Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(10):280-288

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis characterization and anti-inflammatory activity of indole derivatives bearing-4-oxazetidinone

S. Muralikrishna, P. Raveendrareddy, L. K. Ravindranath, S. Harikrishna and P. Ashok Gajapathi Raju

Department of Chemistry, S. K. University, Anantapur

ABSTRACT

Schiff base synthesis of pyrazolone derivatives containing Indole moiety bearing-4-oxazetiding ring were synthesized by the condensation of 2-(3-(3chloro -1-(4-substitued phenyl)-4-oxozetiding -2-yl(1H-Indole –yl Aceto hydrazone with ethyl 2-(2-(4-substitued phenyl hydrazone)(-4,-4,-4 tri frouro-3-oxo butanoate) this reaction was subjected in schiff base reaction .The structure of these newly synthesized compounds were characterized by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis.

Keywords: Azetidinones, Schiff base, β- Lactam, pyrazolones, indole

---

INDRODUCTION

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 skeleton and development of the drug. The classical indole drugs are indomethacin and indoxole. Indole derivatives 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 .

Pyrazole derivatives have been reported to possess diverse biological activities such as antimicrobial [1, 2], antibacterial [3,4], antifungal [5, 6], herbicidal [7], insecticidal [8], anti-inflammatory[9-11], anticonvulsant [12], antitumor [13], anti-oxidant [14,15].

Azetidinones are of great biological interest, especially as anti-tubercular [16], antibacterial[17],[18],[19],[20] 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 [21],[22], anticonvulsant [23], anti-inflammatory [24] and cardiovascular activities [25], antimycobacterial activity[26], antibacterial activity [27], antihypertensive activity [28].

EXPERIMENTAL SECTION

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 visualization 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.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 –analyzer. All the chemicals used in the present investigation were purchased from Aldrich chemicals ;U.S.A. indole- 3-carbaldehyde was prepared by a reported method

RESULTS AND DISCUSSION

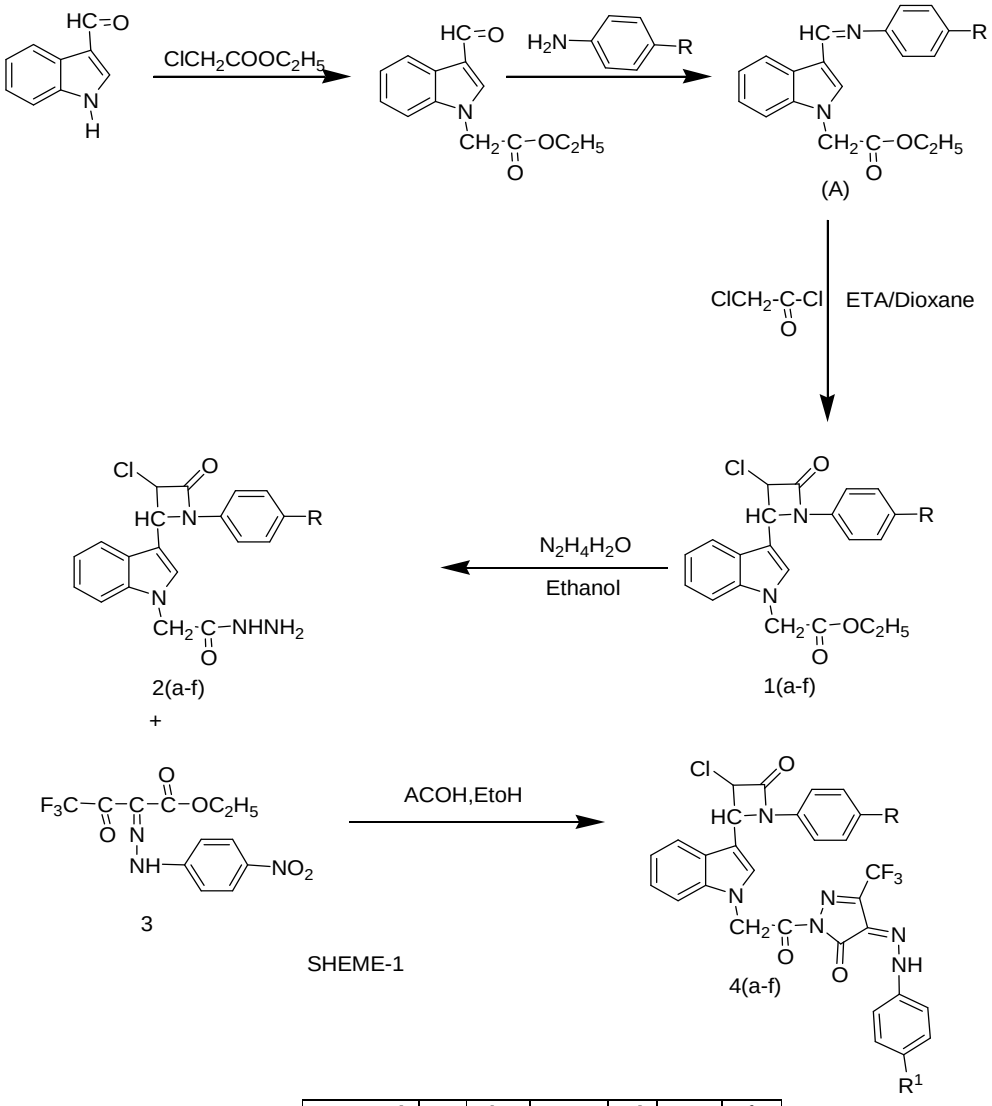
indole-3-carbaldehyde(1) and chloro ethyl acetate were dissolved in dimethyl formamide solvent and to this reaction mixture anhydrous K_2CO_3 was added and the reaction mixture was stirred at room temperature(35^0C) for 8 hours. The yield -2-(3-formyl-1H-indol-1-yl)acetate. The compound on treatment with substituted aniline afford Ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate (A). The compound- (A) on reaction with chloro ethyl acetate and ETA, dioxane compound (1) is Ethyl 2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetate(5) formed. The compound (1) is condensed with hydrazine hydrate in presence of afford 2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)aceto hydrazide2(a-f).The compound (2) is condensed with Synthesis of ethyl 2-(2-(4-nitrophenyl)hydrazono)-4-4-4-trifluoro-3-oxobutanoate(3) in presence of acetic anhydrate in ethanol afford 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one4(a-f).These reactions are summarized in the scheme-1.Yields were moderate to affair(55-70%). The purity of the compounds was monitored by TLC.

Synthesis of 2-(3-formyl-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 monitored by TLC using cyclohexane and ethylacetate solvent mixture (7:3) as eluent the reaction mixture was kept overnight. 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 crystalline 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 further purification. Yield 75%,m.p.:143-145^0C

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).

^{1}HNMR Spectra (δ_{PPm}): The ^{1}HNMR spectra of 2-(3- formyl-1H-indol-1-yl) acetate(2) was recorded in DMSO-d6 solvent. The NMR signal of 2-(3- formyl-1H-indol-1-yl) acetate(2) was found at $\delta_{PPm,}$ 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) and 6.92 , 7.58 (m, 10H, C_8H_5N indole nucleus).

synthesis of Ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate (A)
Equimolar quantity of aniline(3) and ethyl-2-(-3-formyl-1H-indol-1-yl)acetate(2) were dissolved in absolute alcohol, to this three drops of acetic acid is added then heated on a steam bath for 5-6hrs at 100^0C. After standing for 24hrs at room temperature, the product was dried and recrystalised from warm absolute alcohol. The separated solid was identified as ethyl 2-(-3-(((-4-nitro phenyl)imino)methyl)-1H-indol-1-yl)acetate. Yield 75%,m.p.:154-156^0C



SHEME-1

compound	4a	4b	4c	4d	4e	4f
R	H	CH_3	OCH_3	Br	NO_2	CF_3
R^1	H	H	H	H	H	H

IR Spectra (√, cm^{-1}):

IR (KBr) spectrum of ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate 1(a)was recorded in the range 4000-667cm^{-1} and IR absorption signals were found at 3032 (√ Ar-H), 2980 and 2960 (√ aliphatic CH_2 and CH_3), 1760 (√ CO of ester group), 1610(√ C=N group) and 1182(√ C-O-C of ester group).

^{1} H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ;

^{1}H NMR Spectra ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate 1(a)was recorded in DMSO-d6 solvent. The NMR signal of ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate(A) was found at $\delta_{PPm,}$ 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) and 6.92 , 7.58 (m, 10H, C_8H_5N indole nucleus and C_6H_5 phenyl nucleus) and 8.44(s, 1H, N=CH group).

The compound (A) was converted into azetidine-2-one on treatment with chloro acetyl chloride. The formation compound was confirmed by IR,NMR data.

NMR spectra; 1.29(t, 3H,CH_3 of C_2H_5), 4.78(s, 2H N-CH_2-C=O), 4.13(q, 2H,-O-CH_2 Of OC_2H_5), 6.92-7.58(m, 10H, Ar-H, 8.44(N=CH).

IR spectra; The compound (A) shows signals at, 1610(C=N), 1760 (ester –C=O), 3032(Ar-H),1182(-C-O-C).

Table: 2.2 1H NMR spectra of ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate (A)

Synthesis of ethyl 2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetate 1(a)
Equimolar quantities of ethyl 2-(3-(((phenyl) imno)methyl)1-1H-Indol -1yl) acetate (A) was converted into azetidine- 2-one on treatment with chloro acetyl chloride Yield 75%,m.p.:155-150^{0}C. This general procedure was extended to substituted indoles to synthesis azetidin -2-one derivative 5(a-f) the structure of 1 (a-f) were established by IR and H^1 NMR data

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of ethyl 2-(3-(3-chloro -1-(4-substituted phenyl) -4 oxaezetidine -2-yl) -1H - Indol -1-yl)acetate 1(a) show signals 1.30 (t,3H,CH_3 of C_2H_5), 4.75 (s,2H N-CH_2-C =O), 4.15 (q,2H,-O-CH_2 Of OC_2H_5), 5.16(d,1H,-CH of azetidine attached to phenyl ring), 5.44(d,1H,-CH of azetidine attached to -Cl), 6.94-7.59 (m,10H,Ar-H). IR(KBr) spectra ; The compound 1(a) shows signals at, 1578(C=N),1177(-C-O-C-),1765(-C=O),826(CCl) are due to stretching vibrations of –C=O , C=N,C-O-C , CCl respectively . *Anal.* Cacld. for (382);C,67.02;H,5.05;N,7.44 found(%);C:65.88,H:5.00,N:7.32

Ethyl 2-(3-(3-chloro-1-(4-methyl phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetate 1(b).
^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of ethyl 2-(3-(3-chloro -1-(4-methyl phenyl) -4 oxaezetidine -2-yl) -1H - Indol -1-yl)acetate 1(b) show signals1.33 (t,3H,CH_3 of C_2H_5), 4.78 (s,2H N-CH_2-C =O), 4.18 (q,2H, O-CH_2 Of OC_2H_5),5.18 (d,1H,-CH of azetidine attached to phenyl ring), 5.48 (d,1H,-CH of azetidine attached to -Cl), 6.94-7.60 (m,9H,Ar-H), 2.23(s,3H, CH_3 attached to phenyl ring). IR(KBr) spectra ; The compound 1(a) shows signals at, 1565(C=N),1175(-C-O-C-),1760(-C=O),820(CCl) are due to stretching vibrations of –C=O , C=N,C-O-C, CCl respectively. Yield 70%,m.p 140-150^{0}C *Anal*. Cacld. For (396); C, 67.69; H,5.38;N,7.17 found(%);C:66.58,H:5.33,N:7.06

Ethyl 2-(3-(3-chloro-1-(4-methoxy phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetate 1(c).
^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- Synthesis of ethyl 2-(3-(3-chloro -1-(4-methoxyphenyl) -4 oxaezetidine -2-yl) -1H - Indol -1-yl)acetate 1(c) show signals 1.34 (t,3H,CH_3 of C_2H_5), 4.79 (s,2H N-CH_2-C =O), 4.19 (q,2H,-O-CH_2 Of OC_2H_5),5.20 (d,1H,-CH of azetidine attached to phenyl ring), 5.46 (d,1H,-CH of azetidine attached to -Cl), 6.96-7.62 (m,9H,Ar-H), 2.26 (s,3H,OCH_3 attached to phenyl ring). IR(KBr) spectra ; The compound 1(c) shows signals at, 1560(C=N), 1170 (-C-O-C-), 1755(-C=O),815(CCl) are due to stretching vibrations of –C=O , C=N,C-O-C , CCl respectively . Yield 65%,m.p.:130-140^{0}C *Anal.* Cacld. for (412);C,64.07;H,5.09;N,6.85 found(%);C:64.00,H:5.13,N:6.79

Ethyl 2-(3-(3-chloro-1-(4-bromo phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetate 1(d).
^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of ethyl 2-(3-(3-chloro -1-(4-bromo phenyl) -4 oxaezetidine -2-yl) -1H - Indol -1-yl)acetate 1(d) show signals1.37 (t,3H,CH_3 of C_2H_5), 4.82 (s,2H N-CH_2-C =O), 4.21 (q,2H,-O-CH_2 OfOC_2H_5) , 5.23 (d,1H,-CH of azetidine attached to phenyl ring), 5.48 (d,1H,-CH of azetidine attached to -Cl), 6.98-7.65 (m,9H,Ar-H). IR(KBr) spectra ; The compound 1(d) shows signals at, 1563(C=N),1173(-C-O-C-),1763(-C=O),818(CCl) are due to stretching vibrations of –C=O , C=N,C-O-C , CCl respectively . Yield 66%,m.p.:170-180^{0}C *Anal*. Cacld. for (460);C,54.78;H,3.91;N,6.08 found(%);C:54.63,H:3.93,N:6.07

Ethyl 2-(3-(3-chloro-1-(4-nitro phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetate 1(e).
^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of ethyl 2-(3-(3-chloro -1-(4-nitro phenyl) -4 oxaezetidine -2-yl) -1H - Indol -1-yl)acetate 1(e) show signals 1.39 (t,3H,CH_3 of C_2H_5), 4.85 (s,2H N-CH_2-C =O), 4.23 (q,2H,-O-CH_2 Of OC_2H_5), 5.25 (d,1H,-CH of azetidine attached to phenyl ring), 5.50 (d,1H,-CH of azetidine attached to -Cl), 6.99-7.67 (m,9H,Ar-H). IR(KBr) spectra ; The compound 1(e) shows signals at, 1555(C=N),1160(-C-O-C-),1745(-C=O),814(CCl) are due to stretching vibrations of –C=O , C=N,C-O-C , CCl respectively . Yield 70%,m.p.:185-190^{0}C *Anal*. Cacld. for (427);C,59.01;H,4.21;N,9.83 found(%);C:58.95,H:4.24,N:9.82

Ethyl 2-(3-(3-chloro-1-(4-tri fluoro methyl phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl) acetate 1(f).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- synthesis of ethyl 2-(3-(3-chloro -1-(4-nitro phenyl) -4 oxaezetidine -2-yl) -1H - Indol -1-yl)acetate 1(f) show signals 1.40 (t,3H,CH_3 of C_2H_5), 4.90 (s,2H N-CH_2-C =O), 4.25 (q,2H,-O-CH_2 Of OC_2H_5), 5.28 (d,1H,-CH of azetidine attached to phenyl ring), 5.52 (d,1H,-CH of azetidine attached to -Cl), 7.2--7.70 (m,9H,Ar-H).). IR(KBr) spectra; The compound 1(f) shows signals at, 1580(C=N), 1180(-C-O-C-),1770(-C=O),830(CCl) are due to stretching vibrations of –C=O , C=N,C-O-C , CCl respectively . Yield 71%,m.p.:180-185^{0}C *Anal*. Cacld. for (705);C,56.00;H,4.21;N,6.22 found(%);C:58.61,H:4.02,N:6.21.

Synthesis of 2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)aceto hydrazide(2).

A solution of (5a) (0.01mol) and hydrazine hydrate (0.015mol) in ethanol(20ml) was refluxed for 5hrs. The reaction mixture was cooled and poured in to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallised from ethanol to afford 2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)aceto hydrazide(6).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of 2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)aceto hydrazide(2)) show signals at 4.36 (s,2H N-CH_2-C =O), 4.95 (s,1 H,-N-NH), 5.20 (d,1H,-CH of azetidine attached to phenyl ring), 6.9-8.3(m,14H,due to 5H of indole $C_{,6}H_{6,}$ C_6H_4 of phenyl ring), 5.49 (d,1H –CH of azetidine attached to –cl).). IR(KBr) spectra ; The compound 1(f) shows signals at 3494(-NH),3330(Ar-H),2920(-CH- of aliphatic),1680(C=O, amide),3494(-NH_2),820(CCl). Yield 65%,m.p.:175-185^{0}C.

Synthesis of 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one(4)

In a solution of 6(a-f) in (0.01 mol),(10ml) ethanol , and(0.01) ethyl acetoacetate were added and the mixture was refluxed for 12hrs in presence of catalytic amount glacial acetic acid. Excess of ethanol was removed by distillation and crystalline residue obtained was filtered, washed with ethanol, dried and recrystallized to get the compounds 8(a-f) in good yields.

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of Synthesis of 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one4(a)) show signals at 4.36 (s,2H N-CH_2-C =O), 4.95 (s,1 H,-N-NH), 5.20 (d,1H,-CH of azetidine attached to phenyl ring), 6.94-8.34(m,14H,due to 5H of indole $C_{,6}H_{6,}$ C_6H_4 of phenyl ring 5.49 (d,1H –CH of azetidine attached to –cl). IR(KBr) spectra ; The compound 4(a) shows signals at 3158(-NH-),1780(-C=O),2,260(C=N),580(CCl),1770(-C=O),750(C-F).The ^{13}C spectrum of ($CDCl_3$) shown δ:138.4-C_1,121.9-$C_{2,}$117.2- $C_{3,}$149.2- C_4(nitro phenyl),63.1- C_5,59.6- C_6,162.2- C_7(azetidine ring),121.6- C_8,141.7- C_9,129.0-$C_{10,}$124.4.0- C_{11} (phenylring),116.5- C_{12},126.5- C_{13},127.8- C_{14},119.0- C_{15},122.2- C_{16},120.7- C_{17},111.8- C_{18},137.6-C_{19}(indole ring),41.0- C_{20},171.0- $C_{21,}$155.0- $C_{22,}$122.0- C_{23},128.6- $C_{24,}$162.5- C_{25}(pyrazolone ring) Yield 57%,m.p.:150-160^{0}C*Anal*.Cacld. for (637);C,54.63;H,2.98;N,15.38 found(%);C:54.60,H:3.00,N:15.37

Synthesis of 1-(2-(3-(3-chloro-1-(4-methyl phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(b)

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of Synthesis of 1-(2-(3-(3-chloro-1-(4-methyl phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one4(b) show signals at 4.37 (s,2H N-CH_2-C =O), 4.95 (s,1 H,-N-NH), 5.21 (d,1H,-CH of azetidine attached to phenyl ring), 6.95-8.35(m,14H,due to 5H of indole $C_{,6}H_{6,}$ C_6H_4 of two phenyl rings) ,5.50 (d,1H –CH of azetidine attached to –cl),2.23(s,3H,CH_3,attached to phenyl ring) IR(KBr) spectra ; The compound 4(b) shows signals at 3150(-NH-),1775(-C=O),2,255(C=N),578(CCl),1765(-C=O),745(C-F).The ^{13}C spectrum of ($CDCl_3$) shown δ: 138.4-C_1,121.9- $C_{2,}$117.2- $C_{3,}$149.2- C_4(nitro phenyl),63.1- C_5,59.6- C_6,162.2- C_7(azetidine ring),121.5-C_8,138.7- C_9,129.3- $C_{10,}$134.0- C_{11},24.3-C_{12}(tollyl group),116.5- C_{13},126.5- C_{14},127.8- C_{15},119.0- C_{16},122.2-C_{17},120.1- C_{18},111.8- C_{19},137.6- C_{20}(indole ring),41.0- C_{21},171.0- $C_{22,}$155.0- $C_{23,}$122.0- C_{24},128.6- $C_{25,}$162.5-$C_{26,}$(pyrazolone ring). Yield 55%,m.p.:143-150^{0}C *Anal*. Cacld. for (651);C,55.29;H,3.22;N,15.05 found(%);C:55.27,H:3.25,N:15.04

Synthesis of 1-(2-(3-(3-chloro-1-(4-methoxyphenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(c)

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):δ:- of Synthesis of 1-(2-(3-(3-chloro-1-(4-methoxy phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-

5(4H)-one4(c)) show signals at 3.24(s,3H,OCH_3 attached to phenyl ring), 4.37 (s,2H N-CH_2-C =O), 4.95 (s,1 H,-N-NH), 5.22 (d,1H,-CH of azetidine attached to phenyl ring), 6.96-8.33,(m,14H,due to 5H of indole C_6H_6, C_6H_4 of two phenyl rings) ,5.51, (d,1H –CH of azetidine attached to –cl),2.23(s,3H,CH_3,attached to phenyl ring). IR(KBr) spectra ; The compound 4(c) shows signals at 3145(-NH-),1770(-C=O),2,250(C=N),576(CCl),1740(-C=O),750(C-F).The ^{13}C spectrum of ($CDCl_3$) shown δ:138.4-C_1,21.9- C_2,117.2- C_3,149.2- C_4(nitro phenyl),63.1- C_5,59.6- C_6,162.2- C_7(azetidine ring),121.5- C_8,138.7-C_9,129.3-C_{10},134.0-C_{11},55. 9-C_{12}(methoxy phenylgroup),116.5-C_{13},126.5- C_{14},127.8- C_{15},119.0- C_{16},122.2- C_{17},120.1- C_{18},111.8- C_{19},137.6- C_{20}(indole ring),41.0- C_{21},171.0-C_{22},155.0- C_{23},122.0- C_{24},128.6- C_{25},162.5- C_{26},(pyrazolone ring). Yield 54%, m.p.:135-145^{0}C *Anal*. Cacld. fo(667);C,53.97;H,3.14;N,14.69 found(%);C:53.94,H:3.17,N:14.68

Synthesis of 1-(2-(3-(3-chloro-1-(4-bromophenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(d).

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:- of Synthesis of 1-(2-(3-(3-chloro-1-(4-bromo phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substitutedphenyl)hydrazono)-3(trifluoromethyl)-1H-pyrazol-5(4H)-one4(d)) show signals at 4.40 (s,2H N-CH_2-C =O), 4.98 (s,1 H,-N-NH), 5.24 (d,1H,-CH of azetidine attached to phenyl ring), 6.96-8.46 (m,14H,due to 5H of indole C_6H_6, C_6H_4 of two phenyl rings), 5.53 (d,1H –CH of azetidine attached to –cl) IR(KBr) spectra; The compound 4(d) shows signals at 3152(-NH-),1774(-C=O),2,254(C=N),574(CCl),1755(-C=O),750(C-F).The ^{13}C spectrum of ($CDCl_3$) shown δ:138.4--C_1,121.9-C_2,117.2- C_3,149.2- C_4(nitro phenyl),63.1- C_5,59.6- C_6,162.2- C_7(azetidine ring),123.8- C_8,140.7- C_9,131.9-C_{10},118.0- C_{11} (halo phenyl ring),116.5- C_{12},126.5- C_{13},127.8- C_{14},119.0- C_{15},122.2- C_{16},120.7- C_{17},111.8- C_{18},137.6-C_{19}(indole ring),41.0- C_{20},171.0- C_{21},155.0- C_{22},122.0- C_{23},128.6- C_{24},162.5- C_{25}(pyrazolone ring) Yield 56%,m.p.:160-170^{0}C *Anal.* Cacld. for (460);C,54.78;H,3.91;N,6.08 found(%);C:54.63,H:3.93,N:6.07

Synthesis of 1-(2-(3-(3-chloro-1-(4-nitrophenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(e).

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:- Synthesis of 1-(2-(3-(3-chloro-1-(4-nitro phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substitutedphenyl)hydrazono)-3--(trifluoromethyl)-1H-pyrazol-5(4H)-one4(e)) show signals at 4.44 (s,2H N-CH_2-C =O), 5.15(s,1 H,-N-NH), 5.28 (d,1H,-CH of azetidine attached to phenyl ring), 6.98-8.45 (m,14H,due to 5H of indole C_6H_6, C_6H_4 of two phenyl rings), 5.58 (d,1H –CH of azetidine attached to –cl) IR(KBr) spectra; The compound 4(e) shows signals at 3150(-NH-),1760(-C=O),2,252(C=N),572(CCl),1762(-C=O),755(C-F).The ^{13}C spectrum of ($CDCl_3$) shown δ: 138.4-C_1,121.9- C_2,117.2- C_3,149.2- C_4(nitro phenyl),63.1-C_5,59.6- C_6,162.2- C_7(azetidine ring),122.5- C_8,147.8- C_9,121.3- C_{10},144.0- C_{11} (azetidine attached to nitro phenyl ring),116.5- C_{12},126.5- C_{13},127.8- C_{14},119.0- C_{15},122.2- C_{16},120.7- C_{17},111.8- C_{18},137.6- C_{19}(indole ring),41.0-C_{20},171.0- C_{21},155.0- C_{22},122.0- C_{23},128.6- C_{24},162.5- C_{25}(pyrazolone ring) Yield 60%,m.p.:180-190^{0}C *Anal*. Cacld. for (682);C,51.02;H,2.63;N,16.42 found(%);C:51.00,H:2.66,N:16.41

Synthesis of 1-(2-(3-(3-chloro-1-(4-trifluoro methyl phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(f).

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:- Synthesis of 1-(2-(3-(3-chloro-1-(4-trifluoro methyl phenyl)-4-oxoazetidine-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(f) show signals at 4.38 (s,2H N-CH_2-C =O), 4.96(s,1 H,-N-NH), 5.22 (d,1H,-CH of azetidine attached to phenyl ring), 6.95-8.39 (m,14H,due to 5H of indole C_6H_6, C_6H_4 of two phenyl rings), 5.51 (d,1H –CH of azetidine attached to –cl) IR(KBr) spectra; The compound 4(f) shows signals at 3105(-NH-),1785(-C=O),2,300(C=N),585(CCl),1775(-C=O),765(C-F).The ^{13}C spectrum of ($CDCl_3$) shown δ: 138.4-C_1,121.9-C_2,117.2- C_3,149.2- C_4(nitro phenyl),63.1- C_5,59.6- C_6,162.2- C_7(azetidine ring),121.5- C_8,138.7- C_9,129.3-C_{10},134.0- C_{11},55.9-C_{12}(trifluoro tollyl group),116.5- C_{13},126.5- C_{14},127.8- C_{15},119.0- C_{16},122.2- C_{17},120.1-C_{18},111.8- C_{19},137.6- C_{20}(indole ring),41.0- C_{21},171.0- C_{22},155.0- C_{23},122.0- C_{24},128.6- C_{25},162. C_{26},(pyrazolone ring) Yield 58%,m.p.:175-185^{0}C *Anal.* Cacld. for (705);C,51.06;H,2.55;N,13.90 found(%);C:51.04,H:2.57,N:13.

PHARMACOLOGICAL STUDIES:

All the newly synthesized compounds **1(a-f),2(a-f),4(a-f)** were tested in vivo in order to evaluate their anti-inflammatory and analgesic activities by using student's t test. These compounds were screened for their anti-inflammatory and analgesic activities at a dose of 50 mg/kg p.o. exhibited substantive anti-inflammatory activity of varying degree from 9.3-30.1% and analgesic activity evolution varying degree 6.4-33.0% are given in(Table -1).

The characteristic feature of this series is the substituents by the substituted phenyl at presence of moiety at second position of indol nucleus. It was observed that compound **4(e)**showed maximum anti-inflammatory30.1% inhibition of edema and analgesic 33.0% activities. This compound showed better anti-inflammatory activity and equipotent analgesic activity than standard drug phenyl butazone at the dose of 25, 50 and 100 mg/kg p.o.

PHARMACOLOGICAL EVALUATION:

The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70 to 95 days weighing 120 to175 g. Acute toxicity was tested in albino mice (15-25g). Food (chaw pallet) and water was given to the animals ad libitum. The compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

Anti-inflammatory activity:

This study was done by following the procedure of Winter et al[22]. The rats were divided into three groups(control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline), 0.05 mL was injected under the planter aponeurosis of the right hind paw of each rat. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1hr before the carrageenan injection. The paw volume of each rat was measured before 1 hr and after 3 hr of carrageenan treatment with the help of a Plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below.

Percentage of inhibition of oedema = (1-Vt/Vc) ×100

Where Vt and Vc are the volume of oedema in drug, treated and control group, respectively.

Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Davis at el [23]. Test compounds were given to the animals at the dose of 50mg/kg, 30 min later the animals were injected interperitoneally with 0.25 mL /mouse of 0.5% acetic acid. The mean number of writhes for each experimental groups and percentage decrease compared with the control group was calculated after 60 min.

Ulcerogenic activity

Ulcerogenic liabilities of newly synthesized compounds were checked by the method of Verma el al[24]. Albino rats were fasted for 24 hr prior to drug administration. All animals were sacrificed 8hr after drug treatment and then their stomachs and small intestines were microscopically examined to assess the incidence of hyperaemia, shedding of epithelium, petechial and frank hemorrhages and erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.

Acute toxicity

Acute Lethal dose (ALD50) of all the compounds were investigated by the method of Smith, Q.E. [25]..

RESULTS AND DISCUSSION

All the newly synthesized compounds **1(a-f),2(a-f),4(a-f)** were tested in vivo in order to evaluate their anti-inflammatory and analgesic activities. These compounds were screened for their anti-inflammatory and analgesic activities at a dose of 50 mg/kg p.o. exhibited substantive anti-inflammatory activity of varying degree from 9.3-30.1% and analgesic activity of varying degree 6.4-33.0% are given in **Table 1**.The characteristic feature of this series is substituted phenyl moiety at second position of indole nucleus. It was observed that compound **4(e)** showed maximum anti-inflammatory 30.1% inhibition of edema and inhibition of 33.0% of writhes. This compound showed better anti-inflammatory and analgesic activities than standard drug phenyl butazone at the three graded doses of 25, 50 and 100 mg/kg p.o. but showed lesser activity than reference drug indomethacin. Further more the substitution with chloro group at 2nd position of phenyl ring showed better activities than other groups. ALD50 of all compounds is > 1000 mg/kg p.o.

Table- I: Anti inflammatory, analgesic, ulcerogenic and toxicity data of compounds 1(a-f),2(a-f),4(a-f)

Comp. No.	Dose (mg/kg p.o.)	Anti inflammatory activity % edema inhibition relative to control.	Analgesic activity % decrease of writhes in 60 min after treatment relative to control	UD50	ALD50
1(a)	50	9.3	6.4	-	>1000
1(b)	50	9.8	6.8	-	>1000
1(c)	50	10.2	7.2	-	>1000
1(d)	50	10.5	7.5	-	>1000
1(e)	50	11.4	8.7	-	>1000
1(f)	50	11.6	9.8	-	>1000
2(a)	50	10.9	8.9	-	>1000
2(b)	50	11.2	9.5	-	>1000
2(c)	50	11.5	9.8	-	>1000
2(d)	50	12.0	10.2	-	>1000
2(e)	50	12.5	10.4	-	>1000
2(f)	50	13.6	10.8	-	>1000
4(a)	50	21.5	22.5	-	>1000
4(b)	50	24.5	24.8	-	>1000
4(c)	50	24.1	24.1	-	>1000
4(d)	50	25.8	27.2	-	>1000
4(e)	50	30.1	33.0	-	>1000
4(f)	50	29.5	28.3	-	>1000
Phenylbutazone	25 50 100	17.6** 36.3*** 65.6***	18.4* 34.1*** 68.8 ***	65.46	
Indomethacin	5 7.5 10	52.2 63.1 93.2			

**P < 0.05, **P < 0.01, ***P < 0.001.*

CONCLUSION

1. Furthermore the substitution with phenyl group having a chloro group at p-position showed better activities than other group.
2. The azetidinones showed better anti-inflammatory and analgesic activities.

Acknowledgement
My sincere thanks to UGC authorities for providing financial assistance to continue research in better manner. I am very thankful to S.K. University authorities for providing such an environment for doing better research very much. It's my pleasure to express my thanks to Department of Chemistry for giving an opportunity to do research. I express my sincere thanks to my research Supervisor Prof P. Raveedra Reddy. I express my sincere thanks to Prof LK Ravindranath, who is giving valuable guidance during my research.

REFERENCES

[1] N. Shah, H. Ziauddin, M. Baseer, *Der Pharmacia Sinica*, **2011,** 2, 69.
[2]. R. Sharma, *Der Pharmacia Sinica*, **2011**, 2, 73.
[3]. S. Gomha, H. Hassaneen, *Molecules*, **2011,** 16, 6549.
[4]. E.M.N. Abdel-Hafez, G.A.A. Abuo-Rahma, M. Abdel-Aziz, M.F. Radwan, H.H. Farag, *Bioorg. Med. Chem.*, **2009**, 17, 3829.
[5]. T.E. Ali, *Eur. J. Med. Chem.*, **2009**, 44, 4385.
[6]. N. Rai, B. Kalluraya, B. Lingappa, S. Shenoy, V.G. Puranic, *Eur. J. Med. Chem.*, **2008**, 43, 1715.
[7]. M. Witschel, *Bioorg. Med. Chem.*, **2009**, 17, 4221.
[8]. G. Lahm, T. Stevenson, T. Selby, J. Freudenberger, D. Cordova, L. Flexner, C.A. Bellin, C. Dubas, B. Smith, K. Hughes, J. Hollingshaus, C. Clark, E. Benner, *Bioorg. Med. Chem. Lett.*, **2007**, 17, 6274.
[9]. A. Youssef, M.White, E. Villanueva, I.M. El-Ashmawy, A. Klegeris, *Bioorg. Med. Chem.*, **2010**, 18, 2019.
[10]. P. Sauzem, P. Machado, M.A. Rubin, G.S. Sant'Anna, H.B. Faber, A.H. De Souza, C.F. Mello, P. Beck, R.A. Burrow, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, *Eur. J. Med. Chem.*, **2008**, 43, 1237.

[11]. P. Kapupara, B. Suhagia, A. Bhandari, N. Jivani, *Der Pharmacia Sinica*, **2011**, 2, 194.
[12]. M. Abdel-Aziz, G.E.A. Abuo-Rahma, A.A. Hassan, *Eur. J. Med. Chem*., **2009**, 44, 3480.
[13]. S. Rostom, *Bioorg. Med. Chem.*, **2010**, 18, 2767.
[14]. E. Musad, R. Mohamed, B.A. Saeed, B.S. Vishwanath, K.M.L. Rai, *Bioorg. Med. Chem. Lett.*, **2011**, 21, 3536.
[15]. K. Hazra, L.V.G. Nargund, P. Rashmi, J.N.N.S. Chandra, B. Nandha, *Der Chemica Sinica*, **2011**, 2, 149.
[16] P. Kagthara, S. Teja, D. Rajeev, H. Parekh, *Indian J. Heterocycl. Chem.*, **2000,** 10, 9.
[17] G. Singh, B. Mmolotsi, *Farmaco.*, **2005,** 60, 727.
[18] H. Patel, V. Patel, *Oriental J. Chem.*, **2004,** 17, 425.
[19] P. Sharma, A. Kumar, S. Sharma, *Indian J. Chem*., **2004,** 43, 385.
[20] Kumar, P. Sharma, R. Sharma, P. Mohan, *Ind. J. Chem.*, **2003,** 42, 416.
[21] S. Srivastava, R. Dua, S. Srivastava, *Proc. Nat. Acad. Sci. India., Sec. A: Phys. Sci.* **2010**, 80, 117.
[22] P. Trivedi, N. Undavia, A. Dave, K. Bhatt, N. Desai, *Indian J. Chem.*, **1993**, 32B (7), 760.
[23] H. Panwar, R. Verma, V. Srivastava, Kumar, *Indian J. Chem.*, **2006,** 45B, 2099.
[24] N. Siddiqui, A. Rana, S. Khan, S. Haque, M. Alam, W. Ahsan, M. Arshada, *Acta Chim. Slov.*, **2009,** 56, 462.
[25] S. Srivastava, S. Srivastava, S. Srivastava, *Ind. J. Chem,*, **2000,** *39B*, 464.
[26] P. Anna, Nikaljea, P. Mudassir, S. Ashok, Narutea, S. Ghodkea, D. Rajanib, *Der Pharmacia Sinica.*, **2012,** 3 (2), 229-238.
[27] M. Gunwanti, P. Gothwal, Y. Srivastava, *Der Chemica Sinica*, **2011,** 2 (3), 47-50.
[28] M. Sharma, D. Kohlia, S. Sharmab, A. Sharma, *Der Pharmacia Sinica*, **2010,** 1 (1), 82-94.