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Synthesis and antimycobacterialactivity against*Mycobacterium tuberculosis* (MTB) H37Rv of some novel Indolederivatives.

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Abstract - Tuberculosis treatment remnants a contest that necessitates new antitubercular agents due to the development of multidrug-resistant Mycobacterium strains. This paper defines the synthesis, characterization and the antitubercular activity of some new 2-ethyl 1-alkyl 5-chloro-3-(pyridin-3-yl)-1H-indole-1,2-dicarboxylatederivatives, alkyl 2-(alkylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate and 2-ethyl 1-alkyl 5-chloro-3-cyclopropyl-1H-indole-1,2-dicarboxylate, alkyl 2-(methylcarbamoyl)-5-chloro-3-cyclopropyl-1H-indole-1-carboxylatederivatives, which were synthesized by the C-C coupling (Suzuki coupling) reaction. This reaction involve coupling of ethyl 3-bromo-5-chloro-1H-indole-2-carboxylate [obtained by the Fischer Indole reaction followed bybromination reaction of ethyl -5-chloro-1H-indole-2-carboxylate] with cyclopropylboronic acid or pyridine-3-yl boronic acid in presence of Palladium(II) diphenylphosphinoferrocene dichloride and sodium carbonate in 1,4-dioxane. All the synthesized compound were characterized by elemental analysis, ^{1}H NMR and LCMS and also screened for their in- vitro antitubercular activity against *Mycobacterium tuberculosis*.

Key words: Indolederivative,antitubercular activity, minimum inhibitory concentration, minimum fungicidal concentration.

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I. INTRODUCTION

Tuberculosis is a transmittable disease with extraordinary impermanence. About 30 lacs of individuals die every yeardue to complication of TB globally[1] and approximately 80lacs new cases each year, most of them occur in developing countries.[2]Medicines such as isoniazid and rifampicin have historically been successful in the treatment of TB infections. Prolonged use of available drugs has led to the emergence of multidrug resistant *Mycobacterium tuberoculosis* strain.[3]Resistance led to the development of second-line drug like thiacetazone (which is very effective in combination withisoniazid).[4]

Recently, a numeral of thiacetazone derivatives have been produced and defined for the activity against *M. tuberculosis*, *M. avium*, and other mycobacterial species.[5–7] Results indicate that some S-alkylisothiosemicarbazones and SRI-286 can be useful in the therapy and epitomizeanexemplary for the progress of novel antimycobacterial drugs. 1H-Indole-2,3-dione is an endogenous composite acknowledged in humans and its effect has been studied in a diversity of systems. Biological properties of 1H-indole- 2,3-dione shows an significantpart as prophylactic agent against quite a lot of viral diseases.[8]

In modern years, Schiff and Mannich bases of 1H-indole- 2,3-diones are conveyed to unveil broad-spectrum chemotherapeutic activities such as antiviral,[9–11] anti- tuberoculosis,[12,13] antifungal, and antibacterial activities.[14,15]

For the reason that said and as a perpetuation of our works on 1H-indole derivatives, we have synthesized 2-ethyl 1-alkyl 5-chloro-3-(pyridin-3-yl)-1H-indole-1,2-dicarboxylatederivatives, alkyl 2-(alkylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate and 2-ethyl 1-alkyl 5-chloro-3-cyclopropyl-1H-indole-1,2-dicarboxylate, alkyl 2-(methylcarbamoyl)-5-chloro-3-cyclopropyl-1H-indole-1-carboxylate derivatives, in order to getnovel and furthereffective anti-tuberoculosis compounds. These new derivatives along with available drugs were evaluated for in vitro anti-tuberoculosis activity against *Mycobacterium tuberculosis*H37Rv.

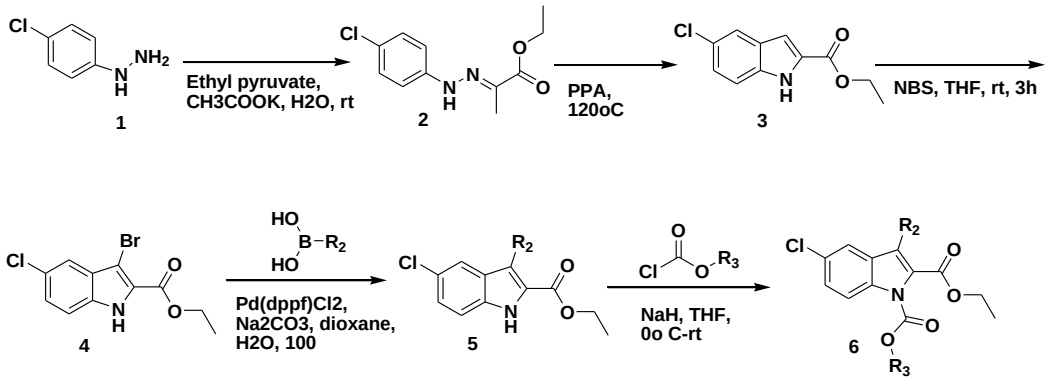
II. RESULTS AND DISCUSSION

Reagent grade chemicals were used without further purification. The purity and mass of the synthesized compounds was checked. ^{1}H NMR spectral was recorded in CDCl3 /DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Bruker DRTX-400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). Elemental analysis was performed using a (EURO EA 3000 instrument). Merck silica gels (100 to 200 and 230 to 400 mesh size) were used for analytical TLC and Column chromatography respectively.

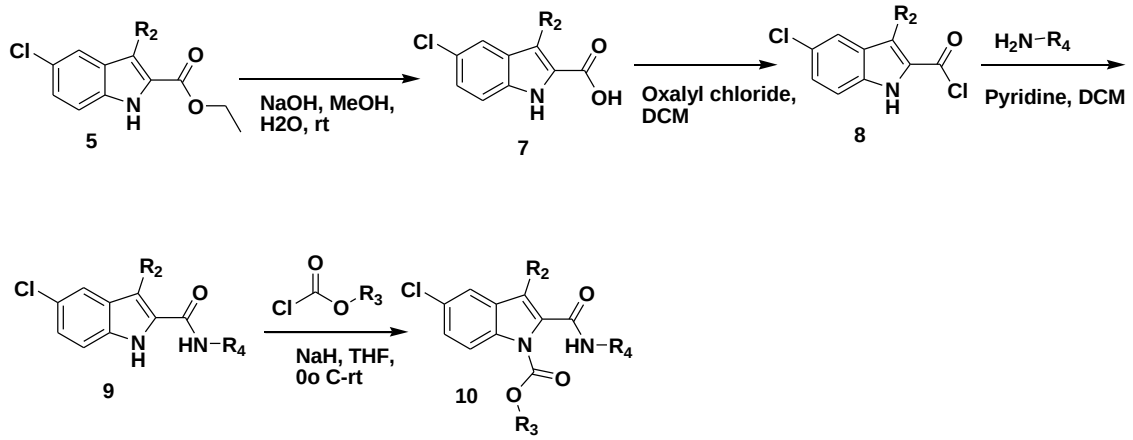
In the present investigation N-substituted carbamates and 2-substituted amides withN-substituted carbamateswere synthesized using multistep procedure by synthesizing indole with Fischer Indole synthesis[16]followed by Suzuki reaction and amide coupling. Synthetic pathways for the synthesis of targets compounds are shown in scheme-1 and scheme-2 with the hope of discovering new antimicrobial andantimalarial agents. In comparison with several control drugs available in market in different categories. Newly synthesized derivatives have been evaluated for antitubercular activity against standard strains. So it was aimed to investigate the efficacy of the antitubercular 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 compounds showed [M^+ + H] peaks, since the electrosprayionizationmethod was employed. Thestructures of all derivatives were confirmed by spectral analysis and results are presented in the experimental section.[17]

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. Aromatic protons of indole ring appeared at δ 7.13, 7.24–7.27, 7.41 – 7.44 and 7.73 in DMSO (*d6),* while in $CDCl_3$ these were observed at δ 7.31–7.35 and 7.66 as singlet bands and doublet bands.[17]

Scheme-1



Scheme-2



Experimental Section

The chemicals and solvents were purchased from Sigma-Aldrich Co. (Taufkirchen, Munich, Germany), Merck LifesciencePvt. 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 LifesciencePvt. Ltd. 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 o Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA) using the ESI (+) method.[17]

Example 1: Synthesis of diethyl 5-chloro-3-(pyridin-3-yl)-1H-indole-1,2-dicarboxylate: All derivatives were synthesized by following multistep synthesis that include Fischer Indole synthesis, which was followed by bromination reaction with NBS reagent. After bromination Suzuki coupling gives the required intermediate, which was then protected with respective chloroformate to obtained the titled compound as reported earlier.[171]**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).

Example 2: Diethyl 5-chloro-3-cyclopropyl-1H-indole-1,2-dicarboxylate: Compound was synthesized similar to example-1. **^{1}H NMR (IA-CH02-A1); $CDCl_3$ (δppm)**: 8.02-7.99 (1H, d, *J*= 9.2 Hz), 7.62-7.59 (1H, m), 7.34-7.32 (1H, d, *J*= 8.8 Hz), 4.46 (4H, m), 1.95-1.92 (1H, m), 1.45-1.39 (6H, m), 0.99-0.94 (2H, m), 0.79-0.77 (2H, m).

Example 3: 2-ethyl 1-methyl 5-chloro-3-cyclopropyl-1H-indole-1,2-dicarboxylate: Compound was synthesized similar to example-1. **1H NMR (IA-CH01-A2); CDCl3 (δppm):** 8.03-7.99 (1H, d, J= 9.2 Hz), 7.62-7.59 (1H, m), 7.34-7.32 (1H, d, J= 8.8 Hz), 4.46 (2H, m), 3.99 (3H, s), 1.95-1.92 (1H, m), 1.45-1.41 (3H, m), 0.99-0.94 (2H, m), 0.79-0.77 (2H, m).

Example 4: Synthesis of ethyl 2-(1-(tert-butoxycarbonyl)piperidin-4-ylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate: All derivatives were synthesized byfollowing multistep synthesis that includes Fischer Indole synthesis, this was followed by

bromination reaction with NBS reagent. After bromination Suzuki coupling gives the required intermediate, which was then hydrolysed by NaOH in MeOH and H_2O.Amide coupling was done via the synthesis of acid chloride and the titled product was obtained by protecting with respective chloroformate as reported earlier.[171]**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).

Example 5: Synthesis of Isopropyl 2-(cyclopropylcarbamoyl)-5-chloro-3-(pyridin-3-yl)-1H-indole-1-carboxylate: Compound was synthesized similar to example-4. **1H NMR (DMSO-d6) (δppm):** 8.96 (NH, m), 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 (2H, d, J= 8.8 Hz), 5.73-5.71 (NH, bs), 5.19 (1H, m), 2.71-2.69 (1H, m), 1.23 (6H, d, J= 6.8 Hz), 0.66 (2H, m), 0.35 (2H, m).

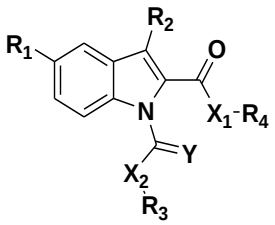
Antitubercular Studies

All the compounds were screened for their in vitro antimycobacterial activity against *Mycobacterium tuberculosis* (MTB) H37Rv. The primary screening was carried out by agar dilution method using double dilution technique recommended by the National committee for clinical laboratory standards [12]. Isoniazid and thiacetazone were used as standard drugs. MTB H37Hv was grown in Middle brook 7H11 broth medium supplemented with 10% OADC (Oleic acid, albumin, dextrose and catalase,1,10,100 mg/L). In brief 10^3 and 10^4 colony forming unit (CFU) were inculcated in to 7H11 medium. The minimum inhibitory concentration (MIC) was defined as the minimum concentration of compound required to 90% inhibition of bacterial growth.

In vitro Anti Mycobacterial Activity

All the compounds were screened for their in vitro antimycobacterial activity against mycobacterium tuberculosis (MTB) H37Rv.

Table- List of synthesized indole derivatives and their Antimycobacterial activity.



Where R1 is Cl- and X2 = Y = -O- in substituted derivatives.

Compound	**X_1**	**R_2**	**R_3**	**R_4**	**Antimycobacterial Activity (MIC in mg / ml)**
IA-CH02-A1	O	c-Prop	Et	Et	11.3
IA-CH02-A2	O	c-Prop	Me	Et	14.7
IA-CH02-A3	O	c-Prop	prop	Et	23.1
IA-CH02-A4	O	c-Prop	iso-prop	Et	25.8
IA-CH02-A5	O	c-Prop	Ph	Et	18.3
IA-CH02-A6	O	c-Prop	Benzyl	Et	21.8
IA-CH02-A7	NH	c-Prop	Et	4-(Boc)-Pip-	4.7
IA-CH02-A8	NH	c-Prop	Et	4-(t-Bu)PhC_2H_4-	7.6
IA-CH02-A9	NH	c-Prop	Et	4-(CF_3)PhC_2H_4-	7.3
IA-CH02-B1	O	3-Py	Et	Et	11.2
IA-CH02-B2	O	3-Py	Me	Et	17.4
IA-CH02-B3	O	3-Py	prop	Et	23.6
IA-CH02-B4	O	3-Py	iso-prop	Et	21.9
IA-CH02-B5	O	3-Py	Ph	Et	16.3
IA-CH02-B6	O	3-Py	Benzyl	Et	19.1
IA-CH02-B7	NH	3-Py	Et	4-(Boc)-Pip-	1.7
IA-CH02-B8	NH	3-Py	Et	4-(t-Bu)PhC_2H_4-	4.1
IA-CH02-B9	NH	3-Py	Et	4-(CF_3)PhC_2H_4-	7.2
IA-CH02-C1	NH	3-Py	Et	c-Prop	9.5
IA-CH02-C2	NH	3-Py	Et	Me	8.3
Isoniazid					0.125
Thiacetazone					0.125

MIC=Minimum inhibitory concentration that is the lowest concentration to inhibit 90% of mycobacterium tuberculosis H37Rv growth: Isoniazid and thiacetazone were used as standard.

III. CONCLUSION

The series of novel substituted indole derivatives were synthesized in reasonably good yields. They were characterized by 1H NMR, Liquid chromatography mass spectrometry and elemental analyses. All the newly synthesized compounds were screened for antitubercular activity. Some of the compound shows moderate to weak activity. Synthesized Indole derivativesshowed moderate antitubercular activity with MIC of 1.7µg/ml.

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