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Synthesis of 1,3,4 Oxadiazole derivatives containing Indole moiety bearing-Thiazolidinone and Anti-inflamatory activity of Thiazolidinone

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Abstract: Schiff base synthesis of 1,3,4oxadiazole derivatives containing Indole moiety bearing thiazolidinone ring were synthesised by thecondensation of 2-(3-(4-oxo-3-(p-tolyl)thiazolidin-2-yl)-1H-indol-1-yl)-N-(1,1,1-trifluoropropan-2- ylidene)acetohydrazide with acetic anhydride.To this reaction was subjected in schiff base reaction. It forms 2-(1-((4-acetyl-5-methyl-5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol -3yl)-3-(p-tolyl)thiazolidin-4-one.The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis.
Keywords: 1, 3, 4oxadiazole, Schiff base, thiazolidinone, indole.

Indroduction

Hetero cyclic compounds represents 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 skelton and development of the drug.The classical indole drugs are indomethacin and indoxole. Indole derivetives found to posses high which includes,antibacterial,analgesic,antipyretic, antifungal,antiflamatory,anthelmintic, cardiovascular,anticonvalsant and selective COX-2 inhibitary activities.

Thiazolidinones moiety is associated with variety of biological activities including antifungal[1], anti-inflammatory [2], anticonvulsant[3], antitubercular[4],antihistaminic[5].

Among the five member heterocyclic compounds, 1,3,4-oxadizoles has become an important synthon for the development new therapeutic agents. Compounds with 1,3,4-oxadiazole core substantiate for broad spectrum of biological activities including antimicrobial[6], antifungal[7], anti-inflammatory[8], anticonvulsant[9], antioxidant, analgesic[10] and mutagenic activity[11]. Compounds containing quinoline moiety are most widely usedas antimalarials[12], antibacterials[13], antifungals[14], anticancer agents[15]and potential HIV-1 integrase inhibitors[16-17].

Materials and Methods

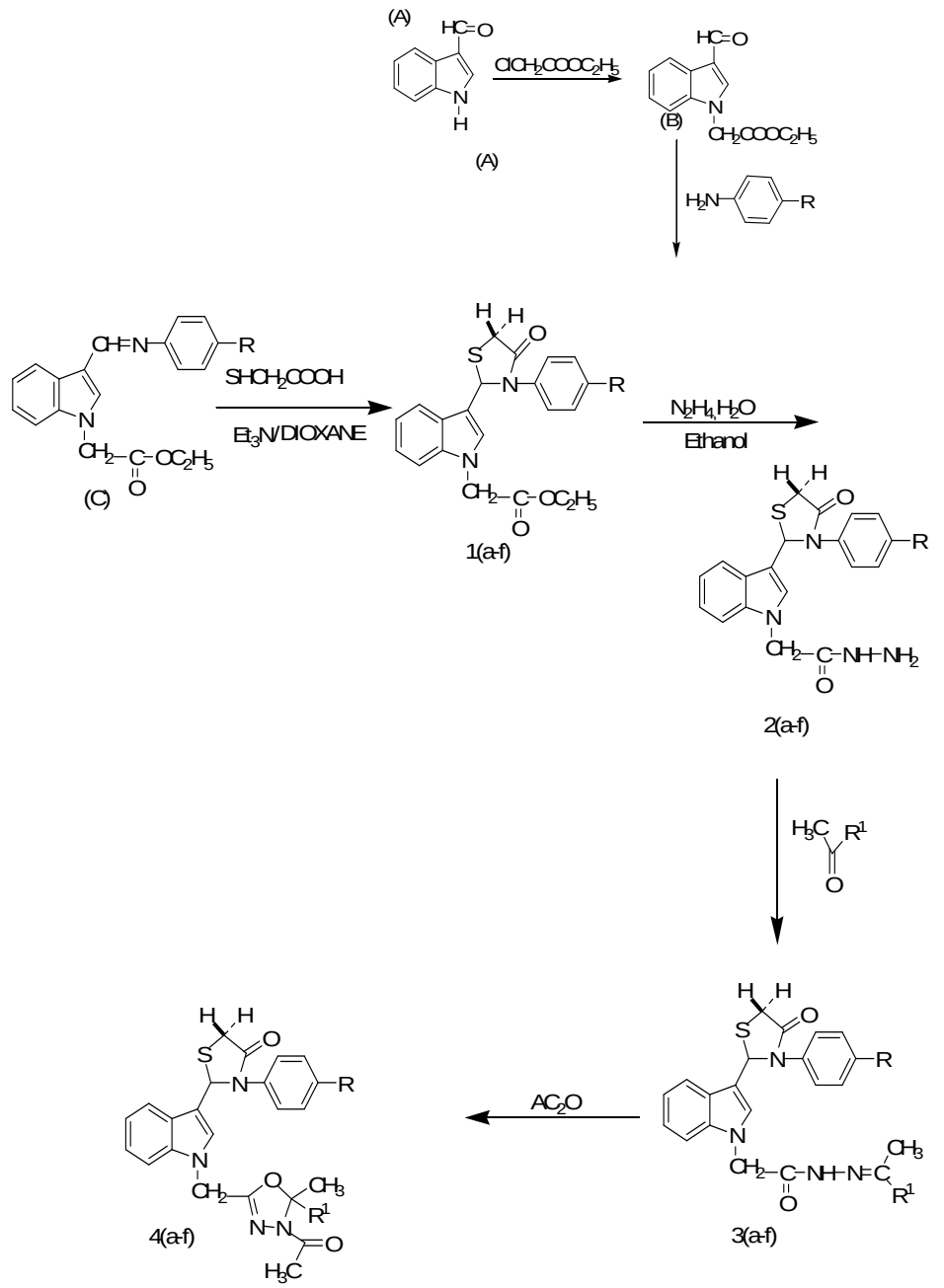
Melting points were determined on open capillaries using a cintex melting point apparatus.T.L.C. analysis were performed on precoatedsilicagel (E-Merck Kieselgel 60 F_{254}) plates and visualisation was done by exposing to iodine vapour .Solvent were purified by standard procedures before use .Column 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.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 perchased from Aldrich chemicals ;U.S.A. indole- 3-carbaldehyde was prepared by a reported method.

Results and Discussion

Indole 3-carbaldehyde compound[A] and chloro ethyle autate were disloved in DMF solvent yield compound [B]on treatment with substituted online forms compound[C] .compound[C] was treated with a mixture of Schiff bases and mercepto auticaid to afford ethyle 2-[3-[3-[4-substituted phenyl]-4-oxothiezolidine-2-yl]1H-indole[1-yl]autate compound 1[a-f]yield 58%.Compound[1]onaminetion with hydrazine hydrate afford a2-(3-(3(4-substituted phenyl)-4-oxothiazolidin-2-yl)-1H-indole-1-41)acetohydrezide(2). Compound2(e-f)yield 65%. Compound (2) on condensed with substituted lcetone to obtained 2-(3-(4-oxo-3-(p-tdyle)thiezolidine-2-yl)_N-(1,1,1-trifiuoropropane-2-ylidene) auto hydrezide(3). Compound3(a-f) yield 84% compound 3(a-j)on treatment with aceticanhydride to afford 2-(1-((4-acetyl-5-methy-5—(trifluromethyle)-4,5-dihydro-1,3,4-oxadizol-2-yl)methyl)-1H-indole(-3yl)-3-(p-tolyl)thiezolidin-4-one(4(a-j) yield 56%. The purity of the compounds was monitored by TLC; mass spectrum of 4(a) was recorded by ESI-MS technique showed the molecular ion signal at 502. The structure of these compounds monitored by ^{1}H NMR,^{13}CNMR,Mass, IR, and elemental analysis.

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

An equimolar mixture of indole-3-carbaldehyde(A)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^{0}C.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^{0}C.



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

Scheme-1

The IR(KBr) spectrum of 2-(3- formyl-1H-indol-1-yl) acetate 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 was recorded in DMSO-d6 solvent. The NMR signal of 2-(3- formyl-1H-indol-1-yl) acetate 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) and6.92 , 7.58 (m, 10H, C_8H_5N indole nucleus).

Synthesis of Ethyl 2-(3-phenyl imino)methyl-1H-Indole-1-yl-acetate (C)

Equimolar quantity of aniline(3) and ethyl-2-(-3-formyl-1H-indol-1-yl)acetate(B) were dissolved in absolute alcohol, to this three drops of aceticacid 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)me thyl)-1H-indol-1-yl)acetate. Yield 75%,m.p.:154-156^0C

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 NMRSpectra 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 (c) was converted into thiazolidinone-2-one on treatement with mercapto acetic acid in presence of ETA/dioxane. The formation compound was conformed by IR,NMR data.

NMR spectra ;1.32(t,3H,CH_3 of OC_2H_5),2.33(s,1H ,-CH of thiazolidinone attached to indole ring)3.70 (s,2H N-CH_2-C =O), 4.25 (q,2H,-O-CH_2 Of OC_2H_5),3.90(d,1H,Ha of -CH_2 of thiazolidinone),3.99(d,1H,Hb of –CH_2 of thiazolidinone),7.2-7.30(m,10H,due to 5H of indole ,5H of phenyl ring).

^{1}IR spedtra ; The compound (1) shows signals at, 1616 (C=N),1170 (-C-O-C-),1723 (-C=O),(C-S-C),695

Synthesis of ethyl 2-(3-(3-(4- phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate1(a).

A mixture of schiffs base (0.01mol) and mercaptoacetic acid (0.01mol) dissolved in dioxane (20ml), anhydrous zinc chloride (0.5mg) was added and refluxed for 8hours.The reaction was cooled and the resulting solid was washed with sodium bicorbonate solution and recrystalised from absolute alcohol. The formation compound was conformed by IR,NMR spectral data .

NMR spectra ;1.32(t,3H,CH_3 of OC_2H_5),2.33(s,1H ,-CH of thiazolidinone attached to indole ring)3.70 (s,2H N-CH_2-C =O), 4.25 (q,2H,-O-CH_2 Of OC_2H_5),3.90(d,1H,Ha of -CH_2 of thiazolidinone),3.99(d,1H,Hb of –CH_2 of thiazolidinone),7.2-7.30(m,10H,due to 5H of indole ,5H of phenyl ring).

IR spedtra ; The compound 1(a) shows signals at, 1616 (C=N),1170 (-C-O-C-),1723 (-C=O),(C-S-C),695

Synthesis of ethyl 2-(3-(3-(4methyl phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate1(b).
^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):
1.35 (t,3H,CH_3 of C_2H_5), 2.25(s,3H,CH_3 attached to phenyl ring), 2.35(s,1H,-CH of thiazolidine attached to indole ring),3.72 (s,2H N-CH_2-C =O), 3.92 (d,1H,Ha of –CH_2 of thiazolidine), 4.02(d,1H,Hb of –CH_2 of thiazolidine),4.28,(q,2H, O-CH_2 Of OC_2H_5), 7.22-7.32(m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra; The compound 1(b) shows signals at, 1612 (C=N),1165 (-C-O-C-),1720 (-C=O),(C-S-C),693

Synthesis of ethyl 2-(3-(3-(4methoxy phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate1(c).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 1.37 (t,3H,CH_3 of C_2H_5), 2.27(s,3H,CH_3 attached to phenyl ring), 2.37(s,1H,-CH of thiazolidine attached to indole ring),3.72 (s,2H N-CH_2-C =O), 3.93 (d,1H,Ha of –CH_2 of thiazolidine), 4.05(d,1H,Hb of –CH_2 of thiazolidine),4.29(q,2H, O-CH_2 Of OC_2H_5), 7.25-7.35(m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra ; The compound 1(c) shows signals at, 1610(C=N),1160 (-C-O-C-),1715 (-C=O),(C-S-C),691

Synthesis of ethyl 2-(3-(3-(4-chloro phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate1(d).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 1.39 (t,3H,CH_3 of C_2H_5), 2.35(s,1H,-CH of thiazolidine attached to indole ring),3.73 (s,2H N-CH_2-C =O), 3.95 (d,1H,Ha of –CH_2 of thiazolidine),4.10(d,1H,Hb of –CH_2 of thiazolidine), 4.29 (q,2H,-O-CH_2 of OC_2H_5),7.28-7. 35 (m,9H,due to 5H of indole,5H of phenyl ring)

IR spedtra ; The compound 1(d) shows signals at, 1605(C=N),1155 (-C-O-C-),1710 (-C=O),(C-S-C),690

Synthesis of ethyl 2-(3-(3-(4-nitro phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate1(e).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 1.40 (t,3H,CH_3 of C_2H_5), 2.37 (s,1H,-CH of thiazolidine attached to indole ring),3.75 (s,2H N-CH_2-C =O), 3.97 (d,1H,Ha of –CH_2 of thiazolidine),4.12 (d,1H,Hb of –CH_2 of thiazolidine), 4.30 (q,2H,-O-CH_2 of OC_2H_5),7.29-7. 36 (m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra ; The compound 1(e) shows signals at, 1600(C=N),1140 (-C-O-C-),1705 (-C=O),(C-S-C),698.

Synthesis of ethyl 2-(3-(3-(4-trifluoro methyl phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate1(f).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 1.42 (t,3H,CH_3 of C_2H_5), 2.39 (s,1H,-CH of thiazolidine attached to indole ring),3.77 (s,2H N-CH_2-C =O), 3.99 (d,1H,Ha of –CH_2 of thiazolidine),4.15 (d,1H,Hb of –CH_2 of thiazolidine), 4.32 (q,2H,-O-CH_2 of OC_2H_5),7.31-7. 37 (m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra ; The compound 1(f) shows signals at, 1625(C=N),1175 (-C-O-C-),1730 (-C=O),(C-S-C),700.

Synthesis of 2-(3-(3-(4-substituted phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetohydrazide(2):

A solution of 1(a) (0.01mol) and hydrazine hydrate (0.015) in ethanol (20ml) was refluxed for 5 hours.The reaction mixture was cooled and poured in to icecold water with stirring. The seperated solid was filtered, washed with water and recrystalised from ethanol.

NMR spectra; 2.35(d,1H,-CH of thiazolidine attached to indole ring). 4.36 (s,2H N-CH_2-C =O), 4.98 (s,1 H,-N-NH), 4.05(d,1H,Ha of -CH_2 of thiazolidine), 4.10(d,1H,Hb of –CH_2 Of thiazolidine),4.28(s,2H,-NH_2)

6.9-8.3(m,10H due to 5H of indole,5H of phenyl ring).

IR spedtra ; The compound 6a shows signals at,1620(C=N),1175(C-O-C),1730(C=O),698(C-S-C).

Synthesis of 2-(3-(4-oxo-3-(p-tolyl)thiazolidin-2-yl)-1H-indol-1-yl)-N-(1,1,1-trifluoropropan-2-ylidene) acetohydrazide(3)

To the solution of 2(a) (0.01mole) in hot methanol (25ml), acetophenone(0.01) and a drop of glacialacetic acid were added. The solid that seperated on refluxing for 3 hours was filtered wash with cold methanol and recrystalised from methanol to give 7(a).M.P.236^{0}C,yield 84%.

NMR spectra ; 2.37 (d,1H,-CH of thiazolidine attached to indole ring),2.54(s,1H,N=C-CH_3), 3.75 (s,2H N-CH_2-C =O), 4.90 (s,1 H,-N-NH), 4.10 (d,1H,Ha of -CH_2 of thiazolidine), 4.15 (d,1H,Hb of –CH_2 Of thiazolidine), 7.1-8.3(m,10H due to 5H of indole,5H of phenyl ring).

IR spedtra; The compound 3(a) shows signals at,1680(C=O,imide),1620(C=N), 3185(-NH),2950(-CH of aliphatic),3200(Ar-H), 700 (C-S-C).

Synthesis of 2-(1-((4-acetyl-5-methyl-5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3-(p-tolyl)thiazolidin-4-one(4)

A mixture of3(a) (0.01mole) and excessive acetic anhydride (10ml) was refluxed for two hours.

The excessive aceticanhydride was distilled off and the residue was poured in to crushed ice. The solid thus obtained was filtered, washed with water and recrystalised from aqueous methanol to furnished obtained compound. M.P.185^{0}C, yield 56 %.

NMR spectra; 2.40 (d,1H,-CH of thiazolidine attached to indole ring),2.42(s,3H,CH_3),2.46(s,3H,-CO-CH_3),3.77(s,2H,-N-CH_2), 4.12 (d,1H,Ha of -CH_2 of thiazolidine), 4.16 (d,1H,Hb of –CH_2 Of thiazolidine), 7.2 -8.5 (m,10H due to 5H of indole,5H of phenyl ring).

IR spedtra; The compound 4(a) shows signals at,1680(C=O), ,1622 (C=N), 3130 (-NHof oxadizole),C-F(750) ,3200(N-H), 750(C-O -C) .

Synthesis of 2-(1-((4-acetyl-5-methyl-5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3-(p-tolyl)thiazolidin-4-one(4a)

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):; 2.40 (d,1H,-CH of thiazolidine attached to indole ring),2.42(s,3H,CH_3),2.46(s,3H,-CO-CH_3),3.77(s,2H,-N-CH_2), 4.12 (d,1H,Ha of -CH_2 of thiazolidine), 4.16 (d,1H,Hb of –CH_2 Of thiazolidine), 7.2 -8.5 (m,10H due to 5H of indole,5H of phenyl ring).

IR spedtra; The compound 4(a) shows signals at,1680(C=O), ,1622 (C=N), 3130 (-NHof oxadizole),C-F(750) ,3200(N-H), 750(C-O -C) .

Synthesis of 2-(1-((4-acetyl -5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3-(p-tolyl)thiazolidin-4-one(4b).

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 2.23(s,3H,attached to phenyl ring), 2.41 (s,1H,-CH of thiazolidine attached to indole ring),2.43(s,3H,-CH_3),2.48(s,3H,-CO-CH_3),3.78(s,2H,-N-CH_2) , 4.14 (d,1H,Ha of –CH_2 of thiazolidine),4.17 (d,1H,Hb of –CH_2 of thiazolidine), 7.3 -8.6 (m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra ; The compound 4(b) shows signals at,1680(C=O), ,1620 (C=N), 3100 (-NHof oxadizole),745(C-F) ,3195(N-H), 743(C-O -C) .

Synthesis of 2-(1-((4-acetyl -5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3(4-methoxy phenyl)thiazolidin-4-one(4c)

^{1} H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 2.25(s,3H,attached to phenyl ring), 2.43 (s,1H,-CH of thiazolidine attached to indole ring),2.44(s,3H,-CH_3),2.50(s,3H,-CO-CH_3),3.79(s,2H,-N-CH_2) , 4.16 (d,1H,Ha of –CH_2 of thiazolidine),4.19 (d,1H,Hb of –CH_2 of thiazolidine), 7.45 -8.65 (m,9H,due to 5H of indole,5H of phenyl ring) .

IR spedtra ; The compound 4(c) shows signals at,1680(C=O), ,1620 (C=N), 3098 (-NHof oxadizole),740(C-F) ,3190(N-H), 741(C-O -C) .

Synthesis of 2-(1-((4-acetyl -5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3(4-Choloro phenyl)thiazolidin-4-one(4d)

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 2.39 (s,1H,-CH of thiazolidine attached to indole ring),2.45(s,3H,-CH_3),2.49(s,3H,-CO-CH_3),3.80(s,2H,-N-CH_2), 4.17 (d,1H,Ha of–CH_2 of thiazolidine),4.20 (d,1H,Hb of –CH_2 of thiazolidine), 7.46 -8.68 (m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra; The compound 4(d) shows signals at,1680(C=O), ,1618 (C=N), 3105 (-NHof oxadizole),750(C-F) ,3188(N-H), 755(C-O -C).

Synthesis of 2-(1-((4-acetyl -5-(trifluoromthyl)-4,5-dihyro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3(4-nitro phenyl)thiazolidin-4-one(4e)

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS):2.44 (s,1H,-CH of thiazolidine attached to indole ring),2.45(s,3H,-CH_3),2.48(s,3H,-CO-CH_3),3.77(s,2H,-N-CH_2), 4.19(d,1H,Ha of –CH_2 of thiazolidine),4.21 (d,1H,Hb of –CH_2 of thiazolidine), 7.44 -8.68 (m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra; The compound 4(e) shows signals at,1680(C=O), ,1615 (C=N), 3110 (-NHof oxadizole),755(C-F) ,3185(N-H), 748(C-O -C).

Synthesis of 2-(1-((4-acetyl-4,5-dihyro-5-methyl-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3-(4-trifluoro methyl) phenyl)thiazolidin-4-one(4f)

^{1}H NMR spectra(300MHZ,(CD)$_2$ SO,TMS): 2.46 (s,1H,-CH of thiazolidine attached to indole ring),2.45(s,3H,-CH_3),2.49(s,3H,-CO-CH_3),3.77(s,2H,-N-CH_2), 4.20(d,1H,Ha of –CH_2 of thiazolidine),4.23 (d,1H,Hb of –CH_2 of thiazolidine), 7.47 -8.69 (m,9H,due to 5H of indole,5H of phenyl ring).

IR spedtra ; The compound 4(f) shows signals at,1680(C=O), ,1621 (C=N), 3125 (-NHof oxadizole),765(C-F) ,3198(N-H), 760(C-O -C).

Phatrmacological 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-inflammatoryand analgesic activities at a dose of 50 mg/kg p.o.exhibited substantive anti-inflammatory activity of varying degree from 9.5-35.3%,31.8% and analgesic activity evolution varying degree 6.4-32.4%,30.6% are given in (Table -1).

The characteristic feature of this series is the substituents by the substituted phenyl moiety at second position of indole nucleus. It was obsereved that compound **4(c)**showed maximum anti-inflammatory35.3% inhibition of oedema and analgesic 32.4% 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.

Conclusion:

1. Further more the substitution with phenyl grouphaving a chloro group at p-position showed betteractivities than other group.

2. The thiazolidinone showed better anti-inflammatoryand analgesic activities.

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[18]. The rats were divided into three groups (control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension ofcarrageenan (1% in 0.9% saline), 0.05 mL was injected under the planter aponeurosis of the right hind paw ofeach 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 ofeach 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 [19]. 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 at el[20]. 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 haemorrhages and erosion ordiscrete ulceration with or without perforation. Thepresence 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. [21].

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 andanalgesic 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 9.5-35.3%,31.8%and analgesic activity of varying degree 6.4-32.4%,30.6% are given in **Table 1**.The characteristic feature of this series is substituted phenyl moiety at second position of indole nucleus. It was obsereved that compound **4(c)** showed maximum anti-inflammatory 35.3% inhibition of oedema and inhibition of 32.4% 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, ulcorogenic and toxicity data of compounds 1(a-f),2(a-f),4(a-f)

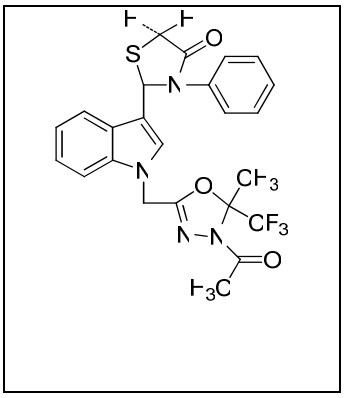
Comp. No.	Dose (mg/kg p.o.)	Anti inflammatory activity % oedema inhibition relative to control.	Analgesic activity % decrease of writhes in 60 min after treatment relative to control	UD50	ALD50
1(a)	50	9.5	6.4	-	>1000
1(b)	50	9.9	6.8	-	>1000
1(c)	50	10.3	7.2	-	>1000
1(d)	50	10.8	7.5	-	>1000
1(e)	50	11.5	8.7	-	>1000
1(f)	50	11.8	9.8	-	>1000
2(a)	50	11.0	8.9	-	>1000
2(b)	50	11.4	9.5	-	>1000
2(c)	50	11.7	9.8	-	>1000
2(d)	50	12.2	10.2	-	>1000
2(e)	50	12.5	10.4	-	>1000
2(f)	50	13.8	10.8	-	>1000
4(a)	50	25.6	25.8	-	>1000
4(b)	50	29.9	29.5	-	>1000
4(c)	50	35.3	32.4	-	>1000
4(d)	50	29.5	28.3	-	>1000
4(e)	50	31.8	30.6	-	>1000
4(f)	50	29.5	28.3	-	>1000
Phenylbut azone	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.

Charactrization of above compounds Table-1.1

Compound	Molecular Formulae	Yield	M.P.O^0 C	% of Analysis					
				C		H		N	
				Calcd	Found	Calcd	Found	Calcd	Found
1a	$C_{21}H_{22}N_2O_2S$	58%	245	68.85	68.82	6.05	6.01	7.65	7.64
1b	$C_{22}H_{24}N_2O_2S$	55%	240	69.47	69.44	6.36	6.31	7.4	7.36
1c	$C_{22}H_{24}N_2O_3S$	52%	220	66.66	66.64	6.1	6.06	7.5	7.07
1d	$C_{21}H_{21}ClN_2O_2S$	59%	235	63	62.91	5.28	5.25	7.00	6.99
1e	$C_{21}H_{22}N_3O_4S$	60%	250	61.31	61.3	5.14	5.1	10.22	10.21
1f	$C_{22}H_{21}F_3NO_2S$	65%	255	60.85	60.82	4.87	4.83	6.46	6.45
4a	$C_{24}H_{21}F_3N_4O_3S$	56%	185	57.37	57.36	4.21	4.18	11.16	11.15
4b	$C_{25}H_{23}F_3N_4O_3S$	54%	190	58.14	58.13	4.49	4.45	10.86	10.85
4c	$C_{25}H_{23}F_3N_4O_4S$	52%	180	56.39	56.38	4.35	4.32	10.53	10.52
4d	$C_{24}H_20F_3N_4O_3S$	50%	182	53.73	53.68	3.75	3.73	10.44	10.43
4e	$C_{24}H_20F_3N_5O_5S$	55%	185	52.68	52.65	3.68	3.65	12.8	12.79
4f	$C_{24}H_{21}F_3N_4O_3S$	50%	180	57.37	57.36	4.21	4.18	11.16	11.15

^{13}C NMR spectra:



^{13}C NMR spectra: The ^{13}C NMR spectra of 2-(1-((4-acetyl-5-methyl-5-(trofluoromethyl)-4,5-dihydro -1,3,4-oxadiazole-2-yl)-1H-indol-3-yl)-3-phenylthiazolidin-4-one 8(a-f) was record in $CDCl_3$ showed the following signals at dppm:
23.7,37.5,127.6,33.5,158.2,60.0,168.2,71.1,127.7,118.8,119.8121.7,109.6,137.5,126.5,112.4,71.1,127.5, 128.9,128.0,141.7,171.2,96.4 and these signals are due to at
C_1,C_2,C_3,C_4,C_5,C_6,C_7,C_8,C_9,C_{10},C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{17},C_{18},C_{19},C_{20},C_{21},C_{22},C_{23},C_{24},C_{25} .

Table-1.2

Compd	4(a)	4(b)	4(c)	4(d)	4(e)	4(f)
C_1	23.7	23.7	23.7	22.9	23.7	23.4
C_2	37.5	168.2	168.2	168.5	168.2	168.5
C_3	127.6	37.5	37.5	30.0	37.5	21.2
C_4	33.5	127.6	127.6	104.9	127.6	75.4
C_5	158.2	96.4	96.4	158.2	96.4	158.2
C_6	60.0	158.2	158.2	59.2	158.2	59.7
C_7	168.2	60.0	60.0	127.7	60.0	127.7
C_8	71.1	127.7	127.7	118.8	118.8	118.8
C_9	127.7	118.8	118.8	119.8	119.8	119.8
C_{10}	118.8	119.8	119.8	121.7	121.7	121.7
C_{11}	119.8	121.7	121.7	109.6	109.6	109.6
C_{12}	121.7	109.6	109.6	137.5	137.5	137.5
C_{13}	109.6	137.5	137.5	126.5	127.7	126.5
C_{14}	137.5	112.4	112.4	112.4	126.5	112.4
C_{15}	126.5	126.5	71.1	71.1	112.4	71.1
C_{16}	112.4	71.1	33.5	33.5	71.1	33.5
C_{17}	71.1	33.5	122.6	145.0	33.5	133.8
C_{18}	127.5	133.5	114.5	133.8	147.8	145.0
C_{19}	128.9	138.2	158.9	125.3	131.1	125.3
C_{20}	128.0	129.2	55.8	132.1	124.1	132.1
C_{21}	141.7	136.8	134.0	124.1	143.5	124.1
C_{22}	171.2	133.4				
C_{23}	96.4	21.3				
C_{24}		171.2				
C_{25}						

Conclusions:

1. Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The thiazolidinone showed better antibactirial and antifungal activities.
3. 1,3,4 oxadiazoles and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, antiflammatory.

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