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SYNTHESIS CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 2-(3-(2-CHLORO-3-OXO-4-PHENYLCYCLOBUTYL)-1H-INDOL-1-YL)-N'-(THIAZOL-2-YL) ACETOHYDRAZIDE

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ABSTRACT

This article is aimed to synthesize, characterize and biological activity of a series of synthesis of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(thiazol-2-yl) acetohydrazide 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°C) for 8 hrs. 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 ethyl 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetate (1) by using of conditions (1) $ClCH_2COCl$/Et3N/Dioxane. Schiff base synthesis of thiazole derivatives containing Indole moiety bearing azetidine ring were synthesised by the condensation of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetohydrazide (2) with potassium thio cyanide and substituted ketones. Then 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(thiazol-2-yl)acetohydrazide 4(a) was obtained. The structure of these newly synthesized compounds was characterised by ^{1}H NMR, ^{13}C NMR, Mass, IR, and elemental analysis. The antimicriobial activity of the novel compounds was screened by agar disc diffusion method.

Key words: Antibacterial activity, Antifungal activity, DMF, Indole, Schiff base, Thiazole, Azetidinone.

INDRODUCTION

Heterocyclic compounds represents an important class of biological molecules. The heterocyclic 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-*

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Trichophyton schoenleinii was the first microorganism that was proven to cause an infections 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].

Azetidinones are of great biological interest, especially as anti-tubercular[7], antibacterial[8-11]. 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 azetidinewith attendantcontrol of functional group and stereochemistry. Azetidinone derivatives are reported to show a variety of antimicrobial[12,13], anticonvulsant[14], anti-inflammatory[15] and cardiovascular activities[16], antimycobacterial activity[17], antibacterial activity[18], antihypertensive activity[19].

EXPERIMENTAL

Materials and methods

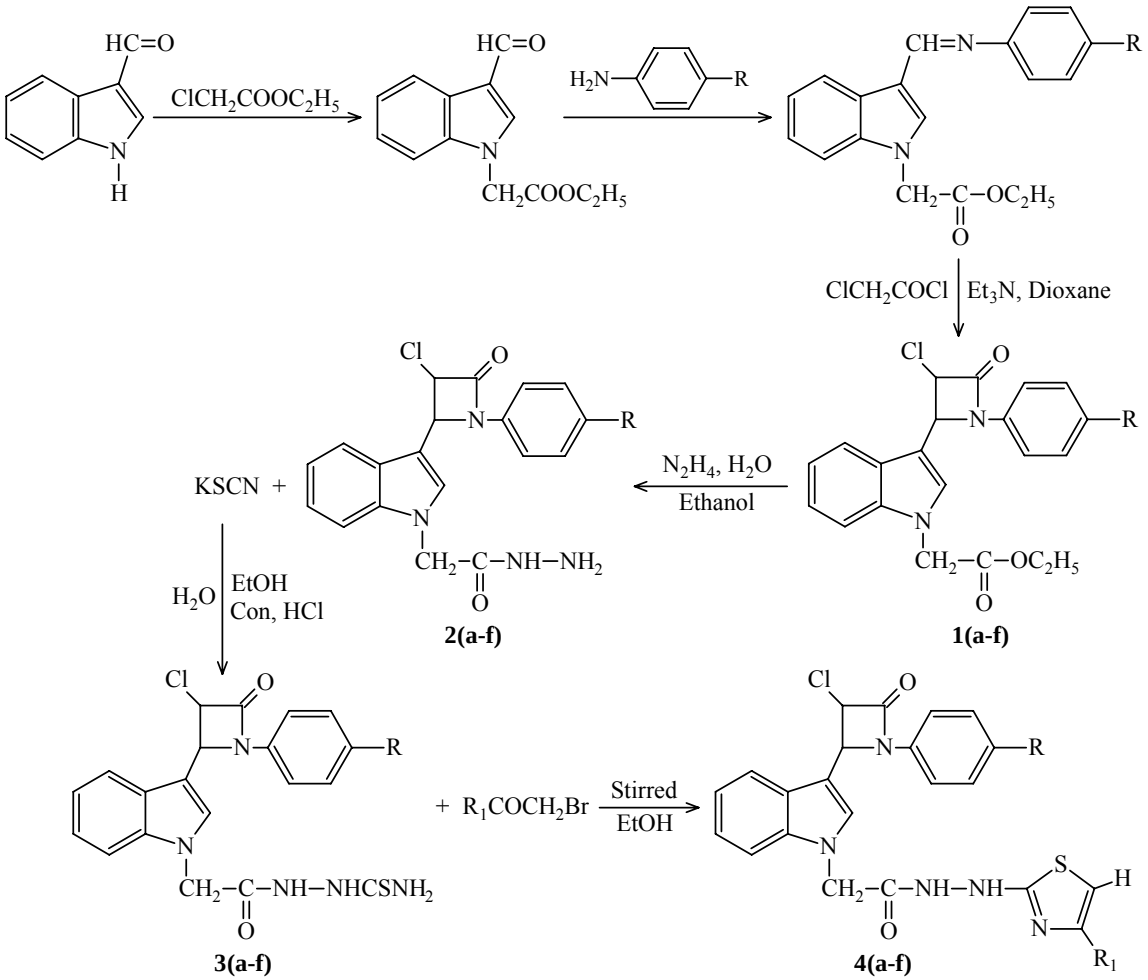
Melting points were determined on open capillaries using a cintex melting point apparatus. T. L. C. analysis were performed on precoatedsilicagel (E-Merck Kieselgel 60 F_{254}) plates and visualisation was done by exposing to iodine vapour. Solvent were purified by standard procedures before use. Column chromatography was conducted by using Silica gel with different solvent systems as elutes. IR Spectra were recorded on Perkin-Elmer spectrum BX series FTIR spectrometer. ^{1}H-NMR spectrum were recorded on varian zemini 300 MHz and 200 MHz spectrometers using TMS as internal standard (chemical shifts in & ppm) ^{13}C NMR spectra were recorded on a Brucker 75 MHz 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 1. 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 hrs 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 m.p. 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	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

Scheme 1

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 where found at 3032 (ν-Ar-H)**,** 2980 and 2960 (ν aliphatic CH_2 and CH_3), 1760 (ν CO of ester group), and 1182 (ν C-O-C of ester group).

^{1}H NMR Spectra (δ_{PPm}): The ^{1}H 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 $\delta_{PPm,}$ 1.29 (t, 3H, J = 13.2 Hz, CH_3 of ethyl group), 4.13 (q, 2H, J = 13.2 Hz, 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 (3) and ethyl-2-(-3-formyl-1H-indol-1-yl)acetate were dissolved in absolute alcohol, to this three drops of acetic acid is added then heated on a steam bath for 5-6 hrs at 100^{o}C. After standing for 24 hrs 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 (ν, cm^{-1}): IR (KBr) spectrum of ethyl 2-(3-phenyl imino)methyl-1H-Indole-1-yl-acetate (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 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 (300 MHZ, $(CD)_2$ SO, TMS) δ: ^{1}H NMR Spectra ethyl 2-(3-phenyl imino)metbyl-1H-indole-1-yl-acetate (A) was recorded in DMSO-d 6 solvent. The NMR signal of ethyl 2-(3-phenyl imino)methyl-1H-Indole-1-yl-acetate(A) was found at $\delta_{PPm,}$ 1.29 (t, 3H, J = 13.2 Hz, CH_3 of ethyl group), 4.13 (q, 2H, J = 13.2 Hz, CH_2 of ethyl group), 4.78 (s, 2H, N-CH_2 group) and 6.92, 7.58 (m, 10 H, C_8H_5N indole nucleus and C_6H_5 phenyl nucleus) and 8.44 (s, 1 H, N=CH group). The compound **(A)** was converted into tetrazole on treatement with **(1)** PCl_3, 100^0C, 1 hr (2) NaN_3 (ice cold), $ZnCl_2$, sodium acetate, acetone, water, RT. The formation compound was conformed 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}H 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, 10 H, Ar-H, 8.44 (N=CH). Table: 2.2 ^{1}H NMR spectra of ethyl 2-(3-phenyl imino)methyl-1H-indole-1-yl-acetate **(A)**.

Synthesis of ethyl 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetate (1)

Schiffs base (0.004 mol) and PCl_5 (0.004 mol) was heated at 100^0C 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 (0.0075 mol) and excess of sodium acetate in water (25 mL) and acetone (30 mL) 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 conformed by IR, NMR, Mass spectral data.

IR spedtra; The compound **(1)** shows signals at, 1610 (C=N), 1760 (ester –C=O), 3032 (Ar-H), 1182 (-C-O-C). ^{1}H 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).

Synthesis of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetohydrazide (2)

A solution of (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed for 5 hrs. 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-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetohydrazide **(2)**.

^{1}H NMR spectra (300 MHZ, $(CD)_2$ 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, 13H, due to 5H of indole, 4H of phenyl ring). IR data: 1615 (C=N), 3220 (NH), 1690 (-C=O), 2125 (N≡N), 3496, 342 (-NH_2 two bands).

Synthesis of 2-(2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl) acetyl) hydrazine-carbothioamide (3)

A solution of **(2a)** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed for 5 hrs. 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-(2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetyl) hydrazinecarbothioamide **(3)**.

^{1}H NMR spectra: 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, 13H, due to 5H of indole C_6H_6, C_6H_4 of phenyl ring), 5.49 (d, 1H –CH of azetidine attached to –Cl), 3.32 (s, 2H, -NH_2), 9.68 (s, 1H, -NH), 9.36-10.27 (2H due to NH-NH group appeared as two broad signals). IR spedtra: The compound 3(a) shows signals at, 3494 (-NH), 3330 (Ar-H), 2920 (-CH- of alifatic), 1680 (C=O, amide), 3494 (-NH_2), 820 (CCl).

Synthesis of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(thiazol-2-yl) acetohydrazide (4a)

A mixture of 2-(2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetyl) hydrazinecarbothioamide **(3)** (0.01 mol), in DMF (10 mL) and various bromoacetyl derivatives (0.01) in ethanol (10 mL), was stirred at room temperature for 1-2 hrs. The solid separated was filtered, dried and recrystalized from ethanol –DMF mixture. The yield, melting point and other characterization data of compounds prepared by this procedure are given in the Table 1.

^{1}H NMR spectra (300 MHZ, $(CD)_2$ SO, TMS) δ: 4.32 (s, 2H N-CH_2-C =O), 4.80 (s, 1 H, -N-NH), 5.18 (d, 1H, -CH of azetidine attached to phenyl ring), 6.85-8.20 (m, 12H, due to 5H of indole $C_{,6}H_6$, of phenyl ring, 1H of thiazole ring), 5.35 (d, 1H –CH of azetidine attached to –Cl). IR data of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(thiazol-2-yl)acetohydrazide. 1630 (C=N), 3220 (NH), 1675 (-C=O), 2135 (N≡N), 3496, 342 (-NH_2 two), 1180 (C=S).

2-(3-(2-Chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-methylthiazol-2-yl) acetohydrazide (4b)

^{1}H NMR spectra (300 MHZ, $(CD)_2$ SO, TMS) δ: 2.25 (s, 3H, CH_3 attached to phenyl ring), 4.29 (s, 2H N-CH_2-C =O), 4.70 (s, 1 H, -N-NH), 5.10 (d, 1H, -CH of azetidine attached to phenyl ring), 6.70-8.10 (m, 11 H, due to 5H of indole $C_{,6}H_5$, of phenyl ring, 1H of thiazole ring), 5.25 (d, 1H –CH of azetidine attached to –Cl). IR data of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-methylthiazol-2-yl)acetohydrazide 4(b) 1620 (C=N), 3220 (NH), 1665 (-C=O), 1270 (N≡N), 3456, 3342 (-NH_2 two), 1170 (C=S).

2-(3-(2-Chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-methoxythiazol-2-yl) acetohydrazide (4c)

^{1}H NMR spectra (300 MHZ, $(CD)_2$ SO, TMS) δ: 2.27 (s, 3H, OCH_3 attached to phenyl ring), 4.25 (s, 2H N-CH_2-C=O), 4.65 (s, 1 H, -N-NH), 5.05 (d, 1H, -CH of azetidine attached to phenyl ring), 6.50-8.05 (m, 11 H, due to 5H of indole $C_{,6}H_{5,}$ of phenyl ring, 1H of thiazole ring), 5.10 (d, 1H –CH of azetidine attached to –Cl). IR data of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-methoxythiazol-2-yl)acetohydrazide 4(c) 1620 (C=N), 3220 (NH), 1665 (-C=O), 1220 (N≡N), 3256, 3142 (-NH_2 two), 1110 (C=S).

N'-(4-Bromothiazol-2-yl)-2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl) acetohydrazide (4d)

^{1}H NMR spectra (300 MHZ, $(CD)_2$ SO, TMS) δ: 4.20 (s, 2H N-CH_2-C =O), 4.50 (s, 1 H, -N-NH), 5.05 (d, 1H, -CH of azetidine attached to phenyl ring), 6.40-8.30 (m, 11 H, due to 5H of indole $C_{,6}H_5$ of phenyl ring, 1H of thiazole ring), 5.60 (d, 1H –CH of azetidine attached to –Cl). IR data of N'-(4-bromothiazol-2-yl)-2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)acetohydrazide 4(d) 1690 (C=N), 3220 (NH), 1630 (-C=O), 1250 (N≡N), 3556, 3444 (-NH_2 two), 1170 (C=S).

2-(3-(2-Chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-nitrothiazol-2-yl) acetohydrazide 4(e)

^{1}H NMR spectra (300 MHZ, $(CD)_2$ SO, TMS) δ: 4.10 (s, 2H N-CH_2-C=O), 4.20 (s, 1 H, -N-NH), 5.05 (d, 1H, -CH of azetidine attached to phenyl ring), 6.20-8.10 (m, 11H, due to 5H of indole $C_{,6}H_{5,}$ of phenyl ring, 1H of thiazole ring), 5.10 (d, 1H –CH of azetidine attached to –Cl). IR data of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-nitrothiazol-2-yl)acetohydrazide 4(e) 1680 (C=N), 3200 (NH), 1650 (-C=O), 1270 (N≡N), 3506, 3414 (-NH_2 two), 1130 (C=S).

2-(3-(2-Chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-(trifluoromethyl)thiazol-2-yl) acetohydrazide 4(f)

^{1}H NMR spectra (300 MHZ, $(CD)_2$ SO, TMS) δ: 4.25 (s, 2H N-CH_2-C =O), 4.15 (s, 1 H, -N-NH), 5.05 (d, 1H, -CH of azetidine attached to phenyl ring), 6.00-8.00 (m, 11H, due to 5H of indole $C_{,6}H_{5,}$ of phenyl ring, 1H of thiazole ring), 5.20 (d, 1H –CH of azetidine attached to –Cl). IR data of 2-(3-(2-chloro-3-oxo-4-phenylcyclobutyl)-1H-indol-1-yl)-N'-(4-(trifluoromethyl)thiazol-2-yl)acetohydrazide 4(f) 1650 (C=N), 3200 (NH), 1620 (-C=O), 1210 (N≡N), 3526, 3424 (-NH_2 two), 1190 (C=S).

Table 1: Charactrization of synthesized compounds

Compound	Yield (%)	M.P. (°C)	% Analysis					
			C		H		N	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
1	58	245	68.85	68.82	6.05	6.01	7.65	7.64
2	55	240	69.47	69.44	6.36	6.31	7.4	7.36
3	52	220	66.66	66.64	6.1	6.06	7.5	7.07
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

Antibacterial activity

The antibacterial 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 of 250 µglmL and 500 µglmL using DMSO as a solvent the cefaclor 10 µglmL disc was used as a standard. (Himedia, Laboratories Ltd., Mumbai). The test results presented in the Table 2, 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* NCCS 1196 and *cadida albicans* NCCS34471 Compounds were treatd at the concentrations of 500 µglm and 1000 µglmL using DMSO as solvent. The standard used was clotrimazole 50 µglmL against both organisms. The test results were presented in the Table 3.

Table 2: Antibacterial activity by disc diffusion method of indole linked thiazole having azetidinone 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 3: Antifungal activity by disc diffusion method for indole linked thizole having azetidinone 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

(i) The substitution with phenyl group having a chloro group at p-position showed better activities.

(ii) The azetidinone showed better antibactirial and antifungal activities.

(iii) Thiazoles and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, anti-inflammatory.

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