Synthesis, Characterization and Biological Evaluation of 1,3,4 Oxadiazole Derivatives Containing Indole Moiety Bearing-Tetrazole

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ABSTRACT
Schiff base synthesis of 1,3,4 oxadiazole derivatives containing Indole moiety bearing thiazolidinone ring were synthesized by the condensation of 2-(3-(4-oxo-3-(p-tolyl) 1H-tetrazol-5-yl)-1H-indol-1-yl)-N-(1,1,1-trifluoropropan-2-ylideneacetohydrazide with acetic anhydride. To this reaction was subjected in schiff base reaction. It forms 2-(1-(4-acetyl-5-methyl-5-(trifluoromethyl)-4,5-dihyro-1, 3, 4-oxadiazol-2-yl) methyl)-1H-indol-3yl)-3-(p-tolyl) 1H-tetrazol-5-yl). The structure of these newly synthesized compounds was characterized by $^1$H NMR, $^{13}$CNMR, Mass, IR, and elemental analysis.

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 a wide range of biological activities. Indoles are one of the most important alkaloid molecules found extensively in biological systems, which play a vital role in many of the biochemical processes. 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 includes, antibacterial, analgesic, antipyretic, antifungal, inflammatory, anthelmintic, cardiovascular, anticonvulsant and selective COX-2 inhibitory activities.

Tetrazole and its derivatives have attracted much attention because of their unique structure and applications asanthihypertensive, antialergic, antibiotic and anticonvulsant agents1-7.

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 substantiates for broad spectrum of biological activities including antimicrobial, antifungal, antiinflammatory, anti-convulsant, antioxidant, analgesic and mutagenic activity. Compounds containing quinoline moiety are most widely used as antimalarials, antibacterials, antifungals, anticancer agents. And potential HIV-1 integrase inhibitors.

Results and Discussion

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$_2$CO$_3$ was added and the reaction mixture was stirred at room temperature (35°C) for 8 hours and the progress of the reaction was monitored by TLC using cyclohexane and ethyl acetate solvent mixture (7:3) as eluent the reaction mixture was kept overnight. After completion of the reaction the solvent was evaporated on Rota-evaporator. The gummy solid was separated and it was recrystallised from -2-propanol-petroleum ether (80°C) 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°C. 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°C.
The IR(KBr) spectrum of 2-(3-formyl-1H-indol-1-yl) acetate was recorded in the range 4000-667 cm⁻¹ and the absorption signals were found at 3032 (ν–Ar-H), 2980 and 2960 (ν aliphatic CH₂ and CH₃), 1760 (ν CO of ester group), and 1182 (ν C–O-C of ester group).

¹H NMR spectra (δ ppm)

The ¹H NMR 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 δ_ppm, 1.29 (t,3H, J=13.2Hz, CH₃ of ethyl group), 4.13 (q, 2H, J=13.2Hz, CH₂ of ethyl group), 4.78(s, 2H, N-CH₂ group) and 6.92 , 7.58 (m, 10H, C₈H₅N indole nucleus) and 8.44(s, 1H, N=CH group).

The compound (A) was converted into tetrazole on treatment with (1) PCl₃, 100°C, 1hr (2) NaN₃ (ice cold), ZnCl₂, Sodium acetate, acetone, water, RT. The formation compound was confirmed by IR, NMR data.

NMR spectra

1.29(t,3H,CH₃ of C₂H₅), 4.78(s,2H N-CH₂-C =O), 4.13(q,2H, O-CH₂ Of OC₂H₅), 6.92-7.58(m,10H,Ar-H,8.44(N=CH).

IR spectra (ν, cm⁻¹)

IR (KBr) spectrum of ethyl 2-(3-phenyl imino)methyl-1H-Indole-1-yl-acetate I(a) was recorded in the range 4000-667 cm⁻¹ and IR absorption signals were found at 3032 (ν–Ar-H), 2980 and 2960 (ν aliphatic CH₂ and CH₃), 1760 (ν CO of ester group), 1610(ν C=No group) and 1182(ν C=O-C of ester group).

NMR spectra

1.32(t, 3H, CH₃ of OC₂H₅), 3.70 (s,2H N-CH₂-C =O), 4.25 (q,2H, O-CH₂ of OC₂H₅), 7.2-7.30(m,10H, due to 5H of indole, 5H of phenyl ring).
IR spectra
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)-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate1(b). \(^1\)H NMR spectra (300MHZ, (CD)\(_2\) SO, TMS)
1.35 (t,3H,CH\(_3\) of C\(_2\)H\(_3\)), 2.25(s,3H,CH\(_3\) attached to phenyl ring,3.72 (s,2H N-CH\(_2\)-C =O), 4.28,(q,2H, O-CH\(_2\) Of OC\(_2\)H\(_3\)), 7.22-7.32(m,9H,due to 5H of indole,5H of phenyl ring).

IR spectra
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)-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate1 (c). \(^1\)H NMR spectra (300MHZ, (CD)\(_2\) SO, TMS)
1.37 (t, 3H, CH\(_3\) of C\(_2\)H\(_3\)), 2.27 (s, 3H, CH\(_3\) attached to phenyl ring), 4.29 (q, 2H, O-CH\(_2\) Of OC\(_2\)H\(_3\)), 7.25-7.35 (m, 9H, due to 5H of indole, 5H of phenyl ring).

IR spectra
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-(4chloro phenyl)-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate1(d). \(^1\)H NMR spectra (300MHZ, (CD)\(_2\) SO, TMS)
1.39 (t,3H,CH\(_3\) of C\(_2\)H\(_3\)), 3.73 (s,2H N-CH\(_2\)-C =O), 4.29 (q,2H,O-CH\(_2\) of OC\(_2\)H\(_3\)),7.28-7.35 (m, 9H, due to 5H of indole, 5H of phenyl ring)

IR spectra
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-(4nitro phenyl)-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate1(e). \(^1\)H NMR spectra (300MHZ, (CD)\(_2\) SO, TMS)
1.40 (t,3H,CH\(_3\) of C\(_2\)H\(_3\)), 3.75 (s,2H N-CH\(_2\)-C =O), 4.30 (q,2H,O-CH\(_2\) of OC\(_2\)H\(_3\)),7.29-7.36 (m, 9H, due to 5H of indole, 5H of phenyl ring)

IR spectra
The compound 1(e) shows signals at, 16 (0(C=, ),1140 (-C-O-C, ),1705 (-C=,),(C-S-),698

Synthesis of ethyl 2-(3-(3-(4trifluoro methyl phenyl)-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate1(f). \(^1\)H NMR spectra(300MHZ,(CD)\(_2\) SO,TMS)
1.42 (t,3H,CH\(_3\) of C\(_2\)H\(_3\)), 3.77 (s,2H N-CH\(_2\)-C =O), 4.32 (q,2H,O-CH\(_2\) of OC\(_2\)H\(_3\)),7.31-7.37 (m, 9H, due to 5H of indole, 5H of phenyl ring)

IR spectra
The compound 1(f) shows signals at, 16 (5(C=, ),1175 (-C-O-C, ),1730 (-C=,),(C-S-),,700

Synthesis of 2-(3-(3-(4substituted phenyl) -1H-tetrazol-5-yl) -1H-indol-1-yl) acethyldrazide (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 into ice cold water with stirring. The separated solid was filtered, washed with water and recrystalised from ethanol.

NMR spectra
4.36 (s,2H N-CH\(_2\)-C =O), 4.98 (s,1 H\(_2\)-N,NH), 4.28(s,2H,-NH\(_2\))
6.9-8.3 (m, 10H due to 5H of indole, 5H of phenyl ring).
IR spectra  

The compound 2 (a) 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) 1H-tetrazol-5-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 glacial acetic acid were added. The solid that separated on refluxing for 3 hours was filtered wash with cold methanol and recrystallised from methanol to give 7(a). M.P. 236°C, yield 84%.

NMR spectra  

2.54(s,1H, N=CH2), 3.75 (5.2H N-CH2C=O), 4.90 (s, 1H, N-NH), 7.1-8.3 (m, 10H due to 5H of indole, 5H of phenyl ring).

IR spectra  

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-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl) methyl)-1H-indol-3-yl)-3-(p-tolyl) 1H-tetrazol-5-yl (4)  

A mixture of 3(a) (0.01mole) and excessive acetic anhydride (10ml) was refluxed for two hours.

The excessive acetic anhydride was distilled off and the residue was poured into crushed ice. The solid thus obtained was filtered, washed with water and recrystallised from aqueous methanol to furnished obtained compound. M.P. 185°C, yield 56%.

NMR spectra  

2.42(s,3H,CH3), 2.46 (s,3H,CO-CH3), 3.77(s,2H,-N-CH2), 7.2 -8.5 (m, 10H due to 5H of indole, 5H of phenyl ring).

IR spectra  

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

Synthesis of 2-(1-((4-acetyl-5-methyl-5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl) methyl)-1H-indol-3-yl)-3-(p-tolyl) 1H-tetrazol-5-yl (4a)  

1H NMR spectra (300MHZ, (CD)2 SO, TMS)  

2.42(s,3H,CH3), 2.46(s,3H,CO-CH3), 3.77(s,2H,-N-CH2), 7.2 -8.5 (m, 10H due to 5H of indole, 5H of phenyl ring).

IR spectra  

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

Synthesis of 2-(1-((4-acetyl-5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl) methyl)-1H-indol-3-yl)-3-(p-tolyl) 1H-tetrazol-5-yl (4b)  

1H NMR spectra (300MHZ, (CD)2 SO, TMS)  

2.23(s,3H,attached to phenyl ring), 2.43(s,3H,-CH3), 2.48(s,3H,-CO-CH3), 3.78(s,2H,-N-CH2), 7.3 -8.6 (m, 9H, due to 5H of indole, 5H of phenyl ring)

IR spectra  

The compound 4(b) shows signals at, 1680(C=O), 1620 (C=N), 3100 (-NH of oxadizole), 745(C-F), 3195(N-H), 743(C=O -C) .
Synthesis of 2-(1-((4-acetyl -5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)3-(4-methoxy phenyl) 1H-tetrazol-5-yl (4c)

$\textbf{1}H$ NMR spectra (300MHz, (CD)$_2$ SO, TMS)

2.25(s,3H,attached to phenyl ring), 2.44(s,3H,-CH$_3$), 2.50 (s,3H,-CO-CH$_3$),3.79(s,2H,-N-CH$_2$), 7.45 - 8.65 (m,9H,due to 5H of indole,5H of phenyl ring)

IR spectra

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

Synthesis of 2-(1-((4-acetyl -5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3-(4-Chloro phenyl) 1H-tetrazol-5-yl (4d)

$\textbf{1}H$ NMR spectra (300MHz,(CD)$_2$ SO,TMS)

2.45(s,3H,-CH$_3$ ), 2.49(s,3H,-CO-CH$_3$), 3.80(s,2H,-N-CH$_2$), 7.46 - 8.68 (m,9H,due to 5H of indole,5H of phenyl ring)

IR spectra

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

Synthesis of 2-(1-((4-acetyl -5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-3-(4-nitro phenyl) 1H-tetrazol-5-yl (4e)

$\textbf{1}H$ NMR spectra(300MHZ,(CD)$_2$ SO,TMS)

2.45(s,3H,-CH$_3$),2.48(s,3H,-CO-CH$_3$),3.77(s,2H,-N-CH$_2$), 7.44 - 8.68 (m,9H,due to 5H of indole,5H of phenyl ring)

IR spectra

The compound 4(e) shows signals at,1680(C=O), 1615 (C=N), 3110 (-NH of 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-trifluoromethyl) phenyl 1H-tetrazol-5-yl (4f)

$\textbf{1}H$ NMR spectra(300MHZ,(CD)$_2$ SO,TMS)

2.45(s,3H,-CH$_3$), 2.49(s,3H,-CO-CH$_3$),3.77(s,2H,-N-CH$_2$), 7.47 - 8.69 (m,9H,due to 5H of indole,5H of phenyl ring)

IR spectra

The compound 4(f) shows signals at,1680(C=O), 1621 (C=N), 3125 (-NH of oxadizole),765(C-F), 3198(N-H), 760(C-O - C)

**Anti-Bacterial Activity**

The anti bacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were *staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106. The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

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

The test results presented in the table - 1, suggest that 4a,4d,4e exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

**Antifungal activity**

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of *aspergillus*
niger NCCS1196 and cadida albicans NCCS34471

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

Conclusion

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

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- I express my sincere thanks to my research Supervisor Prof P. Raveedra Reddy.
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References


Table 1. Antibacterial activity by disc diffusion method of indole-linked 1, 3, 4 oxadiazole having tetrazole 4(a-f)

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Table 2. Antifungal activity by disc diffusion method for indole linked 1, 3, 4 oxadiazole having tetrazole 4(a-f)

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