Synthesis of some novel indole derivatives as potential antibacterial, antifungal and antimalarial agents.

B.P. Yadav 1*, Iftakhar Ahmad2, Meenakshi Thakur2
1Department of Chemistry, Meerut College, Meerut (U.P.) 250001, India
2Department of Chemistry, Mewar University, Chittorgarh (Raj.) 312901, India

Abstract - The rise of antimicrobial resistance (AMR) and antimalarial resistance are complex and severe health issue nowadays as many of microbial strains had become resistant to the available antibiotics. For discovery of new compounds Indole derivatives are chosen as they are well known for their wide range of biological activities such as antimicrobial, anti-inflammatory, and antitumor activities. The synthesis of new series of 2-alkyl 1-alkyl 5-chloro-3-substituted indole-carboxylates have been prepared and assayed for their antibacterial, antifungal and antimalarial activities against human pathogens viz., Escherichiacoli, Pseudomonasaerogenosa, Staphylococcus aureus, Streptococcuspyogenus, Candidaalbicans, Aspergillusniger, Aspergillus clavatus and antimalarial activity against Plasmodium falciparum. Since the activity of antibacterial drugs depends upon its concentration in vitro characterization of antibacterial activity commonly includes the determination of minimum inhibitory concentration (MIC). The objective of this study was to evaluate the MIC values and mean half maximal inhibitory concentration (IC50) values of newly designed heterocyclic compounds.

Key words:- Antimalarial, Antimicrobial, Indole, methicillin-resistant, vancomycin-resistant.

I. INTRODUCTION

Antibiotics revolutionized medicine in the 20th century, and have together with vaccination lead to the near eradication of diseases in the developed world. Antimicrobial and antimalarial infection have taken up centre stage as they are amongst the most common disease and it is dreaded that they would be most prevalent disease in human in future. The rise of antimicrobial resistance and antimalarial resistance are complex and severe health issue. The increased rate of infection due to resistance of available drugs has reached at its alarming level[1]. Infectious disease due to gram-positive bacteria such as methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant Enterococcus faecium (VREF), and penicillin resistant Streptococcus pneumoniae are the leading cause of morbidity and mortality to the community today[2]. During last few years an increase of invasive microbial and fungal infection has been observed, particularly in immune-suppressed patients, which are now the cause of morbidity and mortality as well. Therefore, there is urgent need to develop new antimicrobial agents[3]. Heterocyclic compounds have attracted attention due to their diverse biological and pharmacological properties. Benzo derivatives such as indole are important moieties in medicinal chemistry because of their wide range of biological activities like antibacterial[4], antifungal (Isatin & Indole-oximes)[5-6], antiviral[7], antitumor[8], anticancer[9], anticonvulsant[10], antidepressant (L-Tryptophan- a natural product)[11] and anti-inflammatory[12]. Hiari et al reported that 3-Aryl & 3-Heteroaryl substituted indole derivatives shows very good antimicrobial activity. The compound shows in fig.-1 exhibits MIC = 7 µg/cm3 against E. coli & S. aureus[13]. Panwar et al. reported that substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents. The compounds (Fig. - 2) were found to exhibit most inhibitory effect against E. coli & S. aureus[14].
The aplysinopsins are tryptophan-derived indole-containing marine natural products isolated from sponges, corals, a sea anemone and nudibranch. Aplysinopsins are widely distributed in the Pacific, Indonesia, Caribbean, and Mediterranean regions. Up to date, around 30 analogues occurring in Nature have been reported, however these aplysinopsins derivatives differ in chemical reactivity. The aplysinopsins have aroused considerable interest as potentially useful medicines. They have toxicity against many cancer cells and as well as anti-plasmodial and antimicrobial activity[15].

II. RESULTS AND DISCUSSION

In the present investigation Indole was chosen for synthesis of novel molecules as antimicrobial agents due to reported antimicrobial activity of indole nucleus. N-substituted carbamates and 2-substituted amides withN-substituted carbamates were synthesized using multistep procedure by synthesizing indole with Fischer Indole synthesis[16] followed by Suzuki reaction and amide coupling. Synthetic pathways for the synthesis of targets compounds are shown in scheme-1 and scheme-2 with the hope of discovering new antimicrobial and antimalarial agents. In comparison with several control drugs available in market in different categories. Newly synthesized derivatives have been evaluated for antibacterial, antifungal and antimalarial activity against standard strains. So it was aimed to investigate the efficacy of the antimicrobial and antimalarial effect of different derivatives on the same homologous structure of indole compounds. Their Structures were elucidated with \(^1\)H NMR, and mass spectroscopy and their purity was established through elemental analysis. Mass spectra of the compoundshowed [M+\(^{+}\) + H] peaks, since the electrospray ionization method was employed. The structures of all derivatives were confirmed by spectral analysis and results are presented in the experimental section. In the \(^1\)H NMR spectra of the compounds, the signal of NH proton was observed at \(\delta\) 12.05–12.35 in DMSO (\(d_6\))(deuterated dimethyl sulfoxide) and at \(\delta\) 9.05 – 9.20 in CDCl\(_3\) (deuterated chloroform) solvent. Aromaticprotons of indole ring appeared at \(\delta\) 7.13, 7.24–7.27, 7.41 – 7.44 and 7.73 in DMSO (\(d_6\), while in CDCl\(_3\) these were observed at \(\delta\) 7.31–7.35 and 7.66 as singlet bands and doublet bands.

Compounds were evaluated for the antimicrobial and antimalarial activity and compared with the activity of standard drugs available. All the derivatives synthesized were tested in vitro for antibacterial activity against E. coli/MTCC442, P. aerogenosa/MTCC441, S. aureus/MTCC96 and S. Pyogenus/MTCC443. All the derivatives were tested for the antifungal activity against C. albicans/MTCC227, A. niger/MTCC282 and A. clavatus/MTCC1323 and antimalarial activity were tested against a single strain Plasmodium falciparum. The activity of antibacterial drugs depends upon its concentration in vitro characterization of antibacterial activity commonly includes the determination of minimum inhibitory concentration (MIC)[17-20] in vitro characterization of antimalarial activity commonly includes the determination of IC\(_{50}\)[21]. Each synthesized drugs was diluted with DMSO obtaining 2000 \(\mu\)g/ml concentrations as a stock solution for biological screening. Primary screening was done at 1000 \(\mu\)g/ml to 250 \(\mu\)g/ml concentrations and secondary screening was done at 200 \(\mu\)g/ml to 6.25 \(\mu\)g/ml concentrations. The standard drugs employed while assessing antimicrobial activities were Gentamycin, Chloramphenicol, Ampicillin, Ciprofloxacin and Norfloxacin for antibacterialactivity; Nystatin and Greseofulvin for antifungal activity and Chloroquine and Quinine for antimalarial activity. We have used the Broth Dilution Method[22] to evaluate the antibacterial activity. It is one of the non-automated in vitro bacterial susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms.

Some compounds exhibits broad antibacterial activity with MIC values of 25 – 250 \(\mu\)g/ml against E. coli, P. aerogenosa, S. aureus and S. Pyogenus and its isolate except for derivative IA-CH02-A3 that had a MIC value of 25 \(\mu\)g/ml against S. aureus and compound IA-CH02-A6 and IA-CH02-B1 had a MIC values of 500 \(\mu\)g/ml against S. aureus. Compound IA-CH03-A3 had a MIC value of 62.5 \(\mu\)g/ml against E. coli and P. aeruginosa. All the derivatives had lower antibacterial activities than the standard drugs (Table-1). Among the new compounds IA-CH02-A3 derivatives was found most potent with a MIC value of 37.5\(\mu\)g/ml.

In the antifungal assay compounds exhibits broad antifungal activity with MIC values of 125 – 1000\(\mu\)g/ml against C. albicans, A. niger and A. clavatus and its isolate except for derivative IA-CH02-A1 and IA-CH02-B3 that had a MIC value of 250\(\mu\)g/ml against all the three strains and compound IA-CH02-C1 had a MIC values of 125\(\mu\)g/ml against C. albicans. All the derivatives had lower antifungal activities than the standard drugs. Among the new compounds IA-CH02-C1 derivatives was found most potent with a MIC value of 125 \(\mu\)g/ml (Table-2). While in antimalarial assay compounds exhibits IC\(_{50}\) Values in a range of 0.50 \(\mu\)g/ml to 1.58 \(\mu\)g/ml against Plasmodium falciparum. Among the new compounds IA-CH02-A4 derivative had a IC\(_{50}\) value of 0.50 \(\mu\)g/ml and derivative IA-CH02-A5-I had a IC\(_{50}\) value of 1.58 \(\mu\)g/ml. All the derivatives had lower activity than standard drugs Chloroquine and Quinine, which had the IC\(_{50}\) values 0.02 \(\mu\)g/ml and 0.27 \(\mu\)g/ml respectively. Among all new derivatives IA-CH02-A4 was found most potent with the lowest IC\(_{50}\) value (Table-2).
III. EXPERIMENTAL SECTION

3.1 Materials & Methods

The chemicals and solvents were purchased from Sigma-Aldrich Co. (Taufkirchen, Munich, Germany), Merck Lifescience Pvt. Ltd. (Vikhroli, Mumbai, India) and Fisher Scientific (Pittsburgh, PA, USA) and used without further purification. Silica gel (with Mesh size 230-400) was used for column chromatography and TLC plates were purchased from Merck Lifescience Pvt. Ltd. (Vikhroli, Mumbai, India) and ethyl acetate: hexanes were used as mobile phase. NMR spectra were recorded on Bruker 400 MHz NMR spectrometer in CDCl3 and DMSO; tetramethylsilane (TMS) was used as an internal standard. The mass spectra were recorded on Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA) using the ESI(+) method.

3.2 General Procedure

3.2.1 Synthesis of (E)-ethyl 2-(2-(4-chlorophenyl)hydrazono)propanoate: To the stirred solution of 4-chlorophenyl hydrazine (5.0 g, 0.0279 moles) in Water (10.0 ml) at rtCH3COOK (5.5 g, 0.0558 moles) was added and followed by dropwise addition of ethyl pyruvate (3.1 ml, 0.0279 moles), and reaction mixture was stirred for 1 h at same temperature. After precipitation, reaction mixture was filtered off and crude was purified by column chromatography to afford desired product.

3.2.2 Synthesis of 5-chloro-1H-indole-2-carboxylate: To the stirred solution of (E)-ethyl 2-(2-(4-chlorophenyl)hydrazono)propanoate (3.1 g, 0.0129 moles) in preheated PPA (80.0 gm) at 110°C, and reaction mixture was stirred for 1 h at same temperature. After completion of reaction, this was quenched with ice-water and extracted with ethyl acetate then washed with water and dried over Na2SO4. Evaporated under reduced pressure and crude was purified by flash chromatography using 50% ethyl acetate: hexanes as mobile phase. Mass spectra were recorded on Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA) using the ESI(+) method.

3.2.3 Synthesis of ethyl 3-bromo-5-chloro-1H-indole-2-carboxylate: To the stirred solution of ethyl 3-bromo-5-chloro-1H-indole-2-carboxylate (10.0 gm, 0.052 moles) in THF (150 ml) at 0°C, NBS (8.4 g, 0.052 moles) was added. Reaction mixture was stirred for 14 h at RT. After completion of reaction, water was poured into reaction mixture and stirred for 30 min., resulting solid was filtered off to afford desired product 13.2 g, 0.043 moles as white solid. 1H NMR CDCl3: 9.07 (1NH, bs), 7.66 (1H, s), 7.35-7.33 (2H, d, J = 8.8 Hz), 4.47-4.45 (2H, q, J = 7.2 Hz), 1.46 (3H, t, J = 7.2 Hz), [M+1= 302.52].

3.2.4 Synthesis of ethyl 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylate: To the stirred solution of ethyl 3-bromo-5-chloro-1H-indole-2-carboxylate (4.0 gm, 0.052 moles) in 1,4-dioxane (40 ml) at RT, a solution of Na2CO3 (3.5 g, 0.033 moles) in water (5.0 ml) was added. To the reaction mixture pyridine-3-boronic acid (2.56 g, 0.02 moles) was added and it was degassed with argon purging for 30 min. After that Pd(dppf)Cl2 (2.1 g, 0.0026 moles) was added and reaction mixture was stirred for 14 h at 100°C. After completion of reaction, reaction mixture was filtered off, crust was purified by flash chromatography using 50%-ethyl acetate: hexanes as eluent to afford desired product 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylate (2.8 g, 0.0093 moles) as white solid. 1H NMR CDCl3: 8.69 (1NH, bs), 8.58 (1H, s), 7.94-7.92 (1H, d, J = 8.0 Hz), 7.57-7.55 (1H, d, J = 9.2 Hz), 7.52-7.45 (3H,m), 7.36-7.34 (1H, d, J = 8.8 Hz), 4.26-4.21 (2H, q, J = 6.4 Hz), 1.17 (3H, t), [M+1= 301.67].

3.2.5 Synthesis of diethyl 5-chloro-3-(pyridin-3-yl)-1H-indole-1,2-dicarboxylate: Ethyl 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylate (0.2 gm, 0.0007 moles) was taken with dry THF in a RBF. To the stirred solution NaH (53 mg, 0.0013 moles) was added at 0°C and reaction mixture was allowed to stir for 30 min. After that period ECF (ml, 0.0008 moles) was added and mixture was allowed to stir at RT for 2 hrs. After completion of reaction, this was quenched with ice-water and extracted with ethyl acetate then evaporated under reduced pressure and crude was purified by column chromatography to afford desired product diethyl 5-chloro-3-(pyridin-3-yl)-1H-indole-1,2-dicarboxylates yellow oil. 1H NMR DMSO (d6): 8.58 (1H, s), 7.94-7.92 (1H, d, J = 8.0 Hz), 7.57-7.55 (1H, d, J = 9.2 Hz), 7.52-7.45 (3H,m), 7.36-7.34 (1H, d, J = 8.8 Hz), 4.29-4.22 (4H, m), 1.24 (3H, t), 1.17 (3H, t); [M+1= 373.07].
3.2.6 Synthesis of 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylic acid: To the stirred solution of 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylate (3.0 gm, 0.01 moles) in EtOH (20 ml) was added an aqueous solution of NaOH (0.8 gm, 0.02 moles) in H2O (10 ml) at RT. Reaction mixture was allowed to stirred at rt for 6 hrs. After completion excess of ethanol was evaporated and diluted with water. Aqueous layer was washed with diethyl ether. Aqueous layer was separated and pH was adjusted to 5-6 and extracted with ethyl acetate. Ethyl acetate layer was concentrated under reduced pressure to afford desired product 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylic acid as yellow solid.\textsuperscript{1}H NMR DMSO (d6): 12.1 (COOH, s), 8.69 (1NH, bs), 8.58 (1H, s), 7.94-7.92 (1H, d, J= 8.0 Hz), 7.57-7.55 (1H, d, J= 9.2 Hz), 7.52-7.45 (3H, m), 7.36-7.34 (1H, d, J= 8.8 Hz), [M\textsuperscript{+}+1]= 273.07.

3.2.7 Synthesis of 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carbonyl chloride: To the stirred solution of 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylic acid (2.0 gm, 0.007 moles) with DCM (20 ml) was added thionyl chloride (0.8 ml, 0.011 moles) was added and reaction mixture was allowed to stirred at rt for 4 hrs. After completion of reaction, it was concentrated and dried under reduced pressure to afford desired product 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carbonyl chloride as HCl salt. Crude salt was carried to next step without analysis and purification.

3.2.8 Synthesis of tert-butyl 4-(5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxamido) piperidine-1-carboxylate: To the stirred solution of tert-butyl 4-aminopiperidine-1-carboxylate (1.0 gm, 0.005 moles) with DCM in a RBF pyridine (1.06 ml, 0.01 moles) was added. To the above stirred solution 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxyl chloride (1.74 gm, 0.006 moles) was added and reaction mixture was allowed to stirred at RT for 4 hrs. After completion of reaction DCM was evaporated and crude was added with water and extracted with ethyl acetate. Organic layer was concentrated under reduced pressure and crude was purified by column chromatography to afford respective compounds tert-butyl 4-(5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxamido)piperidine-1-carboxylate. \textsuperscript{1}H NMR CDC\textsubscript{13}: 8.69 (1NH, bs), 8.58 (1H, s), 7.94-7.92 (1H, d, J= 8.0 Hz), 7.57-7.55 (1H, d, J= 9.2 Hz), 7.52-7.45 (3H, m), 7.36-7.34 (1H, d, J= 8.8 Hz), 7.53-7.51 (NH, bs), 4.13-4.11 (1H, m), 3.5-3.47 (4H, m), 2.26-2.23 (2H, m), 2.1-2.05 (2H, m), 1.47 (9H, s), [M\textsuperscript{+}+1]= 455.13.

3.2.9 Synthesis of ethyl 2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate: tert-butyl 4-(5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxamido)piperidine-1-carboxylate (0.2 gm, 0.0004 moles) was taken with dry THF in a RBF. To the stirred solution NaH (35 mg, 0.0009 moles) was added at 0°C and reaction mixture was allowed to stirred for 30 min. After that period ECF (0.05 ml, 0.0006 moles) was added and reaction mixture was allowed to stirred at RT for 4 hrs. After completion of reaction, it was quenched with ice-water and extracted with ethyl acetate then evaporated under reduced pressure and crude was purified by column chromatography to afford desired product ethyl 2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate as yellow oil. \textsuperscript{1}H NMR CDC\textsubscript{13}: 7.94-7.92 (1H, d, J= 8.0 Hz), 7.57-7.55 (1H, d, J= 9.2 Hz), 7.52-7.45 (3H, m), 7.36-7.34 (1H, d, J= 8.8 Hz), 7.53-7.51 (NH, bs), 4.29-4.22 (2H, q, J= 7.6 Hz), 4.13-4.11 (1H, m), 3.5-3.47 (4H, m), 2.26-2.23 (2H, m), 2.1-2.05 (2H, m), 1.47 (9H, s), 1.24 (3H, t), [M\textsuperscript{+}+5]= 27.09.

4. Figures & Tables
Table-1 - In-vitro Antibacterial activity of newly synthesized indole derivatives in comparison with control drugs.

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<th>X₁</th>
<th>X₂</th>
<th>Y</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
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<th>P. Aer</th>
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Reference Drugs:
1. Gentamycin | 0.05 | 1.0 | 0.25 | 0.5 |
2. Ampicillin | 100 | --- | 250 | 100 |
3. Chloramphenicol | 50 | 50 | 50 | 50 |
4. Ciprofloxacin | 25 | 25 | 50 | 50 |
Synthesis of some novel indole derivatives as potential antibacterial and antifungal agents

IV. CONCLUSION

In conclusion, the right hand region of our lead MTCC inhibitor structure appears to be quite tolerant to structural modifications. Few derivatives showed good antibacterial, antifungal activity and antimalarial activity, but less as compared to the standard drugs. So, these types of derivatives of Indole can serve as future therapeutic leads for the discovery of antimicrobial drugs. It can be concluded that this class of compounds certainly holds promise towards good active leads in medicinal chemistry. The results of our efforts to further optimize the biological profile of this series of dual MTCC inhibitors will be forthcoming.

V. ACKNOWLEDGEMENTS

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Synthesis of some novel indole derivatives as potential drug candidates.

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