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Synthesis Characterization and antitumor activity of thiazole derivatives containing indole moiety bearing-tetrazole

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ABSTRACT

Schiff base synthesis of thiazole derivatives containing Indole moiety bearing tetrazole ring were synthesised by the condensation of 2-(3-(3chloro -1-(4-substitued phenyl)-tetrazole -2-yl(1H-Indole –yl Aceto hydrazone with potassium thio cyanide and substituted ketones.To this reaction was subjected in schiff base reaction .The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis.

Keywords: Tetrazole, Schiff base, thiazole, indole

INDRODUCTION

Hetero cyclic compounds represents an important class of biological molecules. The hetero cyclic molecules which posses indole, pyrazole and azetidine 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 derivatives found to posses high which includes,antibacterial,analgesic,antipyretic,antifungal,antiflamatory,anthelmintic,cardiovascular,anticonvalsant and selective COX-2 inhibitary activities, 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 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].

Tetrazole and its derivatives have attracted much attention because of their unique structure and applications asantihypertensive,, antialergic, antibiotic and anticonvulsant agents [7-14]. Development of tetrazole chemistry hasbeen 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 advanced lead 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 were performed on precoated silicagel (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 purchased from Aldrich chemicals ;U.S.A. indole- 3-carbaldehyde was prepared by a reported method

RESULTS AND DISCUSSION

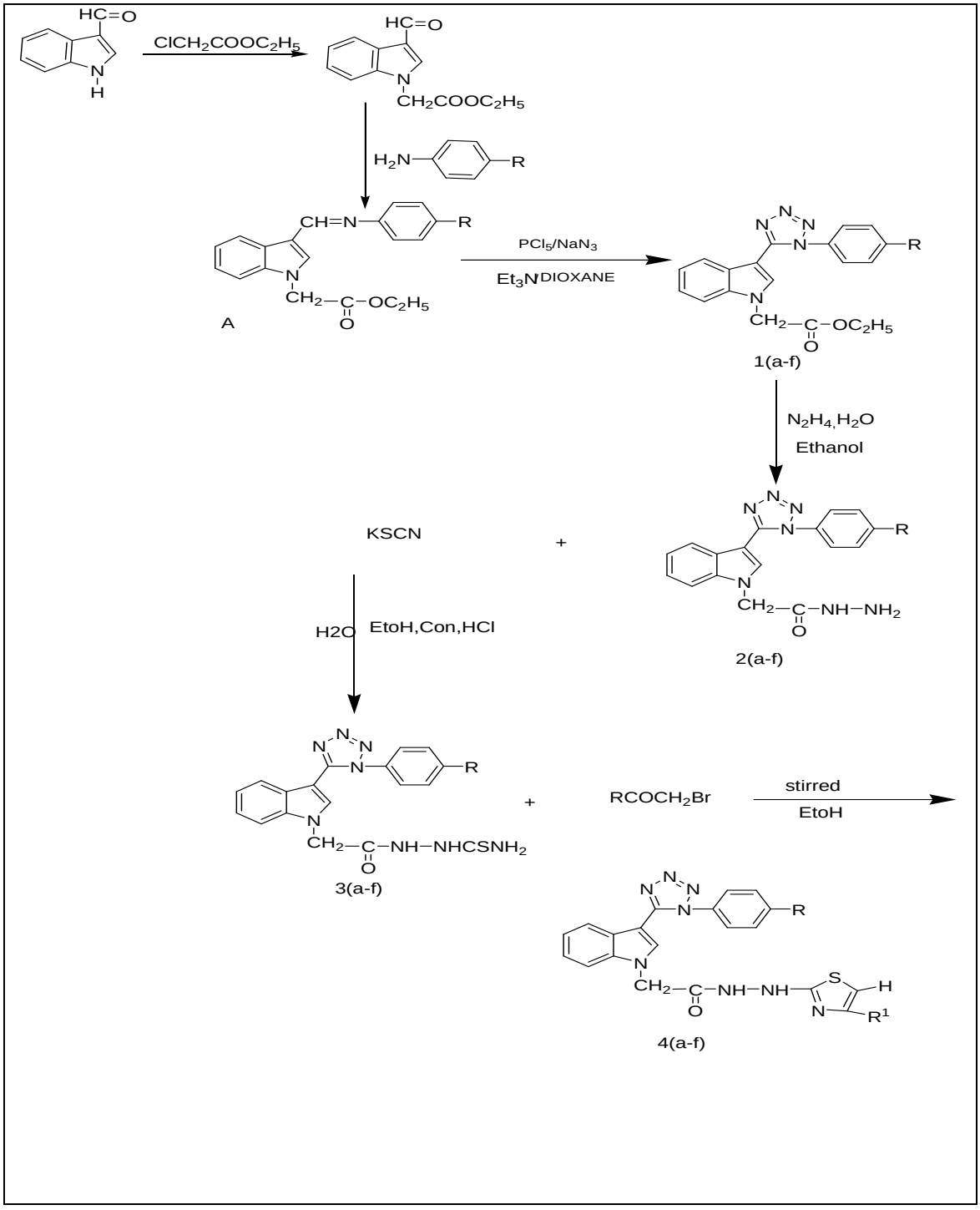
The target compounds were synthesized via the route as shown in Scheme above. The synthon required for thesynthesis of the target molecules indole-3-carbaldehyde was prepared by a reported method. Filtered and recrystal lized from ethanol. These reactions are summarized in the scheme-1.Yields were moderate to affair(55-70%). The purity of the compounds was monitored 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 monitored 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 separated 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.:143-145^0C

The IR(KBr) spectrum of 2-(3- formyl-1H-indol-1-yl) acetate(2) 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(2) was recorded in DMSO-d6 solvent. The NMR signal of 2-(3- formyl-1H-indol-1-yl) acetate(2) 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)metbyl-1H-Indole-1-yl-acetate (A)
Equimolar quantity of aniline(3) and ethyl-2-(-3-formyl-1H-indol-1-yl)acetate(2) 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



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

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 (A) was converted into azetidine-2-one on treatement with chloro acetyl chloride. 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 spectra ; 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 conformed by IR,NMR,MASS spectraldata.

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 spectra; 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)

Antitumor activity
The biological activity of all synthesized target compounds was tested in vitrofor antitumor activity using the Alamar Blue assay[27] on a panel of five human tumor cell lines at Zentaris, Germany. The cytotoxicity was evaluated on five different cell lines, cervix cancer (KB/HELA), ovarian carcinoma (SK-OV-3), brain cancer (SF-268), nonsmall-cell lung cancer (NCl-H460), and adenocarcinoma colon cancer (RKOP-27). The first screening was carried out at a predefined concentration of 3.16 µg/ml. If the compound led to more than 50% inhibition at this concentration it was evaluated for EC50 mean values (lM) from at least two experiments on those five different cell lines. It turned out that the amino nitrile 3showed significant cell-growth inhibitory activity (>50%) at a fixed concentration of 3.16 µg/mL. Subsequent determination of EC50 concentrations from dose-response curves gavevalid values for four cell lines (in the case of NCI H-460, EC50 was above the highest test concentration). The results are summarized in Table 1

In-vitro antitumor activity (% cell-growth inhibition at fixed concentration and EC50values) for synthesized compounds.

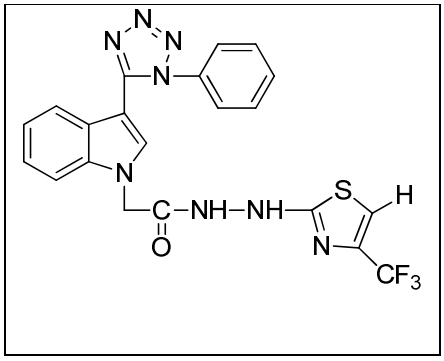
Single point		**Dose Response**
KB/HELA SKOV-3 SF-268 NCI-H46 RKOp27		KB/HELA SKOV-3 SF-268 NCI-H46 RKOp27
Comp No.	%INH [3.16µg/ml]	EC50 [µg/ml]
4(A)	-25 -1 5 5 7	
4(B)	-20 -31 34 50 60	EC50> - - - - -
4(C)	-18 -03 5 -2 3	- - - - -
4(D)	-15 0 3 3 8	
4(E)	-08 5 7 16 22	- - - - - -
4(F)	-03 12 13 38 25	

KB/HELA cervical carcinoma; SK OV-3: ovarial carcinoma; SF-268: CNS cancer; NCI- H460:non-small-cell lung cancer; RKOp27: colon adenocarcinoma

Characterization of above compounds

COMPOUND	YIELD	M.P.O^{0}C	%ANALYSIS					
			C		H		N	
			COLD	FOUND	COLD	FOUND	COLD	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

^{13}C NMR spectra: The ^{13}C NMR spectra of 2-(3-(1-phenyl-1H-tetrazol-5-yl)-1H-indol-1-yl)-N-(4-(trifluoromethyl)thiazol -2-yl)acetohydrazide was record in $CDCl_3$ showed the following signals at dppm: 163.5,128.5,129.6,128.7,106.7,129.2,136.5,109.6,121.7,119.8,121.4,128.8,46.1,164.4,171.9,104.3,123.9,148.6 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}.



compd	4(a)	4(b)	4(c)	4(d)	4(e)	4(f)
C1	163.5	163.5	163.5	163.5	163.5	163.5
C2	128.5	125.5	120.8	126.6	134.6	131.8
C3	129.6	134.8	122.3	129.5	128.1	135.2
C4	128.7	129.0	114.3	128.8	123.9	123.1
C5	106.7	138.4	160.6	134.3	147.9	131.0
C6	129.2	21.3	55.8	106.7	106.7	124.1
C7	136.5	106.7	106.7	129.2	129.2	106.7
C8	109.6	129.2	129.2	136.5	136.5	129.2
C9	121.7	136.5	136.5	109.6	109.6	136.5
C10	119.8	109.6	109.6	121.7	121.7	109.6
C11	121.4	121.7	121.7	119.8	119.8	121.7
C12	128.8	119.8	119.8	121.4	121.4	119.8
C13	46.1	121.4	121.4	128.8	128.8	121.4
C14	164.4	128.8	128.8	46.1	46.1	128.8
C15	171.9	46.1	46.1	164.4	164.4	46.1
C16	104.3	164.4	164.4	171.9	171.9	164.4
C17	123.9	171.9	171.9	104.3	104.3	171.7
C18	148.6	104.3	104.3	123.9	123.9	112.1
C19		123.9	123.9	148.6	148.6	137.0
C20		148.6	148.6			
C21						
C22						

CONCLUSION

1. Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The tetrazoles showed better antibacterial and antifungal activities.

thiazoles and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, antitumor activity

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