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SYNTHESIS CHARECTERIZATION AND BIOLOGICAL EVALUATION OF ACYCLIC NUCLEOSIDE AND THEIR CONDENSED PYRENYL DERIVATIVES CONTAINING INDOLE MOIETY BEARING -2-THIAZOLIDINONE

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ABSTRACT

This study is aimed to synthesize,characterize and screen the biological activity of a series of Synthesis of Synthesis of 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) was prepared by 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(35^0C) for 8 hours .To afford 2-(3-formyl-1H-indol-1-yl)acetate(3). To this reaction mixture Equimolar quantity of 4,5-dihydro pyrene-1-amine(4) 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 to obtain Ethyl2-(3-((1,9dihydro pyrene-6-yl imino)methyl)-1H-indol-1-yl)acetate(5).To this reaction mixture thioacetic acid and TEA,Dioxane was added and the mixture stirred at roomtemperature for 30min.compound Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetate(6)was obtained. 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 0^0C.To obtain 2-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4-one(8).The reaction mixture is treated with aniline(9) to obtain of 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) was obtained. The structure of these newly synthesized compounds was characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis. The antimicriobial activity of the novel compounds was screened by agar disc diffusion method.

KEYWORDS; Indole-3-carboxaldehyde, DMF,phenyl derivatives , Ureas,thiocarboxilic acid,halo esters

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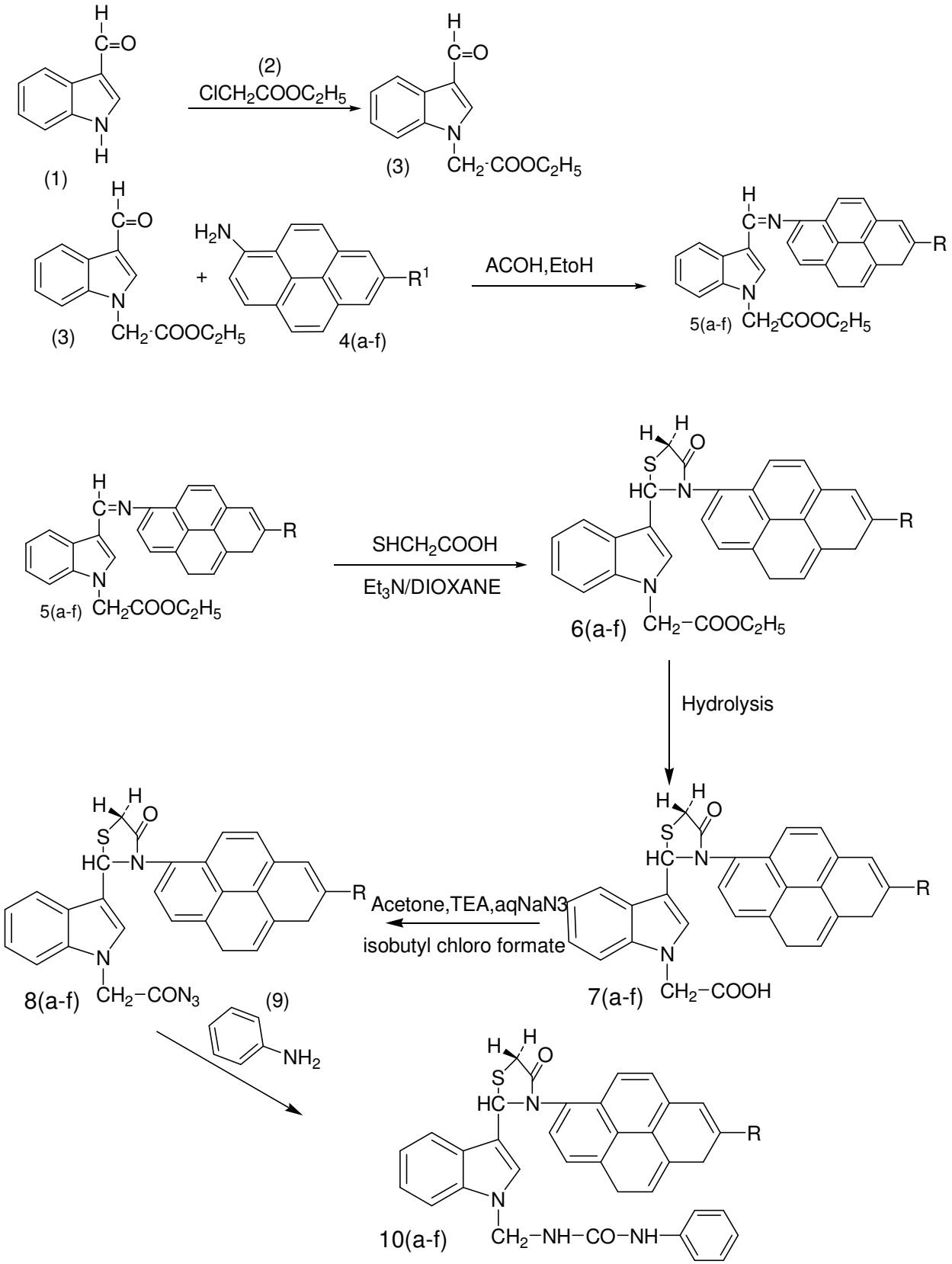
INTRODUCTION

Hetero cyclic compounds represent an important class of biological molecules.The hetero cyclic molecules which ,posses indole,1,3,4 oxadiazole and thiazolidinone 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 skeleton and development of the drug.The classical indole drugs are indomethacin and indoxole. Indole derivatives found to possess high which ncludes,antibacterial,analgesic,antipyretic,antifu ngal,antiflamatory,anthelmintic,cardiovascular,a nticonvalsant and selective COX-2 inhibitary activities . Indole and its derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activities(1-7). Major efforts have been directed by the nucleoside chemists to words the synthesis of analogues of acyclovir and other acyclo nucleosides with various side chains and aglycons(20) thiazolidinones moiety is associated with variety ofbiological activities including antifungal[9]., anti-inflammatory[10]., anticonvulsant[11]., antitubercular[12].,antihistamine[13].Considerin g that both molecules as well as ayclic nucleoside withvarious side chains are potent pharmacophores the combinations of these two moieties may result in interesting biological activities and this is the aim of the present investigation Indole 3-carboxaldehyde (1)was alkylated with the appropriate alkylating agent (2) using anhydrous K_2CO_3 and pyrene amines was added. .The reaction proceeded at room temparature with in few minutes to yield the corresponding acyclic nucleoside derivatives(3) in good yields(76-92%).New indole Schiff base derivatives having a pyrene nucleous were synthesized through a condensation reaction between an acyclic nucleoside type of indole-3caoboxadehyde (1) and 1-aminopyrene in refluxing ethylalcohol for 6h to give schiff bases 5a,c,e-g in good yield (78-87%)

R	1	2	3	4	5	6	7
Compound	H	CH_3	OCH_3	Cl	NO_2	CF_3	Br



N-Alkylated indole -3-carboxaldehyde (3) eg were condensed with N-acetyl pyrene4(a)in refluxing ethanol and in the presence of 1%KOH to yield the ethylenic compounds 5(a-f)eg in the good yield (80-84%).

The HNMR spectra for compounds 5(a-f)eg showed the pattern for the CH=CH Group as an AB system which appears at δ785 and 752 ppm as two doublets with the coupling constant J=159Hz.The ^{13}C NMR spectra showed a peak in the range 195-200 ppm characteristic for C=0 conjugated to pyryne which also confirimed the structurer micro analysis and FAB MS Compounds 6(a-f)eg and 10(a-f)e.g were examined for possible antiviral activity againists HIV-1using MT-4cell as target cell compounds 10a and 10e were found moderately active against HIV-1 with the effective doses ED_{50}=10and 18μM,respectively.The selectivity was low as the toxic doses for the compounds 10a and 10e were found to be CD_{50}=70 and 32 μM respectively. Compounds 10a and 10e were toxic to the MT-4cell ,but no activity was found against HIV-1 at non-toxic concentractions .The compounds were also screened against herpes simplex virus (HSV-1)replication using vero cell as target cells.but no activity was found .

Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetate(6)

To a solution of Ethyl2-(3-((1,9dihydro pyrene-6-yl imino)methyl)-1H-indol-1-yl)acetate(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 thiazolidine-4-one derivatives 5(a-f). The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetate(6) was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3250(-NH),3100(√-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-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetate(6) 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), 3.90(d,1H,Ha of -CH_2 of thiazolidinone),3.99(d,1H,Hb of –CH_2 of thiazolidinone),,7.04-8.31(complex,m,6H,five aryl protons of the indole ring,one α-proton of the indolyl ring),), pyrene group (multiplets at 7.90- 8.25).

Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetic acid(7)

The synthesis of the synthon Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetate(6) to this solvent mixture tetrahydro furan/methylalcohol/H_2O(1:1:1)ratio,aqNaOH(2 N) 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 vacuum 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 Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetic acid(7) The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of compound Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetic acid7(a)was recorded in the range 4000-667cm^{-1} and the absorption signals were found at 3260(-NH),2950 (OH) 3100(√-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 Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetic acid7(a) was found at 4.92(s,1H,N-NH), 3.95(d,1H,Ha of -CH_2 of thiazolidinone),4.20(d,1H,Hb of –CH_2 of thiazolidinone),,7.01-8.29(complex,m,6H,five aryl protons of the indole ring,one α-proton of the indolyl ring),) pyrene group (multiplets at 7.93- 8.29). ,10.5-12(broad signal of –COOH of –OH) *Synthesis of 2-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4- one(8)* . Earlier we have identified various useful methodologies for the synthesis of indole derivatives containing thiazolidin-4-one heterocyclic moieties.Here we are describing the synthesis of substituted urea derivatives processing indole moiety containing thiazolidin-4-one. In the present investigation the required synthons Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetic acid(7).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 reaction was monitored by TLC with acetone . ethyl acetate (6:4) as mobile phase .The reaction mixture 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 vacuum 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-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4-one(8) The structures of this newly synthesized compounds were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of compound 2-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4-one(8)was recorded in the range 4000-667cm-1 and the absorption signals were found at 3260(-NH), 3100(√-Ar-H), 2990 and 2960 (√ aliphatic CH2 andCH3),1740(carbonyl group), 1680(C=N) , and 1195(C=S).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of 2-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4-one(8) 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 8(a) was found at 4.38(s,2H,- N-CH_2 –N-),4.92(s,1H,N-NH), 3.97(d,1H,Ha of -CH_2 of thiazolidinone),4.30(d,1H,Hb of –CH_2 of thiazolidinone),,7.04-8.31(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,one)),. pyrene group (multiplets at 7.90- 8.22).

Synthesis of 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) To a mixture of pure 2-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4-one(8) (1eq),in aniline (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 vacuum to give crude residue,purified by column chromatography 60-120 mesh silica gel to give 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) The structures of this newly synthesized compounds 10(a-f) were charecterised by H-NMR and IR spectral data. The IR(KBr) spectrum of compound 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) 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 andCH_3), 2140(NΞN),1775 (√Azetidine C=O), 1630(C=N) and 680(√C-S-C).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo

thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) was recorded in DMSO-d6 solvent. The NMR signal of 1-((3-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10) was found at 4.38(s,2H,- N-CH_2 –N-),4.92(s,1H,N-NH), 3.99(d,1H,Ha of -CH_2 of thiazolidinone),4.35(d,1H,Hb of –CH_2 of thiazolidinone),,7.04-8.31(complex,m,7H,five aryl protons of the indole ring,one α-proton of the indolyl ring,)),. pyrene group (multiplets at 7.85- 8.35).

EXPERIMENTAL SECTION

Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetate(6)

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%.

Ethyl2-(3-(3-(1,9-dihydro pyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)acetic acid(7)

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 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_2 SO_4, filtered and evaporated under vaccum to give a 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-(1-(2-azido-2-oxoethyl)-1H-indol-3-yl)-3-(1,9-dihydropyren-6-yl)thiazolidin-4-one(8).

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_2 SO_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-(3-(1,9-Dihydropyrene-6-yl)-4-oxo thiazolidin-2-yl)-1H-indol-1-yl)methyl)-3-phenyl urea(10)

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 vacuum 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).

ANTI-MICROBIAL ACTIVITY

Media and chemicals

Nutrient Broth, Nutrient agar and 5 mm diameter antibiotic assay were obtained from Hi-Media Laboratories Limited, India. Barium chloride dehydrate GR, concentrated sulphuric acid GR, Dimethyl sulphoxide GR, Sodium chloride AR and Potassium dichromate were obtained from Ranbaxy Laboratories Ltd, Chemical Division India. The standard bacterial and fungal strains were procured from National Centre for Cell Science (NCCS), Pune, India.

Glass wares and Apparatus

Glass Petri dish, Glass tubes, Beakers, Erlenmeyer flasks, Bacterial loop and measuring cylinder. All the glass wares were of Borosilicate grade. Digital electronics balance (Shankar Scientific supplies, India), Yorco Horizontal Laminar air flow bench (Yorco sales Pvt. Ltd, New Delhi, India), Ausco incubator, Zone reader (Cintex industrial Corporation, India), hot air oven, autoclave and UV/Visible spectrophotometer (Shimadzu corporation, Japan).

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).

Disc Diffusion Method

A suspension of Staphylococcus aureus was added sterile nutrient agar at 45ºC. The mixture was transferred to sterile Petri dishes to give a depth of 3 to 4 mm and allowed to solidify. Precautions were observed to reduce uniform layer of medium on the plate. Sterile discs 5mm in diameter (made from Whatman Filter paper) were immersed in the solutions of synthesized compounds (250 µg/ml) and maintain an untreated control sample for comparison. Leave the plates to stand for 1hour at room temperature as a period of pre-incubation diffusion to minimize the effects of variations in different time. Then the plates were incubated at 37ºC for 24 hours and observed for antibacterial activity. .

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 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.

Disc Diffusion Method

A suspension of Aspergillus Niger NCCS 1196 was added to sterile sabouraud dextrose agar at 45ºC. The diameters of the zone of inhibition were measured for the plates in which the zone of inhibition was observed. The average zone of inhibition was calculated with that of standard. A similar procedure was carried out for studying the antifungal activity the other organisms (Candida albicans).

Determination of Minimum Inhibitor Concentration

Medium: Nutrient Broth Test tubes: 16 x 100 mm glass tubes with loose fitting metal caps.

Method (Broth Dilution Method)

Standardized Inoculums (matched to McFarland BaSO4 standard) of suspension of organisms were prepared. A series of glass tubes containing different concentration of test compounds dissolved in DMSO and spiller in Nutrient Broth were incubated with one drop of inoculum and mixed gently by shaking the rack. Two growth control tubes were also prepared without the addition of test compound and its optical density was determined as follows. 0.1 ml of control was mixed with 0.9 ml of Sterile Saline and with 0.2µL loop, an Agar plate was inoculated. The control should contain 1 x 10-5 colony forming units/ml=20colonies. Incubate the tubes for 24 hours at 37ºC in air. The MIC of the compounds was presented in given tables.

Antibacterial activity by disc diffusion method for indole linked thiazolidinone 10(a-f)

Comp	R	Zone of inhibition (mm)			
		staphylococcus aureus NCCS 2079	*Bacillus cereus* NCCS 2106	*Escherichia coli* NCCS 2065	*Pseudo-manas aeruginosa.* NCCS 2200
10a	H	15	19	14	14
10b	CH_3	14	13	16	16
10c	OCH_3	12	13	12	15
10d	Cl	17	16	10	14
10e	NO_2	18	18	14	15
10f	CF_3	16	15	18	17
Cefaclor		19	22	19	20

Antifungal activity by disc diffusion method for indole linkedThiazolidinone 10(a-f)

Compound	*Zone of inhibition (mm)*	
	Aspergillus niger NCCS 1196	*Candida albicans* NCCS 2106
4a	18	18
4b	17	15
4c	22	17
4d	19	19
4e	22	22
4f	18	14
Clotrimazole	25-30	25-30

Characterization and biological activity of thiazolidinone is shown in the given reference
- Synthesis of 1,3,4 oxadiazole derivatives containing indole moiety bearing thiazolidinone and anti-inflammatory activity of thiazolidinone
International journal of chemtech Research vol.6,NO.1,pp183-194,Jan-March2014*

CONCLUSION

1.Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2.The thiazolidinone showed better antibacterial and antifungal activities.
3.indoles and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, antiflammatory.

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