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Synthesis Charecterization and biological evaluation of 4-amino-N'-(thiazol-2-yl) benzohydrazide

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A B S T R A C T

Synthesis of mannish bases derivatives containing aromatic rings were synthesized by the condensation 4-aminobenzohydrazide (1) with KSCN. It forms 2-(4-aminobenzoyl) hydrazine carbothioamide (3). The Compound (3) is treatment with substituted alpha halo ketones to obtained 4-amino-N'-(thiazol-2-yl) benzohydrazide (4). The structure of these newly synthesized compounds were characterized by ^{1}H NMR, $^{13}CNMR$, Mass, IR, and elemental analysis**.**

Keywords: KSCN, DMF, Hydrazine Hydrate, Alpha Halo Ketones

A R T I C L E I N F O

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1. Introduction

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].

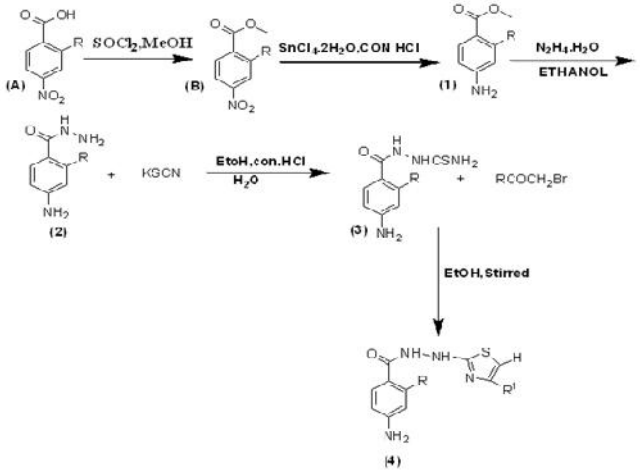
The geophilic species are natural habitats in the soil, natural habitats of the zoophilic dermatophytes are domestic and wild animals [3]. *Geotrichum candidum* was believed to be part of the normal flora of human skin and gastrointestinal tract. *Geotrichum* is frequently isolated from milk and is recorded 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]. Thiazole 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 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 thiazole heterocyclic incorporated drugs approved by the FDA [19-20]. The medicinal activity of thiazole functionality is due to its ability to serve as bioequivalent (bioisostere) of the carboxylic acid group. 1, 5-disubstituted thiazole can be used as isosteres of the*cis*-amide bond of peptides [21-23].

Biphenyl thiazole 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 thiazole 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 linked to thiazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive a heteroaromatic or acyclic system by means of a methylene group.

2. Materials and Methods:

Melting points were determined on open capillaries using a Centex melting point apparatus .T.L.C. analysis were performed on precoatedsilicagel (E-Merck Kieselgel 60 F_{254}) plates and visualization was done by exposing to iodine vapor .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 Gemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm) C^{13}NMR spectra were recorded on a bucker 75MHz spectrometer . mass spectra were scanned on a Varian MATCH -7 and Joel JMSD-300 mass spectrometer at 70ev. elemental analysis were carried out on caroler 106 and per kin –analyzer. All the chemicals used in the present investigation were purchased from Aldrich chemicals, U.S.A. in dole- 3-carbaldehyde was prepared by a reported method.



compd	4(a)	4(b)	4(c)	4(d)	4(e)	4(f)
R	H	CH_3	OCH_3	Cl	NO_2	CF_3
R^1	H	H	H	H	H	H

SCHEME 1

3. Results and Discussion

Synthesis of methyl 4-aminobenzoate (1)

A mixture of(b) (0.01mole) and excessive of con.HCl (15ml) and tin chloride monohydrate (0.05mol) was refluxed for two hours. The reaction progress was monitored by T.L.C. After completion of reaction cool at RT then filtered celite bed and concentrated the filtrate under reduced pressure to get color less solid.M.P.125^{0}C, yield 65 %

^{1}H NMR spectra (300MHZ,$(CD)_2$ SO,TMS): 7.19-7. 55 (m,4H,due to 4H of Benzene ring,),2.25(S,due to 2H of –NH_2) , 3.99((S,due to 3H of –CH_3)

IR spedtra: The compound (C) shows signals at, 1690(C=N), 1790 (-C=O), 3500(-NH_2), 3250(-NH)

Synthesis of 4-aminobenzohydrazide (2)

A solution of 1 (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 separated solid was filtered, washed with water and recrystalised from ethanol.

^{1}H NMR spectra (300MHZ,$(CD)_2$ SO,TMS): 7.10-7. 25 (m, 4H,due to 4H of Benzene ring,), 2.55(S,due to 2H of –NH_2) , 8.55(S,due to 1H of –NH)

IR spedtra, the compound (1) shows signals at, 1690 (C=N), 1790 (-C=O), 3500(-NH_2), 3250(-NH)

Synthesis of 2-(4-aminobenzoyl) hydrazine carbothioamide (3)

A mixture of 4-aminobenzohydrazide (2) (0.5212gr, 0.01563 mol), potassium thiocyanate (1.96gr, 0.02mol),

con.HCl (1ml),ethyl alcohol (10ml) and water (20ml) were refluxed for three hours. The solid obtained after cooling was collected by filtration, washed with water, dried and recrystalised from ethanol-DMF mixture to afford 2-(4-aminobenzoyl) hydrazine carbothioamide (3)

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS): 6.10(S, due to 2H of $–NH_2$),8.35(S,1H,due to the-NH attached to keto group),6.65-7.95(m,4H attached to the benzene ring), 4.95(s.1H attached to NH of thiazole ring),7.73(s.1H attached to amide group)

IR spedtra: The compound (3) shows signals at, 1660(C=N), 1790 (-C=O), 3500(-NH_2), 3250(-NH)

Synthesis of 4-amino-N'-(thiazol-2-yl)benzohydrazide(4)

A mixture of 2-(4-aminobenzoyl) hydrazine carbothioamide (3) (0.3012gr, 0.0007675mol), in DMF(10ml) and various bromoacetyl derivatives (1.9904gr, 0.01mol)in ethanol (10ml),was stirred at room temperature for 1-2 hours. The solid separated was filtered, dried and recrystalized from ethanol –DMF mixture.

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS): ;, 6.20(S,due to 2H of $–NH_2$),8.05(S,1H,due to the-NH attached to keto group),6.25-7.75(m,4H attached to the benzene ring), 4.25(s.1H attached to NH of thiazole ring),6.55-7.45(s,2H attached to thiazole ring) .

IR spedtra: The compound (4) shows signals at, 1690(C=N), 1720 (-C=O), 3570(-NH_2), 3150(-NH)

Table 1: Charactrization of above compounds

Compound	Molecular formulae	Yield	M.P.O^{0}C	% of Analysis					
				C		H		N	
				Calcd	Found	Calcd	Found	Calcd	Found
1	$C_8H_9NO_2$	60%	210	68.85	68.82	6.05	6.01	7.65	7.64
2	$C_7H_9N_3O$	54%	223	69.47	69.44	6.36	6.31	7.4	7.36
3	$C_8H_{10}N_4OS$	65%	215	66.66	66.64	6.1	6.06	7.5	7.07
4	$C_{10}H_{10}N_4OS$	62%	205	63	62.91	5.28	5.25	7.00	6.99

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 Bacillus cereus 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 -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 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-3.

Table 2: Antibacterial activity by disc diffusion method for phenyl thiazole 4(a.f)

Compound	Zone of inhibition (mm)			
	Staphylococcus aureus	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
4a	12	17	16	14
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 phenyl thiazole 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	25

4. Conclusion

- Furthermore the substitution with phenyl group having a chloro group at p-position showed better activities.
- Mannish bases and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, antiflammatory.

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