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Synthesis of some novel indole derivatives aspotential antibacterial, antifungaland antimalarial agents.

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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 compoundsIndole 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-subs-1H-indole-carboxylates have been prepared and assayed for their antibacterial, antifungal and antimalarial activities against human pathogens viz., *Escherichiacoli, Pseudomonasaerugenosa, Staphylococcusaureus, 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 (IC_{50}) 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 amongthe 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 drugshas 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-supressed 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 diversebiological 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/cm^{3}against *E. coli* &*S. aureus*[13].Panwar et al. reported that substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospectiveantimicrobial agents. The compounds (Fig. - 2)were found to exhibit most inhibitory effect against *E. coli* &*S. aureus*[14].

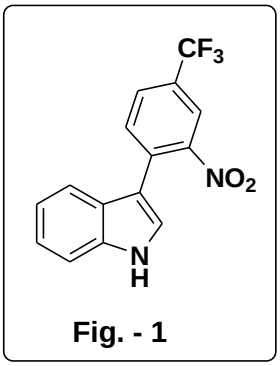


Fig. - 1

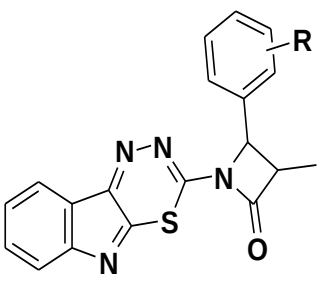


Fig. - 2

The aplysinopsins are tryptophan-derived indole-containing marine natural products isolated from sponges, corals, a sea anemone and nudibranch. Aplysinopsins are widely distributed inthe 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 compoundsshowed [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 δ 12.05–12.35 in DMSO (*d6)*(deuterated dimethyl sulfoxide) and at δ 9.05 – 9.20 in $CDCl_3$ (deuterated chloroform) solvent. Aromaticprotons of indole ring appeared at δ 7.13, 7.24–7.27, 7.41 – 7.44 and 7.73 in DMSO (*d6)*, while in $CDCl_3$ thesewere observed at δ 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. aerugenosa***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 μg/ml concentrations as a stock solution for biological screening. Primary screening was done at 1000 μg/ml to 250 μg/ml concentrations and secondary screening was done at 200 μg/ml to 6.25 μg/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 μg/ml against *E. coli, P. aerugenosa, S. aureus* and *S. Pyogenus* and its isolate except for derivative **IA-CH02-A3** that had a MIC value of 25 μg/ml against *S. aureus* and compound **IA-CH02-A6** and **IA-CH02-B1** had a MIC values of 500 μg/ml against *S. aureus*. Compound **IA-CH03-A3** had a MIC value of 62.5 μg/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 37.5μg/ml.

In the antifungal assay compounds exhibits broad antifungal activity with MIC valuesof 125 – 1000μg/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 250μg/ml against all the three strains and compound **IA-CH02-C1**had a MIC values of 125μg/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 μg/ml (Table-2).While in antimalarial assay compounds exhibits IC_{50}values in a range of 0.50 μg/ml to 1.58 μg/ml against *Plasmodium falciparum.* Among the new compounds **IA-CH02-A4** derivative had a IC_{50} value of 0.50 μg/ml and derivative **IA-CH02-A5-I** had a IC_{50} value of 1.58 μg/ml.All the derivatives had lower activity than standard drugs Chloroquine and Quinine, which had the IC_{50} values 0.02 μg/ml and 0.27 μg/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 usedwithout further purification. Silica gel (with Mesh size 230-400) was used for column chromatography and TLCplates were purchased from Merck Lifescience Pvt. Ltd. (Vikhroli, Mumbai, India) and ethyl acetate: hexaneswere used as mobile phase. NMR spectra were recorded on Bruker 400 MHz NMR spectrometer in CDCl3and DMSO; tetramethylsilane (TMS) was used as an internal standard. The mass spectra were recorded o Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA) usingthe ESI(+) method.

3.2 General Procedure

3.2.1 Synthesis of (E)-ethyl 2-(2-(4-chlorophenyl)hydrazono)propanoate: To the stirredsolution of 4-chlorophenyl hydrazine (5.0 g, 0.0279 moles) in Water (10.0 ml) at rtCH_3COOK (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 hr at same temperature. After precipitation, reaction mixture was filtered off to afford desired product (E)-ethyl 2-(2-(4-chlorophenyl) hydrazono) propanoate (3.1 g, 0.0129 moles) as brown solid. ^{1}H NMRDMSO (d6):9.94 (1NH, bs), 7.33-7.308 (2H, d, *J*= 8.8 Hz), 7.27-7.24 (2H, d, *J*= 9.2 Hz), 4.22-4.16 (2H, q, *J*= 7.2 Hz), 2.05 (3H, s), 1.24 (3H, t, *J*= 7.2 Hz), [M^++1= 241.29].

3.2.2 Synthesis of 5-chloro-1H-indole-2-carboxylate: To the stirred solution of (E)-ethyl2-(2-(4-chlorophenyl)hydrazono) propanoate (3.1 g, 0.0129 moles) in preheated PPA (80.0 gm) at 110ºC, and reaction mixture was stirred for 1 h at same temperature. After completion of reaction, reaction mixture was poured into ice-water thus precipitate was filtered off to afford desired product ethyl 5-chloro-1H-indole-2-carboxylate (1.4 g, 0.0063 moles) as off-white solid.^{1}H NMR DMSO (d6):12.09 (1NH, bs), 7.73 (1H, s), 7.47-7.44 (1H, d, *J*= 8.8 Hz), 7.41-7.38 (1H, d, *J*= 8.8 Hz), 7.13 (1H, s), 4.37-4.32 (2H, q, *J*= 7.2 Hz), 1.34 (3H, t, *J*= 7.2Hz), [M^++1= 224.61].

3.2.3 Synthesis of ethyl 3-bromo-5-chloro-1H-indole-2-carboxylate: To the stirred solution of ethyl 5-chloro-1H-indole-2-carboxylate (10.0 gm, 0.052 moles) in THF (150 ml) at 0ºC, NBS (8.4 g, 0.052 moles) was added. Reaction mixture was stirred for 14 h at RT. After completion of reaction 35 ml of 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.^{1}H NMR $CDCl_3$: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 Na_2CO_3 (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)Cl_2 (2.1 g, 0.0026 moles) was added and reaction mixture was stirred for 14 h at 100ºC. After completion of reaction, reaction mixture was filtered off and crude was purified by flash chromatography using 5-50% ethyl acetate: hexanes as eluent to afford desired product ethyl 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylate (2.8 g, 0.0093 moles) as white solid.^{1}H NMR DMSO (d6):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 0ºC and reaction mixture was allowed to stirred for 30 min. After that period ECF (ml, 0.0008 moles) was added and reaction mixture was allowed to stirred 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-dicarboxylateas yellow oil.^{1}H 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].

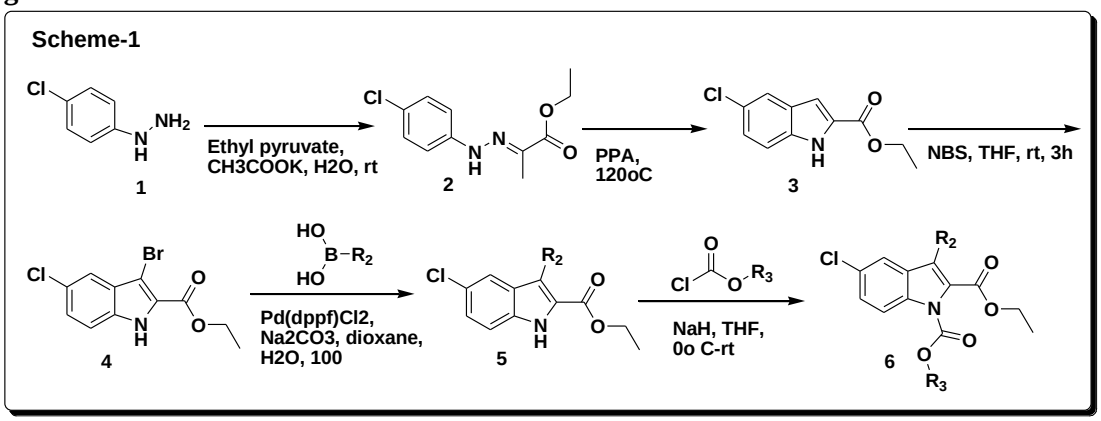
3.2.6 Synthesis of 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylic acid: To the stirred solutionof 5-chloro-3-(pyridin-3-yl)-1H-indole-2-carboxylate (3.0 gm, 0.01 moles) in EtOH (20 ml) was added an aqueous solution of NaOH (0.8 gm, 0.02 moles) in H_2O (10 ml) at RT. Reaction mixture was allowed to 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.^{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^++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-carbonylchloride 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-carbonyl 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. ^{1}H NMR $CDCl_3$: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), 5.73-5.71 (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^++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 0ºC 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, 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 productethyl 2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate as yellow oil.
^{1}H NMR $CDCl_3$: 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), 5.73-5.71 (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^++1=5 27.09].

4. Figures & Tables



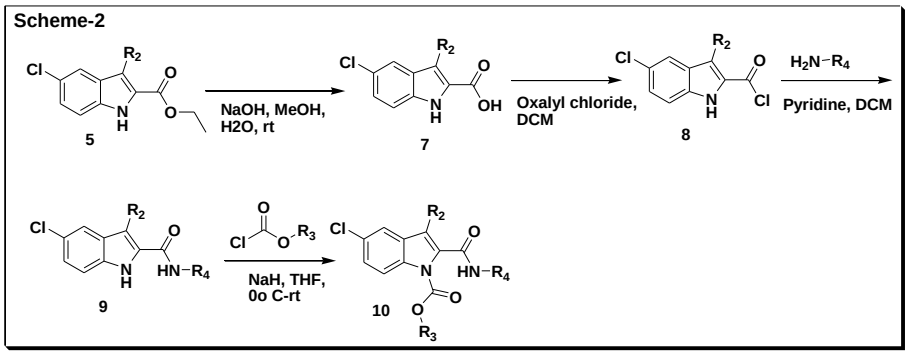
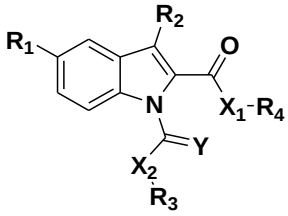


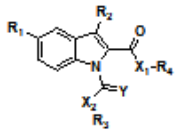
Table-1- In-vitro Antibacterial activity of newly synthesized indole derivatives in comparison with control drugs.



Where R_1 is Cl- substituted derivatives.

Compound I.D.	**X_1**	**X_2**	**Y**	**R_2**	**R_3**	**R_4**	***E. coli***	***P. Aer sa***	***S. aure***	***S. pyog***
IA-CH02-A1	O	O	O	c-Prop	Et	Et	250	200	200	250
IA-CH02-A2	O	O	O	c-Prop	Me	Et	100	200	250	250
IA-CH02-A3	O	O	O	c-Prop	prop	Et	100	125	37.5	100
IA-CH02-A4	O	O	O	c-Prop	iso-prop	Et	100	250	62.5	100
IA-CH02-A5	O	O	O	c-Prop	Ph	Et	200	100	250	200
IA-CH02-A6	O	O	O	c-Prop	Benzyl	Et	100	250	500	125
IA-CH02-A7	NH	O	O	c-Prop	Et	4-(Boc)-Pip-	62.5	125	125	200
IA-CH02-A8	NH	O	O	c-Prop	Et	4-(t-Bu)PhC_2H_4-	200	100	250	250
IA-CH02-A9	NH	O	O	c-Prop	Et	4-(CF_3)PhC_2H_4-	125	62.5	125	200
IA-CH02-B1	O	O	O	3-Py	Et	Et	62.5	200	500	500
IA-CH02-B2	O	O	O	3-Py	Me	Et	100	500	100	250
IA-CH02-B3	O	O	O	3-Py	prop	Et	62.5	250	100	125
IA-CH02-B4	O	O	O	3-Py	iso-prop	Et	200	100	125	500
IA-CH02-B5	O	O	O	3-Py	Ph	Et	500	125	62.5	125
IA-CH02-B6	O	O	O	3-Py	Benzyl	Et	500	200	100	200
IA-CH02-B7	NH	O	O	3-Py	Et	4-(Boc)-Pip-	62.5	100	250	100
IA-CH02-B8	NH	O	O	3-Py	Et	4-(t-Bu)PhC_2H_4-	125	500	200	200
IA-CH02-B9	NH	O	O	3-Py	Et	4-(CF_3)PhC_2H_4-	100	250	125	100
IA-CH02-C1	NH	O	O	3-Py	Et	c-Prop	500	250	500	200
IA-CH02-C2	NH	O	O	3-Py	Et	Me	250	200	500	500
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

Table-2- In-vitro Antifungal and Antimalarial activity of newly synthesized indole derivatives in comparison with control drugs.



Where R_1 is Call- substituted derivatives.

Compound I.D.	X1	X2	Y	R2	R3	R4	*C. albicans*	*A. niger*	*A. clavatus*	*P. falciparum IC50*(µg/ml)
IA-CH02-A1	O	O	O	c-Prop	Et	Et	500	500	500	0.70
IA-CH02-A2	O	O	O	c-Prop	Me	Et	1000	1000	1000	1.16
IA-CH02-A3	O	O	O	c-Prop	prop	Et	500	>1000	>1000	0.90
IA-CH02-A4	O	O	O	c-Prop	iso-prop	Et	>1000	>1000	>1000	0.50
IA-CH02-A5	O	O	O	c-Prop	Ph	Et	>1000	>1000	>1000	1.58
IA-CH02-A6	O	O	O	c-Prop	Benzyl	Et	500	>1000	>1000	0.60
IA-CH02-A7	NH	O	O	c-Prop	Et	4-(Boc)-Pip-	250	500	250	0.95
IA-CH02-A8	NH	O	O	c-Prop	Et	4-(t-Bu)PhC_2H_4-	500	>1000	1000	1.16
IA-CH02-A9	NH	O	O	c-Prop	Et	4-(CF_3)PhC_2H_4-	500	1000	1000	1.00
IA-CH02-B1	O	O	O	3-Py	Et	Et	>1000	>1000	>1000	0.90
IA-CH02-B2	O	O	O	3-Py	Me	Et	1000	>1000	>1000	1.45
IA-CH02-B3	O	O	O	3-Py	prop	Et	500	500	500	0.95
IA-CH02-B4	O	O	O	3-Py	iso-prop	Et	500	>1000	>1000	0.70
IA-CH02-B5	O	O	O	3-Py	Ph	Et	1000	>1000	>1000	1.26
IA-CH02-B6	O	O	O	3-Py	Benzyl	Et	1000	>1000	>1000	1.50
IA-CH02-B7	NH	O	O	3-Py	Et	4-(Boc)-Pip-	250	1000	500	0.80
IA-CH02-B8	NH	O	O	3-Py	Et	4-(t-Bu)PhC_2H_4-	1000	>1000	1000	0.92
IA-CH02-B9	NH	O	O	3-Py	Et	4-(CF_3)PhC_2H_4-	>1000	500	500	1.37
IA-CH02-C1	NH	O	O	3-Py	Et	c-Prop	125	500	500	0.95
IA-CH02-C2	NH	O	O	3-Py	Et	Me	500	>1000	1000	1.12
Reference Drugs:										
1. Nystatin							100	100	100	---
2. Greseofulvin							500	100	100	---
3. Chloroquine							---	---	---	0.02
4. Quinine							---	---	---	0.27

IV. CONCLUSION

In conclusion, the right hand region of our lead MTCC inhibitor structure appears tobe 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 ofderivatives 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 biologicalprofile of this series of dual MTCC inhibitors will be forthcoming.

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