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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACIVITY OF SUBSTITUTED 2-AMINOBENZOTHIAZOLE

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ABSTRACT: -
Heterocyclic compounds and their derivatives have gained popularity due to their prominent medicinal importance, as well as in organic chemistry. The versatile and synthetically accessible 2-aminobenzothiazole scaffolds have the all-round character for multiple applications obviously because they are synthetically accessible. Benzothiazole is a representative class of sulfur containing heterocyclics. Four substituted 2-aminobenzothaizoles were prepared from ammonium thiocyanate and substituted aniline in presence of HCl and ethanol by conventional method. The substituted products were characterized through IR, NMR and Mass spectroscopic methods. The synthesized compounds like substituted 2-aminobenzothiazoles and their derivatives studied for the MIC value by dissolving in ethanol. The effect of electron withdrawing and donating group was studying using serial dilution method.
KEYWORDS: -Substituted anilines, 2-aminobenzothiazoles, Ammonium thiocyanate, Para amino benzoic acid, Microbial activity.

I INTRODUCTION: -

Chemistry is the study of the composition, structure, properties and interaction of matter in our day to day life. Benzothiazole is a representative class of sulfur containing heterocyclic and involves a benzene ring fused to thiazole ring. Various and different marine and terrestrial natural compounds, have been known to have the benzothiazole ring system. This system was a propagator of vulcanization, accelerator and an antioxidants, plant growth regulators, anti- inflammatory agents and enzyme inhibitor, Due to its highly active biological and pharmaceutical activity[1]. In the field of medicinal chemistry also benzothiazole has its own significance rendering an extensive range of biological activity including anticancer[2] antibacterial[3], antituberculosis[4], antidiabatic, antihelmintic, antitumor[5], antiviral[6], antioxidant, anti- inflammatory[7], anti-glumated anti-perkinsonism, anticonvulsant, muscle relaxenent activities, neuroprotective, the synthesis of benzothiazole has gained accolades for its potency in vital and pharmaceutical activities. Naturally, different methods have been developed and implemented with varied ways to for its derivatives. Condensations reactions with various chemicals have helped to synthesized the benzothiazole ring.
Among them, the condensation reaction of 2- aminobenzothiazole with a carbonyl or cyno group containing substrate is the most commonly used method[8]. Radii and co-workers[9] found that benzothiazole could be synthesized from the condensation of 2-aminobenzothiazole and aromatic aldehydes in refluxing toluene at 110^0C. Sun and co- workers reported a copper catalyzed method for the formation of 2- substituted benzothiazole via. condensation of 2-aminobenzothiazole with nitriles. Moreover, many other researchers have opted for many other methods to synthesize benzothiazoles by the reaction of ortho- halogenated aniline with isocynate, carbondisulfide and

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piprediene, aldehydes and sulfur, carbondisulfide and thiol, acid chloride and Lawson's reagent[10]. In addition, an alternativemethod is the intramolecular cyclization of ortho-halogenated analogs [11].
Sahoo and collegeous indicated that benzothiazoles could be synthesized from ortho-halothioureas using both Cu(I) and Pd (II) transition metal as a catalyst. Unfortunately, the greatest disadvantage of the traditional processes is that the yield may be scarce, the selectivity may be poor, the reaction conditions may be harsh, and the utilization of toxic reagents or metal may be unpalatable to humans. It may therefore seem advisable to curtail the use of raw materials, catalyst, solvents, reagents, bi-products that are not human friendly and health hazardous. Nevertheless, reactants, chemical reagents and solvents that are against the Green chemistry should be avoided for community safety and human health security. All the same, ecologically, environmentally friendly synthetic routes. In the preparation of benzothiazoles shall lead to a safer and secure venture.
In recent years, causion remains the buzzword, with the concepts, ideas and notions of Green chemistry so global, it becomes our duty to avoid environment harzards like[12-13] of too many resources and help develop metal-free catalysts. The strategy to provide medical care without being harsh to nature will only serve the purpose of being positive in and out conditions have attracted researcher's attention. Chacko et al. have designed and synthesized a novel series of 2-aminnobenzithizole derivatives as potent anticancer agents. They are known for their biological activity as antiproliferative. anti-bacterial, antifungal etc.
Benzothiazole with substitution at C_2 position like 2-aminobenzothiazole, 2- mercaptobenzothiazole and 2-arylbenzothiazole is widely explored by researchers in the process of drug design and discovery[14].
Literature survey shows that the substituted 2- aminobenzothiazoles have many important properties like anticancer, antidiabetic, antibacterial etc. As it has high pharmaceutical scope thus synthesis and charecterization of this compounds were consider for research work.

ANTIMICROBIAL ACTIVITY: -

Chemotherapeutic agents are chemical substances used for the treatment of infectious diseases. The chemotherapeutic agent's attack and destroy the invading organisms. Without injuring or destroying the cells on the infected host. The interaction between potent chemicals and living system contribute to the understanding of life processes and Chemotherapeutic agents are chemical substances used for the treatment of infectious diseases. The chemotherapeutic agent's attacks and destroy the invading organisms without injuring or destroying the cells on the infected host. The interaction between potent chemicals and living system contribute to the understanding of life processes and provide effective methods for the treatment, prevention and diagnosis of many diseases.
Chemical substances used for this purpose are called "Drugs" and their action on living system are referred to as "drug effect". The treatment of diseases with chemotherapeutic substances has been known since the 1500s but only since 1935 this therapy has been widely practiced. The mass is well aware of the existence of many chemical agents said to be effective in destroying micro-organisms.
"Any chemical moiety which inhibits the growth of micro-organism kills it called as Antimicrobial Activity." The history of drugs is as old as ancient civilization. However, the Greeks were the first who liberated medicine from superstition and magic Hippocrates, a Greek a physician known as the "Father of medicine".
Although natural products of microbial origin that exist widely in natural have been proven to be effective and inherently biodegradable due to the complexity of their structure[15-16]. Moreover, it has been reported that the mode of antimicrobial action is likely due to the inactivation of essential enzymes. Additional, computer docking techniques plays an as mechanist tic studies by placing a molecule into the binding site of the target macromolecule in a non-covalent fashion. Medical sciences have reached their zenith in the clinical world and yet the greatest threat as of now is the bacterial pathogens becoming resistant to drugs administered on a regular basis. As a consequence, there is an alarming increase in the mortality rate caused due to gram-positive and gram-negative

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bacterial diseases. The uncontrolled population and an aspiration for the comfort with modernization have leads to this menace. This leads to the discovery of a new effective antimicrobial drug agent to curb bacterial mortality rate[17]. Researchers have taken up this as a challenge to generate a better scaffold for an undaunted fight against bacterial viruses. The ultimate focus is on two aspects namely, an increase in the potent bacterial antigen drugs and getting of a new bacterial pathogen. The structural characteristic and the rate of activity are the important aspects of synthesizing effective drugs.

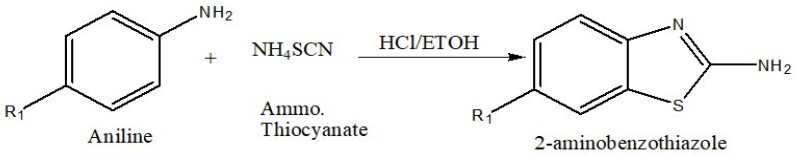
Initially, heterocyclic compounds were considered as parent compounds for any effective bacterial drug. An in-depth study of the vast antimicrobial literature data shows that heterocyclic compounds have played a significant role in the clinical field of science[18].

2. EXPERIMENTAL: -

All the reagents and solvents were purchased from universal, fluca and these were used without any further purification. The melting point of all the compounds was determined by an open capillary thermal melting point apparatus. IR spectra were recorded as KBr pellets on a Bruker IR Spectrophotometer. ^{1}HNMR spectra were recorded in $CDCl_3$ on JEOL Delta-550 spectrometer (400MHz).

2.1 SYNTHESIS: -

Equimolar concentration of substituted aniline (0.025 M) and ammonium thiocyanate (0.025 M) dissolved in ethanol containing 2-3 drops of concentrated hydrochloric acid was added and the mixture was refluxed for 7 hrs. It was cooled in ice bath then diluted with water and neutralized with 5% NaOH. The resulting solid was recrystallized with ethanol to yield compound as a purified product. The following reaction shows scheme.



Where R is $-NO_2$, -Cl, $-OCH_3$.

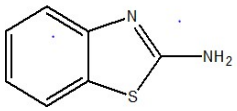
The following were synthesized names L_1, L_2, L_3, L_4.

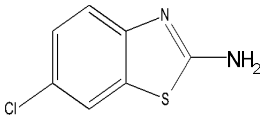
Products	Name	Colour	M.P.	%Yield
L_1	2-aminobenzothiazole	Offwhite	129	74
L_2	6-nitro-1,3-benzothiazol-2-amine	Yellow	240	67
L_3	6-chloro-1,3-benzothiazol-2-amine	White	201	79
L_4	N-(2-amino-1,3-benzothiazol-6-yl) acetamide	White	179	82

Structure of L_1, L_2, L_3 and L_4.

L_1 2-aminobenzothiazole

L_2 6-nitro-1,3-benzothiazol-2-amine





L_3 6-chloro-1,3-benzothiazol-2-amine

L_4 N-(2-amino-1,3-benzothiazol-6-yl) acetamide

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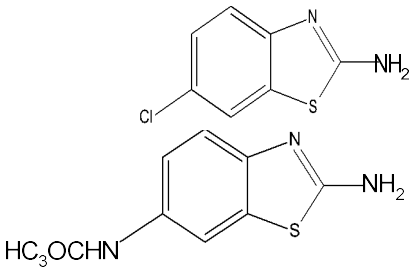

3 RESULT & DISCUSSION

3.1 IR SPECTROSCOPY: -

L_1- The IR spectrum for L_1 showed characteristics absorption bands at (3394-3271cm^{-1}) & (1641cm^{-1}) due to thiazole ring. Other bands appeared at (1641cm^{-1}), (800cm^{-1}) & (3055cm^{-1}) which attributed to (C=N) aromatic (C=C) benzene ring and (C-H) in aromatic ring respectively.

L_2-The IR spectrum for L_2 showed characteristics absorption bands at (1340cm^{-1}) for symmetric andasymmetric -NO_2 group.

L_3-The IR spectrum for L_3 showed characteristics absorption bands at (3377cm^{-1}) for -NH_2 stretch. Otherbands appeared at (1613cm-^{1}) for (–C=N) group. The band appeared at (1281cm-^{1}) for (-C-Cl)

L_4- The IR spectrum for L_4 showed characteristics absorption bands at (cm^{-1}) for -OCH_3 group.

3.2 ^{1}HNMR SPECTROSCOPY: -

The ^{1}HNMR spectrum of compound L_1 showed clear signal at (1.974 δ ppm) belongs to NH aromaticprotons respectively (7.5-8.07 δ ppm) aromatic H protons.

The ^{1}HNMR spectrum of compound L_2 showed clear signal at (1.594 δ ppm) belongs to NH aromaticprotons respectively (6.06-8.12 δ ppm) aromatic H protons.

The ^{1}HNMR spectrum of compound L_3 showed clear signal at (2.77 δ ppm) belongs to NH aromaticprotons respectively, (6.97-7.95 δ ppm) belong to aromatic H protons.

The ^{1}HNMR spectrum of compound L_4 showed clear signal at (3.06 δ ppm) belongs to aromatic Hprotons, (3.7 δ ppm) OH aromatic protons, (6.6-7.2 δ ppm) belongs to aromatic H protons.

3.3 MASS SPECTROSCOPY: -

L_2 Peak due to the loss of heterocyclic ring containing N, S and C gives fragmentation at m/z=138.

Peak due to the loss -NH_2 group gives fragmentation at m/z=121.

Peak due to the loss of -NO_2 group and carries + charge on ring gives fragmentation at m/z=92.

Peak due to the loss of carbon carries + charge on ring and gives fragmentation at m/z=80

L_3 Peak due to the loss of –CNH group from heterocyclic ring, and N attached with benzene ringcarries + charge gives fragmentation at m/z=157.

L_4 Peak due to the loss of -CH_2=C=O and gives fragmentation at m/z=165.

Peak due to loss of heterocyclic ring containing N, S, C and -NH_2 group gives fragmentation at m/z=135.

Peak due to the loss of methyl group gives fragmentation at m/z=120.

Peak due to the loss of -HCO group gives fragmentation at m/z=93.

3.4 SERIAL DILUTION METHOD: -

Nutrient broth was prepared by dissolving 13 g of dehydrated medium, pH of which was adjusted to 7.4. 5ml of the medium was distributed in each test tube. All the tubes were sterilized at 121^{0}C for 20 minutes. 0.2 g of test compound was dissolved in 70% ethanol to give final concentration of 1×10^{-2} M. Various amounts of theabove stock solution was aseptically added to the various nutrient broth tubes (0.5, 1.0, 1.2, 1.4, 1.6, 1.8, 0…5.8, ml). Fresh culture of the test bacterium was inoculated in each tube (0.2 ml culture). The inoculum size of thetest tube bacterium was adjusted to give approximate 10^{7} CFU (Colony Forming Unit). All the tubes were incubated at 37^{0}C for 24 hours Un-inoculated tube was kept as a control in which nutrient broth and 5ml of the solvent was

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taken. After 24 hours of incubation, all the tubes were observed for MIC against test bacterium. This was observed by the absence of visual turbidity in the tube receiving the highest dilution of the test compounds.

TABLE NO: - 2 MINIMUM INHIBITORY CONCENTRATION IN MICRO G ML^{-1}

Sr.No	Name of Compound	E. Coli	S. Typhi	P. Vulgaries	S. Aureus
L_1	2-aminobenzothiazole-aniline	4600	5400	6800	3600
L_2	6-nitro-2-aminobenzo thiazole-p-nitroaniline	2800	2400	3300	2200
L_3	6-chloro-1,3-benzothiazol-2-amine	1900	1800	2000	1600
L_4	N-(2-amino-1,3-benzothiazol-6-yl)Acetamide	4200	4800	5900	3200

Above table showed that L_1 and L_4 compounds have comparable MIC value against P. Vulgaries. It is observed that the MIC value of compounds between 1800- 2800µg /ml is active in inhibiting the growth of organism tested. Generally, less is the concentration more is the active compound. As -NO_2, -Cl groups are electron withdrawing groups and -NH_2 group is electron donating, it is observed that -NH_2 group is more active. Due to +R effect of -OCH_3 group which arises due to the lone pair of oxygen atom, it become more electron donating group. Thus it is observed that the antimicrobial activity of L_1 and L_4 compounds containing electron donating groups is more as compare to compounds L_2 and L_3 compounds containing electron withdrawing groups.

CONCLUSION: -

The compounds L_1, L_2, L_3 and L_4 are successfully prepared by using conventional method. These compounds were characterized by using ^{1}HNMR, IR and MASS spectroscopy. It has been observed that the presence of -NH_2 group and -OCH_3 group increases the activity against P. Vulgaries bacteria.

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