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Synthesis, characterization and pharmacological evaluation of novel Indole derivatives

Sumander Reddy Asireddy, Abhilash Avuti, Narender Boggula, Vasudha Bakshi and Ramadevi Kyatham

Abstract
Back ground: Indoles and their derivatives are common heterocyclic compounds in nature. The Indole ring system is an important structural component in many drugs.
Objectives: The present study aims to synthesize novel Indole derivatives and the compounds were evaluated for their *in vitro* anti-microbial activity.
Methods: Novel Indole derivatives were synthesized from indole-3-aldehyde and benzaldehyde. And they were evaluated *in vitro* anti-microbial activity by using cup plate method.
Results: A series of newly synthesized compounds were characterized by physical data and IR spectra. The synthesized compounds were showed significant anti-microbial activity.
Conclusion: The synthesized compounds exhibited good anti-microbial activity in comparison with standard drug streptomycin. These data present a series of new Indole compounds with potential therapeutic effects in microbial diseases.

Keywords: Indole, anti-microbial activity, heterocycles, streptomycin, cup plate method, agar media

Introduction
Heterocyclic compounds are occupying a prime place in heterocyclic chemistry owing to their valuable properties as therapeutic agents, drugs, dyestuffs etc. These compounds are reported to possess antimicrobial, anti-inflammatory, anti-diabetic, heamoregulatory, blood platelet aggregation inhibiting property and also the pesticidal properties. It is also reported in various journals that these compounds are showing very good antibiotic activities. The heterocyclic compounds are very widely distributed in nature and are essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found in nature, nitrogen heterocycles are the most abundant, especially those containing oxygen or sulphur due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals.
Indoles and their derivatives are common heterocyclic compounds in nature. The Indole ring system is an important structural component in many drugs. Indole is a bicyclic aromatic heterocyclic compound which is benzene fused through 2 and 3 position of pyrrole ring.

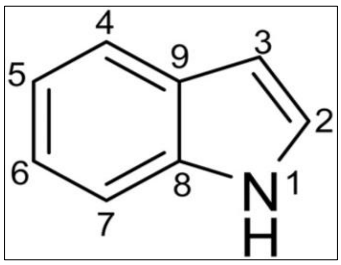


Fig 1: Structure of Indole

Indole has 10 π electrons arising from double bonds and lone pair on nitrogen which are delocalized around the Indole ring. In all resonance structures, some negativity and increased electron density on carbon atoms lead to their description as π-excessive. Because of the delocalization of 10 electrons on 9 atoms (eight carbons and one nitrogen), Indole is called as a π-excessive heterocycle. Because of the π-excessive property, Indole shows enhanced reactivity in electrophilic aromatic substitution, compared to benzene.

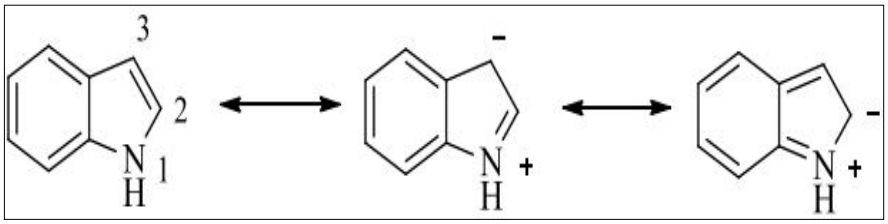


Fig 2: Resonance structures of Indole

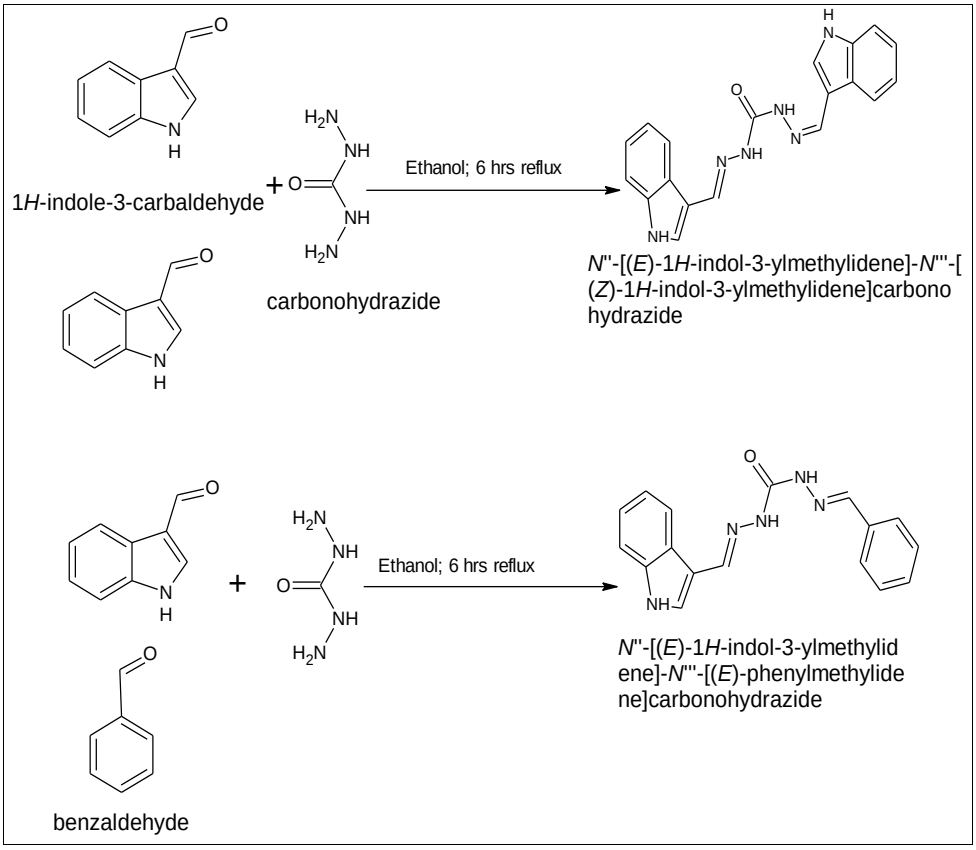
As lone pair of nitrogen is involved in aromatic ring, current Indole behaves as a weak base, like pyrrole. So, Indole and its derivatives are quite reactive towards strong acids. As a result of various molecular orbital calculations, the C-3 site of Indole has the highest electron density and it is the most reactive position towards electrophilic substitution reactions. The C-2 position is the second most reactive site of Indole toward electrophiles. The N-H bond in the Indole skeleton is weakly acidic. Strong bases can be used to deprotonate the N-H proton. So, under basic conditions, N-substitution reactions, such as alkylations, acylations and transition metal catalyzed arylations take place. Indole skeleton is present in the structure of many natural products with high structural complexities and biologically active molecules. For this reason, Indole and Indole derivatives have been used, continuously, in different research areas such as pharmaceuticals, fragrances, agrochemicals, pigments, and material science. Indole and several of their derivatives have been generally associated with various biological and pharmacological properties.

The synthesis of a large number of Indole derivatives have been described to obtain biologically potent compounds. Many such compounds have been found to be promising. A few even have clinical application also. This prominence aroused interest to several chemists and medicinal chemists to prepare day to day newer and newer potential Indole derivatives by molecular conjunction approach and evaluating them for possible pharmacological actions. Since there have been numerous reports, it is highly impossible to cover all such reports in a single review. The present survey aims to synthesize some of new Indole derivatives of specific biological and pharmacological activity and looking for such activity (or) activities by their evaluation experimentally.

The emergence of human pathogenic microorganisms which is resistant to major classes of antibiotics has increased in recent years, due to the indiscriminate use of antimicrobial drugs. This has caused many clinical problems in the treatment of infectious diseases, and the antibiotics that are commonly used are sometimes associated with adverse effects such as hypersensitivity, allergic reactions, and immunosuppression in the host. Thus, the discovery of new antimicrobial agents is an urgent need. The situation seems to be worse in developing countries where many people with life-threatening infections may have no access to effective antimicrobials due to economic constrains. The objective of present study is to synthesize novel Indole derivatives and the compounds were evaluated for their *in vitro* anti-microbial activity.

Materials and methods

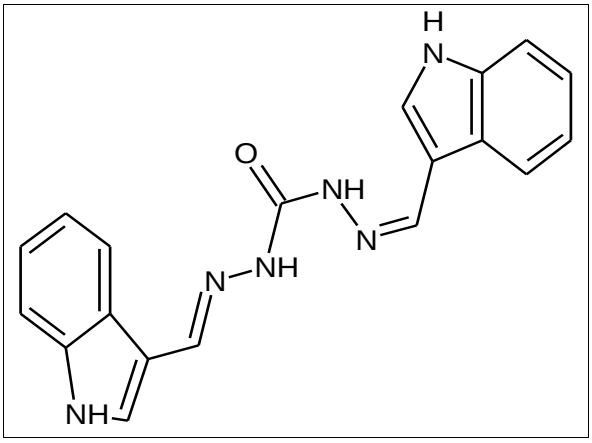
Scheme of work



Procedure

Sample 1

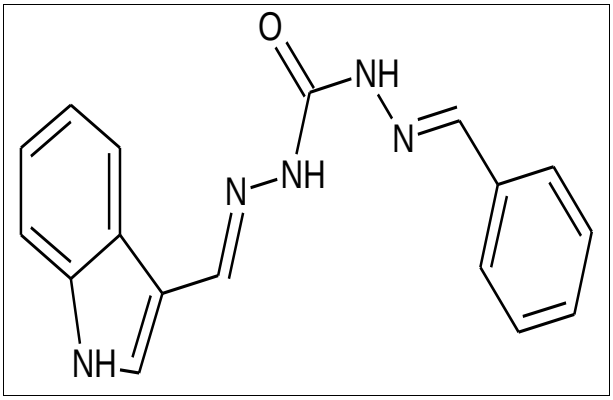
Aqueous solution of corresponding indole-3-aldehyde 2 equivalents in ethanol (20 ml) added slowly to a solution of carbohydrazide 1 equivalent in H_2O (20 ml). A clear solution was obtained after the addition of above solution. Reflux the mixture/solution for 6 hours maintaining the temperature of about 60-70 ^{0}C. At predetermined time intervals, sample was collected and checked for TLC. The compound-1 *N*"-[(*E*)-1*H*-indol-3-ylmethylidene]-*N*"'-[(*Z*)-1*H*-indol-3-ylmethylidene] carbonohydrazide was obtained.



N"-[(*E*)-1*H*-indol-3-yl methylidene]-*N*"'-[(*Z*)-1*H*- indol-3-ylmethylidene] carbonohydrazide

Sample 2

Aqueous solution of corresponding benzaldehyde 2 equivalent in ethanol (20 ml) added slowly to a solution of carbohydrazide 1 equivalent in H_2O (20 ml). A clear solution was obtained after the addition of above solution. Reflux the mixture/solution for 6 hours maintaining the temperature of about 60-70 ^{0}C. At predetermined time intervals, sample was collected and checked for TLC. The compound-2 *N*"-[(*E*)-1*H*-indol-3-ylmethylidene]-*N*"'-[(*E*)-phenylmethylidene] carbonohydrazide was obtained.



N"-[(*E*)-1*H*-indol-3-ylmethylidene]-*N*"'-[(*E*)-phenylmethylidene] carbonohydrazide

Pharmacological evaluation

Anti-microbial activity

The anti-microbial activity can be evaluated by the following techniques

1. Agar streak dilution method
2. Serial dilution method
3. Agar diffusion method
   a. Cup plate method
   b. Cylinder plate method
   c. Paper disc method

In the present study, the agar diffusion technique, cup plate method was used to evaluate the *in vitro* anti-microbial activity of the synthesized compounds.

Procedure

The anti-microbial activity was tested by determining the minimum inhibitory concentration (MIC) for each compound using cup plate method. The following organisms were used in research work.

- Gram –ve bacteria: *Staphylococcus aureus Bacillus subtilis*
- Gram +ve bacteria: *Escherichia coli Pseudomonas*

Prepared stock solutions of given antibiotic i.e. streptomycin and the synthesized samples are diluted. Prepared agar media and nutrient media, by sterilising in an autoclave at 121^{0}C at 151 PSI for 15 minutes. A loopful of the above mentioned cultures were dissolved in mixture of distilled water and to this the sample and streptomycin was added. Then pour the nutrient media into the petriplates until a uniform layer was formed and allow it to solidify. With the help of a cork borer, cut the reservoir at 3 different places indicating low, medium and high concentration zones. Labelled the zones as 10µg/ml, 20µg/ml and 30µg/ml, added the samples into the zones respectively. Allowed it to solidify at room temperature and then kept in a refrigerator for 10 minutes. Then placed all the petriplates in the incubator and set the temperature at 37 ^{0}C and incubated for 24 hours.

Results and discussion

All the synthesized compounds were characterized and screened for their anti-microbial activity.

Table 1: Physical data of novel Indole derivatives

Code	Mol. Formula	Mol. Weight	%Yield	M.P. (^{0}C)
Compound 1	$C_{19}H_{16}N_6O$	344	86	156-158
Compound 2	$C_{17}H_{15}N_5O$	305	88	140-142

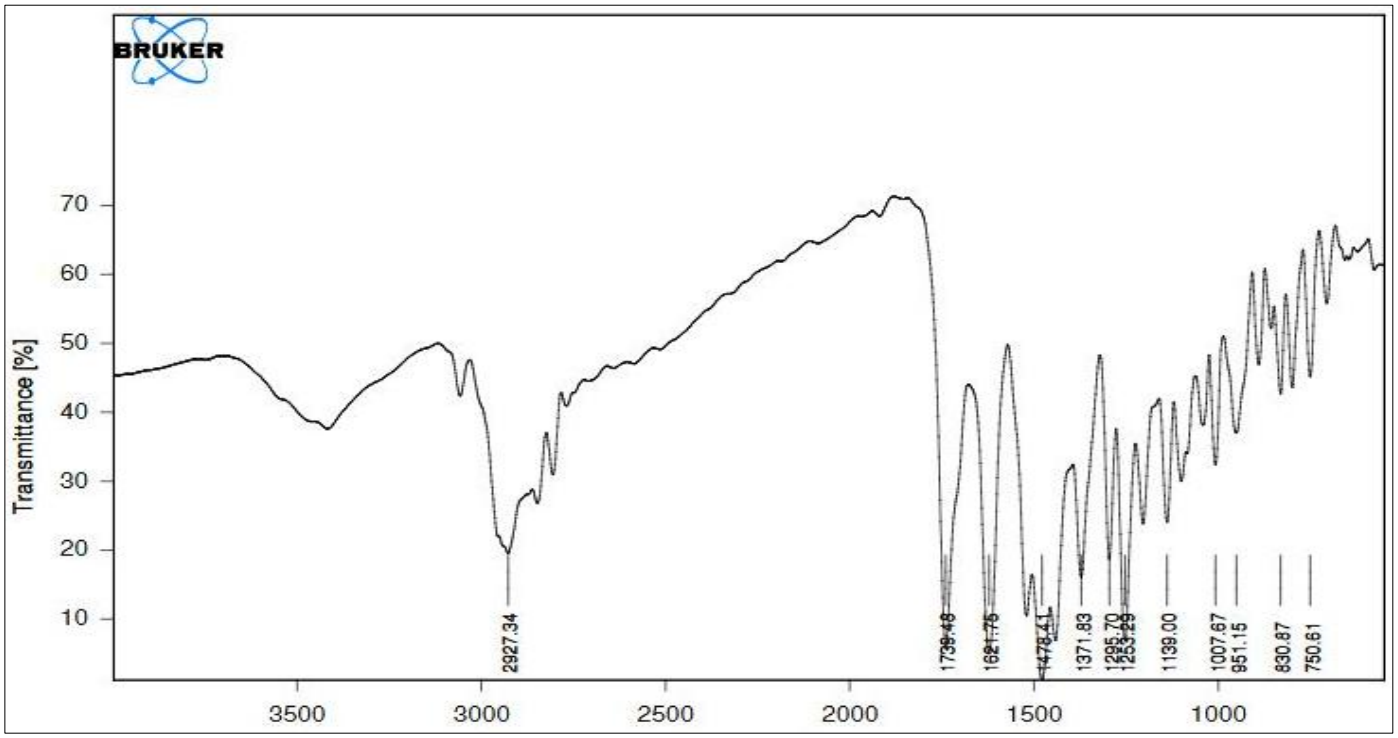


Fig 3: IR spectra of compound-1

IR Spectra: C-H Stretching was observed at 2927cm$^{-1,}$ N-H Stretching was observed at 3650cm^{-1}, N-H Stretching was observed at 3490cm^{-1}, N-H Stretching was observed at 3400cm^{-1}, N-H Stretching was observed at 3100cm^{-1}.

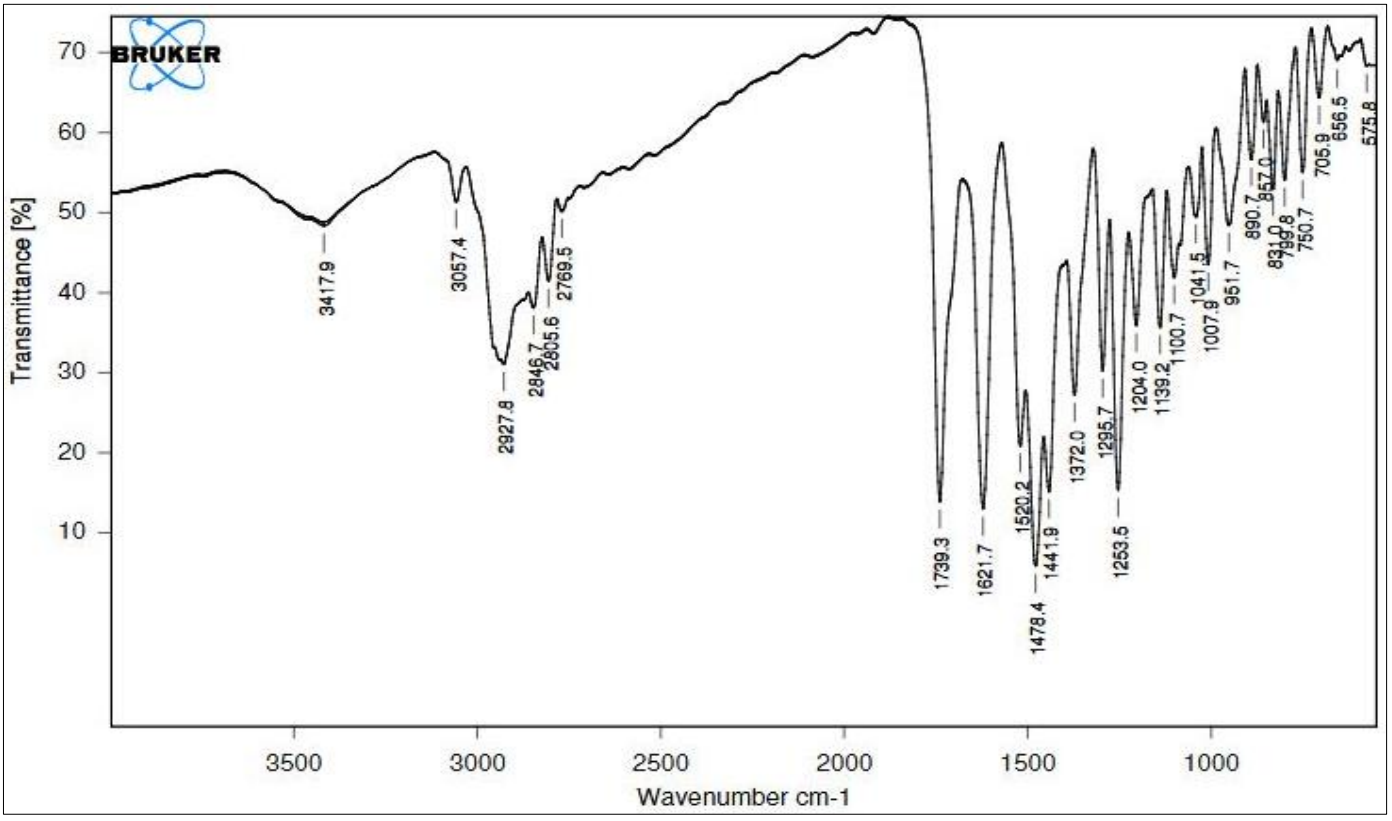


Fig 4: IR spectra of compound-2

IR Spectra: N-H Stretching was observed at 3417cm^{-1}, N-H Stretching was observed at 3540cm^{-1}, N-H Stretching was observed at 3400cm^{-1}, N-H Stretching was observed at 3057cm^{-1}, C-H Stretching was observed at 2927cm^{-1}, C=O Stretching was observed at 1739cm^{-1}.

***In vitro* anti-microbial activity**

All the synthesized derivatives were screened for their *in-vitro* anti-microbial by using activity cup plate method.

Table 2: Anti-microbial activity of compound 1 & compound 2

Samples	Cultures	10µg/ml	20µg/ml	30µg/ml
Standard (Streptomycin)	*Pseudomonas*	3.8	4.8	4.5
	Bacillus subtilis	4.1	5.0	4.6
	Escherichia coli	4.2	3.8	4.5
	Staphylococcus aureus	4.6	4.6	5.3
Compound-1	*Pseudomonas*	1.7	2.2	2.6
	Bacillus subtilis	2.5	3.6	3.9
	Escherichia coli	3.4	3.6	4.0
	Staphylococcus aureus	3.0	3.8	3.4
Compound-2	*Pseudomonas*	2.0	2.4	2.7
	Bacillus subtilis	2.8	3.4	4.1
	Escherichia coli	2.5	3.4	3.7
	Staphylococcus aureus	2.7	3.6	4.0

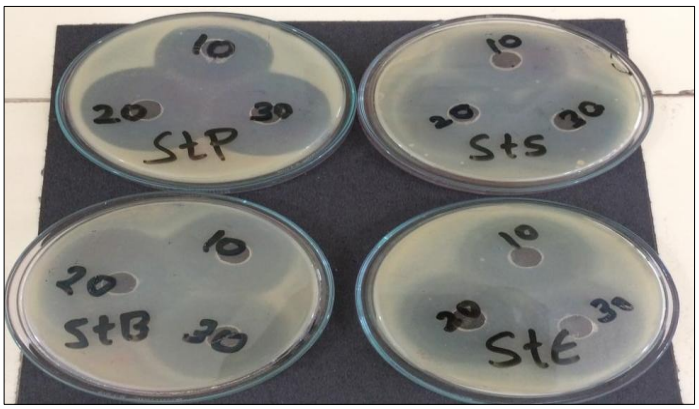


Fig 5: Zone of inhibition for standard drug Streptomycin

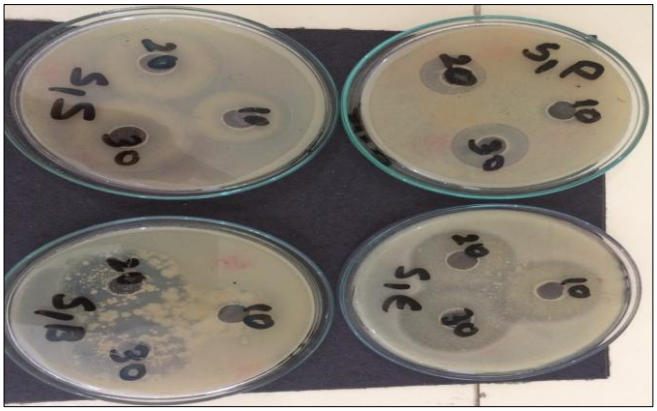


Fig 6: Zone of inhibition for compound-1

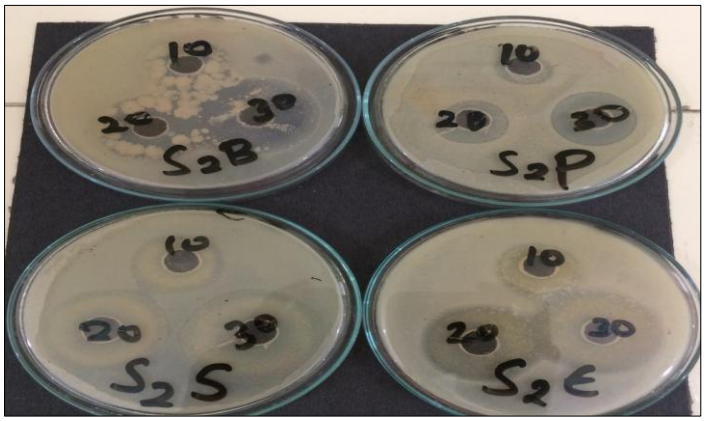


Fig 7: Zone of inhibition for compound-2

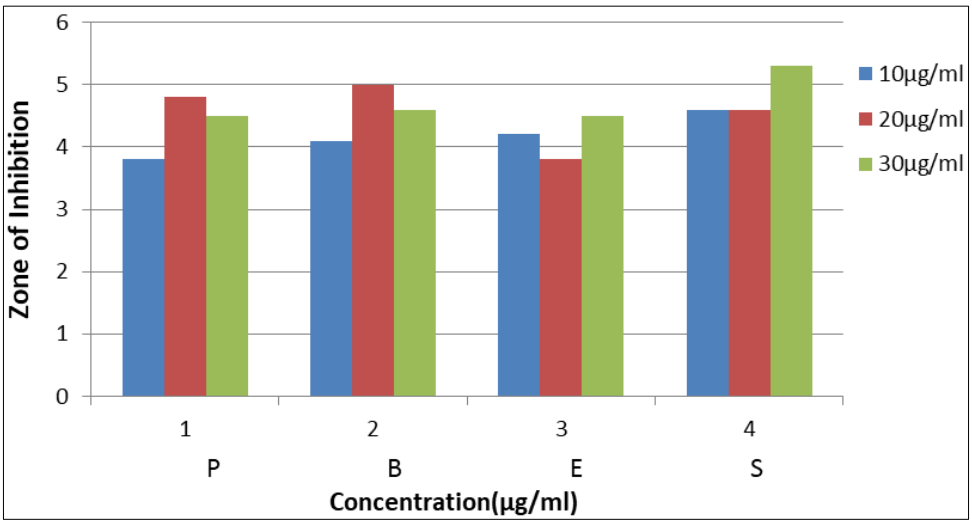


Fig 8: Zone of inhibition for standard drug Streptomycin

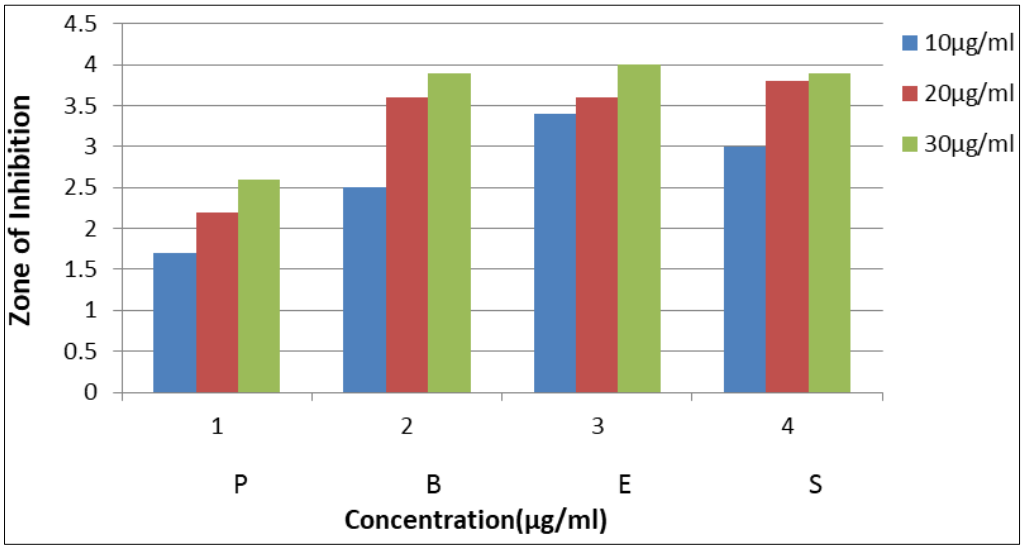


Fig 9: Zone of inhibition for compound-1

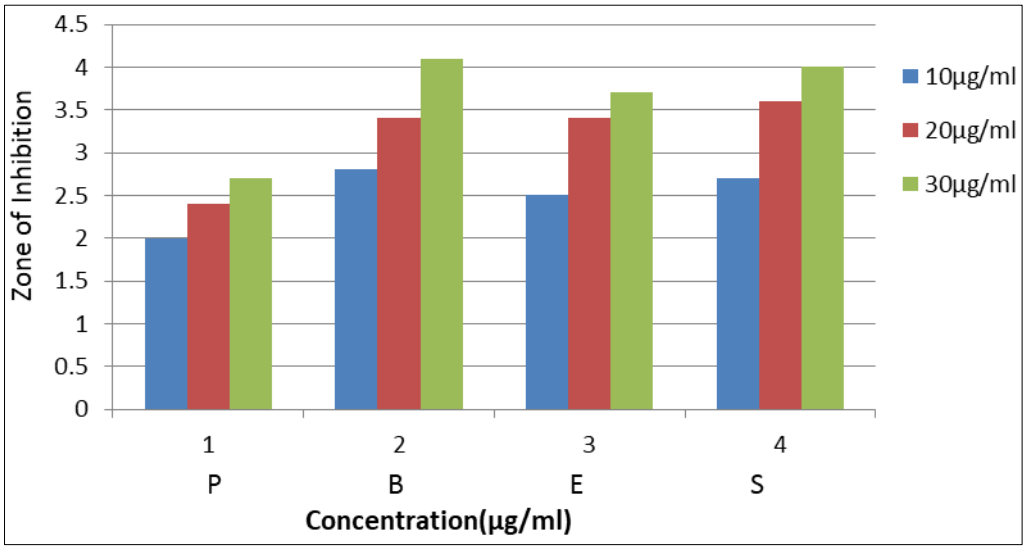


Fig 10: Zone of inhibition for compound-2

Conclusion

We synthesised two Indole derivatives naming *N*"-[(*E*)-1*H*-indol-3-yl methylidene]-*N*"'-[(*Z*)-1*H*-indol-3-ylmethylidene] carbonohydrazide and *N*"-[(*E*)-1*H*-indol-3-yl methylidene]-*N*"'-[(*E*) phenylmethylidene] carbonohydrazide which were confirmed by physical data and IR spectroscopy. Among the synthesized derivatives, compound-1 had shown good activity against *E. coli* and *Staphylococcus*; compound 2 had shown good activity against *Bacillus subtilis* and *Staphylococcus* when compared with standard drug streptomycin. As heterocyclic rings are abundantly present in nature, Indole is commonly found in biologically active natural products and pharmaceuticals. Due to this there has been increased interest in the use of Indole derivatives against many diseases. Further we can conclude that many other derivatives of Indole can be synthesized which will be expected to show potent pharmacological activities in future. Further investigations with appropriate structural modification of title compound may result in therapeutically useful products.

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Authors' Contributions

All authors have made considerable contributions to the work reported in the manuscript.

Conflicts of interest

The authors confirm that this article content has no conflicts of interest.

Sponsorship

Nil.

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