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SYNTHESIS AND SCREENING OF 2-(2-(3-(4-FORMYL-TETRAHYDRO-2-PHENYLTHIOPHENE-3-YL)-1H-INDOL-1-YL)ACETAMIDO)-N^1-(2-OXO-1-(PIPERIDIN-1-YL)METHYL)INDOLIN-3-YLIDENE)METHYLENE)PROPANE HYDRAZINE

S.Muralikrishna*, P.Raveendra Reddy ,L.K.Ravindranath,P.Jagadeeswara Rao

Department of Chemistry, S.K.University, Anantapur-515003,A.P.INDIA
Email ID;-muralisphd@gmail.com

ABSTRACT. Synthesis of 2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-1-(piperidin-1-yl)methyl)indolin-3-ylidene)methylene)propane hydrazine (10) have been reported.They have been prepared by using indole-3-carbaldihide treated with Schiff bases Mercapto acetic acid,DMF solvent. The compound 2-(2-(3-(4-oxo-2-phenyl isothiazolidin-3-yl)-1H-indol-1-yl)acetamido)propane hydrazide(8) condensed with isatin then 2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-indolin-3-ylidene)methylene)propane hydrazine(9) is obtained.

Finally 9(a) compound treated with Mannich bases we obtained 2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-1-(piperidin-1-yl)methyl)indolin-3-ylidene)methylene)propane hydrazine(10) target molecule. The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis. The antimicriobial activity of the novel compounds was screened by agar disc diffusion method. The chemical structures of the newly synthesized compounds were elucidated by their IR, *1*H NMR and Mass spectral data analysis. Further the compounds are used to find out their ability towards anti microbial and nematicidal activity.

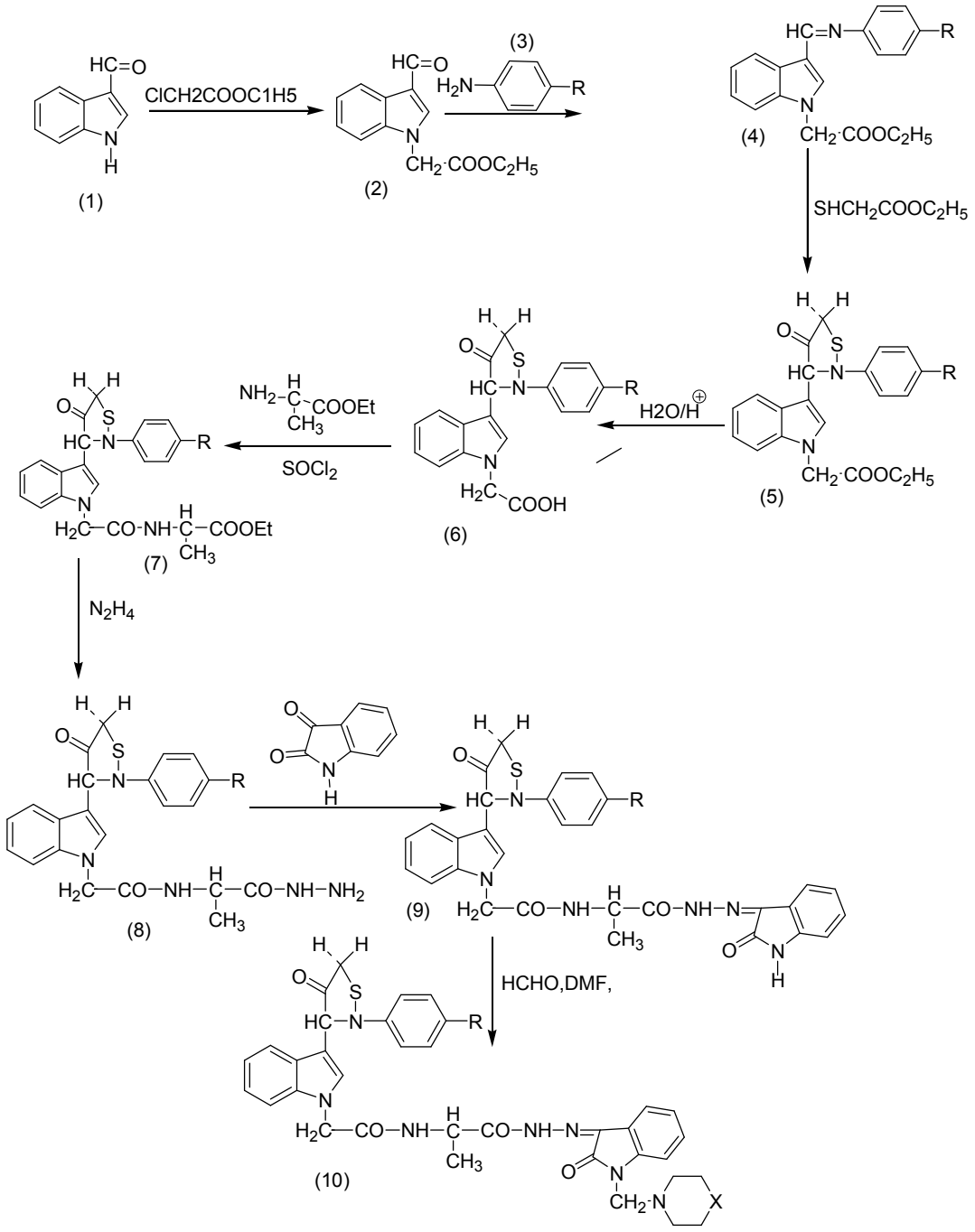
Keywords: Antibacterial activity, Antifungal activity, Indole, mannich base,isatin

Introduction

Recent drug discovery studies have focused on the design and synthesis of small molecules that have an indole nucleus as the core structure and that act as tubulin inhibitors. (1) Drugs that bind to tubulin act by interfering with the mitosis of cells during the M-phase, resulting in mitotic arrest and eventually excess to apoptosis. (2)Therefore, microtubules are a sensitive target for the development of anticancer drugs. Due to the introduction of vinca alkaloids such as vincristine and vinblastine for the clinical therapy of cancer, indole carrying compounds have generated considerable interest. (3−8) A large number of synthetic indole-containing drugs and clinical candidates have been identified over the past few years Chang and co-workers reported a large number of compounds with indole core structure. In addition to the

synthesis and evaluation of the anticancer activity of these compounds, they have revealed some SAR and pharmacophore modeling data. (4,5,9−13) Research on 1- and 3-aroylindoles 9 showed that 3-substituted indole derivatives exhibited significant activity compared with 1-aroylindoles and the electronic effects on the indole ring were important for activity potency(11).

Thiazolidinones moiety is associated with variety of biological activities including antifungal(14)., anti-inflammatory(15)., anticonvulsant(16)., antitubercular(17).,antihistaminic(18).



compound	10(a)	10(b)	10(c)	10(d)	10(e)	10(f)
R	H	CH_3	OCH_3	Cl	NO_2	CF_3
R^1	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2

Experimental section

Chemistry

Chemicals and reagents used in the current study were of analytical grade. The reactions were monitored by thin layer chromatography (TLC) on Merck pre-coated silica GF254 plates. Melting points were determined usinga Mettler Toledo FP62 capillary melting point apparatus (Mettler-Toledo, Greifensee, Switzerland) and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One series FT-IR apparatus (Version5.0.1) (Perkin Elmer, Norwalk, CT, USA), using potassium bromide pellets; the frequencies were expressedin cm−1. The 1 H- and 13C-NMR spectra were recorded with a Varian Mercury-400 FT-NMR spectrometer

(Varian, Palo Alto, CA, USA), using tetramethylsilane as the internal reference, with chloroform-**,$(CD)_2$ SO** as solvent, the chemical shifts were reported in parts per million (ppm) and coupling constants (*J*) were given in hertz (Hz). Elemental analyses were performed on a LECO 932 CHNS instrument (Leco-932, St. Joseph, MI,USA) and analyses for C, H, and N were with in 0.4% of the theoretical values.

RESULTS AND DISCUSSION

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

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 recorded by TLC using cyclohexane and ethylacetate solvent mixture (7:3) as eluent the reaction mixture was kept over night. After completion of the reaction the solvent was evaporated on rota-evaporater. The gummy solid was seperated and it was recrystalised from -2-propanol-petrolium ether(80^0c)solvent mixture. The crystaline solid was found to be -2-(3-formyl-1H-indol-1-yl)acetate. with a yield of 75% and mp 143-145^0C.The indole-3-carbaldehyde used in the present studies was purchased from aldrich company and was used without any farther purification. Yield 75%,m.p.:143-145^0C

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(ν-Ar-H), 2980 and 2960 (ν aliphatic CH_2 andCH_3), 1760 (ν CO of ester group), and 1182(ν 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-d_6 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 (4)

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 acetic acid is added then heated on a steam bath for 5-6hrs at 100^{0}C. 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^{0}C

IR Spectra ($\bar{\nu}$, 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 (ν Ar-H), 2980 and 2960 (ν aliphatic CH_2 and CH_3), 1760 (ν CO of ester group), 1610(ν C=N group) and 1182(ν C-O-C of ester group).

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

^{1}H NMR Spectra of ethyl 2-(3-phenyl imino)metbyl-1H-Indole-1-yl-acetate 1(a)was recorded in DMSO-d_6 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).

Synthesis of ethyl 2-(3-(3-(4- phenyl)-4-oxothiazolidin-2-yl)-1H-indol-1-yl)acetate5(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 confirmed 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)acetate5(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)acetate5(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)acetate5(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)acetate5(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 spectra ; 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)acetate5(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 Spectrum of 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-(4-oxo-2-phenyl iso thiazolidin-3-yl)-1H-indol-1-yl)acetic acid(6)

A solution of 5(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 ice cold 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 Spectrum of the compound 6a shows signals at,1620(C=N),1175(C-O-C),1730(C=O),698(C-S-C) .

Synthesis of Ethyl 2-(2-(3-(4-oxo-2-phenyl isothiazolidin-3-yl)-1H-indol-1-yl)acetamido)propanoate (7)

To the solution of 6(a) (0.01mole) in hot methanol (25ml), acetophenone(0.01) and a drop of glacial aceticacid were added. The solid that segregate on refluxing for 3hours was filtered cleaned 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 7(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-(2-(3-(4-oxo-2-phenyl isothiazolidin-3-yl)-1H-indol-1-yl)acetamido)propane hydrazide(8)

A solution of 7(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 ice cold water with stirring. The segregated 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 Spectrum of The compound 8(a) shows signals at,1620(C=N),1175(C-O-C),1730(C=O),698(C-S-C) .

2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-indolin-3-ylidene)methylene)propane hydrazine(9)

Equimolar quantity of 2-(2-(3-(4-oxo-2-phenyl isothiazolidin-3-yl)-1H-indol-1-yl)acetamido)propane hydrazide(8) and isatin 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 2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-indolin-3-ylidene)methylene)propane hydrazine(9). Yield 75%,m.p.:152-158^0C

IR Spectra (ν, cm^{-1}):

IR (KBr) spectrum of 2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-indolin-3-ylidene)methylene)propane hydrazine 9(a) was recorded in the range 4000-667cm^{-1} and IR absorption signals were found at 3032 (ν Ar-H), 2980 and 2960 (ν aliphatic CH_2 and CH_3), 1760 (ν CO of ester group), 1610(ν C=N group) and 1182(ν C-O-C of ester group).

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

2-(2-(3-(4-formyl-tetrahydro-2-phenylthiophene-3-yl)-1H-indol-1-yl)acetamido)-N^1-(2-oxo-indolin-3-ylidene)methylene)propane hydrazine 9(a) was recorded in DMSO-d^6 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).

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 . The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

The synthesized compounds were used at the concentration of250 µglml and 500µglml using DMSO as a solvent the Cefaclor 10µglml disc was used as a standard .(Himedia,Laboratories Ltd, Mumbai).The test results presented in the table -1,suggest that 4b,4d,4e exhibit high activity against the tesed 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 Penicillium and Trichophton.

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

Table-1 Antibacterial activity by disc diffusion method of indolelinked manich bases. 4(a.f)

Compound	**Zone of inhibition (mm)**			
	Staphylococcus aureus	**Bacillus cereus**	**Escherichia coli**	**Pseudomonas aeruginosa**
10(a)	16	18	13	12
10(b)	14	11	15	10
10(c)	13	12	10	09
10(d)	16	17	12	11
10(e)	18	16	15	17
10(f)	11	14	13	12
Cefaclor	19	22	19	20

.**Table-2** Antifungal activity by disc diffusion method for indole linked mannish bases 4(a-f).

Compound	**Zone of inhibition (mm)**	
	Asperigillus niger	**Candida albicans**
10(a)	14	16
10(b)	15	13
10(c)	17	15
10(d)	18	17
10(e)	23	21
10(f)	15	13
Clotrimazole	25-30	25-30

Conclusions:

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

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