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SYNTHESIS OF THIAZOLE DERIVATIVES CONTAINING INDOLE MOIETY BEARING- -4- OXAZETIDINONE

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ABSTRACT
Schiff base synthesis of thiazole derivatives containing indole moiety bearing-4-oxazetidine ring were synthesised by the condensation of (E)-5-((1H-indol-1-yl)methyl)-N-ethylidene-1,3,4-thiadiazol-2-amine with chloroethylacetate in presence of TEA/DIOXANE to obtain 1-(5-((1H-indol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-methylazetidin-2-one, this reaction was subjected to schiff base reaction .The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis.

KEYWORDS;-Azetidinones, Schiff base, β- Lactam, thiazoles, indole

INDRODUCTION
Heterocyclic compounds represents an important class of biological molecules. The heterocyclic molecules which posses indole, pyrazole and azetidine moieties exhibit wide range of biological activities. Indoles are one of the most important alkaloids molecules found extensively in biological systems, which play vital role in many of the biochemical process. Indole ring constitutes an important basic skelton and development of the drug.The classical indole drugs are indomethacin and indoxole. Indole derivetives found to posses high range of biological activities which includes antibacterial, analgesic, antipyretic, antifungal, antiflamatory, anthelmintic,cardiovascular,anticonvalsant and selective COX-2 inhibitory activities, anticonvalsant,and selective COX-2 inhibitory activities .

Fused aryl hydrazone indole and their N-bridged thiazoles are found to be associated with diverse pharmacological activities, on the other hand it is well known that a number of heterocyclic compounds containing indole and thiazole moieties exhibit a wide variety of biological activities. In the last few years attempts have been made to develop simple and efficient methods for the synthesis of nitrogen bridged heterocyclic compounds utilizing inexpensive starting materials and reagents. Indole containing thiazole systems have received considerable attention in pharmacological activity

Azetidinones are of great biological interest, especially as anti-tubercular [I], antibacterial [II],[III],[IV],[V]. The important and structural diversity of biologically active β -lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidine with attendant control of functional group and stereochemistry. Azetidinone derivatives are reported to show a variety of antimicrobial [VI],[VII], anticonvulsant [VIII], anti-inflammatory [IX] and cardiovascular activities [X], antimycobacterial activity[XI], antibacterial activity [XII], antihypertensive activity [XIII].

MATERIALS AND METHODS

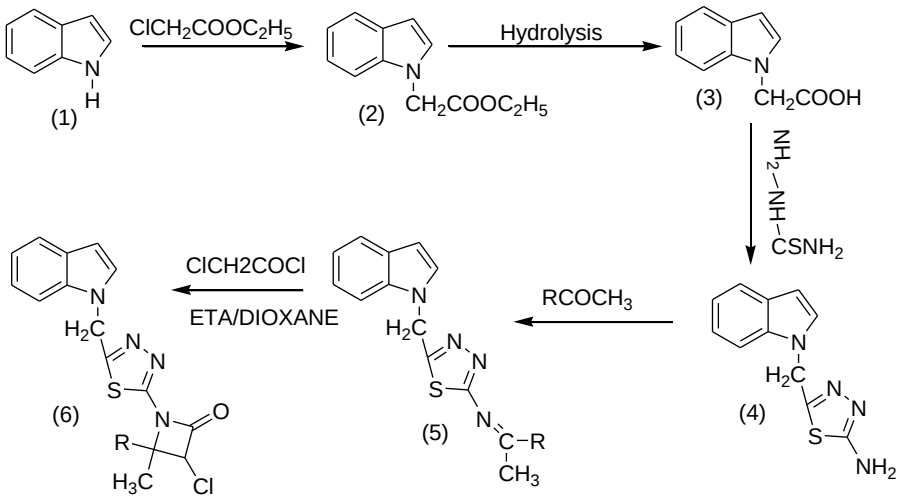
Melting points were determined on open capillaries using a cintex melting point apparatus .T.L.C. analysis were performed on precoated silicagel (E-Merck Kieselgel 60 F_{254}) plates and visualisation was done by exposing to iodine vapour .Solvent were purified by standard procedures before use .Column chromatography was conducted by using Silica gel with different solvent systems as elutes .IR Spectra were recorded with KBr on perkin –elmer spectrum BX series FTIR spectrometer. H^1-NMR spectrum were recorded on varian zemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm). C^{13}NMR spectra were recorded on a brucker 75MHz spectrometer . Mass spectra were scanned on a varian MATCH -7 and jeol JMSD-300 mass spectrometer at 70 ev. Elemental analysis were carried out on carloerba 106 and perkin –analyser . All the chemicals used in the present investigation were purchased from Aldrich chemicals ;U.S.A. Indole was prepared by a reported method.

RESULTS AND DISCUSSION

Schiff base synthesis of thiazole derivatives containing indole moiety bearing-4-oxazetiding ring were synthesised by the condensation of (E)-5-((1H-indol-1-yl)methyl)-N-ethylidene-1,3,4-thiadiazol-2-amine with chloroethylacetate in presence of TEA/DIOXANE to obtain 1-(5-((1H-indol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-methylazetidin-2-one, this reaction was subjected to schiff base reaction .The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR, Mass, IR, and elemental analysis. Biological activity of this compounds can be determined by disc diffusion method.

Synthesis of ethyl 2-(1H-indol-1-yl)acetate:

An equimolar mixture of indole-3-carbaldehyde and chloro ethyl acetate were dissolved in dimethyl formamide solvent and to this reaction mixture anhydrous K_2CO_3 was added and the reaction mixture was stirred at room temperature(35^0C) for 8 hours and the progress of the reaction was monitered by TLC using cyclohexane and ethylacetate solvent mixture (7:3) as eluent the reaction mixture was kept over night. After completion of the reaction the solvent was evaporated on rota-evaporater. The gummy solid was separated and it was recrystalised from -2-propanol-petrolium ether(80^0c)solvent mixture. The crystaline solid was found to be ethyl 2-(1H-indol-1-yl)acetate with a yield of 75% and mp 143-145^{0}C.The indole is used in the present studies was purchased from aldrich company and was used without any purification. Yield 75%,m.p.:143-145^{0}C



COMPOUND	**6(a)**	**6(b)**	**6(c)**	**6(d)**	**6(e)**	**6(f)**
R	**H**	**CH_3**	**OCH_3**	**Br**	**CF_3**	**NO_2**

The IR(KBr) spectrum of 2-(3- formyl-1H-indol-1-yl) acetate(2) was recorded in the range 4000-667cm^{-1} and the absorption signals where found at 3032(√-Ar-H)**,** 2980 and 2960 (√ aliphatic CH_2 andCH_3), 1760 (√ CO of ester group), and 1182(√ C-O-C of ester group).

Synthesis of 2-(1H-indol-1-yl)acetic acid(3):

To a solution of ester (2) (1eq) in tetrahydro furan /MeoH/H_2O(1:1:1) ratio, aq NaOH(2N) was added and stirred (room temp) or reflux for 4-16h. After completion solvent was evaporated under vacuum to give crude residue. The residue was washed with EtOAc(removing impurities). After that residue was acidified with 1N HCl up to P^H-2 to give solid suspension, filtered under vacuum to give fine solid. If solid is not obtained extracted with EtOAc (200ml) twice. The organic layer was collected, washed with water, brine,dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give crude acid product. The crude was purified by column chromatography(60-120 mesh-silica gel, Eluent: 70% EtoH-pet ether) to give compound 2-(1H-indol-1-yl)acetic acid(3).

Synthesis of 5-((1H-indol-1-yl)methyl)-1,3,4-thiadiazol-2-amine(4)

Equimolar quantity of hydrazine carbothioamide and 2-(1H-indol-1-yl)acetic acid(3) were dissolved in absolute alcohol, to this three drops of acetic acid was added then heated on a steam bath for 5-6hrs at 100^{0}C. The progress of the reaction was monitored by cyclohyxane: ethyacetate (7:3) solvent mixture as an eluent. The reaction mixture was kept overnight at room temperature. The solvent was evaporated on rotoevoparator. The semi solid was dried and recrystallized from warm absolute alcohol. The separated solid was identified as 5-((1H-indol-1-yl)methyl)-1,3,4-thiadiazol-2-amine(4).

The yield of 3(a) was found to be 75% with mp with 154-156^{o}C. The similar procedure was adopted for the synthesis of 4(b-f) from 2-(1H-indol-1-yl)acetic acid(3) and hydrazinecarbothioamide3 (a-f).

Synthesis of(E)-5-((1H-indol-1-yl)methyl)-N-ethylidene-1,3,4-thiadiazol-2-amine(5)

To a mixture of 4 and 3(2.18 gr,) and K_2CO_3 (0.69gr,) in methanol (20ml) was added substituted ketones (chloro aceto phenone , chloro acetone) 10mM and the mixture stirred at room temperature for 30min. At the end of this period, the solution was poured into ice cold water and neutralized with dil AcoH. The separated solid was filtered and dried to obtain crude(3).The crude compound obtained above, was recrystalised from hot MeOH to obtain pure5(a).

1-(5-((1H-indol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)-3-chloro-4-methylazetidin-2-one(6)

To a solution of (E)-5-((1H-indol-1-yl)methyl)-N-ethylidene-1,3,4-thiadiazol-2-amine(5)in 1,4 dioxane monocholoroacetylchloride and triethylamine was added drop wise with constant stirring. The reaction mixture was then refluxed on water bath and excess of dioxane was distilled out and resulting mixture was poured on to ice cold HCl, filtered, dried and recrystalised from ethanol to give the desired product. The general procedure was extended to substituted indoles to synthesize azetidine-2-one derivatives 5(a-c).

Monocholoroacetyl chloride(1.1294gr, 0.01mol) was added drop wise to Schiff's base (4.7248gr, 0.0086068mol) and triethylamine (2.02gr, 0.02mol) in dioxane (25ml) at room temperature. The mixture was stirred for 8hrs and left at room temperature for 3days. Pour the contents on crushed ice. The product thus formed was filtered and washed with sodium corbonate solution. The dried product was recrystalised with absolute alcohol. The MP was 182-184^{0}C with a yield of 58%

Anti-Bacterial Activity:

COMPOUND	YIELD	M.P.O^{0}C	% of Analysis					
			C		H		N	
			Calcd	FOUND	Calcd	FOUND	Calcd	FOUND
6a	58%	185	58.33	57.31	3.70	3.73	19.44	19.43
6b	55%	190	59.19	59.17	4.06	4.03	18.83	18.82
6c	53%	180	57.14	57.13	3.89	3.92	18.17	18.18
6d	52%	182	53.73	53.68	54.07	54.01	18.02	18.00
6e	56%	185	52.83	52.82	3.14	3.17	20.53	20.54
6f	51%	180	52.80	52.79	3.00	3.02	16.80	16.79

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were staphylococcusaureus NCCS 2079 . The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

The synthesized compounds were used at the concentration of 250µglml and 500µglml using DMSO as a solvent, the Ciprofloxacin 10µglml disc was used as a standard .(Himedia,Laboratories Ltd, Mumbai).

The test results presented in the table -1,suggest that 6b,6d,6e exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

Antifungal activity

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of Penicillium and Trichophton.

Compounds were treated at the concentrations of 500µglm and 1000µglml using DMSO as solvent. The standard used was Cyclopiroxolamine 50µglml against both organisms. The test results are presented in the table-2.

TABLE.- 1 Antibacterial activity by disc diffusion method of indole linked thiazole. 6(a.f)

Compound	Zone of inhibition (mm)			
	E.Coli	Staphylococcus	Klebsiella	Pseudomonas aeruginosa
6a	6.5(18)	6.5(20)	7.5(18)	7.5(18)
6b	13(15)	13(15)	14(18)	8(18)
6c	12(10)	-	-	12.5(15)
6d	11(14)	-	7.5(12)	-
6e	14(15)	-	7.5(11)	-
6f	9(18)	9(16)	7.5(18)	-
Ciprofloxacin	6.25(30)	6.25(30)	6.25(27)	6.25(28)

Table-;2 Antifungal activity by disc diffusion method for indole linked Thiazole 6(a-f).

Compound	Zone of inhibition (mm)	
	Penicillium	Trichophton
6a	7.5(18)	7.5(18)
6b	12(15)	12(11)
6c	14(10)	-
6d	13(15)	-
6e	11(12)	-
6f	7.5(16)	7.5(18)
Cyclopiroxolamine	7.5(27)	3.12(30)

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