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ORIGINAL ARTICLE **OPEN ACCESS**

Synthesis, Characterization of New Potential Substituted Thiazolyl / Thiazolidinone Derivatives and their Screening Effect as biological, Antifungal Activity

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ABSTRACT
5,5,7-trimethyl-3a , 4 , 5 , 6,7,7a-hexahydro benzo[d] thiazol-2-amine [1] was prepared by reaction between 5,5,7 tri methyl cyclohexanone and thiourea.N Substituted benzylidine 5,5,7 tri methyl 3a ,4,5,6,7,7a hexahydrobenzo (d) thiazol-2 amine (2a- 2e) were prepared by compound 1 and different aromatic aldehydes which showed effected nature against fungi. Synthesis of desire new derivatives 2- (substituted phenyl) -3-(5,5,6,7-trimethyl-3a ,4,5,6,7,7a - hexa hydro benzo [d]thiazol-2-yl)thiazolidin-4-one.3(a-e) showed valuable characteristic and efficacy as antifungal. Chloro and hydroxyl thiazolidinone derivatives showed better inhibition activity as compare to standard drugs, so heterocyclic compounds and its derivative are very useful in field of medicinal chemistry as well as biological, pharmacological aspect. So this thiazolidinone nucleus possesses better biological properties. A new 3(a-e) series of synthesis drug thiazolidinone is very useful and it show clinically efficacy and low toxicity. Purity of thiazolyl /Thiazolidinone derivatives purity check with the help of TLC technique. Structure of new synthesised compounds identified and confirmed by elemental analysis, IR, NMR, and new synthesised drugs screened, regarding their antifungal activity.
Keywords: *Thiazolyl, Thiazolidinone, Antifungal Activity, Griseofulvin.*

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INTRODUCTION

In earlier and present time we see our surrounding different life treating infection cause by fungal disease. Thiazolidinone are useful structural requirement in the field of medicinal chemistry. Thiazolyl / Thiazolidinone drug derivatives exhibit different biological activity like antimicrobial,antibacterial, antifungal. Benzothiazole derivatives have also shown diverse biological activities [1] such as antimicrobial [2] some 1,3thiazolyldiphenyl amine represent antibacterial nature [3, 4] thiazolidinone moiety containing drug as antifungal properties [5] and represent biological active nucleus [6] antimicrobial and insecticidal activity [7] thiazolidinoyl derivative used as a potential anticonvulsant activity [8-10] antimicrobial activity and desire efficacy [11 and its derivatives also work as anti convulsent [12] and antibacterial[13] anti microbial ,anticonvulsant ,and anti inflammatory [14] progress and biological useful aspect [15-18] anti bacterial and microbial effect [20-21] and antifungal property [22] and anti convulsant [23-24] antibacterial ,antifungal, and anticancer [25], represent biological and antioxidant [26] biological protective , effective nucleus ,inhibitor [26-30]. Thiazolyl, Thiazolidinone derivatives which contain small ring heterocyclic nitrogen, sulphur and oxygen electro negative active atom show better results due to their medicinal properties in biological system and it also affected by different rate, older drug show high frequency of renal toxicity and several adverse effect. However this research work, synthesised some novel drug derivatives 3(a –e) which shown the better antifungal activity with less side effects.

MATERIAL AND METHODS

For synthesis work, different reagent were purchased commercially which are (AR) grade and purified standard procedure , a desire reagents dissolve in proper solvents at which reaction was completed at different condition . Melting points were recorded by ordinary glass capillary tube it may be incorrect. The homogeneity of all newly synthesized portion, purity and completion of reaction was confirmed by use of this plate comes with iodine vapor visualized the clear spot. IR spectra recorded with help Perkin Elmer spectrum and FTIR, and confirmed different portion of elemental parts .Beckman spectrometer check different value of UV, VIS (cm^{-1} max.) Brucker (300) DPX help to predict and recorded. ^{1}H NMR

values and the value of chemical shift expressed in ppm (δ) scale using tetra methyl silane as an internal standard , it is use in $CDCl_3$ solvent.

EXPERIMENTAL

1: Synthesis of 5, 5, 7- trimethyl - 3a, 4, 5, 6, 7, 7a-hexahydrobenzo [d] thiazol-2-amine (1)

Take a reagent 5,5,7 tri methyl cyclohexanone (2.8 g, 0.02 mol) in ethyl alcohol (18 ml) , and added thiourea (3.04g , 0.04 mol) and iodine (5.08 g , 0.02 mol) then mixture was properly stirred heat and reflux at right temperature 6 h. completion of reaction checked with help of TLC time to time and then small sample taken in beaker and added one drop of ammonia solution, when crystals were formed and then cool down to 20^0 C in 200 ml water. Basified this solution with liquor ammonia solution and put it for crystallization, after crystallization, crystals extracted through ethyl acetate (100 ml) and crude crystal purified by column chromatography using chloroform as fluent and silica gel (70- 230 mesh) as solid phase. The pure form of crystal show pale white solid, yield of the compound 72 % , MP 55-57 ^{0}C , KBR ν_{max}cm $^{-1}$) IR: 3480 (NH_2), 3270(C,H ring), 2953 (CH_3), 2877, 1562 (C=N), 758 C-S-)

2: General Procedure of Synthesis of N Substituted benzyl dine 5,5,7 tri methyl 3 a , 4 ,5,6,7,7a hexa hydrobenzo (d) thiazol - 2 amine 2 (a- e) .

Take solution of compound 1 (1.96 g, 01 mol) and substituted benzaldehyde (1.12g, 0.01 mol) in 5 ml conc CH_3COOH in RBF and make a solution in benzene (30 ml) respectively then reflux for 4 h in dean Starks apparatus in which water was remove azeobatically. The completion of reactions checked with help of TLC. When the reactions were completed the solvent was removed by distillation and solid compounds were obtained then filtered and recrystallized by ethanol to obtained pure compounds 2(a-e) with colour- light pale ; IR (KBr ν_{max} cm^{-1}): 786 (C- S -C), 1301 (C- N), 1510 (C- C aromatic ring), 1565 (C=N) , 3042 (C-H ring), ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 4.02 (s 3x3H, CH_3), 5.42 (s, 2x2H, CH_2), 6.05 (s, 3x1H, CH of benzothiazole), 6.90 (d, 1 H, =C (H) - Ar) , 7.10 - 8.12 (m , 5H, Ar-H).

3: A general process of synthesis of 2-(substituted phenyl) -3- (5 ,5 ,6,7-trimethyl-3 a ,4 ,5 , 6 ,7,7 a - hexahydrobenzo [d]thiazol-2-yl) thiazolidin-4-one. 3 (a-e):Take the different solution of compound of Schiff base 2(a-e) **(0**.01mol) and thioglycollic acid (0.01 mol) in N, N dimethyl formamide 17 ml and add a pinch of anhydrous $ZnCl_2$, it reflux to 5.5 hr, progress of the reaction was check with the help of TLC using ethyl acetate: toluene 1:4 as an eluent. Excess solvent separated through distilled off and mixture cooled and then resulting portion poured into crushed ice crystal water and put it for formation of crystal at overnight respectively. The crystal were filtered, dried yield 60% light Brown solid , and IR value (K Br ν_{max} cm^{-1}) : 750 (CH- Cl), 786 (-S-C), 1301 (C-N), 1510 (-C-C- aromatic ring), 1565 (- C = N), 3042 (C-H ring), ^{1}HNMR ($CDCl_3$, DMSO - d_6) ppm (δ) : 4.54 (s 3x3H, CH_3), 5.03 (s, 1H, CH- Cl) , 5.97 (s, 2x2H, CH_2) , 6.61 (s , 3x1H, C - H of benzothiazole), 6.70 (d, 1 H , = CH – Ar) , 7.14-8.15 (m, 5H , Ar -H).

Table 1 Physical and Elemental data

Compound N o	R- Group and position	Molecular formula	Molecular weight (g)	mp in ^{0}C	Yield	Recrystalised Solvent	Actual Elemental analysis			Calculated Elemental analysis		
							C	H	N	C	H	N
2a	H	$C_{17}H_{20}N_2S$	384	65	78	ethanol	71.79	7.09	9.85	71.83	7.08	9.84
2b	4 -OH	$C_{17}H_{20}N_2OS$	300	68	75	methanol	67.97	6.71	9.32	67.96	6.72	9.32
2c	4-Cl	$C_{17}H_{19}ClN_2S$	319	67	73	ethanol	64.04	6.01	8.79	64.06	6.00	8.78
2d	Ar 2 -OH	$C_{17}H_{20}N_2OS$	300	72	68	ethanol	67.97	6.71	9.32	68.00	6.72	9.32
2e	4-CH_3	$C_{18}H_{22}N_2S$	298	137	62	ethanol	72.44	7.43	9.39	72.44	7.95	9.37
3a	H	$C_{19}H_{22}N_2OS_2$	359	80	66	methanol	63.65	6.19	7.81	63.65	6.18	7.81
3b	Ar 4- OH	$C_{19}H_{22}N_2O_2S_2$	375	85	63	ethanol	60.93	5.92	7.48	60.93	5.92	7.49
3c	4-Cl	$C_{19}H_{21}ClN_2OS$	393	79	57	ethanol	58.07	5.39	7.13	58.07	5.38	7.13
3d	2-OH	$C_{19}H_{22}N_2O_2S_2$	375	82	51	methanol	60.93	5.92	7.78	60.97	5.92	7.49
3e	4- CH_3	$C_{20}H_{24}N_2OS_2$	372	132	59	ethanol	64.48	6.49	7.52	64.47	6.49	7.52

FUNGAL ACTIVITY

All novel different synthesize derivative were tested against their properties as antifungal nature. Antifungal properties determine, confirm by use disc diffusion procedure [3, 5, 17] against *Candida albicans*, *Candida albicans* ACCT and *Candida krusei* G03. Inhibition nature of stain conformed, recorded in (mm). Antifungal property of its synthesized new compounds, compared with the standard drug Griseofulvin.

RESULT AND DISCUSSION

Table -2 pertaining to the antifungal activity, data of thiazole / thiazolidinone indicates that these compounds showed moderate antifungal activity. Amongst them, compound 3c, 3d were found to be relatively more effective and active against all three stains of fungi showing a zone of inhibition, respectively. It was also noticed from the data that other compounds, substitutes were also showed the order of antifungal activity against only one organism, the antifungal activity of compounds 3a, and 3c showed better activity then compound 2a, 2c due to presence of thiazolidinone moiety.

Table 2 Antifungal activity of compounds 2(a-e), 3(a-e)

Compounds No	Compound	R Group	Fungal Inhibition Zone/mm		
			C. albican	C. albicans ATCC	C. krusei
2a	$C_{17}H_{20}N_2S$	H	9	10	7
2b	$C_{17}H_{20}N_2OS$	4-OH	12	11	9
2c	$C_{17}H_{19}ClN_2S$	Cl	14	12	8
2d	$C_{17}H_{20}N_2OS$	2-OH	12	10	9
2e	$C_{18}H_{22}N_2S$	CH_3	15	13	10
3a	$C_{19}H_{22}N_2OS_2$	H	18	15	13
3b	$C_{19}H_{22}N_2O_2S_2$	4-OH	20	17	15
3c	$C_{19}H_{21}ClN_2OS$	Cl	26	25	19
3d	$C_{19}H_{22}N_2O_2S_2$	2-OH	24	20	14
3e	$C_{20}H_{24}N_2OS_2$	CH_3	25	22	16
3f Reference	Reference	Griseofulvin	25	26	18

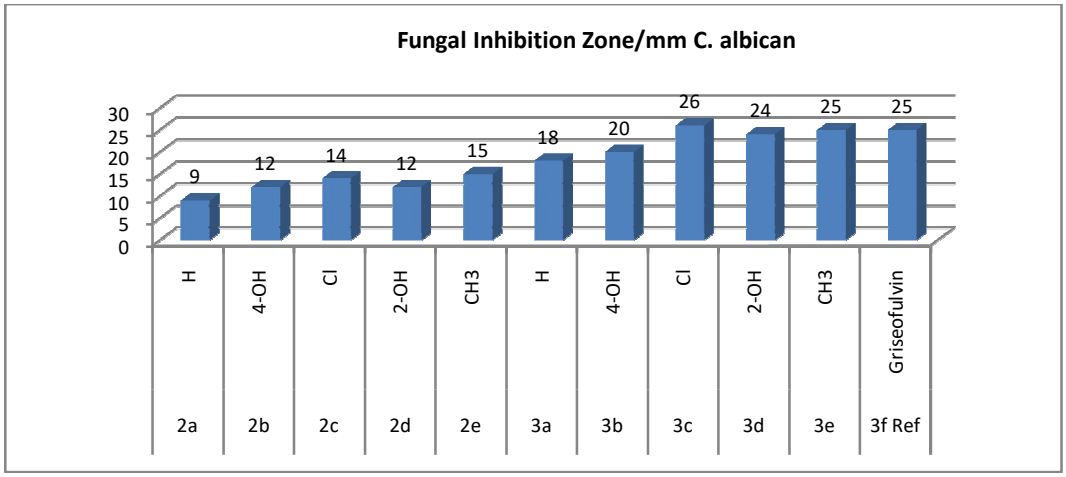


Chart 1: Fungal Inhibition Zone/mm, affectivity against C Albican and various function groups containing thiazolidinone moiety

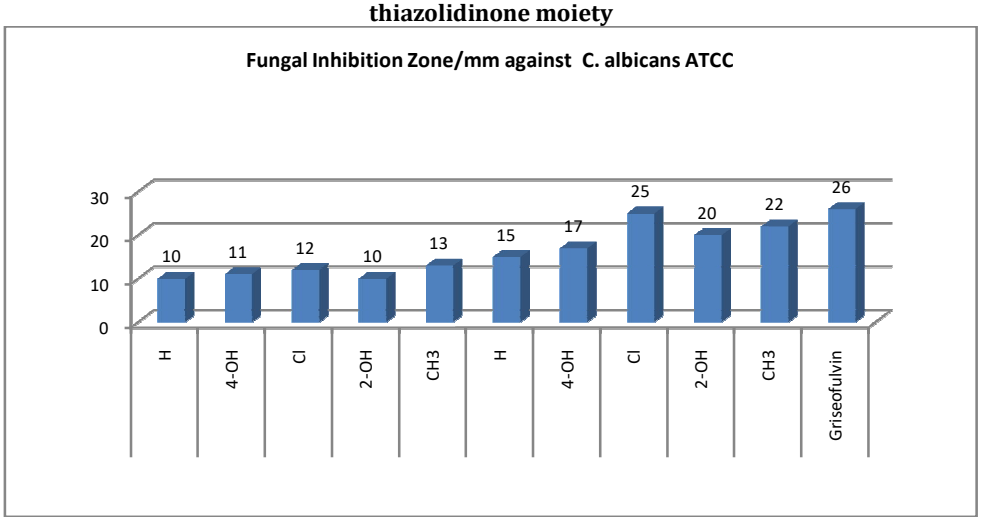


Chart 2: Fungal Inhibition Zone/mm, affectivity against C Albican ATCC and various function groups containing thiazolidinone moiety

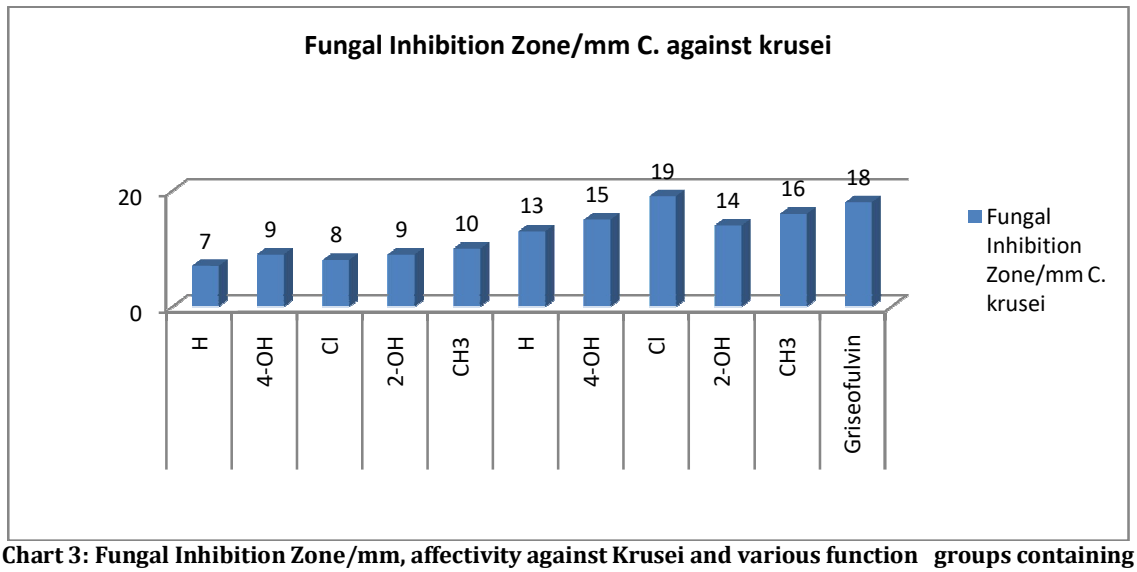


Chart 3: Fungal Inhibition Zone/mm, affectivity against Krusei and various function groups containing thiazolidinone moiety

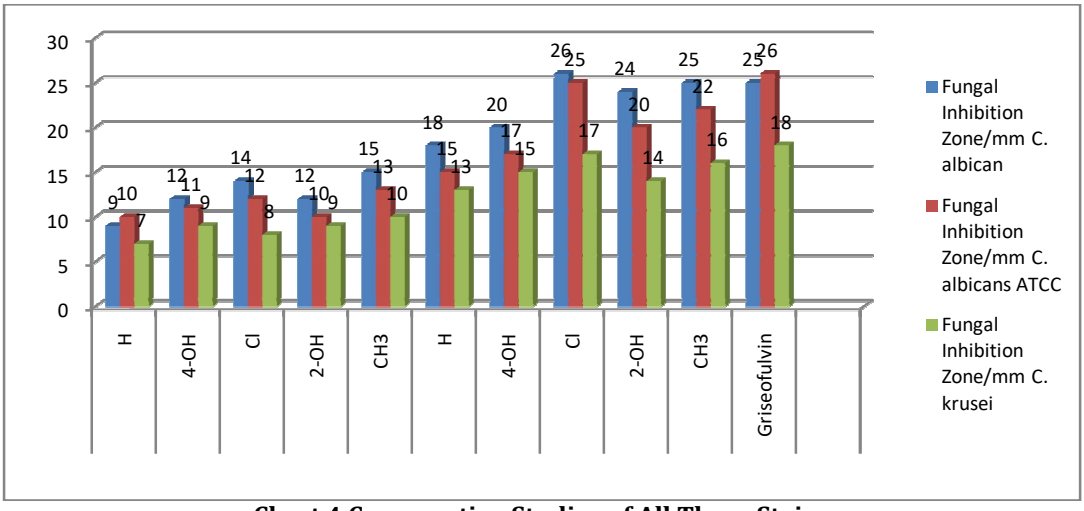
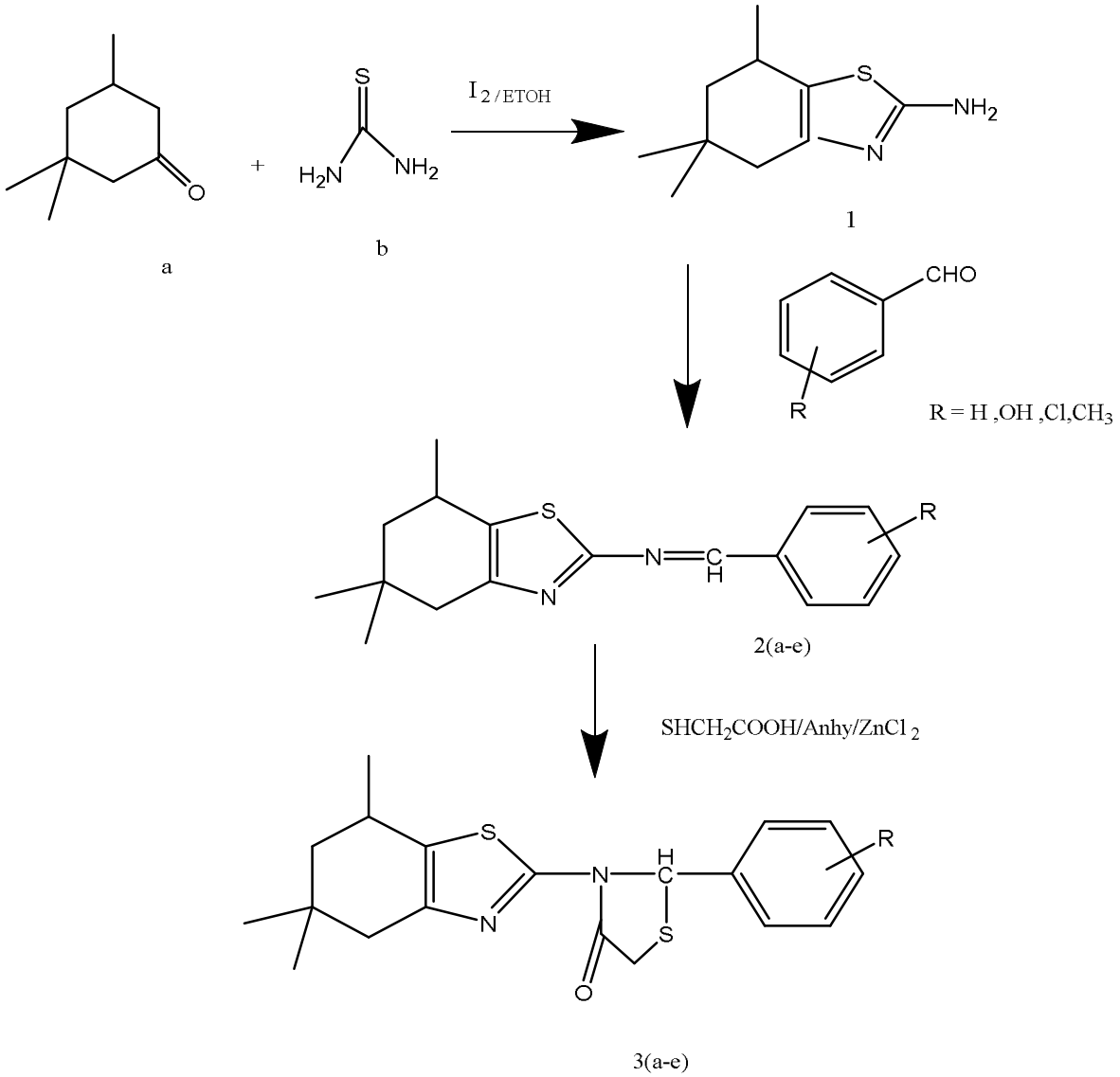


Chart 4 Comparative Studies of All Three Stains

CONCLUSION

Newly novel synthesised drug derivatives of thiazolidinone class of compounds give the better results to protect from different class of diseases and these drugs were very useful to alive system as compare to earlier synthesis drug .these drug may represent activity against biological system. Thiazolyl / thiazolidinone linkage enhance their activity of potent drugs and decrease the toxicity of novel drugs. 4 - Chloro substituted thiazolidinone derivatives 3c which has shown major , moderate but better antifungal activity i.e. 26 mm ,25mm ,19 mm against C albican , Calbican ATCC and C. krusei as compare with reference, standard drug Griseofulvin which represent the value 25 mm, 26mm, 18mm while other compound 3b,3d which is the related derivatives of thiazole , thiazolidinone , aromatics substituted- OH , at 2 and 4 position , which represent the moderate value ie at 4 OH-20 mm,17mm,15mm while at 2 position 24mm, 20mm, 14mm , Chart -1 ,2,3,4 represent the proper value of inhibition zone. 1st chat represent the anti fungal activity against C Albicans while chart 2 show the affectivity C Albicans ATCC while Chart 3 represent the antifungal properly against C krusai while chart 4 indicate comparative study and information of inhibition its affectivity as antifungal.



Schematic Representation, Synthesises Of some thiazolyl / Thiazolidinone Derivatives

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