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Synthesis of ureides containing indole moiety bearing -4-oxazetidinone

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ABSTRACT

The article is aimed to synthesize,characterize and screening the biological activity of a series of Synthesis of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a) Indole-3-carbaldehyde and chloro ethyl acetate were dissolved in DMF.To this reaction mixture anhydrous K_2CO_3 was added and the reaction mixture was stirred at room temperature(35^{0}C) for 8 hours .To afford 2-(3-formyl-1H-indol-1-yl)acetate**(A).** To this reaction mixture Equimolar quantity of hydrazinecarbothioamide were dissolved in absolute alcohol, to this three drops of aceticacid was added then heated on a steam bath for 5-6hrs at 100^{0}C to obtain Ethyl2-(3-((2-carbamoylhydrazono)methyl)-1H-indol-1-yl)acetate(3).To this reaction mixture α-halo ketones (chloro aceto phenone , cloro acetone) 10mM and the mixture stirred at roomtemperature for 30min.compound (3) Ethyl 2-(3-((2-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)hydrazono)methyl)-1H-indol-1-yl)acetate was obtained.To this reaction mixture Monocholoroacetyl chloride(0.01)was added drop wise to schiffs base (0.01) and triethylamine (0.02mol) in dioxane(25ml) at room temperature.To obtain Ethyl 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetate(5).After hydrolysis to this reaction mixture isobutyl chloroformate (1:1eq) was added stirred for 30min, and aq NaN_3 (3eq) was added and stirred for 20min at 0^{0}C.To obtain 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetyl azide.The reaction mixture is treated with mannich bases to obtain of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a) was obtained. The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR , Mass, IR, and elemental analysis. The antimicriobial activity of the novel compounds was screened by agar discdiffusion method.

KEYWORDS: Antibacterial activity, Antifungal activity, Indole, Mannich base , α-halo ketones, thiazole.

INTRODUCTION:

Hetero cyclic compounds represents an important class of biological molecules. The hetero cyclic 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. Indolederivatives found to posses high which includes, antibacterial, analgesic, antipyretic, antifungal, anti-inflammatory, anthelmintic, cardiovascular, anticonvulsant and selective COX-2 inhibitory activities, anticonvulsant and selective COX-2 inhibitory activities

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Acyl azides, in general, and *N*-protected a-amino acid azidesin particular, have occupied a place of their own importance in organic[1], and peptide as well as peptidomimetic[2], syntheses. They are extensively used in the preparation of amides and peptides,and a wide range of other compounds such as nitriles, andseveral classes of heterocycles. [1,3] ,The Curtius rearrangement of acyl azides into isocyanates is of paramount value in synthetic chemistry. It is widely used in the preparation of amines, ureas and carbamates. A number of natural products and pharmacologically important compounds containing uriedo linkages, [4],ureidopeptidomimetics, [5], partially modified retro-inverso (PMRI)peptides, formamides and unnatural amino acids have been prepared *via* this rearrangement. [2,6], Due to such vast utility of acid azides, the development of efficient routes for their synthesis is important.

The two well known routes for the preparation of acid azides are the reaction of NaN_3 with an acid chloride[7], or mixed anhydride. [8], The acid chloride method offers disadvantages at the preparation of acid chloride itself. These include prolonged reaction duration, incompat

ibility with acid cleavable groups,and storage and stability problems associated with moisture sensitive acid chlorides. Also the poor solubility of NaN_3 inorganic reaction medium requires the usage of a phase transfer catalyst, [9],or catalysts such as ZnI_2 [10], to improve the yield of acid azides. Alternately, protocols for the *in situ* generation of acid chlorides using SOCl2/DMF–NaN_3,[11], cyanuric chloride/ *N*-methylmorpholine,[12],triphosgene/triethylamine,[13], *N*,*N*chloromethylenedimethylammonium chloride,[14],followed by coupling with an azide have also been reported. But these methods are not suitable for acids such as *N*-Boc/Z-a-amino acids whose acid chlorides are unstable. Preparation of acid azides *via* mixed anhydrides has been used to advantage. Yet, thismethod uses chloroformates which are inconvenient for handling.Katritzky *et al.*, recently prepared acid azides from acids in atwo step route involving *N*-acyl benzotriazoles as stable and reactive intermediates.[15],Acid azides, such as Boc/Z-amino acidazides, have also been prepared through a multi-step routestarting from acids by hydrazinolysis of the methyl/ethyl esters followed by reaction of the resultant hydrazide with nitrosyl donors like HNO_2.

Azetidinones are of great biological interest, especially as anti-tubercular [16], antibacterial. [17-20] The important and structural diversity of biologically active ß-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[21,22], anticonvulsant[23], anti-inflammatory[24] and cardiovascular activities [25], antimycobacterial activity[26], antibacterial activity[27], antihypertensive activity[28]

MATERIALSAND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus .T.L.C. analysis were performed on precoatedsilicagel (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 KBr on perkin –elmer spectrum BX series FTIR spectrometer.^{1}H-NMR spectrum were recorded on varian zemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm) ^{13}CNMR 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 perchased from Aldrich chemicals ;U.S.A. indole- 3-carbaldehyde was prepared by a reported methode.

EXPERIMENTAL SECTION

Ethyl 2-(3-((2-(4-(4-(trifluoromethyl) phenyl) thiazol-2-yl) hydrazono)methyl) -1H-indol-1-yl)acetate(3).

To a mixture of 1(a) and 2(a),(2.18 gr,) and K_2CO_3 (0.69gr,) in methanol (20ml) was approximate α-halo ketones (chloro aceto phenone , cloro acetone) 10mM and the mixture stirred at roomtemperature 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 pure3(a).

Ethyl 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl) amino) azetidin-2-yl)-1H-indol-1-yl)acetate(5).

Monocholoroacetyl chloride(0.01)was added drop wise to schiffs base (0.01) and triethylamine (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 sodiumcorbonate solution.The dried product was recrystalised with absolute alcohol. The MP was 182-184^{0}C with a yield of 58%.

2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl) amino) azetidin-2-yl)-1H-indol-1-yl)aceticacid(6).

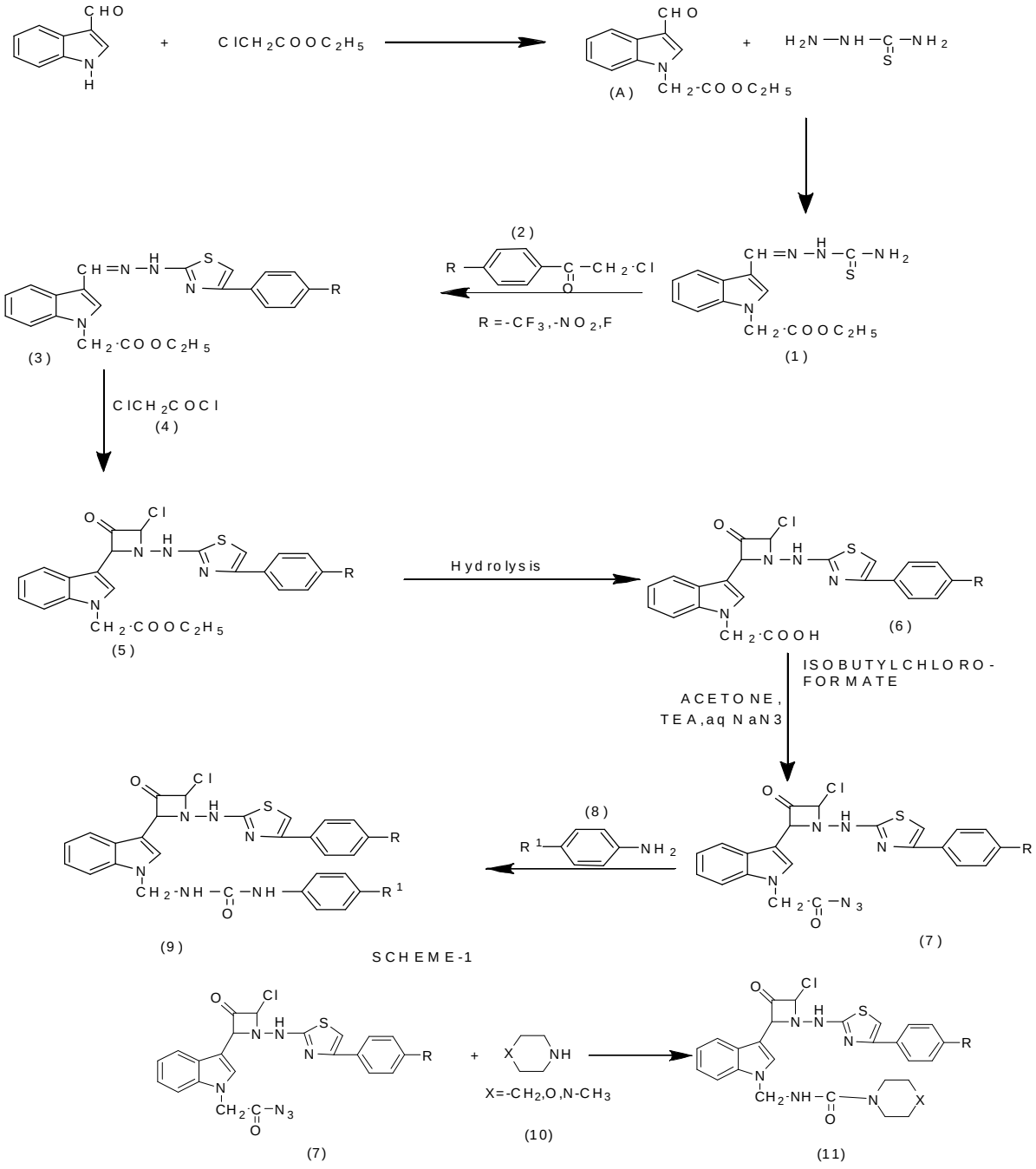
To a solution of ester(5) (1eq) in tetrahydro furan /MeoH/H_2O(1:1:1) ratio, aq NaOH(2N) was added and stirred (room temp) or reflux for 4-16h. after completion solvent was evaporated under vaccum to give crude residue.The residue was washed with EtOAc(removing impurities).After that residue was acidified with 1N HCl up to P^H-2 to give solid suspension, filtered under vaccum 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 vaccum to give crude acid product.The crude was purified by column chromatography(60-120 mesh-silca gel, Eluent: 70% EtoH-pet ether) to give compound 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino) azetidin-2-yl)-1H-indol-1-yl)aceticacid(6).

2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino) azetidin-2-yl)-1H-indol-1-yl) acetyl azide (7).

To a solution of acid (6) (1eq) in acetone, tri ethyl amine (3eq) was added and stirred at 15^{0}C.To that isobutyl chloroformate (1:1eq) was added stirred for 30min, and aq NaN_3 (3eq) was added and stirred for 20min at 0^{0}C. After completion,reaction mixture was poured in ice cold water (20ml), extracted with diethylether (10times).The organic layer was separated, washed with water,brine,dried over anhydrous Na_2SO_4, filtered and evaporated under vaccum to give crude oil.The crude oil was purified by column chromatography(60-120 mesh silicagel,eluent:10% EtOAc-pet ether)to give pure2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetyl azide (7).

1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl) amino) azetidin-2-yl)-1H-indol-1-yl) methyl)-3-phenyl urea (9).

To a mixture of acid azide (7)(1eq), in benzene, primary amine (1eq) in benzene was added and refluxed for 16h.After completion of the reaction, solvent was evaporated under vaccum to gave crude residue, purified by column chromatography (60-120 mesh silica gel, Eluent: 80% EtOAc-pet ether) to give 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a-o).



Compound	9(a)	9(b)	9(c)	9(d)	9(e)	9(f)	9(g)		
R	$-CF_3$	$-CF_3$	$-CF_3$	$-CF_3$	$-CF_3$	$-NO_2$	$-NO_2$		
R^1	-H	$-CH_3$	$-OCH_3$	-Cl	$-NO_2$	-H	$-CH_3$		
Compound	**9(h)**	**9(i)**	**9(j)**	**9(k)**	**9(l)**	**9(m)**	**9(n)**	**9(o)**	
R	$-NO_2$	$-NO_2$	$-NO_2$	-F	-F	-F	-F	-F	
R^1	$-OCH_3$	-Cl	-F	-H	$-CH_3$	$-OCH_3$	-Cl	$-NO_2$	
Compound	**11(a)**	**11(b)**	**11(c)**	**11(d)**	**11(e)**	**11(f)**	**11(g)**	**11(h)**	**11(i)**
R	$-CF_3$	$-CF_3$	$-CF_3$	$-NO_2$	$-NO_2$	$-NO_2$	-F	-F	-F
X	$-CH_2$	O	$N-CH_3$	$-CH_2$	O	$N-CH_3$	$-CH_2$	O	$N-CH_3$

N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl) amino)azetidin-2-yl)-1H-indol-1-yl)methyl) piperidine-1-carboxamide (11).

To a mixture of acid azide (7)(1eq), in benzene, secondary amine (1eq) in benzene was added and refluxed for 16h.After completion of the reaction, solvent was evaporated under vaccum to gave crude residue, purified by column chromatography (60-120 mesh silica gel, Eluent: 80% EtOAc-pet ether) to give N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl) piperidine-1-carboxamide 11(a-i).

RESULTS AND DISCUSSION;

The target compounds were synthesized via the route as shown in Scheme below. The synthon required for thesynthesis of the target molecules indole-3-carbaldehyde was prepared by a reported method.Filtered and recrystallized from ethanol. These reactions are summarised in the scheme-1and sheme-2.Yields were moderate to affair(55-70%). The purity of the compounds was monitered by TLC.

Synthesis of 2-(3-formyl-1H-indol-1-yl)acetate(A)

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 seperated and it was recrystalised from -2-propanol-petrolium ether(80^0c)solvent mixture.The crystaline solid was found to be -2-(3-formyl-1H-indol-1-yl)acetate. with a yield of 75% and mp 143-145^0C.The indole-3-carbaldehyde used in the present studies was purchased from aldrich company and was used without any forther purification. Yield 75%,m.p.:143-145^0C

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

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of 2-(3- formyl-1H-indol-1-yl) acetate(A) was recorded in DMSO-d6 solvent. The NMR signal of 2-(3- formyl-1H-indol-1-yl) acetate was found at $d_{PPm,}$ 1.29 (t,3H, J=13.2Hz, CH_3 of ethyl group), 4.13 (q, 2H, J=13.2Hz, CH_2 of ethyl group), 4.78(s, 2H, N-CH_2 group) and6.92 , 7.58 (m, 10H, C_8H_5N indole nucleus).

Syntheis of Ethyl 2-(3-((2-carbamoylhydrazono) methyl)-1H-indol-1-yl)acetate(1);

Equimolar quantity of hydrazinecarbothioamide and ethyl-2-(-3-formyl-1H-indol-1-yl)acetate(1) were dissolved in absolute alcohol, to this three drops of aceticacid was added then heated on a steam bath for 5-6hrs at 100^0C. The progress of the reaction was monitored by cyclohyxane: ethyacetate (7:3) solvent mixture as an eluent. The reaction mixture was kept over night 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 Syntheis of Ethyl2-(3-((2-carbamoylhydrazono) methyl)-1H-indol-1-yl)acetate(3).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-(3-formyl-1H-indol-1-yl)acetate(2) and hydrazinecarbothioamide3(a-f). The structures of 3(a-f)were established by IR, 1H-NMR. The analytical data of 3(a-f)was shown in the table.

The IR(KBr) spectrum of **Ethyl2-(3-((2-carbamoylhydrazono)methyl)-1H-indol-1-yl) acetate(1)** was recorded in the range 4000-667cm^{-1} and the absorption signals where found at 3185(-NH),3032(v-Ar-H)**,** 2980 and 2960 (v aliphatic CH_2 andCH_3), 1760 (v CO of ester group), 1629(C=N) , and 1185(v C-O-C of ester group), 1158(C=S).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of **Ethyl2-(3-((2-carbamoylhydrazono) methyl)-1H-indol-1-yl) acetate (1)** was recorded in DMSO-d6 solvent. The NMR signal of **Ethyl2-(3-((2-carbamoylhydrazono) methyl)-1H-indol-1-yl) acetate(1)** was found at $d_{PPm,}$ 1.31 (t,3H, J=13.2Hz, CH_3 of ethyl group), 4.15 (q, 2H, J=13.2Hz, CH_2 of ethyl group), 4.80(s, 2H, N-CH_2 group) and6.94 - 7.59 (m, 5H, C_8H_5N indole nucleus), 11. 189(s,1H,-NH),14.7(s,1H,thiol-thione tautomeric proton SH).

Ethyl2-(3-((2-(4-(4-(trifluoromethyl) phenyl) thiazol-2-yl) hydrazono) methyl) -1H-indol-1-yl)acetate(3).

A mixture of ethyl2-(3-((2-carbamoylhydrazono)methyl)-1H-indol-1-yl)acetate(1) and in methanol was added approximately α-halo ketones (chloro aceto phenone , cloro acetone) 10mM and the mixture stirred at roomtemperature 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 pure ethyl 2-(3-((2-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)hydrazono)methyl)-1H-indol-1-yl)acetate(3).The reaction process leading to the synthesis of ethyl 2-(3-((2-(4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)hydrazono)methyl)-1H-indol-1-yl)acetate 3(a-c) and their analytical data given in the tables.

The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of ethyl2-(3-((2-carbamoylhydrazono)methyl)-1H-indol-1-yl)acetate 3(a)was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3200(-NH),3055(v-Ar-H)**,** 2980 and 2965 (v aliphatic CH_2 andCH_3), 1765 (v CO of ester group), 1655(C=N) , and 1195(v C-O-C of ester group), 1175(C=S).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of ethyl2-(3-((2-carbamoylhydrazono)methyl)-1H-indol-1-yl)acetate 3(a)was recorded in DMSO-d6 solvent. The NMR signal of ethyl2-(3-((2-carbamoylhydrazono)methyl)-1H-indol-1-yl)acetate 3(a) 1.31 (t,3H, J=13.2Hz, CH_3 of ethyl group), 4.15 (q, 2H, J=13.2Hz, CH_2 of ethyl

group), 4.80(s, 2H, N-CH_2 group),4.92(s,1H,N-NH),,7.04-8.31 (complex, m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one aldehydimine proton),7.31-7.33 (complex, m,3H,one proton of the thiazolylring, two phenyl protons).

Ethyl 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl)amino) azetidin-2-yl)-1H-indol-1-yl) acetate(5).

To a solution of ethyl 2-(3-((2-(4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)hydrazono)methyl)-1H-indol-1-yl)acetate 3(a) 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 distilledout 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).

The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of Ethyl2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetate 5(a)was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3250(-NH),3100(v-Ar-H)**,** 2985 and 2965 (✓ aliphatic CH_2 andCH_3), 1780 (✓CO of ester group), 1680(C=N) , and 1190(✓ C-O-C of ester group), 1190(C=S).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of Ethyl2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetate5(a)was recorded in DMSO-d6 solvent. The NMR signal of Ethyl2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetate5(a)1.31 (t,3H, J=13.2Hz, CH_3 of ethyl group), 4.15 (q, 2H, J=13.2Hz, CH_2 of ethyl group), 4.80(s, 2H, N-CH_2 group) ,4.92(s,1H,N-NH), 5.4(d,1H,-CH of azetidine attached to indole ring), 5.6(d,1H,-CH of azetidine attached to-Cl),7.04-8.31(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one aldehydimine proton),7.31-7.33(complex,m,3H,one proton of the thiazolylring, two phenyl protons).

2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl) amino) azetidin-2-yl)-1H-indol-1-yl) aceticacid (6).

The synthesis of the synthon Ethyl2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetate5(a) to this solvent mixture tetrahydro furan/methylalcohol/ H_2O(1:1:1)ratio,aqNaOH(2N) was added and reflux for 6 hrs. The progress of the reaction was monitored by cyclohyxane: ethyacetate (4:6) solvent mixture as an eluent. After completion of reaction solvent was evaporated under vaccum to give crude.The residue was washed with ethyl acetate to remove impurities.The residue was acidified with 1N HCl up to P^H-2 to give solid suspension which was filtered under vaccum to give crude solid.The crude was purified by chromatography (60-120mesh-silicagel,eluent:70% ethylacetate-pet ether) to afford acid compound 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)aceticacid 6(a). The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data.

The IR(KBr) spectrum of compound 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)aceticacid 6(a)was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3260(-NH),2950 (OH) 3100(v-Ar-H)**,** 2990 and 2960 (✓ aliphatic CH_2 andCH_3), 1785 (✓ CO of ester group), 1680(C=N) , and 1195(✓ C-O-C of ester group), 1195(C=S).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of was recorded in DMSO-d6 solvent. The NMR signal of compound 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)aceticacid (6) was found at 4.92(s,1H,N-NH),5.4(d,1H,-CH of azetidine attached to indole ring), 5.6(d,1H,-CH of azetidine attached to-Cl),7.01-8.29(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one aldehydimine proton),7.30-7.35(complex,m,3H,one proton of the thiazolylring, two phenyl protons),10.5-12(broad signal of –COOH of –OH) Synthesis of 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetyl azide (7).

Erlier we have identified various useful methodologies for the synthesis of indole derivatives containing azetidin-2-one heterocyclic moieties.Here we are describing the synthesis of substituted urea derivatives processing indole moiety containing azetidin-2-one.

In the present investigation the required synthons 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino) azetidin-2-yl)-1H-indol-1-yl) aceticacid 6(a) used were prepared as per the procedure described in this chapter of this thesis.

At this instance to a solution of 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)aceticacid 6(a) (1eq) in acetone ,TEA(3eq) was added and stirred at -15^{0}C for 20min.To this reaction mixture ISOBUTYL CHLORO FORMATE (1:1eq) was added and stirred for 30 min.To the above reaction mixture aq NaN_3(3eq) was added and stirred for 20min at 0^{0}C. The progress of the rection was monitered by TLC with acetone . ethyl acetate (6:4) as mobile phase .The rection mixtured was cooled poured on ice cold water(20ml),extracted with 10ml diethyl ether (5timesThe organic layer was separated, washed with water,dried over anhydrous Na_2SO_4. The dried organic layer was filtered and evaporated under vaccum to give crude oil. The crude oil was purified by column chromatography by using 60-120 mesh silica gel.The 10% ethyl acetate-pet Ether solvent mixture was used as eluent.After the evaporation of the solvent under vaccum it affords pure 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetyl azide (7).

The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data.

The IR(KBr) spectrum of compound 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetyl azide (7) was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3260(-NH), 3100(v-Ar-H), 2990 and 2960 (v aliphatic CH_2 and CH_3),1740(carbonyl group), 1680(C=N) , and 1195(C=S).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a) was recorded in DMSO-d6 solvent. The NMR signal of 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a) was found at 4.38(s,2H,- N-CH_2 –N-),4.92(s,1H,N-NH),5.4(d,1H,-CH of azetidine attached to indole ring), 5.6(d,1H,-CH of azetidine attached to-Cl),7.04-8.31(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one aldehydimine proton),7.31-7.33(complex,m,8H,one proton of the thiazolylring, seven phenyl protons).

Synthesis of 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl)amino) azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea (9).

To a mixture of pure 2-(3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)acetyl azide 7(a) (1eq),in benzene (1eq) was added and refluxed for 16hrs.progress of the reaction was monitored by TLC with acetone . ethyl acetate (6:4) as mobile phase. After completion of reaction solvent was evaporated under vaccum to give crude residue,purified by column chromatography 60-120 mesh silica gel to give 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a).

The similar procedure was extended for the syn thesis of their compounds of the series 9(a-o) from 7(a).

The structures of this newly synthesized compounds 9(a-o) were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of compound 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a) was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3260(-NH),3100(✓-Ar-H), 2990 and 2960 (✓ aliphatic CH_2 and CH_3), 2140(NΞN),1775 (✓Azetidine C=O), 1630(C=N) and 680(✓C-S-C).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a) was recorded in DMSO-d6 solvent. The NMR signal of 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a) was found at 4.38(s,2H,- N-CH_2 –N-),4.92(s,1H,N-NH),5.4(d,1H,-CH of azetidine attached to indole ring), 5.6(d,1H,-CH of azetidine attached to-Cl),7.04-8.31(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one aldehydimine proton),7.31-7.33(complex,m,8H,one proton of the thiazolylring, seven phenyl protons).

Elemental analysis: Elemental analysis of 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a-o) shown in Table-1.

Table-1. Elemental analysis of of 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a-o)

Compound	R	R^1	MP ^{0}C	Yield %	Mol.Formula	Found (%)	Calculated (%)	
						C	H	N
9(a)	$-CF_3$	-H	182	58%	$C_{29}H_{22}ClF_3N_6O_2S$	57.00 (57.04)	3.63 (3.60)	13.75 (13.77)
9b)	$-CF_3$	$-CH_3$	185	60%	$C_{30}H_{24}ClF_3N_6O_2S$	57.65 (57.69)	3.87 (3.84)	13.45 (13.46)
9(c)	$-CF_3$	OCH_3	190	62%	$C_{30}H_{24}ClF_3N_6O_3S$	56.21 (56.25)	3.77 (3.75)	13.11 (13.12)
9(d)	$-CF_3$	-Cl	195	59%	$C_{29}H_{21}Cl_2F_3N_6O_2S$	53.96 (53.95)	3.28 (3.25)	13.02 (13.05)
9(e)	$-CF_3$	$-NO_2$	205	56%	$C_{29}H_{21}ClF_3N_7O_4S$	53.09 (53.12)	3.23 (3.20)	14.95 (14.96)
9(f)	$-NO_2$	-H	210	57%	$C_{28}H_{22}ClN_7O_4S$	57.19 (57.24)	3.77 (3.74)	16.67 (16.69)
9(g)	$-NO_2$	$-CH_3$	175	54%	$C_{29}H_{24}ClN_7O_4S$	57.85 (57.90)	4.02 (3.99)	16.29 (16.30)
9(h)	$-NO_2$	OCH_3	165	58%	$C_{29}H_{24}ClN_7O_5S$	56.36 (56.40)	3.91 (3.88)	15.86 (15.88)
9(i)	$-NO_2$	-Cl	182	60%	$C_{28}H_{21}Cl_2N_7O_4S$	54.03 (54.01)	3.40 (3.37)	15.75 (15.78)
9(j)	$-NO_2$	-F	170	61%	$C_{28}H_{21}ClFN_7O_4S$	55.49 (55.53)	3.49 (3.47)	16.18 (16.19)
9(k)	-F	-H	180	57%	$C_{28}H_{22}ClFN_6O_2S$	59.94 (60.00)	3.95 (3.92)	14.98 (15.00)
9(l)	-F	$-CH_3$	192	55%	$C_{29}H_{24}ClFN_6O_2S$	60.57 (60.62)	4.21 (4.18)	14.61 (14.63)
9(m)	-F	OCH_3	200	52%	$C_{29}H_{24}ClFN_6O_3S$	58.93 (58.98)	4.09 (4.06)	14.22 (14.23)
9(n)	-F	-Cl	202	56%	$C_{28}H_{21}Cl_2FN_6O_2S$	56.48 (56.47)	3.55 (3.52)	14.11 (14.15)
9(o)	-F	NO_2	205	59%	$C_{28}H_{21}ClFN_7O_4S$	55.49 (55.53)	3.49 (3.47)	16.18 (16.19)

Synthesis of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl)amino) azetidin-2-yl)-1H-indol-1-yl)methyl) piperidine-1-carboxamide (11).

To a mixture of 1-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl) thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea 9(a),1eq (1eq) in benzene,piperidine(1eq) in benzene was added and refluxed for 16hrs. After completion of reaction solvent was evaporated under vaccum to give crude residue,purified by column chromatography 60-120 mesh silica gel to give N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a).

The similar procedure was extended for the syn thesis of their compounds of the series 11(a-i) from 7(a).

The structures of this newly synthesized compounds 11(a-i) were charecterised by H-NMR and IR spectral data.

The IR(KBr) spectrum of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl) phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a) compound was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3190(-NH),2950 (OH) 3100(✓-Ar-H), 2990 and 2960 (✓ aliphatic CH_2 andCH_3), 2140(NΞN),1780(✓azetidine CO), 1645(C=N) , and 695(✓C-S-C).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a) was recorded in DMSO-d6 solvent. The NMR signal of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a) was found at 1.55-1.57(m,6H,$(CH_2)_3$ of piperidine ring,), 2.58(t,4H,-CH_2–N-CH_2– of piperidine ring),4.36(s,2H,-N-CH_2–N-),5.1(d,1H,-CH of azetidine attached to indole ring), 5.5(d,1H,-CH of azetidine attached to-Cl),7.02-8.29(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one aldehydimine proton),7.30-7.32(complex, m,5H,one proton of the thiazolylring, four phenyl protons),9.6(s,1H,-NH).

Elemental analysis: Elemental analysis of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a-i) shown in Table-2.

Antibacterial activity

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram +ve bacteria screened were *Staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106. The gram -ve bacteria screened were *Escherichia coli* NCCS 265 and *Pseudomonas aeruginosa* NCCS 2200.

The synthesized compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/disc and cefaclor 30 µg/disc were used as a standard (Himedia laboratories limited. Mumbai).

Antifungal activity

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of *Aspergillus Niger* NCCS 1196 and *Candida albicans* NCCS 3471 in Table-3.

Compounds were treated at the concentrations of 100 µg/ml, 250 µg/ml, 500 µg/ml and 1000 µg/ml using DMSO as a solvent. The standard used was ketaconazole 50 µg/ml against both the organisms. Antibacterial activity by disc diffusion method for Azetidine **11(a-i)** in Table-4**.**

Table-2. Elemental analysis of N-((3-(4-chloro-3-oxo-1-((4-(4-(trifluoromethyl)phenyl)thiazol-2-yl)amino)azetidin-2-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxamide 11(a-i)

Compound	R	R^1	MP ^{0}C	Yield %	Mol.Formula	Found(%)	Calculated (%)	
						C	H	N
11(a)	-CF_3	-CH_2	185	57%	$C_{28}H_{26}ClF_3N_6O_2S$	55.77 (55.81)	4.35 (4.31)	13.94 (13.95)
11(b)	-CF_3	O	190	58%	$C_{27}H_{24}ClF_3N_6O_3S$	53.60 (53.64)	4.00 (3.97)	13.89 (13.90)
11(c)	-CF_3	N-CH_3	195	59%	$C_{28}H_{27}ClF_3N_7O_2S$	54.41 (54.45)	4.40 (4.37)	15.86 (15.88)
11(d)	-NO_2	-CH_2	200	56%	$C_{27}H_{26}ClN_7O_4S$	55.91 (55.95)	4.52 (4.49)	16.90 (16.92)
11(e)	-NO_2	O	185	55%	$C_{26}H_{24}ClN_7O_5S$	53.65 (53.70)	4.16 (4.13)	16.85 (16.82)
11(f)	-NO_2	N-CH_3	180	52%	$C_{27}H_{27}ClN_8O_4S$	54.50 (54.54)	4.57 (4.54)	18.83 (18.85)
11(g)	-F	-CH_2	175	60%	$C_{27}H_{26}ClFN_6O_2S$	58.64 (58.69)	4.74 (4.71)	15.20 (15.21)
11(h)	-F	O	170	58%	$C_{26}H_{24}ClFN_6O_3S$	56.26 (56.31)	4.36 (4.33)	15.14 (15.16)
11(i)	-F	N-CH_3	200	59%	$C_{27}H_{27}ClFN_7O_2S$	57.09 (57.16)	4.79 (4.85)	17.26 (17.35)

Table-3. Antifungal activity by disc diffusion method

Compound	Zone of inhibition (mm)	
	Aspergillus niger NCCS 1196	*Candida albicans* NCCS 2106
11(a)	14	16
11(b)	15	13
11(c)	17	15
11(d)	18	17
11(e)	23	21
11(f)	15	13
11(g)	12	10
11(h)	13	12
11(i)	18	20
Clotrimazole	25-30	25-30

Table-4. Antibacterial activity by disc diffusion method

Comp	R	R_1	Zone of inhibition (mm)			
			Staphylococcus aureus NCCS 2079	*Bacillus cereus* NCCS 2106	*Escherichia coli* NCCS 2065	*Pseudomanas aeruginosa*. NCCS 2200
11(a)	H	CF_3	16	18	13	12
11(b)	CH_3	CF_3	14	11	15	14
11(c)	OCH_3	CF_3	13	12	10	10
11(d)	Cl	CF_3	16	17	8	09
11(e)	NO_2	CF_3	18	16	10	11
11(f)	CF_3	H	11	14	12	17
11(g)	CF_3	OCH_3	9	13	9	12
11(h)	CF_3	Cl	10	14	11	12
11(i)	CF_3	CF_3	12	15	14	15
Cefaclor			19	22	19	20

Antifungal activity by disc diffusion method for indole linked Thizole having Azetidinone **11(a-i)**

CONCLUSIONS:

1. Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The Urieds showed better antibactirial and antifungal activities.
3. thiazoles and its derivatives were found to play an important role in medicinalchemistry as herbicidal, fungicidal, bacterial, anti-inflammatory.

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