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Synthesis of some novel 1H-indole derivatives with antibacterial activity and antifungal activity

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ABSTRACT

The present research works a series of new 1H-Indole derivatives were synthesized. The title compound was obtained by the reaction of indole with chloroacetylchloride in toluene afforded 2-chloro-1-(indoline-1-yl) ethanone which reacts with 1,4 diamine benzene in chloroform afforded 2-((4-aminophenyl)amino)-1-(1H-indol-1-yl)ethan-1-one, on further reaction with various acetophenone in presence of acetic acid in ethanol gave various final derivatives. After synthesis of compounds, the synthesized compounds were characterized by their IR, 1HNMR spectral data and elemental analysis. These derivatives were screened for their antimicrobial activity (*Paper-disk-plate technique (disc diffusion method)* and *Tube-dilution technique (broth microdilution technique)*, antifungal activity of all synthesized compounds were evaluated against *Aspergillus niger* and *Candida albicans* (ATCC 10231) using Fluconazole as the standard drug using the paper plate method and antibacterial activity against both Gram-positive (***Bacillus subtilis***) and Gram-negative bacteria (***Escherichia coli***) using Ampicillin as standard medication at a concentration of 50µg/ml, 100µg/ml. The collected compounds were evaluated for antibacterial activity and antifungal activity. All compounds exhibit significant antimicrobial activity.

Keywords: *Indole; Antimicrobial activity; Staphylococcus; Antibacterial activity; Bacillus subtilis; Escherichia coli.*

1. INTRODUCTION

Serious infections caused by commonly used antimicrobial-resistant microorganisms have become major health problems of the 21st century, leading to significant increases in morbidity and mortality, prolonged hospital stays and high medical costs. Recognizing the seriousness of this challenge, the World Health Organization (WHO) chose the theme "Antimicrobial resistance: no action today, no treatment tomorrow as the theme for the 2011 World Health Day as a preventive measure [1]. The agents which are valuable against microbes such as bacteria, fungi, and virus are known as Antimicrobial agents. In recent years, the availability of new antimicrobials worldwide is lower than in recent years. During the 37 years, no antimicrobial drug has been developed between the addition of nalidixic acid (1962) and linezolid (2000), and all antimicrobial drugs on the market have been replaced by existing medicine. The growth of a new antimicrobial agent is very expensive and time-consuming, leading to a decrease in the interest of the existing pharmaceutical industry. On average, antiretroviral drug research and development takes 15-20 years and can cost over $ 1 billion [2]. The first antibacterial agent in the world was safety, a remedy for syphilis synthesized by Ehrlich in 1910. In 1935, sulfonamides were developed by Domagk and other researchers. The drug is a synthetic compound and presented safety and efficacy limits [3]. 1928, Fleming discovered penicillin. He discovered that the growth of Staphylococcus aureus was suppressed in a culture vessel surrounded by a contaminated blue mold (Penicilliumgenus fungus), and it was determined that the microorganism would produce substances that could inhibit the growth of other microorganisms. The antibiotic was called penicillin and was used clinically in the 1940s. Penicillin, which is rare in terms of safety and efficacy, has led to antimicrobial chemotherapy that saves the lives of wounded soldiers during World War II [4].

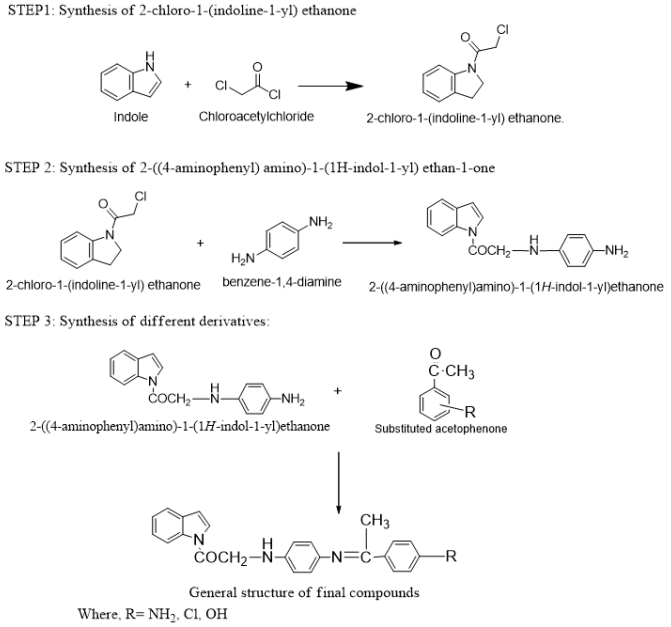

Figure 1. Synthesis scheme of 1H-Indole derivatives.

In the next two decades, new Antimicrobials classes, which led to the golden age of Bacteria was developed. In 1944, streptomycin, an aminoglycoside antibiotic, from soil bacteria Streptomycin gracious. Then, from a soil bacteria were detected chloramphenicol, tetracycline, macrolide and glycopeptide (e.g. Vancomycin). Nalidixic acid and a synthetic antimicrobial agent, a quinolone Antimicrobial obtained in the year 1962 [3].

Antimicrobials developed in the last 60 years are one of the most dramatic examples of modern drugs. Many infectious diseases

previously considered incurable and deadly are now being punished for treatment with fewer pills. The strong and specific activity of antimicrobials is due to their selection for a very specific purpose that is unique to a microorganism or more important to humans. Among these objectives are specific fungal and bacterial cell synthesis enzymes, (beta-lactam antibiotics and antifungal agents), the bacterial ribosome (Chloramphenicol, Tetracycline, Macrolide, Clindamycin, Aminoglycosides, and Streptomycin), the enzyme required for nucleotide synthesis and DNA replication (sulphonamides, Trimethoprim, Quinolones) and virus replication mechanism. These agents also include Mycobacterium infections, disinfectants, and specific drugs used for selected pathogens. Overuse and misuse of antibiotics have led to a significant increase in the prevalence of various drug-resistant pathogens, leading some to believe that we are near the end of the antibiotic chain. Unfortunately, as demand has increased in recent years, the development of new drugs has slowed down. The most sensitive molecular targets of antimicrobial drugs have been identified, and in most cases, their crystallization and characterization. Given the continued development of resistance, significant efforts will be required to maintain drug efficacy and to seek new antimicrobial agents [5,6].

The synthetic procedures mainly based upon structure modification to found a molecule, which has improved safety profile. Among the derivatives of indole, there is a huge quantity of compounds, which display anti-inflammatory activity [8-10]. Indole derivatives are under the category of synthetic compounds with a wide variety of pharmacological activities in the accumulation with anti-inflammatory activity such as antimicrobial [11, 12], analgesic [13], hypoglycaemic [14] anticancer [15], anticonvulsant [16], etc.

In our attempt to find out more effective and safer agents for the dealing of antimicrobial activity conditions, we report the synthesis, spectral characterization (IR, 1HNMR and Mass spectra) and pharmacological evaluation of a series of 2-((4-aminophenyl)amino)-1-(1H-indol-1-yl)ethan-1-one derivatives.

The reaction scheme is presented in figure 1.

2. MATERIALS AND METHODS

All research chemicals were purchased from CDH (Central Drug House Pvt. Ltd, New Delhi, India) and used as such to obtain such reactions. The solvents were dried and purified before use, according to standard procedures. All solvents and anhydrous solutions were transferred through syringes and cannulae previously dried in the oven for at least 12 h and kept in desiccators with KOH. The melting points of the prepared compounds as well as intermediates were determined by open capillary methods and were uncorrected. Thin-layer chromatography (TLC) using coated silica gel plates followed the progress of the reactions; use iodine fumes for spots detection. All glassware was washed with distilled water, dried in an oven, packed in brown paper & then autoclaved at 15 lb/inch^2 pressure (121^0 C) for 15 min.

2.1. Infrared spectroscopy.

The IR spectra of the synthetic compounds were recorded on a potassium bromide channel plate and a SHTMADZU MODEL 8300 FT-IR spectrophotometer at Dr. Bhim Rao Ambedkar University in Lucknow.

2.2. Nuclear magnetic resonance spectroscopy.

^{1}H-NMR spectra of synthesized compounds were recorded in DMSO (dimethyl sulfoxide) using a 300 MHz spectrophotometer using MODEL AV-300 BROKE JES., at IIT, Roorkee. Chemical shifts were recorded in parts per million (ppm, δ) and signals were recorded as s(singlet), d(doublet), t(triplet), q(quatret) and m(multiplet).

Synthesis of 2-chloro-1-(indoline-1-yl) ethanone (A).

Indole (0.02 moles) was dissolved in toluene (100 ml) in a dry 250 ml RBF and heated under reflux. In this refluxing solution, slowly added dropwise chloroacetylchloride (0.01 moles) dissolved in toluene. The reaction mixture was then refluxed for 3 hours. The precipitate was filtered, dried and recrystallized from the appropriate solvent ethanol. The synthesis scheme presented in Figure 1.

Synthesis of 2-((4-aminophenyl) amino)-1-(1H-indol-1-yl) ethan-1-one (B).

An Equimolar amount of compound 1 (0.1 moles) and 1,4diamine benzene (0.1 moles) in chloroform was refluxed in the presence of K_2CO_3 (0.1 moles). Excess solvent was removed in vacuum and the residue was mixed with water, filtered, washed with 2% $NaHCO_3$ and then water. The crude product is crystalline from methanol.

IR (KBr) cm-1: 1525 (C=C Str. Aro.); 1162 (C-N Str.); 3053 (C=H Str.); 3265 (N-H Str.); 1690 (C=O Str.); 747 (C-H Bend.); **1H-NMR (300 MHz, DMSO) δ (ppm):** 6.35-7.93 (10 H, Aro.); 6.24 (2H, NH_2); 4.15 (2H,CH_2); 3.8 (1H, NH).

2.3. General method for the preparation of indole derivatives (C-1 TO C-5).

2-((4-((1-(3-aminophenyl) ethylidene) amino) phenyl) amino)-1-(1H-indol-1-yl) ethanone(C-1)

0.002 mole 2-((4-aminophenyl) amino)-(indolin-1-yl) ethanone (A) was dissolved in 100 ml of ethanol in an RBF and 0.002 moles of 3-amino acetophenone (C-1) was added and 4-5 glacial acetic acid droplets were added. The reaction mixture was stirred for 26 hours. The reaction mixture was concentrated and kept overnight in the refrigerator to afford the product. The product was filtered and recrystallized with ethanol. **IR (KBr) cm-1: 1450 (**C=C Str. Aro.**); 1235 (**C-N Str.**); 3052 (**C=H Str.**); 3048 (**N-H Str.**); 1669 (**C=O Str.**); 748 (**C-H Bend.**); 1H-NMR (300 MHz, DMSO) δ (ppm):** 6.48-8.10 (13H, Aro.); 6.23 (2H,NH_2); 4.15 (2H,CH_2); 4.00 (1H,NH); 1.80 (3H,CH_3).

2-((4-((1-(4-hydroxyphenyl) ethylidene) amino) phenyl) amino)-1-(1H-indol-1-yl) ethanone(C-2)

0.002 mole 2-((4-aminophenyl) amino)-(indolin-1-yl) ethanone (A) was dissolved in 100 ml of ethanol in an RBF and 0.002 moles of 4-hydroxy acetophenone (C-2) was added and 4-5 glacial acetic acid droplets were added. The reaction mixture was stirred for 26 hours. The reaction mixture was concentrated and kept overnight in the refrigerator to afford the product. The product was filtered and recrystallized with ethanol. **IR (KBr) cm-1: 1550 (**C=C Str. Aro.**); 1665 (**C-N Str.**); 2905 (**C=H Str.**); 3410 (**N-H Str.**); 1660 (**C=O Str.); 1580 (C=N Str.); 1165 (O-H); **1H-NMR (300 MHz, DMSO) δ (ppm):** 6.50-8.00 (13H, Aro.); 4.13 (2H,CH_2); 4.00 (1H, NH); 1.82 (3H, CH_3).

2-((4-((1-(4-aminophenyl) ethylidene) amino) phenyl) amino)-1-(1H-indol-1-yl) ethanone (C-3)

0.002 mole 2-((4-aminophenyl) amino)-(indolin-1-yl) ethanone (A) was dissolved in 100 ml of ethanol in an RBF and 0.002 moles of 4-amino acetophenone (C-3) was added and 4-5 glacial acetic acid droplets were added. The reaction mixture was stirred for 26 hours. The reaction mixture was concentrated and kept overnight in the refrigerator to afford the product. The product was filtered and recrystallized with ethanol. **IR (KBr) cm-1: 1497 (**C=C Str. Aro.**); 1177 (**C-N Str.**); 3055 (**C=H Str.**); 3042 (**N-H Str.**); 1676 (**C=O Str.**); 1620 (**C=N Str.**); 1H-NMR (300 MHz, DMSO) δ (ppm):** 6.50-8.10 (13H, Aro.); 6.25 (2H, NH_2); 4.16 (2H, CH_2); 4.00 (1H, NH); 1.80 (3H, CH_3).

1-(1H-indol-1-yl)-2-((4-((1-(4-nitrophenyl) ethylidene) amino) phenyl) amino) ethanone(C-4)

0.002 mole 2-((4-aminophenyl) amino)-(indolin-1-yl) ethanone (A) was dissolved in 100 ml of ethanol in an RBF and 0.002 moles of 4-nitro acetophenone (C-4) was added and 4-5 glacial acetic acid droplets were added. The reaction mixture was stirred for 26 hours. The reaction mixture was concentrated and kept overnight in the refrigerator to afford the product. The product was filtered and recrystallized with ethanol. **IR (KBr) cm-1: 1529 (C=C Str. Aro.); 1253 (**C-N Str.**); 3413 (**N-H Str.**); 1664 (**C=O Str.**); 744 (**C-H Bend.**); 1611 (**C=N Str.**); 1H-NMR (300 MHz, DMSO) δ (ppm):** 6.50-8.11 (13H, Aro.); 1.82 (3H, CH_3); 4.17 ()2H, CH_2); 4.00 (1H, NH).

2-((4-((1-(4-chlorophenyl) ethylidene) amino) phenyl) amino)-1-(1H-indol-1-yl) ethanone(C-5)

0.002 mole 2-((4-aminophenyl) amino)-(indolin-1-yl) ethanone (A) was dissolved in 100 ml of ethanol in an RBF and 0.002 moles of 4-chloroacetophenone (C-5) was added and 4-5 glacial acetic acid droplets were added. The reaction mixture was stirred for 26 hours. The reaction mixture was concentrated and kept overnight in the refrigerator to afford the product. The product was filtered and recrystallized with ethanol. **IR (KBr) cm-1: 1498 (**C=C Str. Aro.**); 1260 (**C-N Str.**); 3066 (**C=H Str.**); 3359 (**N-H Str.**); 1675 (**C=O Str.**); 825 (**C-He Bend.**); 1614 (**C=N Str.**); 747 (**C-Cl Str.**); 1H-NMR (300 MHz, DMSO) δ (ppm):** 6.49-7.9 (13H, Aro.); 4.14 (2H, CH_2); 4.00 (1H, NH); 1.79 (3H, CH_3).

2.4. Biological Studies.

2.4.1. Antimicrobial Activity.

The paper-disk-plate technique (disc diffusion method)

The sensitivity test is performed to determine the range of microorganisms susceptible to mixing under specific conditions. This can be done by distributing the disk. This method is suitable for organisms that grow well at night, such as aerobic anaerobes and normal faculties and fast-growing fungi. This method depends exclusively on the dissemination of the drug from the disc, and the multiplication of the microorganism is generally avoided in the area around the disc absorbed in the drug solution. The inhibition zone around the disc (clear zone) indicates that the body was inhibited by this drug, which was dispersed in agar.

Tube-dilution technique (broth microdilution technique)

The dilution sensitivity method is used to determine the minimum concentration, usually expressed as units or micro-organisms/ml of an agent, necessary to prevent or destroy micro-organisms. Methods for determining antibacterial activity are due to agar or broth base method.

By this method, one can determine the smallest amount of drug substances required to reduce the development of the organism in vitro, this method is referred to as the MIC (Minimum inhibitory concentration). MIC can be determined by the tube dilution technique. Antioxidants are regularly tested at 10 g of sub-dose (2) (twice) of the concentration, and the lowest concentration prevents the growth of the observed organism, which is registered as MIC.

2.4.2. Determination of antibacterial activity.

To determine the antibacterial activity of the synthesized compounds, the inhibition zone (a clear area) around the disc is measured, indicating that the organism inhibited the organism that spread from the disc into the agar. To determine the zone of inhibition Paper disk plate technique was used.

2.4.3. Antifungal Activity.

All the synthesized compounds were evaluated for their antifungal activity against *Aspergillus niger* and *Candida albicans* (ATCC 10231) using Fluconazole as a standard drug by Paper disk plate technique. We have adopted the same method as described in section 4.3.2 except the culture medium and incubation period. Sabouraud dextrose agar was used as a culture medium and the plates were incubated at 25°C for 48 hours. The standard and test compounds were treated at a concentration of 100µg/ml. The solvent control i.e. DMF did not show any activity.

2.4.4. Paper disk plate technique (determination of zone of inhibition)

Preparation of solution of synthetic compound

The 25 mg weight of each correctly formed compound was transferred to a separate 100 ml desk. These compounds were then dissolved in 2 ml. DMSO and volumes in each flask were adjusted to 100 ml with sterile water. This suspension (each at a concentration of 250 µg/ml) was used as the basic suspension. 2 ml and 4 ml of these suspensions were transferred to two 10 ml volumetric flasks and further dilutions were made to 10 ml mark with sterilized distilled water. The finishing suspension contains 50 and 100 µg of each compound per ml of the suspension.

Preparation of stock solution of the standard drug (Ampicillin)

Ampicillin (25 mg) was carefully weighed and transferred into a 100 ml volumetric flask. Dissolve the drug in 2 ml. DMSO was diluted to 100 ml with sterile distilled water. The final solution contained 250 µg/ml standard drugs (Ampicillin). A volume of 2 ml and 4 ml of the solution was transferred into two 10 ml flasks and further diluted to sterile 10 ml with sterile distilled water. The final solution contained 50 and 100 µg of Ampicillin per ml of solution.

Procedure for preparation of media:

Peptone extract (5 g) Beef extract (5 g) and sodium chloride (2.5 g) all biological qualities were weighed and dissolved in 400 ml of distilled water in a 500 ml volumetric flask. And they became hot. 10 g of agar was dissolved in 50 ml of hot distilled water. The two solutions were mixed and the volumetric flask was quenched to 500 ml with hot distilled water. This feed agar medium was sterilized for 15 minutes in an autoclave at a pressure of 15 lb/inch^2 pressure (121^0 C) for 15 min.

The following steps were used to determine the antibacterial activity of the synthesized compounds:

1. The laminar airflow bench was replaced with 70% alcohol and the UV lamp turned on. After 30 minutes, the UV lamp was turned off.

2. All the reagents, media, inoculums and glassware were placed in laminar airflow bench and aseptic conditions were maintained.
3. The plates were inoculated within minutes of the preparation of suspension so that the density did not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculum had dried, the drug solution was poured on the disk & then disk was placed on the agar plate with the help out of a forceps. After inoculation at 37 ^{0}C for 48 hours. The region of embarrassment was calculated using the mm scale.
4. Negatively adjustable plate. On this plate pour only receiving food i.e. they do not contain dilutions of drugs and vaccines.
Positive controlled plate- In this plate, the nutrient agar medium was pour and after its solidification, the inoculum was spread over the exterior of the culture plate. But this Petri-plate did not contain a drug solution.

3. RESULTS

3.1. Physical parameters of synthesized compounds.

Several Indole derivatives were synthesized according to the planned scheme. Percentage yields, the melting point of the synthesized compound, molecular formula, molecular weight and R_f value of all synthesized compounds were calculated and tabulated in table 1. Their physical constants and thin layer chromatography mainly confirmed the cleanness of the synthetic compound.

3.2. Antifungal activity.

The antifungal activity of all synthesized compounds was evaluated against *Aspergillus niger* and *Candida albicans* (ATCC 10231) using Fluconazole as the standard drug using the paper plate method. It does not include intermediate and incubation periods. Sabouraud dextrose agar was used as a medium and the plates were incubated at 25 ° C for 48 hours. Standard and test compounds were treated at 100 g/ml. Solvent control, i.e. DMF, showed no activity.

3.3. Antibacterial activity.

All newly synthesized compounds were evaluated for their in vitro antibacterial activity against both Gram-positive (***Bacillus subtilis***) and Gram-negative bacteria (***Escherichia coli***) using Ampicillin as standard medication at a concentration of 50µg/ml, 100µg/ml. The disc diffusion method was used to determine the provisional antibacterial and antifungal activity. The results recorded for each test compound are shown in Tables 2 and 3.

Table 1. Physical parameters of different indole derivatives.

Compound code	Reaction Time	M.P (°C)	Molecular Formula	Molecular Weight	% Yield	R_f Value
C-1	26hrs	153-156	$C_{30}H_{24}N_4O_3$	788.55	68	0.62
C-2	25hrs	170-174	$C_{31}H_{25}N_3O_2$	471.56	85	0.95
C-3	26 hrs	162-164	$C_{31}H_{26}ClN_3O$	492.02	90	0.88
C-4	24hrs	180-184	$C_{32}H_{27}N_3O_2$	485.59	88	0.93
C-5	26hrs	166-168	$C_{32}H_{28}N_4O_2$	500.60	49	0.92

Table 2. Antibacterial activity of synthesized compounds against *Escherichia coli.*

Standard and Test compound	Zone of inhibition in mm			
	Escherichia coli (ESS 2231)		*Aspergillus niger*	
	100µg	50µg	100µg	50µg
Control	-	-	-	-
Ampicillin	25	21	24	22
C-1	13	12	14	13
C-2	15	13	17	14
C-3	16	15	15	14
C-4	18	15	19	16
C-5	12	10	13	11

Table 3. Antifungal activity data of synthesized compounds against *Bacillus subtilis* or *Aspergillus niger*.

Standard and Test compound	Zone of inhibition in mm			
	Bacillus Subtilis (ACC-132)		*Aspergillus niger*	
	100µg	50µg	100µg	50µg
Control	-	-	-	-
Ampicillin	26	25	25	23
C-1	15	13	12	10
C-2	16	13	16	14
C-3	16	14	15	14
C-4	18	16	14	13
C-5	13	11	12	11

4. CONCLUSIONS

Literature review reveals that Indole derivatives have various types of biological activities including antibacterial, anti-inflammatory, analgesic, and anticancer and anticonvulsant activity. Given these observations, we have synthesized several new Indole derivatives (C1-C5) synthesized according to scheme and evaluated for their antimicrobial activity. In the present effort, five compounds (Indole derivatives) were synthesized. The title compounds were obtained by the reaction of indole with Chloroacetylchloride. The reaction yielded 2-chloro-1-(indoline-1-yl) ethanone, which upon further reaction with 1,4-diamine benzene

gave 2-((4-aminophenyl)amino)-1-(1H-indol-1-yl)ethan-1-one. This upon further reaction with various acetophenone in the presence of glacial acetic acid and ethanol gave diverse final compounds.

The compounds were obtained in solid-state and yields of synthesized compounds were ranging between 60% to 80%. Their melting points and TLC confirmed the purity of all synthesized compounds. The structures of these compounds were characterized based on IR and 1H-NMR spectroscopy. All these synthesized compounds demonstrated significant antibacterial activity as compared to the control group. Among them, the compounds C-3 and C-4 were most potent. All the synthesized compounds demonstrated potent antifungal activity as compared to the control group. Among them, the compound C-2 was most potent.

5. REFERENCES

1. Orme, M.; Sjöqvist, F.; Birkett, D.; Brøsen, K.; Cascorbi, I.; Gustafsson, L.L.; Maxwell, S.; Rago, L.; Rawlins, M.; Reidenberg, M., et al. Clinical Pharmacology in Research, Teaching and Health Care. *Basic & Clinical Pharmacology & Toxicology* **2010**, *107*, 531-559, https://doi.org/10.1111/j.1742-7843.2010.00602.x.
2. Saga, T.; Yamaguchi, K. History of Antimicrobial Agents and Resistant. *Japan Medical Association Journal* **2009**, *52*, 103-108.
3. Powers, J.H. Antimicrobial drug development--the past, the present, and the future. *Clin Microbiol Infect* **2004**, *10 Suppl 4*, 23-31, https://doi.org/10.1111/j.1465-0691.2004.1007.x.
4. Thorarensen, A.; Wakefield, B.D.; Romero, D.L.; Marotti, K.R.; Sweeney, M.T.; Zurenko, G.E.; Rohrer, D.C.; Han, F.; Bryant, G.L. Preparation of novel anthranilic acids as antibacterial agents. Extensive evaluation of alternative amide bioisosteres connecting the A- and the B-rings. *Bioorg Med Chem Lett* **2007**, *17*, 2823-2827, https://doi.org/10.1016/j.bmcl.2007.02.055.
5. Finar, I.L. *Organic Chemistry*. 6th edition, Parson, 2001.
6. Tannock, G.W.; Munro, K.; Taylor, C.; Lawley, B.; Young, W.; Byrne, B.; Emery, J.; Louie, T. A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of Clostridium difficile-infected patients than does vancomycin. *Microbiology* **2010**, *156*, 3354-3359, https://doi.org/10.1099/mic.0.042010-0.
7. Ge, Y.; Biek, D.; Talbot, G.H.; Sahm, D.F. In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. *Antimicrob Agents Chemother* **2008**, *52*, 3398-3407, https://doi.org/10.1128/aac.00149-08.
8. Saravolatz, L.D.; Stein, G.E.; Johnson, L.B. Ceftaroline: a novel cephalosporin with activity against methicillin-resistant Staphylococcus aureus. *Clin Infect Dis* **2011**, *52*, 1156-1163, https://doi.org/10.1093/cid/cir147.
9. Chahine, E.B.; Nornoo, A.O. Ceftobiprole: The First Broad-Spectrum Anti–methicillin-resistant Staphylococcus aureus Beta-Lactam. *Journal of Experimental & Clinical Medicine* **2011**, *3*, 9-16, https://doi.org/10.1016/j.jecm.2010.12.007.
10. Widmer, A.F. Ceftobiprole: a new option for treatment of skin and soft-tissue infections due to methicillin-resistant Staphylococcus aureus. *Clin Infect Dis* **2008**, *46*, 656-658, https://doi.org/10.1086/526528.
11. Higgins, D.L.; Chang, R.; Debabov, D.V.; Leung, J.; Wu, T.; Krause, K.M.; Sandvik, E.; Hubbard, J.M.;Kaniga, K.; Schmidt, D.E., Jr.; Gao, Q.; Cass, R.T.; Karr, D.E.; Benton, B.M.; Humphrey, P.P. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant Staphylococcus aureus. *AntimicrobAgents Chemother* **2005**, *49*, 1127-1134, https://doi.org/10.1128/aac.49.3.1127-1134.2005.
12. Mushtaq, S.; Ge, Y.; Livermore, D.M. Doripenem versus Pseudomonas aeruginosa in vitro: activity against characterized isolates, mutants, and transconjugants and resistance selection potential. *Antimicrob Agents Chemother* **2004**, *48*, 3086-3092, https://doi.org/10.1128/aac.48.8.3086-3092.2004.
13. Jones, R.N.; Huynh, H.K.; Biedenbach, D.J. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. *Antimicrob Agents Chemother* **2004**, *48*, 3136-3140, https://doi.org/10.1128/aac.48.8.3136-3140.2004.
14. Yang, L.P.; Keam, S.J. Spotlight on retapamulin in impetigo and other uncomplicated superficial skin infections. *Am J Clin Dermatol* **2008**, *9*, 411-413, https://doi.org/10.2165/0128071-200809060-00010.
15. Laue, H.; Weiss, L.; Bernardi, A.; Hawser, S.; Lociuro, S.; Islam, K. In vitro activity of the novel diaminopyrimidine, iclaprim, in combination with folate inhibitors and other antimicrobials with different mechanisms of action. *J Antimicrob Chemother* **2007**, *60*, 1391-1394, https://doi.org/10.1093/jac/dkm409.
16. Frampton, J.E.; Curran, M.P. Tigecycline. *Drugs* **2005**, *65*, 2623-2635, discussion 2636-2627, https://doi.org/10.2165/00003495-200565180-00008.
17. Gales, A.C.; Jones, R.N. Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis* **2000**, *36*, 19-36, https://doi.org/10.1016/s0732-8893(99)00092-9.
18. Nilius, A.M.; Ma, Z. Ketolides: the future of the macrolides? *CurrOpinPharmacol***2002**, *2*, 493-500, https://doi.org/10.1016/s1471-4892(02)00198-4.
19. Laue, H.; Weiss, L.; Bernardi, A.; Hawser, S.; Lociuro, S.; Islam, K. In vitro activity of the novel diaminopyrimidine, iclaprim, in combination with folate inhibitors and other antimicrobials with different mechanisms of action. *J Antimicrob Chemother* **2007**, *60*, 1391-1394, https://doi.org/10.1093/jac/dkm409.
20. Sharma, V.; Kumar, P.; Pathak, D. Biological importance of the indole nucleus in recent years: A comprehensive review. *Journal of Heterocyclic Chemistry* **2010**, *47*, 491-502, https://doi.org/10.1002/jhet.349.
21. Sumpter, W.C.; Miller, F.M. *Heterocyclic Compounds with Indole and Carbazole Systems.* Wiley-Interscience, Amsterdam, the Netherlands. 1954.
22. Budarari, S.; O'Neil, M.J.; Smith, A.; Heckelman, P.E. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.*11th edition, Merck&Co., NewYork, NY, USA, 1989.
23. Winters, K.; O'Donnell, R.; Batterton, J.C.; Van Baalen, C. Water-soluble components of four fuel oils: Chemical characterization and effects on growth of microalgae. *Marine Biology* **1976**, *36*, 269-276, https://doi.org/10.1007/BF00389288.
24. Dixit A, Pathak D, Sharma GK. Synthesis, antibacterial and free radical scavenging activity of some newer N-((10-nitro-1H-indolo [1, 2-c] quinazolin-12-yl) methylene) benzenamines. *European Pharmaceutical Journal*. **2020**;1, https://doi.org/10.2478/afpuc-2020-0002
25. Yokoyama, M.T.; Carlson, J.R. Dissimilation of tryptophan and related indolic compounds by ruminal microorganisms in vitro. *Appl Microbiol* **1974**, *27*, 540-548.

26. Lee, J.H.; Lee, J. Indole as an intercellular signal in microbial communities. *FEMS Microbiol Rev* **2010**, *34*, 426-444, https://doi.org/10.1111/j.1574-6976.2009.00204.x.
27. Gribble, G.W. Recent developments in indole ring synthesis—methodology and applications. *J. Chem. Soc. Per. Trans.***2000,***17*, 1045, https://doi.org/10.1039/A909834H.
28. Cacchi, S.; Fabrizi, G. Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions. *Chemical Reviews* **2005**, *105*, 2873-2920.
29. Humphrey, G.R.; Kuethe, J.T. Practical Methodologies for the Synthesis of Indoles. *Chemical Reviews* **2006**, *106*, 2875-2911.
30. Collin, G.; Hartmut, H. Indole. In:*Ullmann's Encyclopedia of Industrial Chemistry*. Volume 10, 2000; pp.361, https://doi.org/10.1002/14356007.a14_167.
31. Bratulescu, G. A new and efficient one-pot synthesis of indoles. *Tetrahedron Letters* **2008**, *49*, 984-986, https://doi.org/10.1016/j.tetlet.2007.12.015.
32. Smith, E.A.; Macfarlane, G.T. Formation of Phenolic and Indolic Compounds by Anaerobic Bacteria in the Human Large Intestine. *Microbial Ecology* **1997**, *33*, 180-188, https://doi.org/10.1007/s002489900020.
33. Kumar P, Kumar A, Mishra AK. Synthesis and Biological Evaluation of Some Bioactive Secondary Aromatic Amine Derivatives of 3, 3-Diphenyl Propionic Acid. Current Bioactive Compounds. 2018 Dec 1;14(4):412-8, https://doi.org/10.2174/1573407213666170616112848
34. Srivastava, A.;Pandeya, S.N. Indole a versatile nucleus in the pharmaceutical field. *Int. J. Cur. Pharm. Rev. Res*. **2010**, *1*, 1-17.
35. Yuan, L.-J. Biooxidation of indole and characteristics of the responsible enzymes. *African journal of biotechnology* **2011**, *10*.
36. Imran, S.; Taha, M.; Selvaraj, M.; Ismail, N.H.; Chigurupati, S.; Mohammad, J.I. Synthesis and biological evaluation of indole derivatives as α-amylase inhibitor. *Bioorganic Chemistry* **2017**, *73*, 121-127, https://doi.org/10.1016/j.bioorg.2017.06.007.
37. Yadav, B.P.; Ahmad, I.; Thakur, M.Synthesis of some novel indole derivatives as potential antibacterial, antifungal and antimalarial agents. *IOSR J. Pharm.***2016**, *6*,27-33.
38. Asif, M.; Singh, A.; Bilkanti, L. In-vivo Anticonvulsant and In-vitro Antitubercular Activity of methyl Indole Derivative of some 6-aryl-4, 5-Dihydropyridazin-3(2H)-ones and their Expected Anticonvulsant Mechanisms. *Iranian Journal of Pharmaceutical Sciences* **2013**, *9*, 67-80.
39. Kaishap, P. Synthesis and study of analgesic, anti-inflammatory activities of bis (indolyl) methanes (bims). *International Journal of Pharmaceutical Sciences and Research* **2012**, *3*, 4247.
40. Koksal, M.; Yarim, M.; DurmazŞahin, I.; Cetin-Atalay, R. Design, synthesis, and biological evaluation of indole-based 1,4-disubstituted piperazines as cytotoxic agents. *Turkish Journal of Chemistry* **2012**, *36*, 515-525, https://doi.org/10.3906/kim-1111-5.
41. El-Nakkady, S.S.; Abbas, S.E.S.; Roaiah, H.; Ali, I.H. Synthesis, antitumor and anti-inflammatory activities of 2-thienyl-3-substitued indole derivatives. *Global Journal of Pharmacology* **2012**, *6*, 166-177.
42. Chavan, R.; More, N.; Bhosale, A.V. Synthesis, Characterization and Evaluation of Analgesic and Anti-inflammatory Activities of Some Novel Indoles. *Tropical Journal of Pharmaceutical Research* **2011**, *10*, 463-473,https://doi.org/10.4314/tjpr.v10i4.12.
43. Mandour, A.H.; El-Sawy, E.R.; Shaker, K.H.; Mustafa, M.A. Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of 1,8-dihydro-1-ary1-8-alkyl pyrazolo(3,4-b)indoles. *Acta Pharm* **2010**, *60*, 73-88, https://doi.org/10.2478/v10007-010-0009-8.
44. Kaur, H.; Kumar, S.; Kumar, A. Synthesis, Antipsychotic and Anticonvulsant Activity of some new pyrazolinyl/isoxazolinylindol-2-ones. *International Journal of ChemTech Research* **2010**, *2*,1010-1019.
45. Aboul-Fadl, T.; Bin-Jubair, F.A.; Aboul-Wafa, O. Schiff bases of indoline-2,3-dione (isatin) derivatives and nalidixic acid carbohydrazide, synthesis, antitubercular activity and pharmacophoric model building. *Eur J Med Chem* **2010**, *45*, 4578-4586, https://doi.org/10.1016/j.ejmech.2010.07.020.
46. Kumar, A. Thiazolyl/oxazolylformazanyl indoles as potent anti-inflammatory agents. *Eur. J. Med. Chem.***2010**,*43*, 2323-30.
47. Sujatha, K.; Perumal, P.; Muralidharan, D.; Rajcndra, M. Synthesis, analgesic and anti-inflammatory activities of bis(indolyl)methanes. *Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry* **2009**, *48*, 267-272.
48. Talaz, O.; Gulcin, I.; Goksu, S.; Saracoglu, N. Antioxidant activity of 5,10-dihydroindeno[1,2-b]indoles containing substituents on dihydroindeno part. *Bioorg Med Chem* **2009**, *17*, 6583-6589, https://doi.org/10.1016/j.bmc.2009.07.077.
49. Bouchikhi, F.; Rossignol, E.; Sancelme, M.; Aboab, B.; Anizon, F.; Fabbro, D.; Prudhomme, M.; Moreau, P. Synthesis and biological evaluation of diversely substituted indolin-2-ones. *European Journal of Medicinal Chemistry* **2008**, *43*, 2316-2322, https://doi.org/10.1016/j.ejmech.2008.01.010.
50. Xiong, Q.; Gao, Z.; Wang, W.; Min, L. Activation of Kv7 (KCNQ) voltage-gated potassium channels by synthetic compounds. *Trends in Pharmacol. Sci.***2008**,*105*, 3128-33.
51. Amir, M.; Javed, S.; Kumar, H. Synthesis and biological evaluation of some 4-(1H-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin-2-ones/thiones as potent anti-inflammatory agents. *Acta pharmaceutica (Zagreb, Croatia)* **2009**, *58*, 467-477, https://doi.org/10.2478/v10007-008-0028-x.
52. Chaudhary, A. Contraceptive property of nitrogen/oxygen sulfur donor heterocyclic compounds. *Rasay. J. Chem.***2008**,*1*, 648-92.
53. Özdemir, A.; Turan-Zitouni, G.; Kaplancikli, Z. Novel Analogues of 2-Pyrazoline: Synthesis, Characterization, and Antimycobacterial Evaluation. *Turkish Journal of Chemistry* **2008**, *32*, 529-538.
54. Kini, S.G.; Bhat, A.R.; Bryant, B.; Williamson, J.S.; Dayan, F.E. Synthesis, antitubercular activity and docking study of novel cyclic azole substituted diphenyl ether derivatives. *European Journal of Medicinal Chemistry* **2009**, *44*, 492-500, https://doi.org/10.1016/j.ejmech.2008.04.013.
55. Husain, A.; Ajmal, M. Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. *Acta Pharm* **2009**, *59*, 223-233, https://doi.org/10.2478/v10007-009-0011-1.
56. El-Atawy MA, Hamed EA, Alhadi M, Omar AZ. Synthesis and Antimicrobial Activity of Some New Substituted Quinoxalines. Molecules. **2019**; 24(22):4198, https://doi.org/10.3390/molecules24224198.
57. Rani, P.; Srivastava, V.K.; Kumar, A. Synthesis and anti-inflammatory activity of heterocyclic indole derivatives. *European Journal of Medicinal Chemistry* **2004**, *39*, 449-452, https://doi.org/10.1016/j.ejmech.2003.11.002.
58. Jia B, Ma YM, Liu B, Chen P, Hu Y, Zhang R. Synthesis, Antimicrobial Activity, Structure-Activity Relationship and Molecular Docking Studies of Indole Diketopiperazine Alkaloids. Frontiers in Chemistry. **2019**;7:837, https://doi.org/10.3389/fchem.2019.00837
59. Katritzky, A.R.; Yang, H.; Jhang, W.M.An efficient conversion of carboxylic acids into Weinreb amides. *Int. J. of Pharm. Sci.* **2002,***1*, 260-273.
60. Sayed M, Kamal El-Dean AM, Ahmed M, Hassanien R. Synthesis of some heterocyclic compounds derived from indole as antimicrobial agents. *Synthetic Communications*. **2018**; 48(4):413-21, https://doi.org/10.1080/00397911.2017.1403627
61. Kaur H, Singh J, Narasimhan B. Indole hybridized diazenyl derivatives: synthesis, antimicrobial activity, cytotoxicity

evaluation, and docking studies. BMC chemistry. **2019**; 13(1):65.https://doi.org/10.1186/s13065-019-0580-0.
62. Altuntas, T.; Yilmaz, N.; Ece, A.; Altanlar, N.; Olgen, S. In Vitro Antibacterial and Antifungal Activity and Computational Evaluation of Novel Indole Derivatives Containing 4-Substituted Piperazine Moieties. *Letters in Drug Design & Discovery* **2018**, *15*, https://doi.org/10.2174/1570180815666180109161948.
63. Gholami, A.; Ebrahiminezhad, A.; Abootalebi, N.; Ghasemi, Y. Synergistic Evaluation of Functionalized Magnetic Nanoparticles and Antibiotics Against Staphylococcus aureus and Escherichia coli. *Pharm Nanotechnol***2018**, *6*, 276-286, https://doi.org/10.2174/2211738506666181031143048.
64. Srivastava, A.K.; Pandey, L.K. Synthesis and biological activity of some novel chalcones and nucleosides containing[1, 3, 4]oxadiazolenone core. *Current Bioactive Compounds* **2018**, *14*, 1-14, https://doi.org/10.2174/1573407214666180911130110.

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