Research Article

Synthesis Characterization and Biological Evaluation of Novel Thiazole Derivatives Containing Indole Moiety Bearing-Tetrazole

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ABSTRACT

Purpose**:** The article is aimed to synthesize,characterize and screening the biological activity of a series of Synthesis of 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 4(a-f). 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**.** To this reaction mixture added aniline,EtoH and three drops of acetic acid is added and then heated on a steam bath for 5-6 hrs.Compound(A) Ethyl 2-(3-phenyl imino)methyl-1H-Indole-1-yl-acetate was obtained. Compound(A) is converted into Ethyl2-(3-(1-phenyl-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate (1) by using of conditions (1)PCl_3,100^0C,1hr (2)NaN_3(ice cold),$ZnCl_2$,Sodium acetate,acetone,water,RT. Schiff base synthesis of thiazole derivatives containing Indole moiety bearing tetrazole ring were synthesised by the condensation of 2-(3-(3-chloro -1-(4-substitued phenyl)-4-tetrazole -2-yl)-1H-Indole –1-yl) Aceto hydrazide with potassium thio cyanide and substituted ketones. Then 1-(2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetyl)-4-(2-(4-substituted phenyl)hydrazono)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one is obtained. The structure of these newly synthesized compounds were characterized by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis. The antimicriobial activity of the novel compounds was screened by agar discdiffusion method.

Keywords: Antibacterial activity, antifungal activity, DMF, indole, schiff base, thiazole, tetrazole

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INDRODUCTION

Hetero cyclic compounds represent an important class of biological molecules. The hetero cyclic molecules which posses indole, thiazole and tetrazole 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, antiinflamatory, anthelmintic, cardiovascular, anticonvalsant and selective COX-2 inhibitary activities.

Dermatophytes are infections of keratinized tissue, that is, the epidermis, hair and nails, caused by a group of specialized fungi. The dermatophytes do not invade subcutaneous or deep tissue. *Dermytophyte- Trichophyton schoenleinii* was the first microorganism that was proven to cause an infectious disease of humans [1]. The dermatophytes species can be categorized as an ecological basic as being geophilic, zoophilic or anthrophilic [2]. The geophilic species are natural habitats in the soil, natural habitats of the zoophilic dermatophytes are domestic and wild animals [3]. *Geotrichum candidum* was believed to be part of the normal flora of human skin and gastrointestinal tract. *Geotrichum* is frequently isolated from milk and is recorded as a spoilage organism on dairy

products [4]. Some fungi are parasitic, especially on plants and others are symbiotic with roots and algae [5]. Fungi cells are quite different from plant cells not only by lacking chloroplasts but also by having a cell wall that contains chitin and not cellulose [6]. Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive, antialergic, antibiotic and anticonvulsant agents [7-14]. Development of tetrazole chemistry has been largely associated with wide scale of applications of these classes of compounds in medicine, biochemistry, agriculture [15-18]. And also a large number of medicinally important tetrazole heterocyclic incorporated drugs approved by the FDA [19-20]. The medicinal activity of tetrazole functionality is due to its ability to serve asbioequivalent (bioisostere) of the carboxylic acid group. 1, 5-disubstituted tetrazoles can be used as isosteres of the*cis*-amide bond of peptides [21-23]. Biphenyl tetrazole compounds play important role in the medicinal chemistry. Losartan was described as the first non-peptide AT1 receptor antagonist and the coined group name was sartans [24-25]. Most of these compounds share the biphenyl tetrazole unit or replacements thereof with the original advancedlead Losartan [26]. All these sartan drugs contain some common structural features represented by a biphenyl fragment bearing an acidic moiety (i.e.: tetrazole, carboxylic- or sulphonamidocarboxyl-group), linked to Tetrazole and its derivatives have attracted much attention because of their unique structure and applications asantihypertensive a heteroaromatic or acyclic system by means of a methylene group.

MATERIALS AND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus. T.L.C. analysis was performed on precoated silica gel (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 –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.

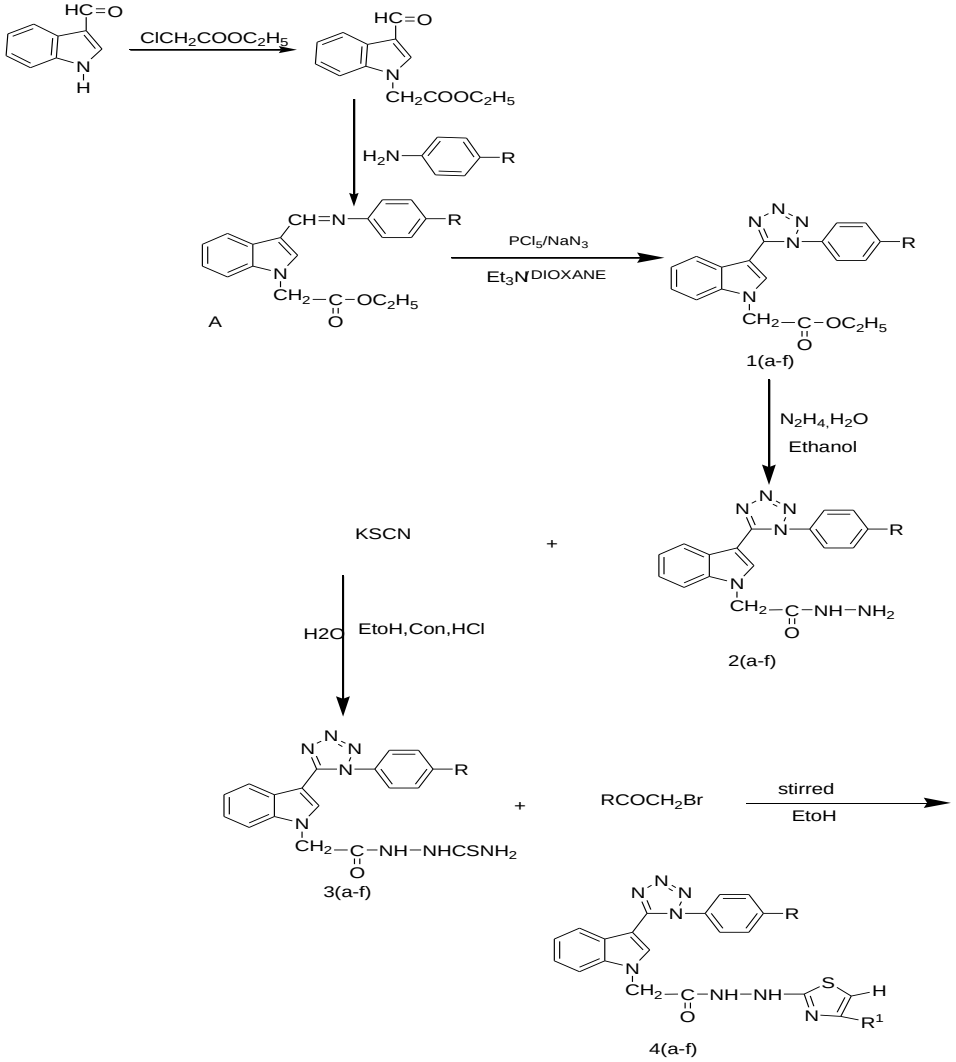
RESULTS AND DISCUSSION

The target compounds were synthesized via the route as shown in Scheme above. The synthon required for the synthesis of the target molecules indole-3-carbaldehyde was prepared by a reported method. Filtered and recrystallized from ethanol. These reactions are summarised in the scheme-1. Yields were moderate to affair (55-70%). The purity of the compounds was monitered 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 monitered 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 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 forther purification. Yield 75%, m.p.:143-145^{0}C



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

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) and 6.92, 7.58 (m, 10H, C_8H_5N indole nucleus).

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

Equimolar quantity of aniline and ethyl-2-(-3-formyl-1H-indol-1-yl)acetate were dissolved in absolute alcohol, to this three drops of aceticacid 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 (√, cm^{-1}):

IR (KBr) spectrum of ethyl 2-(3-phenyl imino)methyl-1H-Indole-1-yl-acetate (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 (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 tetrazole on treatment with (1)PCl_3,100^{0}C,1hr (2)NaN_3(ice cold), $ZnCl_2$, Sodium acetate, acetone, water, RT. 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 spedtra; the compound (A) shows signals at, 1610(C=N), 1760 (ester –C=O), 3032(Ar-H), 1182(-C-O-C).

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

Ethyl2-(3-(1-phenyl-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate 1(a)

Schiffsbase (0.004mol) and PCl_5 (0.004mol) was heated at 100^0 C for one hour. When the evolution of fumes of HCl ceased, excess of PCl_3 was removed under reduced pressure and the residual imidoyl chloride was treated with an ice-cold solution of sodium azide(0.0075mol) and excess of sodium acetate in water (25ml) and acetone (30ml) with stirring. Stirring was continued for overnight, there after acetone was removed under reduced pressure. The remaining aqueous portion was extracted with chloroform was dried. The newly synthesised compound was confirmed by IR, NMR, MASS spectral data.

NMR spectra ;1.34 (t,3H,CH_3 of OC_2H_5), 3.75 (s,2H N-CH_2-C =O), 4.27 (q,2H,-O-CH_2 Of OC_2H_5), 7.25-7.35 (m,10H,due to 5H of indole, 5H of phenyl ring).

IR spedtra; The compound 1a shows signals at, 1620 (C=N), 1175 (-C-O-C-), 1688 (-C=O),2120(NΞN)

Ethyl 2-(3-(3-chloro-1-(4-methyl phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetate 1(b).

^{1} H NMR spectra(300MHZ,$(CD)_2$ SO,TMS): 1.36 (t,3H,CH_3 of OC_2H_5),2.23(s,3H,CH_3 attached to phenyl ring),3.77 (s,2H N-CH_2-C =O), 4.29 (q,2H,-O-CH_2 Of OC_2H_5), 7.30 - 7.35 (m,9 H,due to 5H of indole ,4H of phenyl ring). IR spedtra; The compound 1(b) shows signals at, 1615 (C=N),1170(-C-O-C-),1685(-C=O),2115(NΞN)

Ethyl 2-(3-(3-chloro-1-(4-methoxy phenyl)-4-tetrazole-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 tetrazole -2-yl) -1H - Indol -1-yl)acetate 1(c) show signals 1.37 (t,3H,OCH_3 of OC_2H_5),2.25 (s,3H,CH_3 attached to phenyl ring),3.78 (s,2H N-CH_2-C =O), 4.30 (q,2H,-O-CH_2 Of OC_2H_5), 7.32 -7.36 (m,9 H,due to 5H of indole ,4 H of phenyl ring). IR spedtra ; The compound 1(c)shows signals at, 1612 (C=N),1165 (-C-O-C-),1680 (-C=O),2110(NΞN).

Ethyl 2-(3-(3-chloro-1-(4-bromo phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetate 1(d).^{1} H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:- synthesis of ethyl 2-(3-(3-chloro -1-(4-bromo phenyl) -4 tetrazole -2-yl) -1H - Indol -1-yl)acetate 1(d) show 1.38 (t,3H,CH_3 of OC_2H_5), 3.79 (s,2H N-CH_2-C =O), 4.32 (q,2H,-O-CH_2 Of OC_2H_5), 7.33 -7.38 (m,9 H,due to 5H of indole ,4 H of phenyl ring). IR spedtra ; The compound 1(d) shows signals at, 1605 (C=N),1160 (-C-O-C-),1675 (-C=O),2105(NΞN).

Ethyl 2-(3-(3-chloro-1-(4-nitro phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)acetate 1(e).

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:-synthesis of _of ethyl 2-(3-(3-

chloro -1-(4-nitro phenyl) -4-tetrazole -2-yl) -1H - Indol -1-yl)acetate 1(e) show signals 1.39 (t,3H,CH_3 of OC_2H_5), 3.80 (s,2H N-CH_2-C =O), 4.33 (q,2H,-O-CH_2 Of OC_2H_5), 7.34 - 7.39 (m,9 H,due to 5H of indole ,4 H of phenyl ring) IR spedtra ; The compound 1(e) shows signals at, 1595 (C=N),1155 (-C-O-C-),1665 (-C=O),2100(NΞN).

Ethyl 2-(3-(3-chloro-1-(4-tri fluoro methyl phenyl)-4-tetrazole-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 tetrazole -2-yl) -1H - Indol -1-yl)acetate 1(f) show signals 1.41 (t,3H,CH_3 of OC_2H_5), 3.81 (s,2H N-CH_2-C =O), 4.35 (q,2H,-O-CH_2 Of OC_2H_5), 7.36 - 7.41 (m,9 H,due to 5H of indole ,4 H of phenyl ring). IR spedtra ; The compound 1(f) shows signals at, 1625 (C=N),1180 (-C-O-C-),1690 (-C=O),2125(NΞN).

Synthesis of 2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-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 seperated solid was filtered, washed with water and recrystalised from ethanol to afford 2-(3-(3-chloro-1-(4-substituted phenyl)-4-tetrazole-2-yl)-1H-indol-1-yl)aceto hydrazide(2).

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS): δ:- 3.77 (s,2H N-CH_2-C =O), 4.29 (s,2H of –NH_2), 9.68(s,1H,-NH),7. 35-7.40 (m,9 H,due to 5H of indole ,4H of phenyl ring). IR data of 2-(3-(1-phenyl-1H-tetrazol-5-yl)-1H-indol-1-yl)acetohydrazide . 1615 (C=N),3220(NH),1690 (-C=O),2125(NΞN), 3496,342(-NH_2 two bands).

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

A mixture of 2-(2-(3-(1-phenyl-1H-tetrazole-5-yl)-1H-indol-1-yl)hydrazine carbothiaoamide 4(a) (0.01mol),in DMF(10ml) and various bromoacetyl derivatives (0.01)in ethanol (10ml),was stirred at room temperature for 1-2 hours. The solid separated was filtered, dried and recrystalized from ethanol –DMF mixture. The yield, meltingpoint and other characterization data of compounds prepared by this procedure are given in the table.

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ:- 3.79 (s,2H N-CH_2-C =O), 9.54 (s,1H,-NH),9.38-10.29 (2H due to NH-NH group appeared as two broad signals), 7.32 -7.37 (m,10H due to 5H of indole,5H of phenyl ring), 7.0-7.1(s,1H,thiazole ring),10.65(s,1H,-CO-NH). IR data of 2-(3-(1-phenyl-1H-tetrazol-5-yl)-1H-indol-1-yl)acetohydrazide. 1630 (C=N), 3220(NH), 1675 (-C=O),2135(NΞN),3496,342(-NH_2 two), 1180(C=S)

Table: Antibacterial activity by disc diffusion method of indole thiazole having tetvazole 4 (a.f) Characterization of above compounds

COMPOUND	YIELD	M.P.O^{0}C	% ANALYSIS					
			C		H		N	
			Calcd	FOUND	Calcd	FOUND	Calcd	FOUND
1a	58%	245	68.85	68.82	6.05	6.01	7.65	7.64
1b	55%	240	69.47	69.44	6.36	6.31	7.4	7.36
1c	52%	220	66.66	66.64	6.1	6.06	7.5	7.07
1d	59%	235	63	62.91	5.28	5.25	7.00	6.99
1e	60%	250	61.31	61.3	5.14	5.1	10.22	10.21
1f	65%	255	60.85	60.82	4.87	4.83	6.46	6.45
4a	56%	185	57.37	57.36	4.21	4.18	11.16	11.15
4b	54%	190	58.14	58.13	4.49	4.45	10.86	10.85
4c	52%	180	56.39	56.38	4.35	4.32	10.53	10.52

4d	50%	182	53.73	53.68	3.75	3.73	10.44	10.43
4e	55%	185	52.68	52.65	3.68	3.65	12.8	12.79
4f	50%	180	57.37	57.36	4.21	4.18	11.16	11.15

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 staphylococcusaureus NCCS 2079 and Bacilluscereus 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 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 4a, 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 aspergillus niger NCCS1196 and cadida albicans NCCS34471

Compounds were treatd 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 thiazole having tetrazole 4(a.f)

Compound	Zone of inhibition (mm)			
	Staphylococcus aureus	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
4a	16	18	13	12
4b	14	11	15	10
4c	13	12	10	09
4d	16	17	12	11
4e	18	16	15	17
4f	11	14	13	12
Cefaclor	19	22	19	20

Table 2: Antifungal activity by disc diffusion method for indole linkedThizole having tetrazole 4(a-f)

Compound	Zone of inhibition (mm)	
	Asperigillus niger	Candida albicans
4a	14	16
4b	15	13
4c	17	15
4d	18	17
4e	23	21
4f	15	13
Clotrimazole	25-30	25-30

CONCLUSION

1. Furthermore the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The tetrazoles showed better antibactirial and antifungal activities.
3. thiazoles and its derivatives were found to play an important role in

medicinalchemistry as herbicidal, fungicidal, bacterial, anti-inflammatory.

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