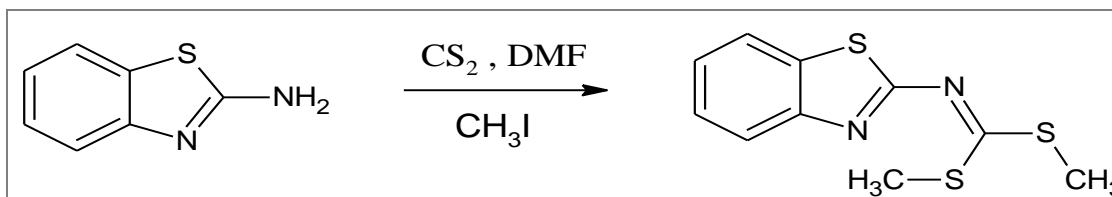
Synthesis of Dibenzyl (1,3 Benzothiazolo-2-yl) Dithioimidocarbonate:

2-amino benzothiazole (0.025 mole) and aqueous sodium hydroxide solution (10M, 4ml) were stirred in 10 ml of dimethyl formamide for 15 mins then drop wise carbon disulphide was added the reaction mixture was stirred for additional 20 min and then benzyl chloride (0.05 mole) was added and was allowed to stir for 3hrs. The reaction mixture was monitored with TLC.

Molecular formula: $C_{20}H_{16}N_2S_3$; Molecular weight: 332; R_f : 0.76;

Melting Point: 140-152 °C; Solubility: Chloroform;

Yield: 79.5; IR (KBr) cm^{-1} : 3461 C-H (Stretching of Aromatic Ring) 2220 C=N (Thiazole) 1568 C=C (Aromatic Ring) 693 C-S

Synthesis of Dimethyl (1,3 benzothiazolo-2-yl) Dithioimidocarbonate:

2-amino benzothiazole (0.025 mole) and aqueous sodium hydroxide solution (10M, 4ml) were stirred in 10 ml of dimethyl formamide for 15 minutes drop wise carbon disulphide was added then reaction mixture was stirred for additional 20 min and then methyl iodide (0.05 mole) was added and allowed to stirred for 3hrs. The reaction mixture was monitored with TLC.

Molecular formula: $C_{10}H_{12}N_2S_3$; Molecular weight: 208;

Melting Point: 130-140 °C; Solubility: Chloroform; R_f : 0.8; Yield: 81%;

IR(KBr) cm^{-1} : 2938 C-H (Aliphatic Alkane) 3010 C-H (Aromatic) 1571 C=C (Aromatic) 694 C-S (Aliphatic Chain) 710-550 C-S

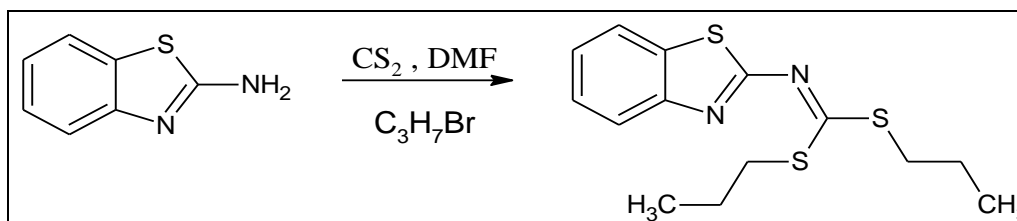
Synthesis of Dipropyl (1,3 benzothiazolo-2-yl) Dithioimidocarbonate:

FIG.1: SYNTHESIS OF DIPROPYL (1,3 BENZOTHIAZO-2YL) DITHIOIMIDOCARBONATE.

2-amino benzothiazole (0.025 mole) and aqueous sodium hydroxide solution (10M, 4ml) were stirred

in 10 ml of dimethyl formamide for 15 mins then drop wise carbon disulphide was added the

reaction mixture was stirred for additional 20 min and then bromopropane (0.05mole) was added and was allowed to stir for 3hrs. The reaction mixture was monitored with TLC.

Molecular formula: $C_{14}H_{20}N_2S_3$; Molecular weight: 264; R_f : 0.82;

Melting Point: 140-150 °C; Solubility: Chloroform; Yield: 83%;

IR (KBr) cm^{-1} : 2151 C-H 1223 C-C (Aliphatic) 1588 C=C (Aromatic) 694 C-S

Synthesis of Diethyl (1,3 benzothiazol-2-yl) Dithioimidocarbonate:

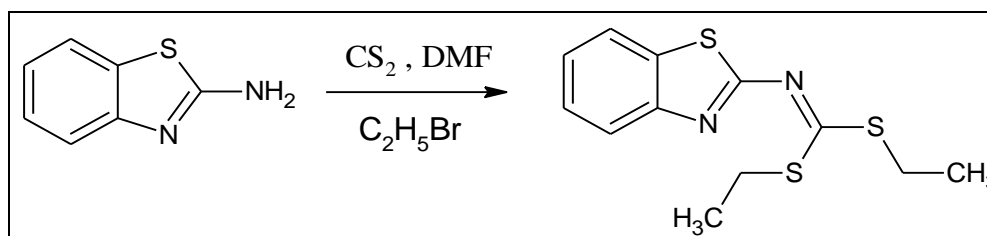


FIG.2: SYNTHESIS OF DIETHYL (1,3 BENZOTHAZO-2YL) DITHIOIMIDOCARBONATE.

2-amino benzothiazole (0.025 mole) and aqueous sodium hydroxide solution (10M, 4ml) were stirred in 10 ml of dimethyl formamide for 15 minutes then carbon disulphide was added drop wise the reaction mixture was stirred for additional 20 min and then bromo ethane (0.05mole) was added and allowed to stir 3hrs .the reaction mixture was monitored with TLC

Molecular formula: $C_{12}H_{16}N_2S_3$; Molecular weight: 236; R_f : 0.39;

Melting Point: 152-160 °C; Solubility: Chloroform; Yield: 82%;

IR(KBr) cm^{-1} :2870 C-H (Aliphatic)1588 C-C (Aromatic)693 C-S972 H-C-S1220 C-C

TABLE 2: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

| Compounds | Molecular formula | Molecular weight | Percentage yield | Melting point (°C) |
|-----------------|----------------------|------------------|------------------|--------------------|
| 3T | $C_7H_8N_2S$ | 152 | 82% | 120-135 |
| 4T ₁ | $C_{20}H_{16}N_2S_3$ | 332 | 79.5% | 140-152 |
| 4T ₂ | $C_{10}H_{12}N_2S_3$ | 208 | 81% | 130-140 |
| 4T ₃ | $C_{14}H_{20}N_2S_3$ | 264 | 83% | 140-150 |
| 4T ₄ | $C_{12}H_{16}N_2S_3$ | 236 | 82% | 152-160 |

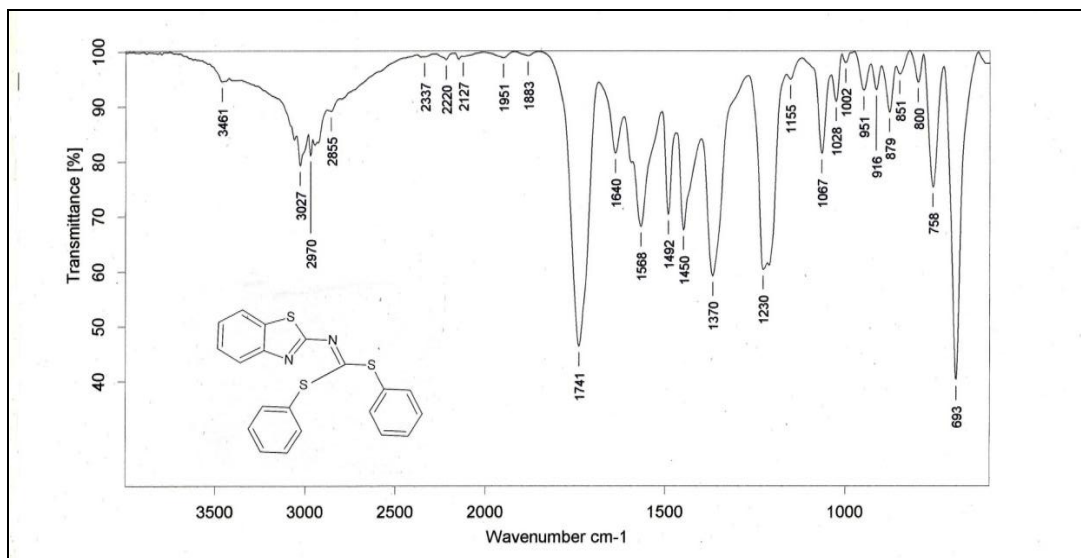


FIG.3: SPECTRUM OF DIBENZYL (1,3 BENZOTHAZO-2YL) DITHIOIMIDOCARBONATE

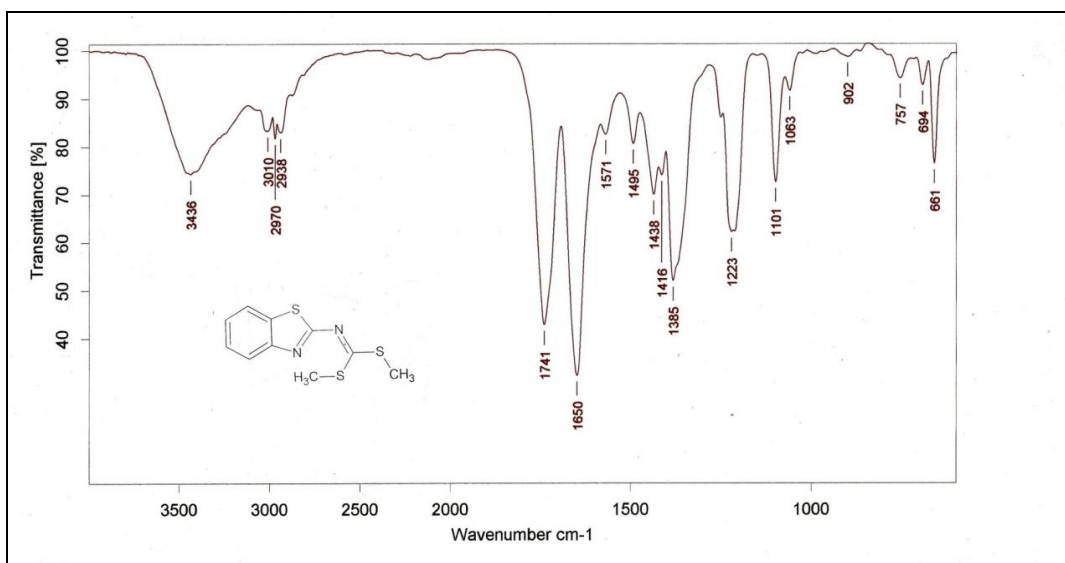


FIG.4: SPECTRUM OF DIMETHYL (1,3 BENZOTHAZO-2YL) DITHIOMIDOCARBONATE

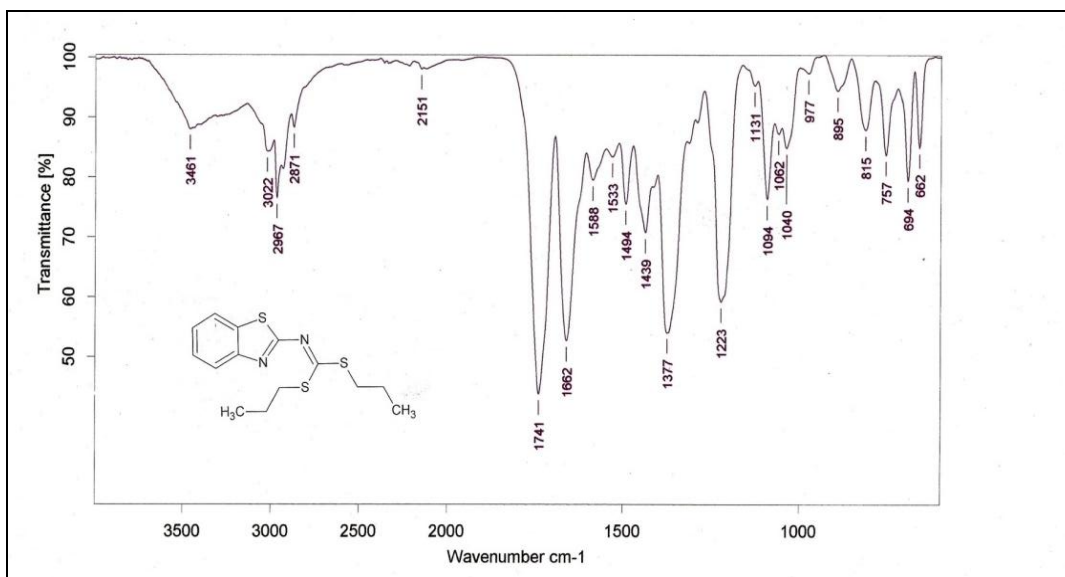


FIG.5: SPECTRUM OF DIPROPYL (1,3 BENZOTHAZO-2YL) DITHIOMIDOCARBONATE

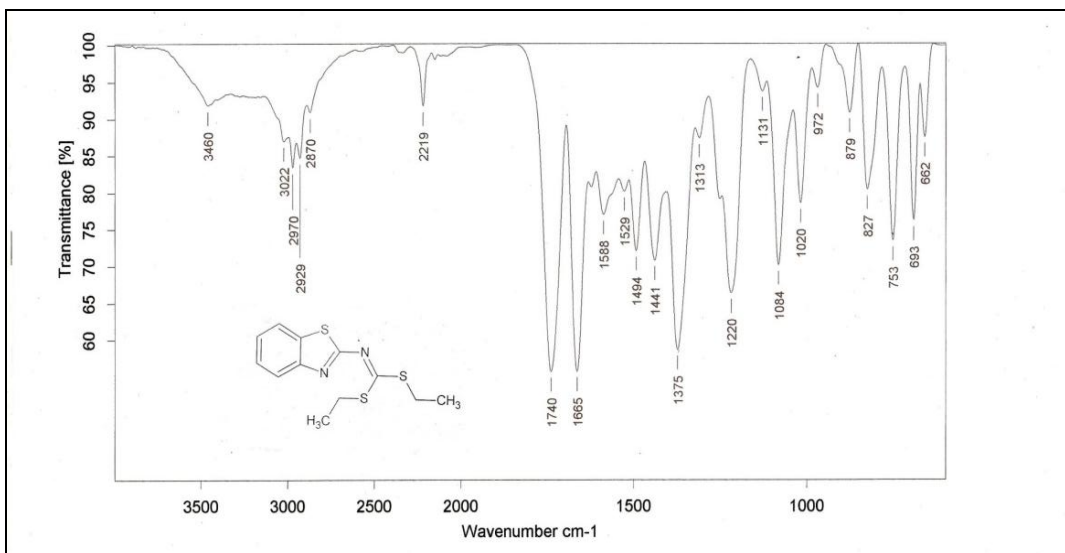


FIG. 6: SPECTRUM OF DIETHYL (1,3 BENZOTHAZO-2YL) DITHIOMIDOCARBONATE

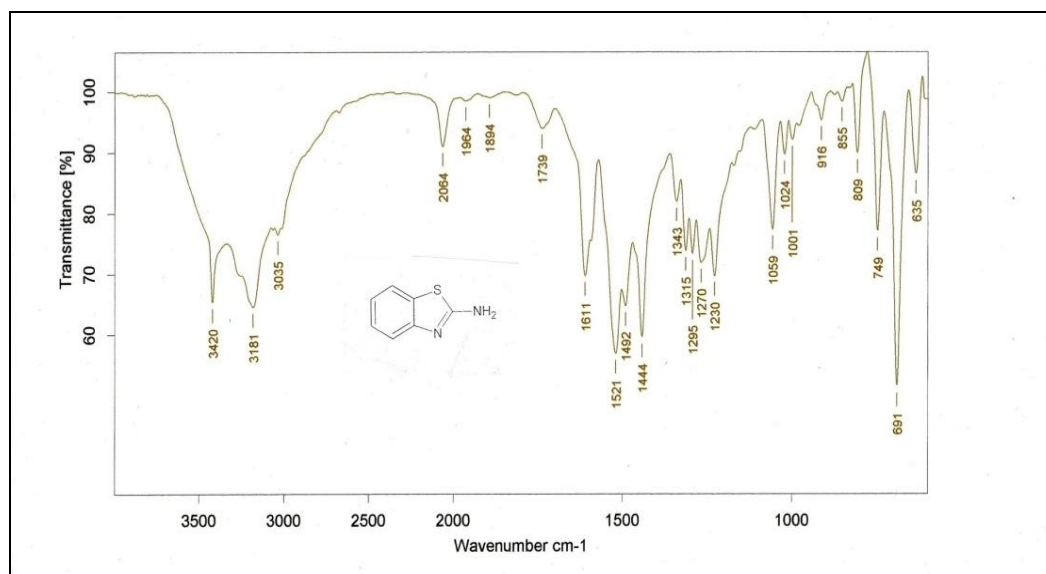


FIG.7: IR SPECTRUM OF 2-AMINO BENZOTHAZOLE

Biological Evaluation:

The objective of this work is to try to find out how this group of substituents in benzothiazole exert their antimicrobial activity. The compounds were synthesized were subjected to biological evaluation.

Antimicrobial activity:

Test Micro-Organisms:

TABLE 3: LIST OF MICRO-ORGANISMS

| S. No. | Micro-organisms | ATCC Codes |
|-------------------|-------------------------------|------------|
| I BACTERIA | | |
| 1 | <i>Proteus vulgaris</i> | 8427 |
| 2 | <i>Enterobacter</i> | 35030 |
| 3 | <i>Staphylococcus aureus</i> | 25923 |
| 4 | <i>Pseudomonas aeruginosa</i> | 27853 |
| 5 | Cons | 12228 |
| II FUNGI | | |
| 6 | <i>Candida albicans</i> | 10231 |
| 7 | <i>Cryptococci</i> | 204092 |
| 8 | <i>Aspergillusniger</i> | 16404 |
| 9 | <i>Trycophytonrubrum</i> | 28188 |
| 10 | <i>Mucor</i> | 16457 |

Preparation of Antibiotic Stock Solutions:

Ciprofloxacin: Standard stock solution for bacterial organisms. 100mg of ciprofloxacin was dissolved in 100ml of distill water. The stock solution was prepared.

Fluconazole: Standard stock solution for fungal organisms. 1.0 mg/ml of fluconazole diluted with methanol, acetonitrile and buffer (20:10:70). Adjust with glacial acetic acid to a P^H of 5.0

Preparation of Test Stock Solution:

The test drugs 2-Aminobenzothiazole (1ml), Dibenzyl (1,3 Benzothiazo-2yl) Dithioimidocarbonate (1ml), Dimethyl (1,3 Benzothiazo-2yl) Dithioimidocarbonate (1ml), Dipropyl (1,3 Benzothiazo-2yl) Dithioimidocarbonate (1ml), Diethyl (1,3 Benzothiazo-2yl) Dithioimidocarbonate (1ml) was dissolved in 10 ml of distilled water.

Anti-microbial susceptibility test:⁷

I. Disc diffusion method

Disc Diffusion Method:⁷

i. Inoculation of Micro-Organisms:

- Dip a sterile swab into the inoculum tube (5 Bacteria and 5 Fungi).
- Rotate the swab against the side of the tube (above the fluid level) using firm pressure, to remove excess fluid. The swab should not be dripping wet.
- Inoculate the dried surface of a MHA and SA plate by streaking the swab three times over the entire agar surface; rotate the plate approximately 60 degrees each time to ensure an even distribution of the inoculum.
- Rim the plate with the swab to pick up any excess liquid.
- Discard the swab into an appropriate container.
- Leaving the lid slightly ajar, allow the plate to sit at room temperature at least 3 to 5 minutes, but no more than 15 minutes, for

the surface of the agar plate to dry before proceeding to the next step.

ii. Preparation of Dried Filter Paper Discs:

Whatmann filter paper no. 1 is used to prepare discs approximately 6 mm in diameter, which are placed in a Petri dish and sterilized in a hot air oven. The loop used for delivering the antibiotics is made of 20 gauge wire and has a diameter of 2 mm. This delivers 0.005 ml of antibiotics to each disc.

iii. Placement of Antibiotic Discs:

- Place the appropriate antimicrobial-impregnated disks on the surface of the agar, using either forceps to dispense each antimicrobial disk one at a time, or a multidisk dispenser to dispense multiple disks at one time.
- Once all disks are in place, replace the lid, invert the plates, and place them in a 37 °C air incubator for 16 to 18 hours (for bacteria) and 7 days (for fungi).

Incubation of Plates:

- A temperature range of 35°C ± 0.5 °C was required.

Measurement of Zone of Inhibition:

TABLE 4: ANTI-BACTERIAL EFFECT OF 2-SUBSTITUTED BENZOTHAZOLE DITHIOIMIDO CARBONATE DERIVATIVES AGAINST SOME BACTERIAL PATHOGENS

| S.No | Microbial Culture | Diameter Of Zone Of Inhibition | | | | | Standard |
|------|-------------------------|--------------------------------|-----------------|-----------------|-----------------|----------------|----------|
| | | 4T ₁ | 4T ₂ | 4T ₃ | 4T ₄ | T ₅ | |
| 1. | <i>Proteus vulgaris</i> | 1.6 | 1.1 | 0.9 | 0.9 | 1.5 | 3 |
| 2. | <i>Enterobacter</i> | 1.3 | 1.2 | 1.2 | 0.9 | 1.2 | 1.2 |
| 3. | <i>S.aureus</i> | 1.8 | 1.6 | 1.6 | 1 | 1.7 | 3.2 |
| 4. | <i>P.aureginosa</i> | 1.7 | 1.4 | 1 | 0.8 | 1.8 | 3.5 |
| 5. | <i>Conus</i> | 1.4 | 1.2 | 0.8 | 0.7 | 1.9 | 1 |

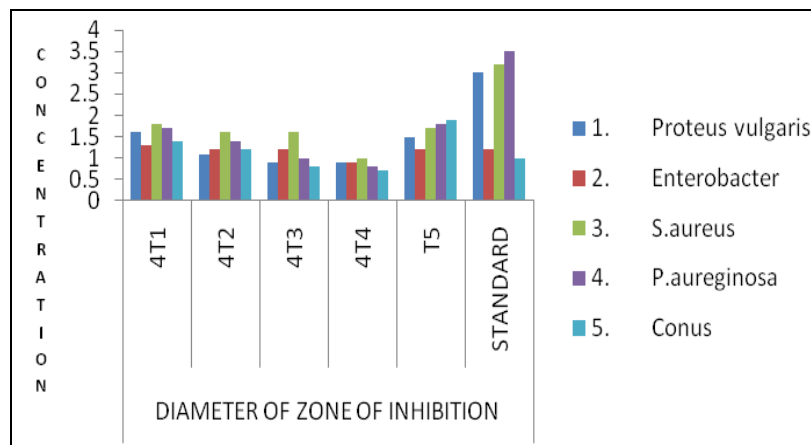


FIG. 7: BAR DIAGRAM OF ANTI-BACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

- Note that temperatures above 35°C may not allow the detection of Organisms.
- Do not incubate plates in CO₂ as this will decrease the pH of the agar and result in errors due to incorrect pH of the media.
- Results were read after 18 hours (for *Enterobacter*, *Proteus vulgaris*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Conus*) and 7 days (for *Candida albicans*, *Cryptococci*, *Aspergillusniger*, *Trycophyton*, *Mucor*) for incubation.

RESULTS AND DISCUSSION:

Antibacterial Activity:

The antibacterial activity of synthetic compounds was tested by using disc diffusion method taking drug at a concentration of 1mg/10ml. The area of zone of inhibition was taken as a parameter of antibacterial activity. The area of zone of inhibition was taken as a parameter of antifungal activity. The area of zone of inhibition of test compound is compared with that of the standard drug i.e., Ciprofloxacin (100 mg/100ml). All the compounds were screened and shown antibacterial activity against following microorganisms *Proteus vulgaris*, *Enterobacter*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Conus*.



FIG. 8: ANTI-BACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (*CONUS*)



FIG. 11: ANTI-BACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (*P. AUREGINOSA*)



FIG. 9: ANTI-BACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (*PROTEUS*)



FIG. 12: ANTI-BACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (*ENTERO BACTERIA*)



FIG. 10: ANTI-BACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (*S. AUREUS*)

Antifungal Activity:

The antifungal activity of synthetic compounds was tested by using disc diffusion method taking drug at a concentration of 1mg/10ml. The area of zone of inhibition was taken as a parameter of antifungal activity. The area of zone of inhibition of test compound is compared with that of the standard drug i.e., Fluconazole (1 mg/ml).

All the compounds were screened for antifungal activity against five fungal organisms, *Aspergillus niger*, *Candida albicans*, *SDA mucor*, *Trycophytonrubrum* and *Cryptococci.*, *Aspergillus niger*, *Candida albicans* and *SDA mucor* shows antifungal activity

TABLE 5: ANTI-FUNGAL EFFECT OF 2-SUBSTITUTED BENZOTHIAZOLE DITHIOIMIDO CARBONATE DERIVATIVES AGAINST SOME FUNGAL PATHOGENS

| S.No | Microbial Culture | Diameter of Zone of Inhibition | | | | | Standard |
|------|---------------------------|--------------------------------|-----------------|-----------------|-----------------|----------------|----------|
| | | 4T ₁ | 4T ₂ | 4T ₃ | 4T ₄ | T ₅ | |
| 1. | <i>A.niger</i> | 0.7 | 1.2 | 1.5 | 1.3 | 0.8 | 2.0 |
| 2. | <i>C.albicans</i> | 0.9 | 0.2 | 0.8 | 0.9 | 0.1 | 1.2 |
| 3. | <i>SDA.mucor</i> | 0.8 | 0.6 | 1.9 | 1.2 | 0.7 | 2.5 |
| 4. | <i>Trychophytonrubrum</i> | 0.5 | 0.1 | 0.1 | 0.2 | 0.1 | 1.0 |
| 5. | <i>Cryptococci</i> | 0.3 | 0.2 | 0.1 | 0.1 | 0.1 | 1.5 |

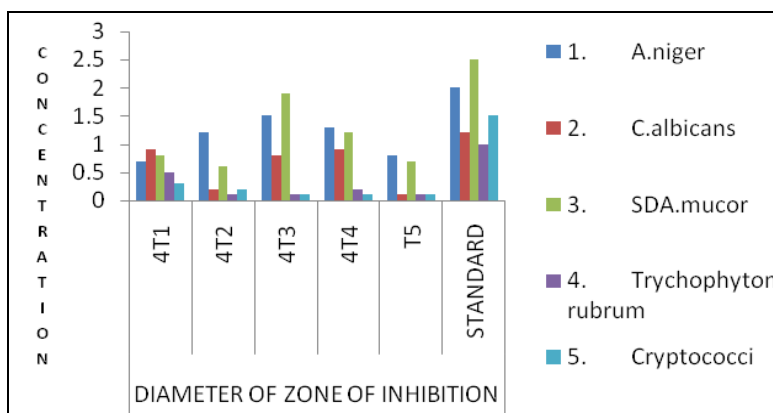


FIG. 13: BAR DIAGRAM OF ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS

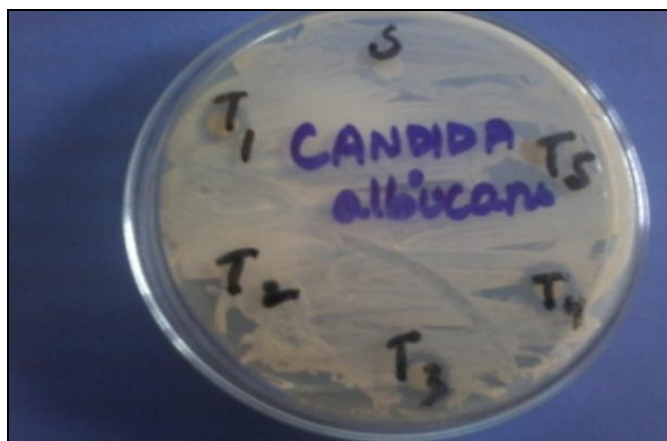


FIG.14: ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS (CANDIDA ALBICANS)

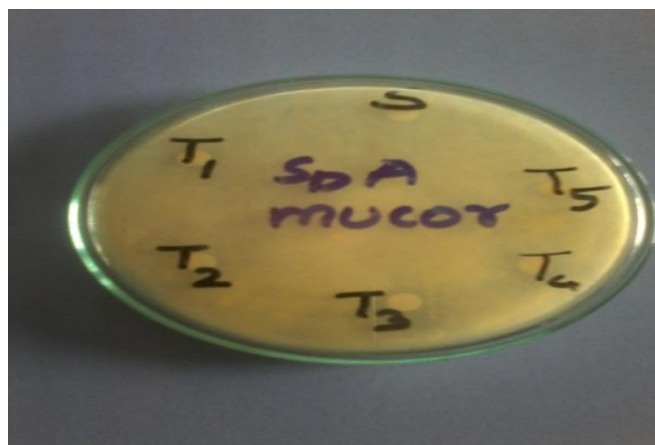


FIG.16: ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS (SDA MUCOR)

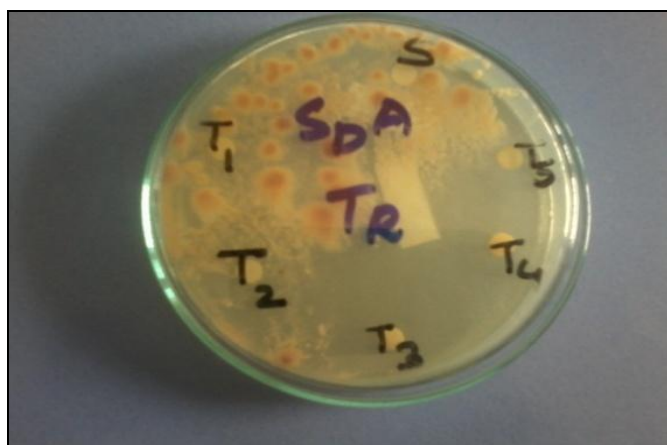


FIG.15: ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS (SDA TR)



FIG.17: ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS (CRYPTO COCCUS)



FIG. 18: ANTI-FUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS (*ASPERGIUS NIGER*)

CONCLUSION: Benzothiazole and its derivatives were synthesized in laboratory by simple methods under normal conditions, with the help of magnetic stirrer. All the compounds were characterized by spectral methods like IR Spectroscopy.

The synthesized compounds were screened for their anti-microbial activity by using nutrient agar media & sabouraud's glucose agar media by disc diffusion method. Some of these compounds showed significant activity against gram positive and gram negative bacteria and fungi.

The proposed compounds were synthesized successfully and characterized. They were evaluated for their antimicrobial activity and the results were found to be encouraging. Most of the compounds were more active against gram positive (*Proteus vulgaris*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*) and gram negative (*Enterobacter*) bacteria and fungi. The promising result in antifungal activity gave us scope for further work in this area.

Antimicrobial Activity:

It was carried out against microorganisms using disc diffusion method. In antimicrobial study compounds 4T₂, 4T₃, 4T₄ exhibited moderate antibacterial activity while 4T₁ have emerged as the most active antibacterial agent and it has shown equipotent activity when compared to the reference standard Ciprofloxacin.

Antifungal activity:

It was carried out against microorganisms using disc diffusion method. In antimicrobial study

compounds 4T₁, 4T₂, 4T₄ exhibited moderate antibacterial activity while 4T₃ have emerged as the most active antibacterial agent and it has shown equipotent activity when compared to the reference standard Fluconazole.

Future Scope: At last, it is worthwhile to study these compounds further by carrying out complete QSAR and molecular modelling studies and which may establish these compounds as lead molecules for antimicrobial activity.

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How to cite this article:

Tasleem: Synthesis and Pharmacological Evaluation of 2-Substituted Benzothiazole Dithiomidocarbonate Derivatives. *Int J Pharm Sci Res* 2015; 6(9): 4058-68. doi: 10.13040/IJPSR.0975-8232.6(9).4058-68.

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