# Analyzing and creating compounds of amino thiazole

**Subramaniam V[1],Akshatha Soratur[2]**
[1,2]Research Assistant
[1]GM Institution of Technology, Davanagere, Karnataka.
[2]Mysore University, Mysore, Karnataka.
Corresponding Author email ID: subramanyamvkumar@gmail.com



## Introduction

Due to the introduction of novel ideas with high predictability and the development of new techniques and technologies, the second half of the 20th century saw a huge advancement in organic synthesis that led to the creation of numerous complex natural and synthetic goods. Due to ongoing attempts to find novel chemicals and techniques, particularly those that enable the stereoselective and chemically efficient assembly of molecular building blocks, tremendous goals have been reached.The interaction between organic chemistry and various life science disciplines, such as biology, pharmacology, and medicine, which are presenting a demand for natural products and synthetic analogues in meaningful scale and high purity, is currently promoting research in this field even more actively. Even though successful research in organometallic chemistry has led to the development of numerous new reagents and catalysts.

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**Heterocyclic compounds:** Natural organic molecules known as heterocyclic compounds contain one or more atoms other than carbon atoms in the form of ring atoms known as hetero atoms. Nitrogen, sulphur, or oxygen are examples of hetero atoms.Numerous heterocyclic substances are found in nature as alkaloids, vitamins, pigments, etc. The majority of them are utilised in the creation of colours and medications, and many of them are significant players in biological processes that take place in plants and animals. Heterocyclic compounds are those with five or six stable aromatic five- or six-membered rings. Furan, Pyridine, Thiopene, Quinoline, etc. are a few examples.

**Indole:**When left at room temperature, indole is solid. It naturally arises in human faeces and has a strong faeinl odour. It is a component of numerous flower smells, including orange blossoms, and perfumes, and has a floral scent at extremely low concentrations [1]. In coal tar, it also appears. The equivalent substituent is known as indolyl. Electrophilic substitution occurs to indole, primarily at position 3.The neurotransmitters serotonin and melatonin, which are generated from tryptophan, are tryptamine alkaloids that contain substituted indoles as structural components. Auxin indolyl-3-acetic acid (IAA), tryptophol, indomethacin, the beta-blocker pindolol, and the naturally occurring hallucinogen dimethyltryptamine are some more indolic substances. Since indole was first extracted by treating the indigo dye with oleum, the name indole is a combination of the words indigo and oleum.

Indole Properties

| | |
|---|---|
| **Chemical Formula** | $C_8H_7N$ |



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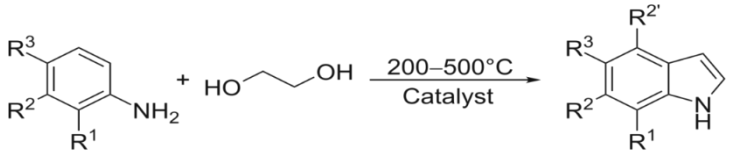
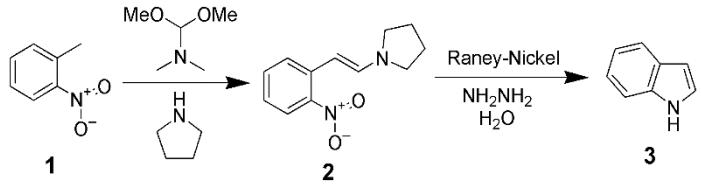
| | |
|---|---|
| **Molar mass** | 117.151 g·mol−1 |
| **Appearance** | White Solid |
| **Odour** | Jasmine/Fecal |
| **Melting point** | 52 to 54 °C |
| **Boiling point** | 253 to 254 °C |
| **Molecular shape** | Planar |

Synthetic routes: Indole and its derivatives can also be synthesized by a variety of methods [5-7]. The main industrial routes start from aniline via vapour phase reaction with ethylene glycol in the presence of catalysts




In general, reactions are conducted between 200 and 500 °C. Yields can be as high as 60%. Other precursors to indole include formyltoluidine, 2ethylaniline, and 2-(2-nitrophenyl) ethanol, all of which undergo cyclization [8].

Leimgruber–Batcho indole synthesis: The Leimgruber–Batcho indole synthesis is a series of organic reactions that indoles produce indoles from o-nitroarenes [9-12]. The first step is the formation of an enamine 2 using N, N dimethyl acetal and pyrrolidine [13]. The desired indole 3 is then formed in a second step by reductive cyclisation.




Fisher indole synthesis: One of the oldest and most reliable methods for synthesizing substituted indoles is the Fischer indole synthesis, developed in 1883 by Emil Fischer. Although the synthesis of indole itself is problematic using the Fischer indole synthesis, it is often used to generate indoles substituted in the second or third positions. Indole can still be synthesized, however, using the Fischer indole synthesis by reacting phenyl hydrazine with pyruvic acid followed



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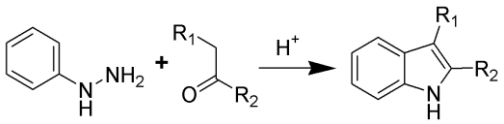
by decarboxylation of the formed indole-2-carboxylic acid. This has also been accomplished in a one-pot synthesis using microwave irradiation [13-14].






Bartoli indole synthesis: The reaction is often unsuccessful without substitution ortho to the nitro group, with bulkier ortho substituents usually resulting in higher yields for the reaction. The steric bulk of the ortho group assists in the [3, 3] sigma tropic rearrangement required for product formation. Three equivalents of the vinyl Grignard reagent are necessary for the reaction to achieve full conversion when performed on nitroarenes, and only two equivalents when performed on nitroarenes.This method has become one of the shortest and most flexible routes to 7-substituted indoles [14][15]. The Leimgruber-Batcho indole synthesis gives similar flexibility and regiospecificity to indole derivatives. One advantage of the Bartoli indole synthesis is the ability to produce indoles substituted on both the carbocyclic ring and the pyrrole ring, which is difficult to do with the Leimgruber-Batchoindole synthesis

**Electrophilic substitution**

The most reactive position on indole for electrophilic aromatic substitution is C3, which is $10^{13}$ times more reactive than benzene. For example, it is alkylated by phosphorylated serine in the biosynthesis of the amino acid tryptophan. Vilsmeier–Haack formylation of indole [16] will take place at room temperature exclusively at C3.

Since the pyrrolic ring is the most reactive portion of indole, the electrophilic substitution of the carbocyclic (benzene) ring generally takes place only after N1, C2, and C3 are substituted. A noteworthy exception occurs when electrophilic substitution is carried out in conditions sufficiently acidic to exhaustively protonate C3. In this case, C5 is the most common site of electrophilic attack [12].

**Carbon acidity and C2 lithiation**

After the N–H proton, the hydrogen at C2 is the next most acidic proton on indole. The reaction of N-protected indoles with butyl lithium or lithium diisopropylamide results in lithiation exclusively at the C2 position. This strong nucleophile can then be used as such with other electrophiles.



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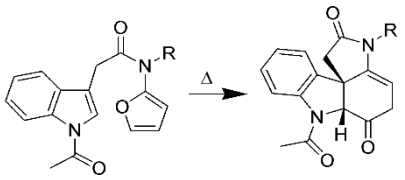
**Cycloaddition of indole**

Only the C2–C3 pi bond of indole is capable of cycloaddition reactions. Intramolecular variants are often higher-yielding than intermolecular cycloadditions. For example, Padwa et al [17]. In this case, the 2-aminofuran is the diene, whereas the indole is the dienophile. Indoles also undergo intramolecular [2+3] and [2+2] cycloaddition



Synthesis of indole derivatives

Protonation of the indole Grignard reagent and other organometallic derivatives of indole.

Preparation and protonation of the sodium salt of indole. The sodium salt of indole was prepared by adding 0.017 mole of indole in ca. 50 ml of benzene to a mixture of sodium hydride (0.46 moles) and Dimethyl sulfoxide (DMSO) 6 ml in ca. 44 ml of benzene. The Dimethyl sulfoxide (DMSO) was necessary in order to achieve a reasonable rate of reaction. The reaction mixture was stirred until the theoretical amount of hydrogen had been evolved (1-6h).The concentration of the sodium salt of indole was then approximately 0.17 M. Protonation was accomplished by the addition of 0.28 mole (16 equiv) of $D_20$. The protonation mixture, a clear two-phase system, was stirred for 5 min and then worked up in the same manner as is described for the Grignard reactions. An analogous experiment was performed by substituting 3-deuterioindole and $H_20$ for indole and $D_2O$.

Effect of periodic replacement of the heteroatom on the spectroscopic Properties of Indole and Benzofuran derivatives.

Benzo-fused five-membered heterocycles, such as indole benzopyrrole ($C_8H_6NH$) benzofuran ($C_8H_6O$) or benzothiophene ($C_8H_6S$), are among the most important domains of aromatic heterocyclic chemistry1, 2 and are of substantial utility in pharmaceutical, agrochemical, and material sciences[3-16] as platforms in pigments, biogenic amino acids or proteins, and alkaloids, as modular components in drugs, and as uniquely effective substituents in organic synthesis. Nitrogen and oxygen are neighbours' in the periodic table, and the similarity in their basic properties has been well documented by experimental chemists. For example, indole and benzofuran [6], exhibit significantly similar planar structures, electronic properties, and



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reactivities and selectivities in organic synthesis, and hence these heterocycles and their derivatives have long been regarded as belonging to the same category. However, these similarities structures of indole and benzofuran derivatives in this Study.



**Structures of indole and benzofuran derivatives in this study**

Reactions of phenyl isocyanate and phenyl isothiocyanate with indole and metal derivatives of indole.

Pyrrole is known to react with phenyl isocyanate and phenyl isothiocyanate to form 2 pyrrolecarboxanilide and pryrolethiocarbanilide, respectively. With the same reagent pyrrolypotassium forms the 1-carboxanilide and 1-thiocarbanilide, whereas pyrrolymagnesium bromide gives mixtures of one and two derivatives. The analogous reactions of indole, indolylpotassium, and indolylmagnesium bromide. When treated with phenyl isocyanate or phenyl isothiocyanate in tetrahydrofuran, indolylpotassium yields indolecarboxanilide [1] or indolethiocarbanilide [2]. It is noteworthy that the same compounds are obtained from the corresponding reactions of indolylmagnesium bromide in tetrahydrofuran, despite the general tendency of this reagent to give 3-substituted indole derivatives [6]. Comparison of the infrared spectra of the crude and purified products shows that these reactions lead to the formation of l substituted indole derivatives only. The structure assigned to 1 is consistent with its infrared spectrum.

**Indole- 2- carboxylic acid**

Properties

| | |
|---|---|
| **Chemical Formula** | **$C_9H_7NO_2$** |
| **Melting point** | 206.5 |
| **Molecular weight** | 161.16 |



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| | | |
|---|---|---|
| **Nature** | | SOLID |
| **Water coefficient** | **Partition** | 2.31 |

Synthesis of derivatives of indole 2 carboxylic acid

Synthesis, biological evaluation, and structure activity relationships of 3-acylindole 2 carboxylic acids as inhibitors of the cytosolic phospholipase A2.

3-Acylindole-2-carboxylic acid derivatives were prepared and evaluated for their ability to inhibit the cytosolic phospholipase A2 of intact bovine platelets. To define the structural requirements for enzyme inhibition, the carboxylic acid group, the acyl residue, and the moiety in position 1 were systematically modified.

Phospholipases A2 (PLA2) are a class of enzymes which catalyze the hydrolysis of membrane glycerophospholipids at the sn-2 position to release fatty acids and lysophospholipids. When the liberated fatty acid is arachidonic acid, subsequent metabolism by the cyclooxygenase and the 5-lipoxygenase enzymes leads to the formation of prostaglandins, which play a major part in the inflammatory response, and leukotrienes, which play a main role in the pathogenesis of asthma.[19][20].

Scheme-1

(i) N, N-Dimethyloctadecanamide, $POCl_3$, benzene; (ii) aqueous KOH, EtOH; (iii) methyl p-toluenesulfonate, $(C_4\ H_9)4N+Br-$, powdered NaOH, $Et_2O$, $CH_2C_{12}$.

Scheme-2

(i) $NaBH_4$, $BF_3$,$Et_2O$, THF, methyl acetate; (ii) aqueous KOH, EtOH;



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Tricyclic indole-2-carboxylic acids highly invivo active and selective antagonists for the glycine binding site of the NMDA receptor.

A series of tricyclic indole-2-carboxylic acid derivatives were synthesized and evaluated by the radio ligand binding assay and the anticonvulsant effects in the mouse NMDA-induced seizure model. The N-methyl-D-aspartate (NMDA) receptor is a member of the glutamate receptor super family and plays important roles for neurotransmission in the central nervous system (CNS) and synaptic plasticity that underlies learning processes and memory.1 The NMDA receptor is associated with a ligand gated calcium ion channel which is activated by cooperation of glutamate and glycine2 and blocked by certain ion channel blockers3 such as phencyclidine (PCP) and dizocilpine (MK-801). Overactivation of the NMDA receptor is, however, thought to be involved in neuronal cell death caused by not only hypoxic conditions such as stroke but also chronic neurodegenerative disorders such as Alzheimer's and Huntington's diseases.[21].



Tricyclic NMDA antagonists acting on the glycine site.

**Materials and methods:**

A brief description of the solvents and reagents used here in the analytical procedures followed and different physio-chemical techniques like TLC, melting point, IR, $^{1}$HNMR and mass spectroscopic are employed for the characterization of the synthesized compounds. The organic solvents like ethanol (E-Merck), methanol (E-Merck),n-hexane(E-Merck),ethyl acetate (E-Merck),were of analytical reagent grade. Distilled water-double distilled water by quartz distillation unit.

**Reagents:**All the chemical reagents were obtained from the standard commercial sources unless otherwise indicated. Anhydrous sodium sulphate (Ranbaxy),

**Analytical techniques:**Thin-layer chromatography (TLC) was the method used to assess the reactions and the purity of the product. In this we used the TLC aluminium sheets-silica gel 60 F254 was purchased from Merck. The plates were developed using n-hexane: ethyl acetate (8:2) as mobile solvent. The spot was located by exposing the TLC plates to iodine vapours. Column chromatography was performed by using activated silica gel [60-120mesh] packed on to the glass column [450 X 40mm] with methanol as solvent. The crude product was loaded and eluted using mixture of n-hexane: ethyl acetate (8:2).The fraction was collected separately and active fraction was concentrated by using rota evaporator.

**Instrumentation:**Melting points of the compounds were determined using SELACO-650 and Veego VMP-III model hot stage melting point apparatus and are uncorrected. Identification and structure elucidation of newly synthesized compounds under study was carried out by using various spectroscopic techniques such as IR, $^{1}$HNMR, mass and elemental analysis. An instrument of FT-IR 021model was used for recording IR spectra of the synthesized compounds. About 2.0-



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3.0mg of compound was prepared as KBr pellet and the IR spectra were recorded.$^{1}$HNMR spectra were recorded on Joel GSX 400,400MHz, spectrophotometer using $CDCl_3$ and DMSO-$d_6$ as solvents with tetramethylsilane (TMS) as internal standard. Mass spectra of the synthesized compound were obtained using a Q-TOF Waters Ultima instrument (No-Q-Tof GAA 082, Water Corporation, and Manchester, UK) fitted with an Electron spray ionization (ESI) source. The data acquisition software used was Version 4.0.Elemental analysis was carried out on elemental Vario EL instrument. Oxygen was used for combustion and Helium as the mobile phase.



**Synthetic procedure: Step-1 Procedure**

An ethanolic solution of indole carboxylic acid (2 mmol) was added to solution of thiosemicarbazide (2 mmol) with constant stirring, few drop of conc. sulphuric acid was added and heated for 4 hours at 80-90 $^{0}$C, after completion of reaction (TLC), cool and poured to ice-cold water, basify with 10% $Na_2CO_3$ solution, filter, dried and recrystalised from suitable solvent.

General Procedure 4(a-d)

Compound (3) (2 mmol) with substituted benzaldehyde (2 mmol) in round bottom flasks was refluxed in 15 mL ethanol at 40 ºC for 3 h in the presence of 1.5 mL glacial acetic acid. In each case, the precipitated base was filtered off, recrystallized from absolute ethanol and dried in vacuum desiccators.

Scheme 2.1: Reaction protocol for the synthesis of benzofuranone derivatives via 4(a-d)

Table 2.1: Chemical structure, yield and melting point of synthesized derivatives 4(a-d)

| Compounds No | R-CHO | Yield | Melting Point |
|---|---|---|---|
| **(4a)** | | 96% | 186$^{0}$ |
| **(4b)** | | 98% | 180$^{0}$ |



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| | | |
|---|---|---|
| **(4c)** | 98% | $191^0$ |
| **(4d)** | 98% | $198^0$ |



Compound (4a)

| | | |
|---|---|---|
| **Physical Appearance** | White solid | |
| **Yield** | 96% | |
| **Molecular Formula** | $C_{17}H_{12}N_4OS$ | |
| **Molecular Weight** | 320.37 | |
| **IR(cm)** | (KBr)$\lambda_{max}$($Cm^{-1}$) 3420-3436 (N-H), 1624 (C=N) | |
| **$^1$H NMR (300 MHz, CDCl3, δ ppm)** | δ= 5.35(S, 1H, -OH), 6.77 (S, 1H, indole-H), 6.99-6.91 (m, 2H, Ar-H), 7.67 (t, 2H, Ar-H), 7.02-7.52 (m, 3H, Ar-H) ,8.36 (S, 1H, =N-H), 11.36 (1H,-NH) | |

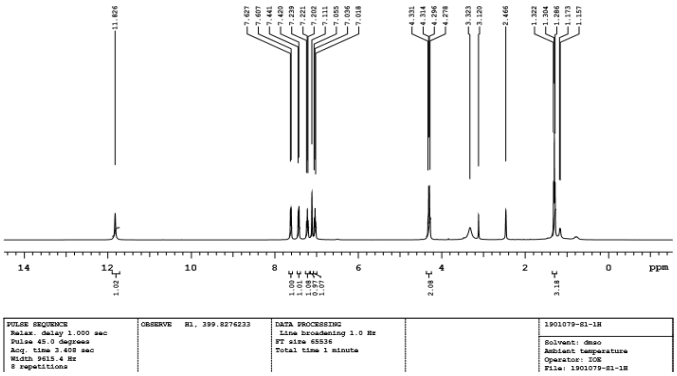


Figure 2.1: $^1$H NMR spectrum of compound 4(a)



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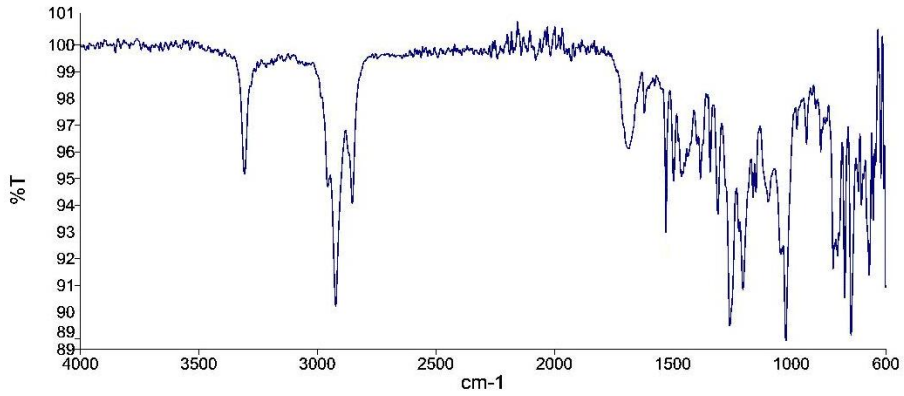


Figure 2.2: IR spectrum of compound 4(a)

Compound (4b)

| | | |
|---|---|---|
| **Physical Appearance** | Yellow Solid | |
| **Yield** | 98% | |
| **Molecular Formula** | $C_{19}H_{16}N_4O_2S$ | |
| **Molecular Weight** | 364.42 | |
| **IR(cm)** | (KBr)$\lambda_{max}$($Cm^{-1}$) 3433-3445 (N-H), 1620 (C=N) | |
| **$^1$H NMR (300 MHz, DMSO, δ ppm)** | δ= 3.83 (s, 6H, $OCH_3$), 6.77 (d,s,1H, Indole-H), 6.99-6.91 (m, 2H, Ar-H), 6.95 (m, 2H, Ar-H) ,7.39 (S,1H,Ar-H) ,7.54 (d, 1H, Ar-H), 7.67 (d,1H, Ar-H) | |

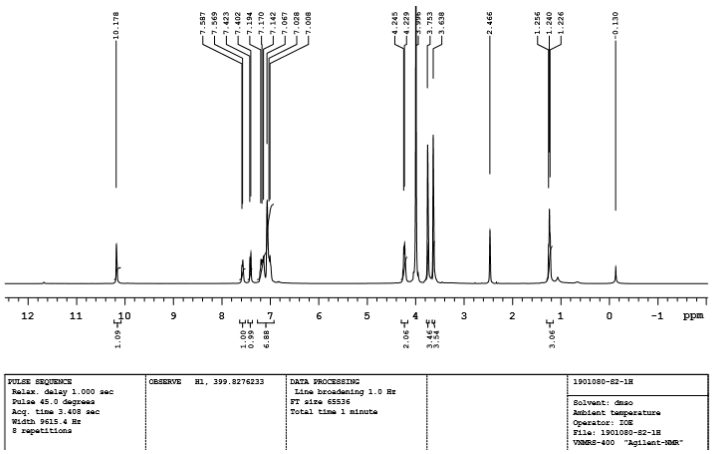


Figure 2.1: $^1$H NMR spectrum of compound (4b)

Compound (4c)



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| | |
|---|---|
| **Physical Appearance** | White Solid |
| **Yield** | 98% |
| **Molecular Formula** | $C_{17}H_{11}ClN_4S$ |
| **Molecular Weight** | 338.04 |
| **IR(cm)** | (KBr)$\lambda_{max}$($Cm^{-1}$) 3436-3440(N-H), 1624 (C=N) |
| **$^1$H NMR (300 MHz, DMSO, δ ppm)** | δ= 6.77 (S, 1H, Indole-H), 6.99 (m, 2H, Ar-H), 7.46-7.52 (m, 2H, Ar-H), 7.67-7.71 (2H, m, Ar-H), 7.91 (d,1H,Ar-H),8.36(s,1H,Indole-H), |

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Compound (4d)

| | |
|---|---|
| **Physical Appearance** | White Solid |
| **Yield** | 98% |
| **Molecular Formula** | $C_{18}H_{14}N_4S$ |
| **Molecular Weight** | 318.40 |
| **IR(cm)** | (KBr)$\lambda_{max}$($Cm^{-1}$) 3426-3435(N-H), 1622 (C=N) |
| **$^1$H NMR (300 MHz, DMSO, δ ppm)** | δ= 2.34 (S, 3H, -$CH_3$), 6.77 (S, 1H, Indole-H), 6.99-6.91 (m, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.54 (d, 1H, Ar-H), 7.67 (t, 1H, Ar-H), 8.36 (S, 1H ,=N-H), |

**Antimicrobial activity:** The search for the substances with antimicrobial activities is an important area of research. In view of the rapid development and also challenging demands in this area, it has become necessary for the scientists to synthesize and screen newer compounds for antimicrobial activity. It is well known fact that heterocyclic compound exhibits antimicrobial effect. This finds application as fungicides, bactericides, herbicides and insecticides. When such heterocyclic compounds are introduced with active functional moieties, they are found to exhibit enhanced microbial activities [37].

The chemical compounds that are toxic to the pathogens are controlling plant disease in the field, in the green house effect and sometimes in storage. The chemicals used oppose the germination, growth and multiplication of the pathogen or directly destroy it by toxicity. According to nature of the pathogen, against which the anti-pathogens are used may be called fungicides, bactericides, nematicides or vermicides. The importance of toxicity in the compounds containing nitrogen and sulphur has been well established in many fungicides.



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For the study of antibacterial activity, two bacterial strains viz., E.coli, and Staphylococcus aureus chosen. The antibacterial activity of a drug or test compound can be tested by wide range of techniques. In many techniques, the principle is the preparations of a concentration gradient of the test compound in a nutrient medium and the observation of growth or inhibition of growth of the organism takes place when the medium is seeded with test organism and incubated. Many factors such as kind of microorganism, the physiological state of the organism, temperature and the environment i.e., the physical and chemical properties of the medium or substance carrying the organism must be considered in the application of any chemical agent to inhibit or destroy microbial population.

**Antibacterial activity: Disc diffusion method**

Antibacterial activity of test compounds was determined against E.coli, and Staphylococcus aureus by Disc diffusion method. The pure cultures of these organisms were obtained from the Department of Botany, University of Mysore, Manasagangotri, and Mysuru-06.

**Resultsand Discussions:**

**Chemistry:**Several procedures were reported for the synthesis of 2-amino-1,3,4-thiadiazoles, in many of these reported methods the thiosemicarbazide was used as the starting material. Among the reported method carboxylic acid with thiosemicarbazide in presence of phosphorous halides was the most important method for the synthesis of 1,3,4,-thiadiazoles. In the present work indole fused thiazole derivatives were synthesized by refluxing the indole carboxylic acid and thiosemicarbazide in presence of phosphorus oxy chloride later coupling reaction was undertaken with deferent aldehydes (Scheme 1). The structures of the compounds were confirmed by $^{1}$H-NMR and IR spectrum.

**Antibacterial activity:** To identify the novel antibacterial efficiency of newly synthesized compounds against bacterial strains in comparison with the standard. Among the tested compounds, compound (4c) was found to show appreciable activity against all bacterial strains (Table 3.1). According to the Structure Activity Relationship (SAR), it is clear that the introduction of chloro substituted on aldehyde moieties to amine-thiazole is more active than the other analogues. Whereas, the tested compounds (4a), (4b) and (4d) have also demonstrated average activity. It is concluded that the presence of 4-chloro aledhyde substitution to =NH2 bond of thiazole system causes significant increase in antibacterial activity.Table 3.1. Inhibitory zone (diameter) mm of the synthesized compounds (4a-d) against tested bacterial strains by well plate method. Each value represents mean ± SD (n=3)

| **Compound** | **Escherichia coli** | | **Staphylococcus aureus** | |
|---|---|---|---|---|
| | 1000 | 500 | 1000 | 500 |
| | **Concentration (µg/mL)** | | | |



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| | | | | |
|---|---|---|---|---|
| **(4a)** | 5±0.02 | 3±0.03 | 1±0.01 | 1±0.01 |
| **(4b)** | 6±0.00 | 4±0.03 | 3±0.01 | 2±0.02 |
| **(4c)** | 18±0.02 | 15±0.01 | 11±0.01 | 8±0.02 |
| **(4d)** | 10±0.04 | 7±0.03 | 6±0.01 | 3±0.01 |
| **Streptomycin** | 22±0.03 | 19±0.01 | 17±0.02 | 15±0.01 |



**Conclusion**

We have created a number of indole fused thaizole derivatives during the course of our research (4a-d). This approach replicates the practical protocol for the target chemicals. Using the disc diffusion method, the produced compounds are assessed for their antibacterial activity. Among the produced analogues, compound (4c) showed the strongest suppression of antibacterial activity, comparable to that of streptomycin. Other derivatives, however, show less action.As a result, our research may show that the interaction of acid with thiasemicarbazide and substituted aldehyde derivatives has an intriguing antibacterial activity. Our research may be helpful both in academia and in the treatment of disorders where free radical oxidation is a key factor. This might call for more thorough biological evolution.

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Figure 1: Molecular mechanisms of



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action of indole and its metabolites on host physiology and disease.

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