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Synthesis and antifungal screening of piperidone derivative with pyrazolone substituents

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Abstract

Ethyl 4-piperidone reacts with different amines in presence of toluene as a solvent and water is removed and Schiff base is formed. Then this Schiff base undergoes reduction and reduced product of Schiff base is obtained. Then it is undergoes for benzoylation, After benzoylation It reacts with two different azides and forms again Schiff base for both azides which further undergoes for clemensen reduction. The reduction product of both azides reacts with ethyl acetoacetate and undergoes cyclization and formed to get the desired cyclized product. product for antifungal screening by zone of inhibition study respect to some gram positive and gram negative microbes reference standard antibiotics. The satisfactory result has been found in the antifungal screening.

Key words: 4-piperidone, antifungal activity.

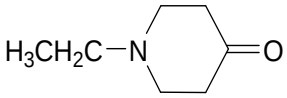
Introduction

The therapeutic problems has achived increasing importants in hospatilization patient,in immunosuppressed patients with AIDS or under going aother disease therapy and organ transplants.In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the imergence of old and new antibiotics resistant created in the last decades a substantial medical name for a new classes of **antifungal drug** is medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others.The fungal infections are superficial and

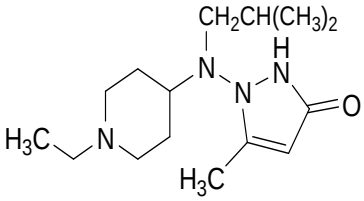
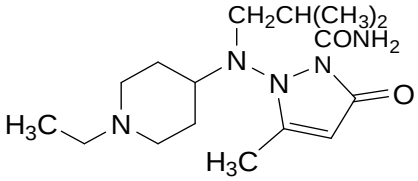
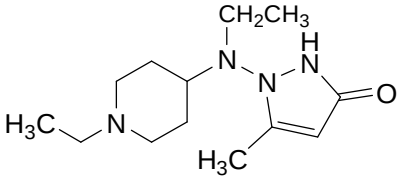
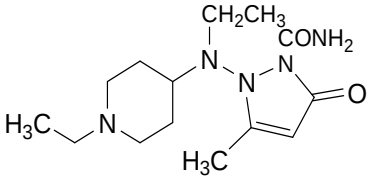
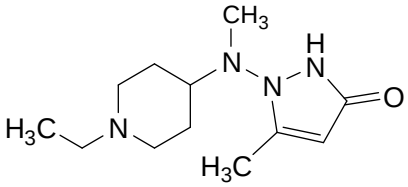
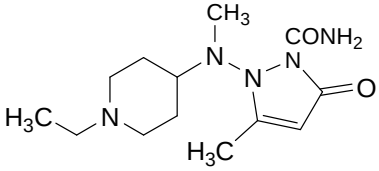
systemic.The causing infections of the hair, mucous memberanes,nails or skin include candida and dermatophyte fungi.drugs are active against fungi like *Candida albicans*, *Aspergillus niger*, etc.[1]

Figure. 1 Fungi

Synthesized compounds



Ethyl 4-piperidone

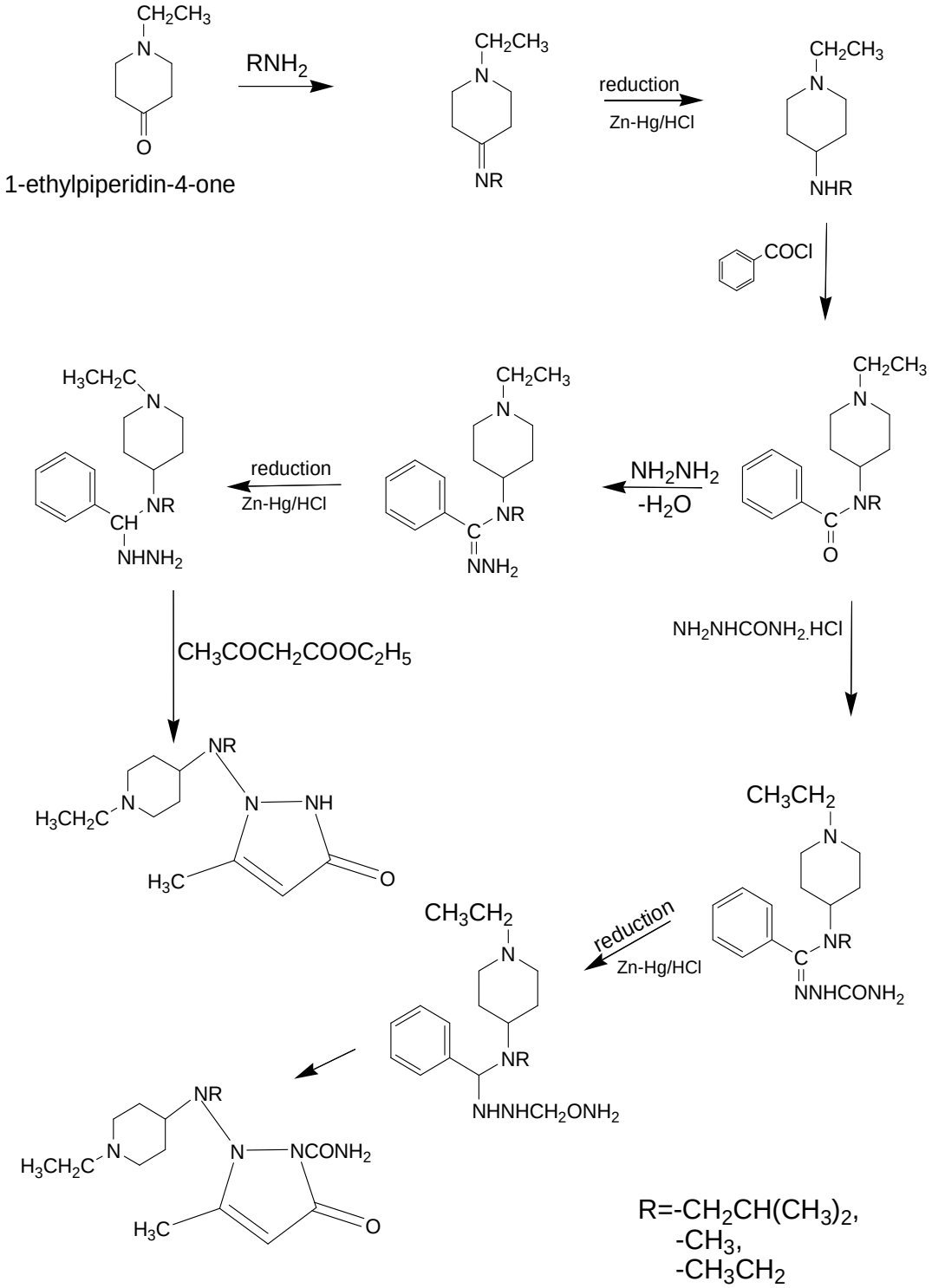
A4b 	**A5b** 	**B4b** 
B5b 	**C4b** 	**C5b** 

Chemistry:

Synthetic procedure:

Ethyl 4-piperidone reacts with different amines [isobutyl amine(A), ethyl amine(B),methylamine(C)]respectivly in presence of toluene as a solvent and water is removed and Schiff base is formed. Then this Schiff base undergoes reduction in presence of Zn-Hg /HCl and reduced product of Schiff base is obtained. Then it is reacted with benzoyl chloride and form benzoylated product, After benzoylation It reacts with two different azides: Hydrazide hydrate and semicarbazide .HCl and forms again Schiff base for both azides which further undergoes for

Scheme



clemensen reduction by reacting with ZnHg/HCl.the reduction product of both azides reacts with ethyl acetoacetate and undergoes cyclization and formed cyclized product.[2-4]

Preparation for Zn-Hg/HCl

A mixture of 200gm of zinc wool ,15gm of mercury(II)chloride,10ml of concentrated HCl and 250ml of water is stirred or shaken for 5minutes.The aqueous solution is decanted and amalgamated zinc is covered with with 150ml of water and 200ml of HCl.The material (about 0.3-0.4mol) to be reduced is then added immediately and reaction proceeds.[5]

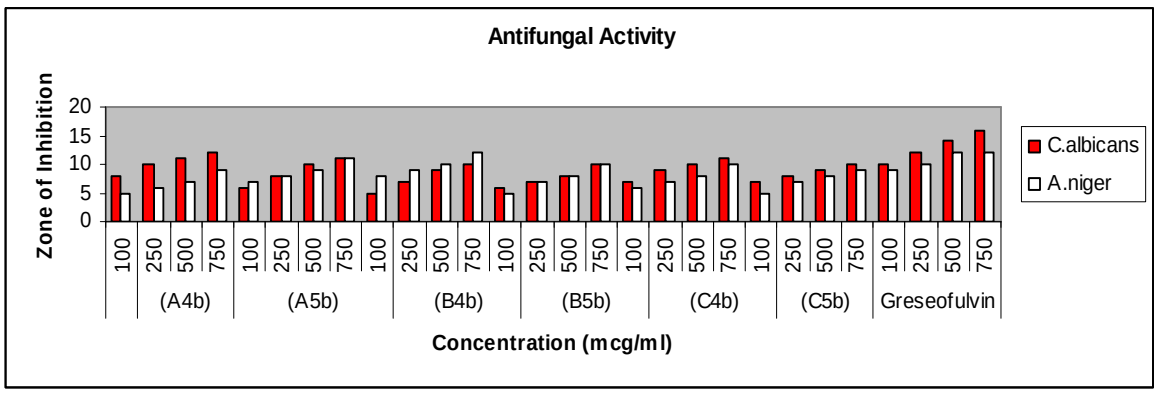
Physicochemical parameters of synthesis compound

Compound	Mol.formula	Mol.wt (g/mol)	M.P. (^{O}C)	Yield (%w/w)	Composition Calculated C, H, N (%)	Composition Found C, H, N (%)
Ethyl -4 -Piperidone	$C_7H_{13}NO$	127.18	45- 47^{0}C	58.60	C,66.05;H,9.50; N,11.50;O,12.40	C,66.10;H,10.30; N,11.01;O,12.58
A4b	$C_{15}H_{28}N_4O$	280.41	110-112	41.58	C,64.10;H,10.02; N,19.90; O, 5.45	C,64.25;H,10.06; N,19.98; O, 5.71
A5b	$C_{16}H_{29}N_5O_2$	329.43	102-104	46.37	C,57.42; H, 9.04; N,21.60; O, 9.70	C,59.42; H, 9.04; N,21.65; O, 9.89
B4b	$C_{13}H_{24}N_4O$	252.25	114-116	38.46	C,60.47; H, 9.59; N,22.20; O, 6.25	C,61.87; H, 9.59; N,22.20; O, 6.34
B5b	$C_{14}H_{25}N_5O_2$	295.38	138-140	43.67	C,56.93; H, 8.53; N,21.71;O,10.56	C,56.93; H, 8.53; N,23.71;O,10.83
C4b	$C_{12}H_{22}N_4O$	238.33	146-148	46.33	C,60.47; H, 9.30; N,21.48; O, 6.71	C,60.47; H, 9.30; N,23.51; O, 6.71
C5b	$C_{13}H_{23}N_5O_2$	281.95	152-154	51.57	C,53.50; H, 8.24; N,24.89;O,11.30	C,55.50; H, 8.24; N,24.89;O,11.37

Antifungal screening method

All the Petri dishes were sterilized in oven at 160°C for I hour. Agar media, Filter paper discs and test solutions were sterilized in autoclave at 121°C 16l bs/square inches. Pouring the molten sterile agar in sterile Petri dishes asceptically. Allow to cool the agar at RT and pouring the bacterial suspension on the petri dishes asceptically.

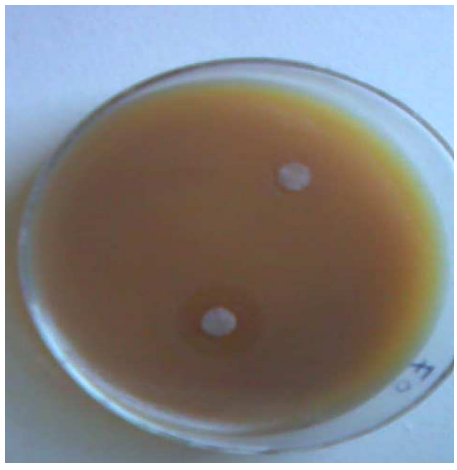
Histogram of antifungal activity



Placing the sterile filter paper discs in appropriate four quadrants of petridishes aseptically after soaking in the sterile test solutions. Incubate the Petridishes at 27°C for antifungal and observed the zone of inhibition.[6]

COMPOUND	CONC.(µg/ml)	Zone of inhibition (mm)	
		C.albicans	***A.niger***
(A4b)	100	8 ±0.6	5 ±0.6
	250	10 ±0.4	6 ±0.2
	500	11 ±0.1	7 ±0.8
	750	12 ±0.8	9 ±0.4
(A5b)	100	6 ±0.3	7 ±0.3
	250	8 ±0.5	8 ±0.4
	500	10 ±0.2	9 ±0.1
	750	11 ±0.7	11 ±0.5
(B4b)	100	5 ±0.5	8 ±0.3
	250	7 ±0.3	9 ±0.2
	500	9 ±0.6	10 ±0.7
	750	10 ±0.8	12 ±0.2
(B5b)	100	6 ±0.2	5 ±0.4
	250	7 ±0.45	7 ±0.5
	500	8 ±0.3	8 ±0.6
	750	10 ±0.6	10 ±0.3
(C4b)	100	7 ±0.4	6 ±0.1
	250	9 ±0.6	7 ±0.4
	500	10 ±0.4	8 ±0.2
	750	11 ±0.3	10 ±0.6
(C5b)	100	7 ±0.2	5 ±0.6
	250	8 ±0.6	7 ±0.4
	500	9 ±0.4	8 ±0.5
	750	10 ±0.7	9 ±0.1
Greseofulvin	100	10 ±0.1	9 ±0.5
	250	12 ±0.5	10 ±0.2
	500	14 ±0.6	12 ±0.4
	750	16 ±0.3	12 ±0.7

Antifungal zone of inhibition



Spectral data of synthesized compounds

Compound Code	U.V. λmax(nm)	IR (cm^{-1})	Mass (m/e)	NMR
A4b	**235.87**	~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide),~1487(C=N imino),~1243(C-N),~3005,3041(Ar C-H)	**282.9**	7.59(8H)d,2.5(2H)q, 3.4(2H)s,3.7(1H)s
A5b	**266.67**	~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino),~1243(C-N),~3005,3041(Ar C-H)	**325**	2.1(3H)s,2.4(2H)q, 3.8(1H)s,8.1(2H)d
B4b	**270.34**	~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino),~1243(C-N),~3005,3041(Ar C-H)	**250.1**	1.4(2H)q,1.3(3H)t, 7.1(8H)d,2.2(1H)m
B5b	**258.43**	~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino),~1243(C-N),~3005,3041(Ar C-H)	**294.1**	-
C4b	**265.64**	~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide), ~1487(C=N imino),~1243(C-N),~3005,3041(Ar C-H)	**237.2**	-
C5b	**266.67**	~3350(N-H), ~1632(C=O), ~1537,1589(-N-Hamide),~1487(C=N imino),~1243(C-N),~3005,3041(Ar C-H)	**279**	1.2(2H)m,7.5(1H)t, 2.1(3H)s,1.4(3H)t

Result

Antifungal activity was performed using turbidometric method using sabourad dextrose both against *C.Albicans* and *A.niger* .Greseofulvin as standard. All synthesized compounds were tested for antifungal activity against *C.Albicans* Compounds A4b.A5b,B4b,B5b,C4b,C5b were shown antifungal activity at hgher concentrations. Standard drug greseofulvin showed inhibition at all concentration (100,250,500,750 μg/ml).All six compounds were found to be less potent compared to greseofulvin.

Conclusion

From IR, Mass and NMR spectra data synthesized compounds are confirm. Among the all synthesized compounds, compound A4b gives a better antimicrobial activity against gram positive(*S.citrus* and *B.subtilis*) and gram negative(*E.coli*) bacteria than other synthesized

compounds. And compound A4b gives a better antifungal activity against fungi (*C.albicans)* than other synthesise compounds.

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